Wiadomości Lekarskie

Medical Advances

Official journal of the Polish Medical Association
Wiadomości Lekarskie has been published since 1928

Volume LXXVIII, Issue 6, JUNE 2025 ISSN 0043-5147 E-ISSN 2719-342X

Wiadomości Lekarskie

Medical Advances

Official journal of the Polish Medical Association
Wiadomości Lekarskie has been published since 1928

ALUNA Publishing

Volume LXXVIII, Issue 6, JUNE 2025

Memory of
dr Władysław
Biegański

Wiadomości Lekarskie Medical Advances is abstracted and indexed in:
PUBMED/MEDLINE, SCOPUS, EMBASE, INDEX COPERNICUS,
MINISTRY OF SCIENCE AND HIGHER EDUCATION, POLISH MEDICAL BIBLIOGRAPHY

Publisher:
ALUNA Publishing
29 Przesmyckiego st.,
05-510 Konstancin – Jeziorna, Poland
www.wydawnictwo-aluna.pl
www.wiadomoscilekarskie.pl
www.wiadlek.pl

Wiadomości Lekarskie
Medical Advances

Official journal of the Polish Medical Association
Wiadomości Lekarskie has been published since 1928

Editorial Team

CONTENTS

ORIGINAL ARTICLES

REVIEW ARTICLES

ORIGINAL ARTICLE

CONTENTS

Healthcare fraud in the United States of America and Ukraine: A comparative legal research

Anzhela B. Berzina[1], Pavlo S. Berzin[2], Ruslan A. Volynets[2], Olga M. Koval[3], Nataliia V. Marushchak[4], Mykhailo B. Holovko[5], Iryna Y. Khmil[1]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2]TARAS SHEVCHENKO NATIONAL UNIVERSITY OF KYIV, KYIV, UKRAINE
[3]KYIV NATIONAL UNIVERSITY OF TECHNOLOGY AND DESIGN, KYIV, UKRAINE
[4]PENITENTIARY ACADEMY OF UKRAINE, CHERNIHIV, UKRAINE
[5]CHERNIHIV POLYTECHNIC NATIONAL UNIVERSITY, CHERNIHIV, UKRAINE

ABSTRACT

Aim: To conduct a comparative legal study of healthcare fraud in the United States of America and Ukraine.

Materials and Methods: This study is based on the analysis of the US federal regulatory legislation (False Claims Act, Anti-Kickback Statute, Stark Law); data from the Fraud Section of the US Department of Justice for the last five years; case law in Ukraine (more than 30 court verdicts were analysed); data from the National Health Service of Ukraine. Dialectical, hermeneutic, comparative, analytical, synthetic, and systems analysis research methods were used.

Results: The criminal legislation acts that provide for criminal liability for healthcare fraud under the laws of the United States and Ukraine are analysed; the criteria for identifying types of healthcare fraud and related criminal offences are defined. It is determined that healthcare fraud has a multidimensional nature, which can manifest itself in different ways, but the common purpose in these manifestations of criminal behaviour is deception or intentional distortion of facts to obtain money or property that is under the control of or owned by any healthcare benefit programme (in the US) or medical guarantees programme (in Ukraine). There are various illegal manipulations with the state programme of medical guarantees. Starting from 2021, the judicial practice of Ukraine lacks a single acceptable approach to the criminal legal assessment of such illegal manipulations.

Conclusions: The experience of the United States in determining the types of criminal offences that constitute healthcare fraud and establishing criminal liability for their commission is appropriate to borrow.

KEY WORDS: fraud, drugs circulation, criminal offence, liability

Wiad Lek. 2025;78(6):967-973. doi: 10.36740/WLek/207347 DOI

INTRODUCTION

Over the past five years, healthcare fraud in the USA has become a serious problem, as the amount of damage from committing this type of white-collar crime increases every year, which also causes an increase in the cost of healthcare programmes for the US federal government. The consolidated report of the Fraud Section of the US Department of Justice (2024) states that the average loss from fraud per person charged in the USA was over $35 million [1]. According to estimates by the National Health Care Anti-Fraud Association, financial losses due to healthcare fraud in the USA amount to billions of dollars every year [2]. The United States has developed effective mechanisms to combat healthcare fraud. Ukraine began the transformation of the healthcare sector in 2017, and the state's purpose was to change the financing model in order to create a competitive environment in the circulation of medical and pharmaceutical products. The National Health Service of Ukraine was created as a manager of budget funds, the main task of which was the implementation of the medical guarantees programme in Ukraine. Judicial practice indicates the presence of fraud schemes with funds allocated by the state within the framework of the medical guarantees programme. Borrowing the experience of other states is extremely important for Ukraine, which seeks to move away from the model that existed before. And the experience of the USA will be invaluable in the further development and reconstruction of Ukraine.

AIM

The aim of the study is to conduct a comparative legal research of healthcare fraud in the United States and Ukraine.

Table 1. Data on healthcare fraud in the United States for 2020-2024

Year	Amount of damages (in USD)	Total accused (individuals)	Individuals convicted by pleading guilty in court
2024	3,33 billion	147	165
2023	3,83 billion	143	186
2022	2,3 billion	158	217
2021	1,76 billion	202	205
2020	3,77 billion	167	144

MATERIALS AND METHODS

This article is based on the analysis of acts of US federal regulatory legislation (False Claims Act (1868), Anti-Kickback Statute (1986) and Stark Law); data of the Fraud Section of the US Department of Justice for the last 5 years (2019-2024), as well as the legislation of the US states (such as California, New York, Texas, New Jersey, etc., a total of 15 states); case law in Ukraine (more than 30 court verdicts taken from the Unified State Register of Court Judgments of Ukraine were researched); data of the National Health Service of Ukraine; data from the official website of the Office of the Prosecutor General of Ukraine. Dialectical, hermeneutic, comparative, analytical, synthetic and system analysis research methods were used.

ETHICS

The authors declare that in preparing the article "Healthcare fraud in the United States of America and Ukraine: comparative legal research" all ethical principles and rules of academic integrity were observed.

RESULTS

In recent years, healthcare fraud has become more complex, resource-intensive, and costly than ever before. This is supported by data collected through publicly available information on healthcare fraud in the United States over the past 5 years, provided by the Fraud Section of the US Department of Justice. The systematized data is provided in Table 1.

Fig. 1 presents quantitative figures for trials and convictions in trials provided by the Fraud Section of the US Department of Justice for 2018–2023 [1].

Analysis of this data shows that healthcare fraud in the United States is a nationwide problem and that there is a statistically significant trend of increasing both the number of such cases and the amount of losses, which is due to the increase in spending on federal government healthcare programmes.

The regulatory laws that define the types and penalties for healthcare fraud in the United States are: 1) the False Claims Act (1868), which imposes liability on individuals and companies (usually federal contractors) who defraud government healthcare benefit programmes. Experts estimate that up to 10% of all healthcare costs are the result of false claims [3]; 2) Anti-Kickback Statute (1986), which prohibits financial payments or inducements for patient referrals or healthcare decisions. This federal law is codified in Title 42 *Public Health and Welfare* U.S. Code [4], and provides for criminal liability for those who knowingly and intentionally offer, solicit, receive, or pay any form of compensation in exchange for a referral to obtain services or products (including drugs) under any federal healthcare programme. The Statute is one of the most important healthcare fraud laws in the United States; 3) the Stark Law is a set of rules that define the federal prohibition on receiving "self-referrals" (self-referral prohibition), regulated by § 1395nn. *Restrictions on Referrals from Certain Therapists*, Title 42 U.S. Code.

These laws provide the US legislature with an understanding of the variations of fraud that show the main schemes that offenders use to avoid liability for illegal acts with healthcare benefit programmes (such as Medicare, Medicaid, etc.).

Types of healthcare fraud in the United States range from the illegal activities of an individual to large-scale operations by medical or pharmaceutical companies. The following criteria have been proposed for dividing types of healthcare fraud in the US: 1) violations of laws prohibiting kickbacks and certain financial arrangements; 2) manipulation of clinical trials/fraud against the Food and Drug Administration; 3) risk adjustment fraud; 4) compounding fraud; 5) illegal substitution of drugs; 6) Medicaid best price fraud; 7) fraud by pharmacy benefit managers; 8) prescription drug programme fraud (Medicare Part D fraud); 9) abuse of the 340B drug discount programme for low-income and uninsured patients; 10) fraudulent billing for services in violation of the False Claims Act; 11) off-label marketing of prescription drugs; 12) telemedicine fraud.

Fig. 2. presents the most common types of healthcare fraud in the United States.

In Ukraine, the transformation of the healthcare system began after the adoption of the Law of Ukraine "On State Financial Guarantees of Medical Services

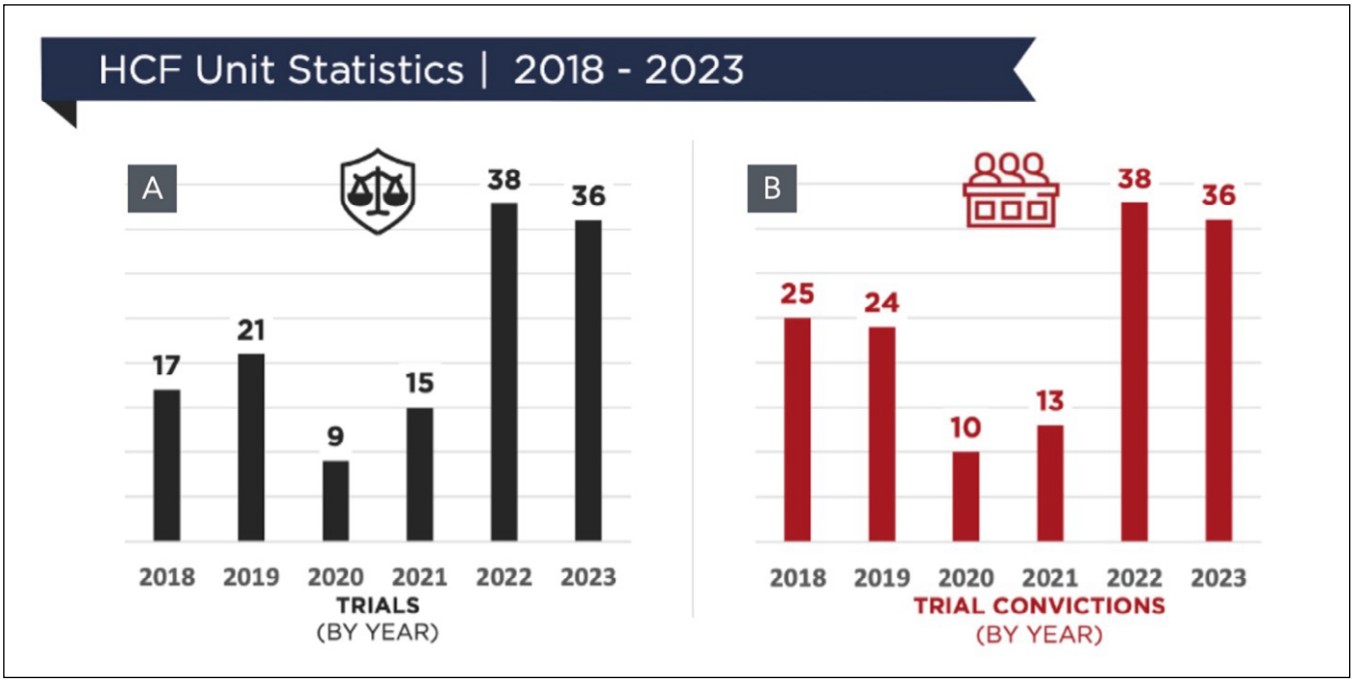

Fig. 1. Data from the Fraud Section of the US Department of Justice for 2018-2023 [1] (A — shows the number of court proceedings in a given year; B — shows the number of court decisions in a given year)

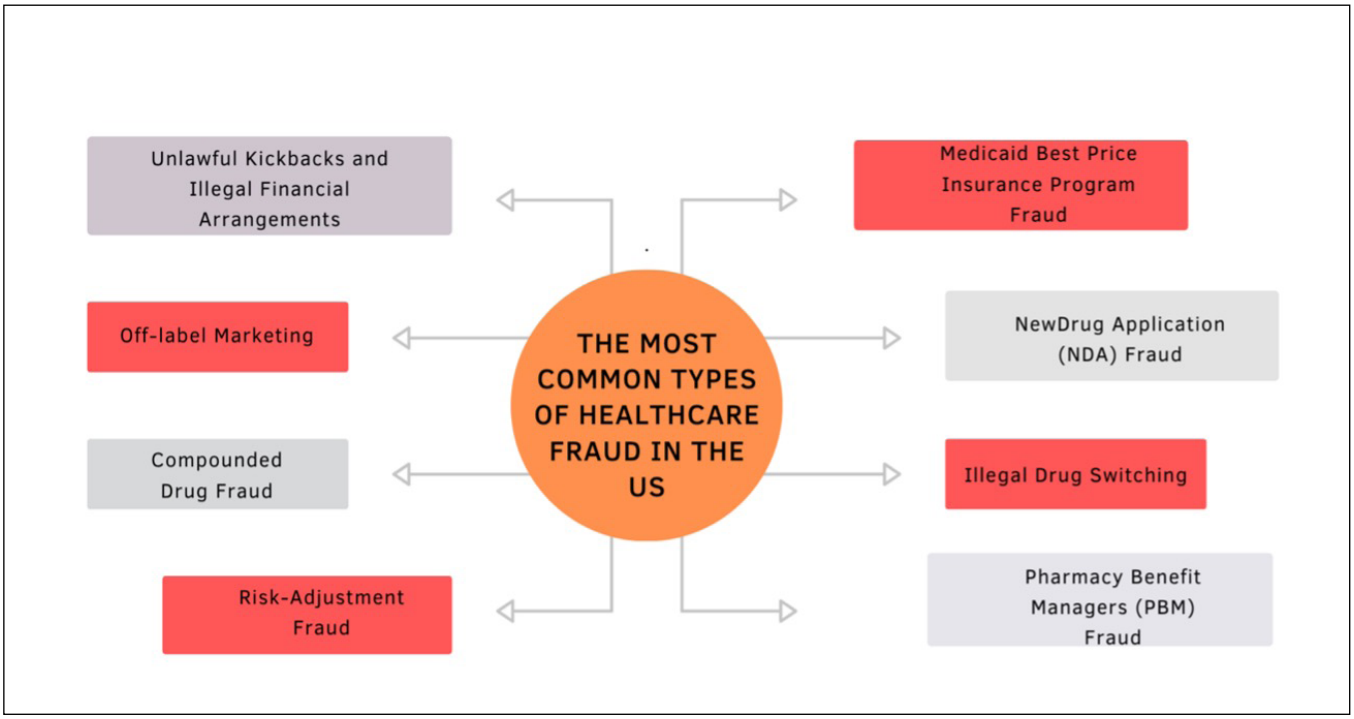

Fig. 2. The most common types of healthcare fraud in the United States

for the Population" (2017) [5]. This law established financial guarantees from the state at the expense of the State Budget of Ukraine for the provision of necessary medical services and drugs of proper quality to patients within the framework of the reimbursement programme. These are components of the medical guarantees programme, which has been in effect in Ukraine since 2017, the emergence of which was due to the beginning of the Medical Reform [6]. An important component of the medical reform was the implementation of the Concept for the Development of Electronic Health Care in Ukraine [7].

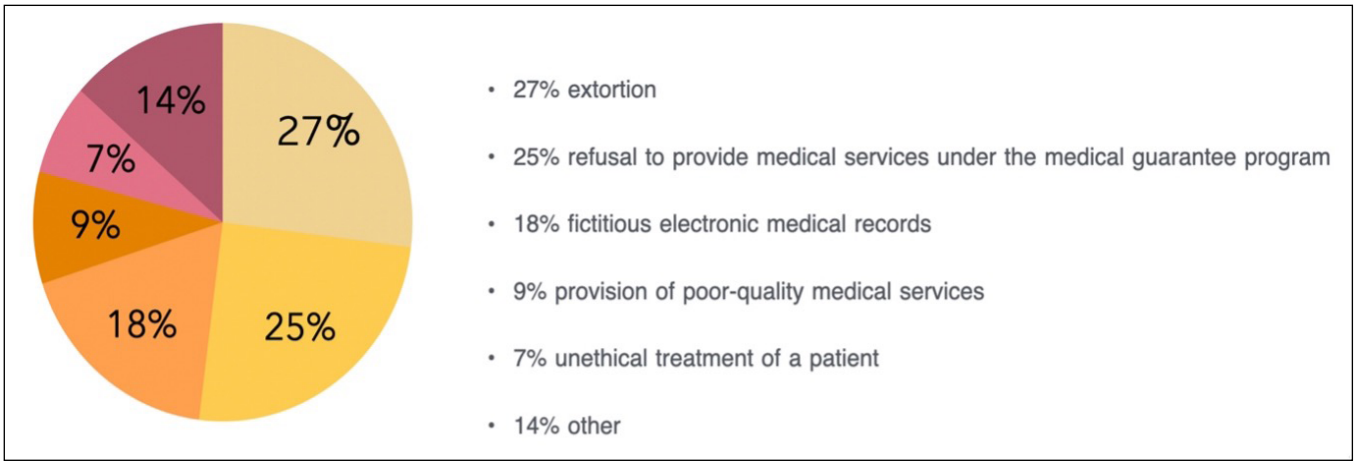

Fig. 3. Data on complaints received from patients regarding the medical guarantees program for 2023 from the National Health Service of Ukraine [8]

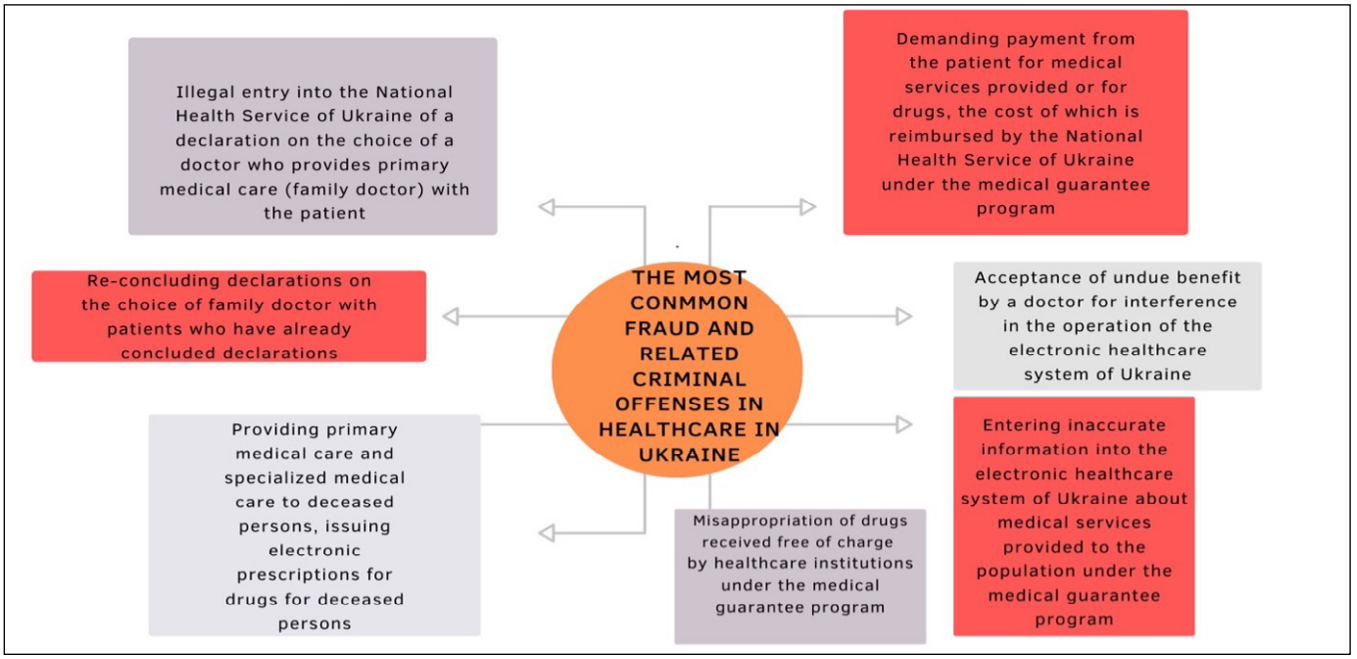

Fig. 4. The most common fraud and related criminal offenses in healthcare in Ukraine

The National Health Service of Ukraine (created in 2017) records complaints about violations of patients' rights; most of them are considered in the procedure of claims work (Fig. 3).

In order to respond to such complaints, the National Health Service of Ukraine monitors the implementation of contracts under the medical guarantees program. This procedure established by the Resolution of the Cabinet of Ministers of Ukraine "On Contracts for Medical Services of the Population under the Medical Guarantees Program" (2018) [9]. Clause 28 of this Resolution stipulates that if, during the monitoring, facts are identified that may indicate the commission of a criminal offense or violations of the terms of provision of medical services, the consideration of which is outside the contractual relations between the provider and the customer and the rights of the customer under the contract, the customer shall transmit information about such facts to the relevant state and law enforcement agencies. If such facts are a criminal offence, criminal liability may arise for their commission.

The most typical criminal offenses with the medical guarantees program include: 1) entering into the e-health system a declaration on the choice of a doctor who provides primary medical care (family doctor) with a patient in the absence of his will and consent or will and consent of his legal representative; re-concluding the declaration on the choice of a doctor who provides primary medical care with a patient who has already concluded it; 2) demanding from the patient payment for medical services provided or payment for drugs, the cost of which is reimbursed by the National Health Service of Ukraine under the medical guarantees program in accordance with the agreement on state financial

guarantees for medical services for the population concluded with a healthcare institution or an individual entrepreneur doctor; 3) provision of primary medical care and specialized medical care to deceased persons, issuing electronic drug prescriptions for deceased persons; 4) entering unreliable information into the e-health system about medical services provided to the population under the medical guarantees program, which may include: a) formation of fictitious reports on medical services provided; b) issuing referrals for laboratory diagnostics, which the patient was not aware of or which were not free of charge; c) drug prescribing under the "Affordable Drugs" program to those persons who did not actually apply for an electronic prescription; d) erroneous clinical coding; 5) acceptance of an unlawful benefit by a doctor for interference in the operation of the e-health system; 6) appropriation of drugs received free of charge by health institutions under the medical guarantees program under agreements with the National Health Service of Ukraine and their further sale.

As a rule, the criminal intent in such criminal offenses is aimed at obtaining from the state the right to receive additional funds provided for the encouragement of the doctor who provides primary medical care for concluding a declaration with the patient on the choice of a doctor. In order to clarify the way the state responds to such criminal offenses, judicial practice was analyzed. But such illegal acts will not always be classified as fraud. It is necessary to distinguish fraud from related criminal offenses in healthcare in Ukraine. The analysis showed that the share of criminal offenses with the medical guarantees program belongs to actions of entering declarations on the choice of a doctor who provides primary medical care into the e-health system in the absence of the will and consent of the patient or his legal representative. These offenses are committed by persons who have the right to access electronic media using a service computer and a personal key with an electronic digital signature and an access identifier to the National Health Service of Ukraine database and are mainly classified under Part 1 or 2 of Article 362 of the Criminal Code of Ukraine [10].

Fig. 4 presents the most common fraud and related criminal offenses in healthcare in Ukraine.

DISCUSSION

Healthcare fraud has a multidimensional nature, which can manifest itself in different ways, but the common purpose in these manifestations of criminal behavior is deception or intentional distortion of facts in order to obtain money or property that is under the control or owned by any healthcare benefit program (in the US) or medical guarantees program (in Ukraine). According to the criminal law of Ukraine, healthcare fraud should be distinguished from related criminal offenses in healthcare.

In search of a definition of the concept of fraud, let us turn to the Dictionary of Criminal Justice Data Terminology of the US Department of Justice, which states that fraud (fraud offense) is a criminal type comprising offenses sharing the elements of the practice of deceit or intentional misrepresentation of facts, with the intent of unlawfully depriving a person of his property or legal rights [11].

Healthcare fraud, as part of white-collar crime in the US, can be traced in the research of such American scholars as G. Becker (1968) [12], P. Kalb (1999) [13], R. Goel (2020) [14], K. Drabiak & J. Wolfson (2020) [15].

In Ukraine, fraud is considered to be the taking of another person's property or the acquisition of property rights through deception or abuse of trust (Article 190 of the Criminal Code of Ukraine) [10]. It has been the subject of consideration by a number of scholars, but healthcare fraud has only been considered indirectly [16-20].

Federal charges of healthcare fraud are based on § 1347. Title 18, US Code, which provides for criminal liability if a person knowingly and intentionally carries out or attempts to carry out a scheme or ruse to defraud any healthcare benefit program by making false claims, statements, or promises to obtain money or property under the control or ownership of any healthcare benefit program [21]. The mechanism of fraud may vary depending on the type of benefit program involved or the purpose of the fraud – either to obtain money or to obtain a valuable service. It is a criminal offense in the US. The punishment depends on the qualifying characteristics.

Healthcare fraud occurs when a person, company, or provider commits fraud under a federal government healthcare or insurance program. In the US these programs include Medicare, Medicaid, TRICARE, or similar programs, and the result is often unfair competition. For example, Medicare (a U.S. government program that provides hospital and voluntary health insurance for people aged 65 and older and certain disabled people under age 65; effective January 1, 1992 [22]) and Medicaid (a federal, state, and local government-funded hospital and health insurance program for people of all ages and income levels) help their beneficiaries pay for prescription drugs [23]. There are different types of Medicare fraud, all of which have the same purpose: to illegally obtain reimbursement from Medicare or Medicaid or similar programs. In Ukraine information about the services provided is recorded in the e-health system,

which is administered by the state enterprise "Electronic Health". Unauthorized access to the e-Health system, improper record keeping, and filing illegal claims for payment for medical services are the most common manifestations of unlawful behavior regarding the state health care guarantee program, which constitutes healthcare fraud or is related to other criminal offenses.

CONCLUSIONS

1. The experience of the United States in determining the types of criminal offenses that constitute healthcare fraud and establishing criminal liability for their commission is appropriate to borrow. Healthcare fraud in the United States is fraud with government healthcare benefit programs (the most common among them are Medicare and Medicaid), which, as a negative phenomenon, emerged in the US almost immediately after the introduction of these programs (in particular, since 1992, when the Medicare program was implemented in the US, and later – other programs). The US law enforcement system was faced with manifestations of healthcare fraud, and medical and pharmaceutical companies, doctors, pharmacists, and intermediaries (such as pharmacy benefit managers) began to implement fraudulent schemes. The experience of the US in combating fraud at both the regulatory and enforcement levels deserves to be borrowed, especially considering the fact that in Ukraine, as part of the healthcare reform, its own healthcare program began to operate in 2017, which is called the medical guarantees program.
2. An important difference between the US and Ukrainian healthcare systems is the lack of mandatory health insurance in Ukraine, as well as the presence of a less developed drugs circulation market and significantly less funding in the state healthcare sector. There are various illegal manipulations with the state medical guarantee program, which is financed from the State Budget of Ukraine, and by their nature, these are healthcare fraudulent actions (in particular, the dispensing of prescription drugs under the "Affordable Medicines" program, medical "kickbacks," and other manifestations of monetary compensation). However, starting from 2021, the judicial practice of Ukraine has lacked a single acceptable approach to the criminal-legal assessment of such illegal manipulations. Therefore, there is an urgent need for such a criminal-legal assessment.

REFERENCES

1. Froud Section. United States Department of Justice. Year in review. 2024. https://www.justice.gov/criminal/media/1385111/dl?inline= [Accessed 11.03.2025]
2. The Challenge of Health Care Fraud. The National Health Care Anti-Fraud Association. https://www.nhcaa.org/tools-insights/about-health-care-fraud/the-challenge-of-health-care-fraud/ [Accessed 11.03.2025]
3. Healthcare & Pharmaceutical Fraud. What potential whistleblowers need to know about reporting fraud in the healthcare industry. https://constantinecannon.com/practice/whistleblower/whistleblower-types/healthcare-fraud/ [Accessed 11.03.2025]
4. 42 USC 1320a-7b: Criminal penalties for acts involving Federal health care programs. https://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section1320a-7b&num=0&edition=prelim [Accessed 11.03.2025]
5. Pro derzhavni finansovi harantiyi medychnoho obsluhovuvannya naselennya [On state financial guarantees for medical care for the population]: Law of Ukraine from 19.10.2017. № 2168-VIII. https://zakon.rada.gov.ua/laws/show/2168-19/card2#Card [Accessed 11.03.2025] (Ukrainian)
6. Medychna reforma [Medical reform]. https://www.kmu.gov.ua/reformi/rozvitok-lyudskogo-kapitalu/reforma-sistemi-ohoroni-zdorovya [Accessed 11.03.2025] (Ukrainian)
7. Kontseptsiya rozbudovy elektronnoyi okhorony zdorov"ya v Ukrayini [The concept of developing e-healthcare in Ukraine]. https://moz.gov.ua/uk/news/koncepciya-rozbudovi-elektronnoyi-ohoroni-zdorov-ya-ukrayini [Accessed 11.03.2025] (Ukrainian)
8. Zvit Natsional'noyi sluzhby zdorov'ya Ukrayiny [Report of the National Health Service of Ukraine]. 2023. https://edata.e-health.gov.ua/storage/files/report-2023-ua-web-1-1.pdf?1742134834 [Accessed 11.03.2025] (Ukrainian)
9. Pro dohovory pro medychne obsluhovuvannya naselennya za prohramoyu medychnykh harantiy [About contracts for medical care for the population under the medical guarantees program]: Resolution of the Cabinet of Ministers of Ukraine from 25.04.2018 № 410. https://zakon.rada.gov.ua/laws/show/410-2018-п#Text [Accessed 11.03.2025] (Ukrainian)
10. Kryminal'nyy kodeks Ukrayiny [Criminal Code of Ukraine]: Kodeks Ukrayiny vid 05.04.2005 r. № 2341-III. https://zakon.rada.gov.ua/laws/show/2341-14#Text [Accessed 10 March 2025] (Ukrainian)
11. U.S. Department of Justice, Dictionary of Criminal Justice Data Terminology. 2nd Ed. Washington, D.C.: Search Group Inc. 1981, p.258.
12. Becker G. Crime and Punishment: An Economic Approach. Journal of Political Economy. 1968;76(2):169-217.
13. Kalb PE. Health Care Fraud and Abuse. JAMA. 1999;282(12):1163–1168. doi:10.1001/jama.282.12.1163. DOI

14. Goel R. Medical professionals and health care fraud: Do they aid or check abuse? Managerial and Decision Economics. 2020;41(4):520-528. doi:10.1002/mde.3117. DOI
15. Drabiak K, Wolfson J. What should health care organizations do to reduce billing fraud and abuse? AMA J Ethics. 2020;22(3):E221-E231. doi:10.1001/amajethics.2020.221. DOI
16. Berzina A, Pletenetska A. Forensic medical and legal analysis of cases of improper performance of professional duties by medical employees, including incorrect prescription of medical product. Pol Merkur Lek. 2025;53(1):94–99. doi:10.36740/Merkur202501113. DOI
17. Dyachuk M. Normatyvnintehratsiya v sferi okhorony zdorov"ya Ukrayiny [Regulatory integration in the healthcare sector of Ukraine]. Klinichna ta profilaktychna medytsyna. 2025;1:153-161. doi:10.31612/2616-4868.1.2025.18. DOI
18. Batyrgareieva V, Babenko A, Kaija S. Corruption in medical sphere of Ukraine: current situation and ways of prevention. Wiad lek. 2019;72(9):1814–1821.
19. Pashkov V, Soloviov O, Harkusha A. Legal characteristics of pharmaceutical activity under the emergency conditions: pandemic and war. Wiad lek. 2022;75(9):2286–2292. doi:10.36740/WLek202209219. DOI
20. Berzin P, Volynets R, Ptashchenko D. Kryminal'ne pravo. Zahal'na chastyna: praktykum: navchal'nyy posibnyk [Criminal law. General part: practical course: textbook] za red. P.S. Berzina. Kyyiv: Alerta. 2023, p.608.
21. 18 U.S.C. 1347. Health care fraud. https://uscode.house.gov/browse/prelim@title18/part1&edition=prelim [Accessed 11.03.2025]
22. Medicare. Cambridge Dictionary. https://dictionary.cambridge.org/dictionary/english/medicare [Accessed 11.03.2025]
23. Medicaid. Cambridge Dictionary. https://dictionary.cambridge.org/dictionary/english/medicaid [Accessed 11.03.2025]

The study was performed as a fragment of the complex scientific project of the Educational and Scientific Institute of Law Taras Shevchenko National University of Kyiv «Legal support for the sustainable development of the economy of Ukraine in the context of European integration» (state registration number 0124U003297; term: 2024-2029).

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Anzhela B. Berzina
Bogomolets National Medical University
13 Taras Shevchenko Ave, 01601 Kyiv, Ukraine
e-mail: anzhela.kasumova@gmail.com

ORCID AND CONTRIBUTIONSHIP
Anzhela B. Berzina: 0000-0002-9885-309X A B C D F
Pavlo S. Berzin: 0000-0003-4146-7910 A D E F
Ruslan A. Volynets: 0000-0002-8134-8572 A B E F
Olga M. Koval: 0000-0003-1509-7258 C E F
Nataliia V. Marushchak: 0000-0001-9636-6274 A E F
Mykhailo B. Holovko: 0000-0002-0406-2319 C E F
Iryna Y. Khmil: 0000-0002-0157-0289 B C E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 18.02.2025
ACCEPTED: 02.06.2025

ORIGINAL ARTICLE

CONTENTS

Microbial contamination of dental unit waterlines systems in Ukraine: results a multicenter study (2020-2022)

Aidyn G. Salmanov[1,2], Taras P. Bondar[1,3], Kostiantyn M. Lykhota[4], Olena Dementieva[3], Evelina A. Chumak[3], Olena I. Ostapko[3], Oleksii Kuvaiev[3], Ella M. Pavlenko[4], Ihor I. Palyvoda[4], Kristina Vataga[4], Mikola A. Boiko[4], Yakush Oleksandr[4]

[1]UKRAINIAN ASSOCIATION OF INFECTION CONTROL AND ANTIMICROBIAL RESISTANCE, KYIV, UKRAINE
[2]THE ZARIFA ALYEVA INTERNATIONAL CENTER OF MEDICAL SCIENCE, KYIV, UKRAINE
[3]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[4]SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: The aim of this study was to evaluate the microbial contamination of dental unit waterlines (DUWLs) and characterize the microbial communities of biofilms in dental chair units (DCUs) from different specialties in Ukrainian dental clinics.

Materials and Methods: A multicentre study was performed between January 1, 2020, to December 31, 2022. Dental water samples and biofilm samples were obtained from 191 DCUs at eighteen dental clinics from seven regions of Ukraine. The genomic DNA of the biofilm samples was extracted, then 16S rDNA were amplified and sequenced.

Results: A total of 1,146 dental water samples were collected, of which 57,4% samples did not meet microbiological parameters of Ukrainian National Standard on drinking water. Sequencing results showed significant differences in bacterial community structure between dental specialties. The largest specific weight of biofilm samples with high bacterial concentrations were detected from orthodontics (54.2%), prosthodontic (47.5%), and oral surgery (44,3%). The 16S rDNA gene sequencing showed high diversity of bacteria (311 genera) were detected in the biofilm samples. Amount of potential human pathogens were detected in the biofilm samples, including *Pseudomonas aeruginosa* (33.7%), *Escherichia coli* (27.3%), *Enterococcus faecalis* (17.4%), *Enterococcus faecium* (9.5%), *Serratia marcescens* (6.8%), *Stenotrophomonas maltophilia* (5.9%), *Staphylococcus aureus* (5.1%), *Burkholderia cepacia* (4.3%), *Acinetobacter lwoffii* (4.8%), *Enterobacter cloacae* (4.6%), *Klebsiella oxytoca* (4.2%), *Streptococcus pneumoniae* (3.9%), *Streptococcus pyogenes* (2.6%), and *Streptococcus* sp, (1.9%).

Conclusions: The most water quality of the DUWLs tested failed to reach the Ukrainian drinking water standard. Furthermore, most DCUs contained pathogens which poses a risk of infection for patients.

KEY WORDS: dental unit waterlines, contamination, microorganisms, biofilm, Ukraine

Wiad Lek. 2025;78(6):974-981. doi: 10.36740/WLek/207349 DOI

INTRODUCTION

In the literature, the transmission of pathogens to patients during dental treatment has been a topic of discussion for many years. This is because using high-speed handpieces without cooling can cause irreversible damage to teeth, spraying water both to clean the working area and to cool the modern dental unit. A complex network of interconnected dental unit waterlines (DUWLs) supply water to dental instruments. Aerosols from dental instruments increase the risk of infection for both the patient and the dentist, due to the constant increase in the germs in the dental office.

Several previous studies showed that the water which reached the dental chair units (DCU) failed to meet national drinking water standards in various countries. The most studies on biofilm formation in DUWLs have focused on a range of individual DCUs. According to the literature, DUWL output water is often becomes contaminated by high densities of microorganisms, principally Gram-negative environmental bacteria including *Pseudomonas aeruginosa* [1, 2] and *Legionella* species, but sometimes contain *Staphylococcus aureus* [3], and *Acinetobacter* species [1]. A wide variety of approaches, many unsuccessful, have been proposed to control a complex network of interconnected plastic dental unit waterlines bacterial biofilm [3]. In Ukraine no studies focused on the water quality and formation of biofilm in dental chair unit waterlines system or individual dental chair units. Therefore, microbial contamination of water from DCUs and the prevalence of opportunistic microorganisms in this water in Ukrainian dental clinics is unknown.

AIM

The aim of this study was to evaluate the microbial contamination of dental unit waterlines (DUWLs) and characterize the microbial communities of biofilms in DCUs from different specialties in Ukrainian dental clinics.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

A multicentre study was performed between January 1, 2020, to December 31, 2022. Our study included eighteen dental clinics from seven regions (Kyiv, Zhytomyr, Kharkiv, Odesa, Mykolaiv, Kherson, and Lviv) of Ukraine. Of these, five were state-owned and seven were private dental clinics. Dental unit waterlines (DUWLs) include air/water syringe, ultrasonic scaler, and narrow-bore plastic tubing that carry water to the dental instruments. The dental chair and ancillary equipment at all dental clinics are used for routine general oral healthcare procedures. These procedures include oral examinations, dental extractions, endodontics, prosthodontic procedures, restorations and prophylaxis among others. All dental clinics used a closed system, where the reservoir bottles were filled with distilled water and attached to the DCUs or fitted at a designated location within the oral healthcare facility to ensure water supply. Inclusion criteria: all participants had to be perform routine dental procedures; dental clinics willing to partake in the study who completed the questionnaire were included in the study. Exclusion criteria: none. In this study a different number of DCUs were included in sampling.

SAMPLING PROTOCOL

All dental clinics participating in the study signed a letter of consent. The microbial contamination of water samples and presence of biofilm associated organisms from swab samples were collected at eighteen dental clinics from seven regions of Ukraine. All dental clinics used closed system DCUs and samples were collected from outlets of municipal taps, dental handpieces, distiller bottles and reservoir bottles. None of the DUWLs are treated with chlorine products or other disinfectants. However, in dental clinics surfaces and the handpieces are routinely treated with disinfectants between patients or are autoclaved.

COLLECTION OF WATER SAMPLES

In this study the exterior surfaces of taps, fast handpieces and DCU tubing were disinfected with an alcohol swab. Water samples were collected aseptically in wide-mouthed sterile glass bottles. The municipal water source water (tap) to the DCU in the dental clinic and water exiting the fast handpieces was allowed to run for one minute before a water sample was collected. Distilled water was used to fill reservoir bottles. Distilled water was used to fill reservoir bottles that were attached to the water system DCUs to supply water to the handpieces. Water samples were collected from distiller bottles as well as from reservoir bottles that were used for DCUs. Water samples were placed in a cooler box on ice and transported to the Zarifa Aliyeva International Center of Medical Science Laboratory and processed within 24 hours.

COLLECTION OF BIOFILM SAMPLES

In this study the conventional swabbing method of field testing with a cotton swab on surfaces for detecting pathogenic bacteria was used. The exterior surfaces of taps, fast handpieces and DCU tubing were disinfected with an alcohol swab. Swab samples were collected from the internal surfaces of distal outlets of taps and the fast handpieces of DCUs, and from internal surfaces of empty distiller bottles and reservoir bottles. Swabs of internal surfaces of sampling sites were collected aseptically using a pre-moistened cotton swab. Swab samples were placed in a cooler box on ice with a temperature not exceeding 4°C and were transported to the Zarifa Aliyeva International Center of Medical Science Laboratory and processed within 24 hours.

MICROBIAL ANALYSIS

In this study water and swab samples were measured against the Ukrainian National Standard, Drinking water, Requirements and control methods of quality DSTU 7525:2014 (2015) for heterotrophic plate counts (HPC) microbial drinking water quality and total coliforms. In this study the water sample was platted onto agar using the constant function of the ScanStation automatic plater (interscience) and spreading it evenly over the agar. This procedure was performed for all water samples. After incubated period all colonies were counted using the ScanStation Automatic colony counter (interscience) and reported as colony forming units, as stipulated in DSTU 7525:2014 (2015). In our study the membrane filtration technique was performed for the propagation and enumeration of total coliform bacteria. Each water sample was filtered through a Millipore Filtration assembly with a sterile membrane nitrocellulose grid filter. The membrane filters were placed on agar, which consists of a chromogenic medium and a

selective supplement. The samples were transported refrigerated to the Lab of the Zarifa Aliyeva International Center of Medical Science (Ukraine) and immediately analyzed. All samples were processed according to EN 12780:2002.

MOLECULAR ANALYSIS

In this study the biofilm samples were centrifuged and the sediment was collected. Then, DNA from biofilm samples was extracted using QIAmp® DNA Mini kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. The quality of DNA extraction was measured by agarose gel electrophoresis. In this study DNA was quantified by ultraviolet spectrophotometer. Extracted genomic DNA was amplified using a set of primers targeting bacterial 16SrRNA genes. Molecular analysis was conducted in the Lab of the Zarifa Aliyeva International Center of Medical Science (Ukraine).

ETHICS

The Ethics Board of the Ukrainian Association of Infection Control and Antimicrobial Resistance has approved the protocols of this study. All participants (dental clinics) were assured of their privacy and anonymity throughout the study and in subsequent reports and articles.

STATISTICAL ANALYSIS

In this study microbiological data were collected in Microsoft® Excel (Microsoft Corporation, WA, USA).

Descriptive statistics were conducted. All the data are presented as numbers and percentages. Levels of microbial contamination were summarised using descriptive statistics (mean, standard deviation, minimum, median, maximum) separately by type, location, and system. A p-value <0.05 was considered statistically significant. Where the p-value was less than 0.05 (<0.05), the hypothesis was rejected.

RESULTS

WATER QUALITY

During the study period (2020-2022), a total of 1,146 dental water samples were collected, of which 57,4% (95% CI: 55.9-58.9) samples did not meet microbial parameters. Only 42.6% of the water samples had bacterial concentrations below the threshold of Ukrainian National Standard DSTU 7525:2014 (2015) and to requirements of the State Sanitary Norms and Rules of the DSanPiN 2.2.4-171-10, section "Indicators of Epidemiological Safety of Drinking Water" (heterotrophic plate counts <100 CFU/mL). In 2022, compared to the baseline level (2020) for the dental water quality there was an increase in the number of non-standard water samples for microbiological indicators. During study period the share of non-standard dental water samples on microbiological parameters in 2022, 2021, and 2020 was 57.4%, 29.7 %, and 30.4%, respectively. The largest specific weight of non-standard (on microbiological parameters) water samples from DUWLs systems was detected in Mykolaiv, Kherson, Zhytomyr region of Ukraine (Table 1).

In this study HPC in both water and swab samples indicated mean counts significantly exceeding the Ukrainian National Standard DSTU 7525:2014, which stipulates that water should not contain more than 1×10^3 CFU mL of heterotrophic bacteria. The mean HPC count for water quality in DUWLs system in Ukrainian dental clinics was the high, 1.94×10^4 CFU mL for municipal tap water and 6.91×10^4 CFU mL in water exiting the handpieces. The average values HPC of DUWLs system of distiller bottles in dental clinics was 4.71×10^4 CFU mL and 5.88×10^4 CFU ml for reservoir bottles.

The high HPCs values in the supply water of dental clinics create optimal conditions for the growth of biofilm and the proliferation of opportunistic microorganisms – potential pathogens of healthcare infections (HAIs). These were indicated by the microbial load detected in this study on the internal surfaces of municipal taps, distiller bottles, reservoir bottles, and handpieces in Ukrainian dental clinics. Number of HPCs of the inner municipal tap surfaces of DCUs (4.1×10^3 CFU mL) and inner surfaces of handpieces (3.93×10^4 CFU/mL) were high exceeded the Ukrainian National Standard DSTU 7525:2014 recommendation for HPC of less than 1×10^3 CFU/mL The inner surfaces of reservoir bottles and distiller bottles were also not compliant with the DCTU 7525:2014 recommendation for HPC and was 8.1×10^4 CFU mL and 2.4×10^4 CFU/mL, respectively.

In present study the total coliforms were determined as an indicator organism of contamination and possible detection of potentially pathogenic bacteria in the DCUs at the various sampling sites. The Ukrainian National Standard, DSTU 7525:2014, for total coliforms stipulates that water should not contain more than 1×100 CFU/100 mL. However, the findings this study indicated that municipal taps supplying DCUs (9.2×100 CFU/100 mL) and water exiting handpieces (8.63×100 CFU/100 mL) did not comply with Ukrainian National Standard, DSTU 7525:2014 (2015). In this study the handpieces (6.2×100 CFU/100 mL), reservoir bottles (6×100 CFU/100 mL), and distiller bottles (1.36×100 CFU/100 mL) also, exceeded total coliform counts the DCTU 7525:2014 recommendation of 1×100 CFU/100 mL.

Table 1. The general information of sampling Dental Chair Units in Ukrainian dental clinics.

Region	Specialty	Number of sample	Age of DUWL				
			<3	4-6	7-10	11-14	≥15
Kyiv	Endodontics	9	1	2	7	0	0
	Orthodontics	18	1	4	6	5	2
	Periodontic	5	0	1	4	0	0
	Oral surgery	27	2	6	16	2	1
	Prosthodontic	22	3	5	9	2	3
Kharkiv	Endodontics	3	0	2	1	0	0
	Orthodontics	4	0	1	1	2	0
	Periodontic	2	0	1	1	0	0
	Oral surgery	5	0	2	3	0	0
	Prosthodontic	3	0	2	1	0	1
Mykolaiv	Endodontics	2	0	0	2	0	0
	Orthodontics	4	1	0	2	1	0
	Periodontic	1	0	1	0	0	0
	Oral surgery	3	1	1	1	0	0
	Prosthodontic	2	0	1	1	0	1
Kherson	Endodontics	2	0	1	1	0	0
	Orthodontics	4	0	0	3	1	0
	Periodontic	1	1	0	0	0	0
	Oral surgery	4	0	2	1	0	0
	Prosthodontic	5	0	2	2	1	2
Odesa	Endodontics	2	0	1	1	0	0
	Orthodontics	8	1	3	4	0	0
	Periodontic	2	1	1	0	0	0
	Oral surgery	7	1	4	2	0	0
	Prosthodontic	6	0	2	4	0	0
Zhytomyr	Endodontics	1	0	1	0	0	0
	Orthodontics	6	0	1	3	1	1
	Periodontic	1	1	0	0	0	0
	Oral surgery	3	0	1	2	0	0
	Prosthodontic	3	0	1	1	1	0
Lviv	Endodontics	2	1	1	0	0	0
	Orthodontics	9	1	3	5	0	0
	Periodontic	2	1	1	0	0	0
	Oral surgery	6	0	2	4	0	0
	Prosthodontic	7	0	2	5	0	0
	Total	**191**	**17**	**58**	**93**	**16**	**11**

MICROBIAL COMMUNITY OF THE BIOFILM

A total of 764 biofilm samples from 191 DCUs of five specialties (i.e., prosthodontics, orthodontics, endodontics, oral surgery, and periodontics) in four time points (i.e., internal surfaces of distal outlets of taps and the fast handpieces of DCUs, and from internal surfaces of empty distiller bottles and reservoir bottles) were collected. The biofilm samples from dental specialties had significantly different bacterial concentrations. Sequencing results showed significant differences in bacterial community structure between dental specialties. The largest specific weight of biofilm samples with high bacterial concentrations were detected from orthodontics (54.2%), prosthodontic (47.5%), and oral surgery (44,3%). Older DCUs were affected more frequently than those under five years of age. Biofilm

Table 2. The overall relative abundance (%) of potential pathogenic microorganism - pathogens of healthcare associated infections (HAI) in dental unit waterlines (DUWLs) system, Ukraine, 2020-2022.

Pathogen	Overall relative abundance (%)
Pseudomonas aeruginosa	33,7
Escherichia coli	27,3
Enterococcus faecalis	17,4
Enterococcus faecium	9,5
Serratia marcescens	6,8
Stenotrophomonas maltophilia	5,9
Staphylococcus aureus	5,1
Burkholderia cepacia	4,3
Acinetobacter lwoffii	4,8
Enterobacter cloacae	4,6
Klebsiella oxytoca	4,2
Streptococcus pneumoniae	3,9
Streptococcus pyogenes	2,6
Streptococcus sp,	1,9

samples with high bacterial concentrations from periodontics and endodontics specialties, was 31.4% and 27.8%, respectively. The biofilm samples with high bacterial concentrations were detected from the fast handpieces of DCUs (43.1%), reservoir bottles (37.8%) the internal surfaces of distal outlets of taps (29.1%), and internal surfaces of empty distiller bottles (17.9%).

Genomic DNA of samples was extracted, and then 16S ribosomal DNA (rDNA) were amplified and sequenced. Microbial community with high diversity of bacteria. In this study the 16S rDNA gene sequencing showed that the bacterial communities of all samples covered 27 classes, 64 orders, 133 families, 311 genera, and 487 species. Microorganisms belonging to multiple genera involved in human diseases were detected including 25 genera of bacteria. Amount of potential human pathogens were detected in the biofilm samples, including 7 genera of bacteria. The potentially human-pathogenic genera of bacteria with relative abundance over 1% were *Pseudomonas aeruginosa* (33.7±2.2%), *Escherichia coli* (27.3±2.4%), *Enterococcus faecalis* (17.4±1.4%), *Enterococcus faecium* (9.5±1.8%), *Serratia marcescens* (6.8±1.7%), *Stenotrophomonas maltophilia* (5.9±1.4%), *Staphylococcus aureus* (5.1±1.3%), *Burkholderia cepacia* (4.3±0.9%), *Acinetobacter lwoffii* (4.8±1.2%), *Enterobacter cloacae* (4.6±1.6%), *Klebsiella oxytoca* (4.2±0.6%), *Streptococcus pneumoniae* (3.9±0.8%), *Streptococcus pyogenes* (2.6±0.7%), and *Streptococcus* sp, (1.9±0.4%). These pathogens were detected in al dental clinics of Ukraine. The overall relative abundances (%) of potential pathogenic microorganism - pathogens of healthcare associated infections (HAI) and that among different groups of DUWL biofilm samples were shown in Table 2.

DISCUSSION

The aim of this study was to evaluate the microbial contamination of DUWLs and characterize the microbial communities of biofilms in DCUs from different specialties in Ukrainian dental clinics. In present study for the first time in Ukraine, microbial contamination of DUWLs and biofilm in DCUs related to dental specialty was comprehensively evaluated, with more abundance of bacterial communities using high-throughput sequencing technology.

The findings of this study revealed that water from DUWLs is heavily colonized by microbial communities. 57,4% of the DUWLs tested samples did not meet microbiological parameters of Ukrainian National Standard on drinking water. Sequencing results showed significant differences in bacterial community structure between dental specialties. The largest specific weight of biofilm samples with high bacterial concentrations were detected from orthodontics (54.2%), prosthodontic (47.5%), and oral surgery (44,3%). The biofilm samples with high bacterial concentrations were detected from the fast handpieces of DCUs (43.1%), reservoir bottles (37.8%) the internal surfaces of distal outlets of taps (29.1%), and internal surfaces of empty distiller bottles (17.9%). The 16S rDNA gene sequencing showed high diversity of bacteria (311 genera) were detected in the biofilm samples. Amount of potential human pathogens were detected in the biofilm samples, including *Pseudomonas aeruginosa, Escherichia coli, Enterococcus faecalis, Enterococcus faecium, Serratia marcescens, Stenotrophomonas maltophilia, Staphylococcus aureus*, *Burkholderia cepacia*, *Acinetobacter lwoffii*, *Enterobacter cloacae, Klebsiella oxytoca, Streptococcus pneumoniae, Streptococcus pyogenes*, and *Streptococcus* sp.

Several previous studies found that the water which reached the DUWLs failed to meet drinking water standards [4-8]. In our study a large proportion water samples of the DUWLs tested did not comply with the Ukrainian drinking water standards. According to the findings of a United Nations survey, Ukraine is ninety-fifth state in the ranking of drinking water quality [9]. According to the statistical report of the Centres for Disease Control and Prevention of the Ministry of Health of Ukraine (CDCP) and the Ukrainian Association of Infection Control and Antimicrobial Resistance, the situation with the quality of drinking water in healthcare institutions is not improving. In 2020, 2021 and 2022, the share of non-standard water samples for microbiological parameters was 21.2%, 29.7% and 43.5%, respectively [10].

Opportunistic pathogens such as *P. aeruginosa*, *E.coli* and Enterococci are prevalent in dental unit water and waterlines [5, 11-14]. In our study *P. aeruginosa* was detected in the source water and handpieces of DCUs, reservoir bottles and distiller bottles. It could be assumed that the waterlines of DCUs were colonised by *P. aeruginosa* to form biofilm. According to the literature, the origin of bacteria that contaminate DUWLs can be attributed to 2 factors: (1) contaminated municipal water that is used in DCUs, and (2) the suck back of patients' saliva into the DUWL because of ineffective or faulty anti-retraction valves [15]. Other authors reported that the contamination may be caused by the water supply [16], the retraction of biological fluids from the handpieces used in oral cavities of patients [17], or probably the continuous biofilm detachment or fragmentation in the narrow waterline tubes [18]. Opportunistic pathogens such as Legionella pneumophila, Pseudomonas aeruginosa, and Staphylococcus aureus have previously been revealed in water samples from DUWL [19, 20]. In addition, other genera such as Stenotrophomonas were also recovered in dental unit waters [21].

The biofilm was possibly sloughed off and was fed into the water supply of the fast handpieces where it contaminated the water at the distal outlets of these instruments. However, there are no legislated parameters relating to the presence of these organisms and microbial water quality. Their presence can encourage the growth of other microorganisms. According to requirements of the State Sanitary Norms and Rules of the DSanPiN 2.2.4-171-10, section "Indicators of Epidemiological Safety of Drinking Water", Appendix 1, "*E.coli*" and "Enterococci" indicators should not be listed. However, national statistical reports do not use data on contamination associated with *E. coli* and other microorganisms. According to statistical reporting, percentage shares of sub-standard samples of drinking water are to be reported in terms of bacteriological indicators. The water supply control and monitoring in healthcare institutions are conducted by various Central executive bodies, there is a need of interdepartmental coordination and unification of relevant reporting under water quality.

Legal regulation of drinking water in Ukraine is governed by legal acts. The main regulatory legal acts regulating the right to drinking water and its quality in Ukraine are Law on Drinking Water and Drinking Water Supply. Rationing of the quality and safety of drinking water is related to the area of subordinate legislation, but in Ukraine there are two standards at the same time: SanPiN 2.2.4-171-10 "Hygienic requirements for drinking water intended for human consumption" and State standards of Ukraine DSTU 7525: 2014 (2015) "Drinking water. Requirements and methods of quality control". According to the Law of Ukraine "On Technical Regulations and Conformity Assessment Procedures", the use of standards or their individual provisions is mandatory for healthcare facilities, if the standards are referred to in technical regulations. SanPiN 2.2.4-171-10 is a binding normative legal act, agreed with all interested ministries and departments. State SanPiN is applied to most water sources. At the same time National standards of Ukraine DSTU 7525:2014 (2015) are optional. Thus, SanPiN 2.2.4-171-10 remains the main valid normative document in the area of drinking water supply and drinking water quality in the Ukraine.

In European Union the quality and safety of drinking water is regulated by Directive 98/83 / EC. The Directive determines that the parametric values shall be complied with: in the case of water supplied from a distribution network, at the point, within premises or an establishment, at which it emerges from the taps that are normally used for human consumption. In order to reduce or eliminate the risk of non-compliance with a parametric value, the Directive requires strict compliance with the requirements of informing the public about changes in the quantity and quality of drinking water. However, in national legislation, insufficient attention is paid to controlling the quality of equipment and materials (pipes, containers, cranes, etc.).

The Ministry of Health of Ukraine currently has no explicit requirements for the quality of water, which is supplied to DCUs, and neither has it issued an infection control policy that regulates to protect their patients and healthcare personnel of dental practice. The Ukrainian National Health Policy also does not contain any regulations related to aspects to curb the transmission of healthcare associated infection or for infection control issues related to the oral healthcare practice.

STRENGTHS AND LIMITATION

In this study for the first time in Ukraine, biofilm in DCUs related to dental specialty was comprehensively evaluated, with more abundance of bacterial communities. For the first time, biofilm in DUWL related to dental specialty was comprehensively evaluated, with more abundance of bacterial communities. The findings of this study revealed that DUWLs are heavily colonized by bacterial communities. There is serious microbial contamination observed in DUWLs is due to opportunistic pathogens. Our findings could help better characterize and assess the cross-contamination risk of dental care.

A limitation of our study is that we studied water samples and biofilm samples deriving only from seven region (29.2%) of Ukraine and it cannot be representative of the overall Ukrainian situation. Further studies are required to address those limitations.In the future, research should be focused on the risks to patients and staff, surveillance of adverse events related to dental treatment and importance of following the advice of dental unit manufacturers. On the basis of comprehensive research on biofilms in Ukraine, further studies on prevention of biofilm accumulation are essential.

CONCLUSIONS

Results this study showed that both patients and dental staff are exposed to healthcare-associated infection risks due to inhalation or spreading of aerosols produced during dental cares. The present study contamination levels of DUWL water were high. The water quality of 57.4% of the DUWLs tested in the seven regions failed to reach the Ukrainian drinking water standard. Results of present study highlights the risk of contaminated source water that is supplied to DCUs, as well as the risk of contaminated water that exits distal outlets of fast handpieces of DCUs. Furthermore, most DCUs contained pathogens which poses a risk of infection for patients. Biofilm accumulation DCUs and multiple kinds of opportunistic pathogen emphasized the risk for healthcare associated infection during dental care and the importance of biofilm control.

REFERENCES

1. Lal B, Ravindra K, Biswal M. Appraisal of microbial contamination of dental unit water systems and practices of general dental practitioners for risk reduction. Environ Sci Pollut Res Int. 2018;25(33):33566-33572. doi: 10.1007/s11356-018-3298-y. DOI
2. Petchphayaprai C, Chotipan C, Sa-Ngiampak P et al. Effectiveness of iodine for continuous decontamination of dental unit waterline. BDJ Open. 2023;9(1):34. doi: 10.1038/s41405-023-00160-w. DOI
3. O'Donnell MJ, Boyle MA, Russell RJ et al. Management of dental unit waterline biofilms in the 21st century. Future Microbiol. 2011;6(10):1209-26. doi: 10.2217/fmb.11.104. DOI
4. Kader CB, de Smidt O, Oosthuysen J. Water Quality and Biofilm Formation in Dental Unit Waterline Systems in Mangaung, South Africa. Int Dent J. 2025:S0020-6539(24)01643-5. doi: 10.1016/j.identj.2024.12.025. DOI
5. Barben J, Kuehni CE, Schmid J. Water quality in dental chair units. A random sample in the canton of St. Gallen. Schweiz Monatsschr Zahnmed. 2009;119(10):976-85.
6. Szymańska J, Sitkowska J. Bacterial contamination of dental unit waterlines. Environ Monit Assess. 2013;185(5):3603-11. doi: 10.1007/s10661-012-2812-9. DOI
7. Arvand M, Hack A. Microbial contamination of dental unit waterlines in dental practices in Hesse, Germany: A cross-sectional study. Eur J Microbiol Immunol (Bp). 2013;3(1):49-52. doi: 10.1556/EuJMI.3.2013.1.7. DOI
8. Alkhulaifi MM, Alotaibi DH, Alajlan H et al. Assessment of nosocomial bacterial contamination in dental unit waterlines: Impact of flushing. Saudi Dent J. 2020;32(2):68-73. doi: 10.1016/j.sdentj.2019.07.003. DOI
9. Salmanov AG, Shchehlov DV, Artyomenko VV et al. Bezpeka patsiyentiv: upravlinnya ryzykamy. [Patient Safety: Risk Management]. Kyiv: AgrarMediaGroup. 2023, p.528. (Ukrainian)
10. Salmanov AG, Artyomenko VV. Klinichna epidemiolohiya ta dokazova medytsyna. [Clinical Epidemiology and Evidence-Based Medicine]. Kyiv: AgrarMediaGroup. 2023, 432 p. (Ukrainian)
11. Tesauro M, Consonni M, Grappasonni I et al. Dental unit water content and antibiotic resistance of Pseudomonas aeruginosa and Pseudomonas species: a case study. J Oral Microbiol. 2022;14(1):2107316. doi: 10.1080/20002297.2022.2107316. DOI
12. Coleman DC, O'Donnell MJ, Shore AC et al. Biofilm problems in dental unit water systems and its practical control. J Appl Microbiol. 2009;106(5):1424-37. doi: 10.1111/j.1365-2672.2008.04100.x. DOI
13. Fan C, Gu H, Liu L et al. Distinct Microbial Community of Accumulated Biofilm in Dental Unit Waterlines of Different Specialties. Front Cell Infect Microbiol. 2021;11:670211. doi: 10.3389/fcimb.2021.670211. DOI
14. Freitas VD, van der Sand ST, Simonetti AB. In vitro biofilm formation by Pseudomonas aeruginosa and Staphylococcus aureus on the surface of high-speed dental handpieces. Revista de Odontologia da UNESP. 2013;39(4):193–200.

15. Salmanov AG, Savychuk NO, Verner OM. Standarty infektsiynoho kontrolyu v stomatolohiyi. Navchal'nyy posibnyk. [Standards of Infection Control in Dentistry. Educational Manual]. Kyiv: AgrarMediaGroup. 2016, 424 p. (Ukrainian)
16. Zhang Y, Ping Y, Zhou R et al. High throughput sequencing-based analysis of microbial diversity in dental unit waterlines supports the importance of providing safe water for clinical use. J Infect Public Health. 2018;11(3):357-363. doi: 10.1016/j.jiph.2017.09.017. DOI
17. Costa D, Mercier A, Gravouil K et al. Pyrosequencing analysis of bacterial diversity in dental unit waterlines. Water Res. 2015;81:223-31. doi: 10.1016/j.watres.2015.05.065. DOI
18. Lal S, Pearce M, Achilles-Day UE et al. Developing an ecologically relevant heterogeneous biofilm model for dental-unit waterlines. Biofouling. 2017;33(1):75-87. doi: 10.1080/08927014.2016.1260710. DOI
19. Güngör ND, Kadaifçiler DG, Peker OÖ. Investigation of the bacterial load and antibiotic susceptibility of dental units. Environ Monit Assess. 2014;186(3):1847-53. doi: 10.1007/s10661-013-3498-3. DOI
20. Spagnolo AM, Sartini M, Cave DD et al. Evaluation of Microbiological and Free-Living Protozoa Contamination in Dental Unit Waterlines. Int J Environ Res Public Health. 2019;16(15):2648. doi: 10.3390/ijerph16152648. DOI
21. Fotedar S, Ganju S. Microbial Contamination of Dental Unit Water Lines in H.P. Government Dental College, Shimla. Saudi J. Dental Res. 2015;6(2):129–132. doi: 10.1016/j.sjdr.2014.11.002. DOI

We thank the participating dental clinics, dentists for their diligent efforts in sampling collection and the Lab of the Zarifa Aliyeva International Center of Medical Science (Ukraine) for microbial and molecular analysis of samples. The findings and conclusions in this study are those of the authors.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Aidyn G. Salmanov

Ukrainian association of infection control and antimicrobial resistance
3 Shuseva St., 04112 Kyiv, Ukraine
e-mail: mozsago@gmail.com

ORCID AND CONTRIBUTIONSHIP

Aidyn G. Salmanov: 0000-0002-4673-1154 A B C D E F
Taras P. Bondar: 0000-0003-0537-8021 A B D F
Kostiantyn M. Lykhota: 0000-0003-0912-6470 B D F
Olena Dementieva: 0000-0002-7049-518X B D F
Evelina A. Chumak: 0000-0003-2967-5346 B D F
Olena I. Ostapko: 0000-0001-6777-5116 B D F
Oleksii Kuvaiev: 0000-0002-0012-333X B D F
Ella M. Pavlenko: 0000-0001-6975-8934 B D F
Ihor I. Palyvoda: 0000-0002-2578-5444 B D F
Kristina Vataga: 0009-0006-5740-5924 B D F
Mikola A. Boiko: 0000-0003-2179-4703 B D F
Yakush Oleksandr: 0009-0008-6212-753X B D F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 16.02.2025
ACCEPTED: 01.06.2025

ORIGINAL ARTICLE

CONTENTS

Rational treatment of mild to moderate community-acquired pneumonia in previously healthy children

Oleksandr H. Buriak, Yurii M. Nechytailo
BUKOVINIAN STATE MEDICAL UNIVERSITY, CHERNIVTSI, UKRAINE

ABSTRACT

Aim: To analyze the features of antibacterial treatment in children hospitalized for community-acquired pneumonia and the potential influence of dysbiosis.
Materials and Methods: The work analyzed medical records of 51 children, aged 2 to 13 years, who were hospitalized with community-acquired pneumonia. Clinical symptoms, severity of the course, structure and duration of basic treatment measures, their cost, and signs of dysbiosis were studied in the patients.
Results: The average duration of hospital treatment for patients with community-acquired pneumonia was 13.3 ± 0.62 days, with 28 cases lasting between 14 and 30 days. Given the community-acquired nature of the infection, the initial use of cephalosporins was irrational and significantly increased the cost of treatment. After one week, signs of intestinal swelling, increased peristalsis, and unstable defecation, assessed as gut dysbiosis, appeared. Some symptoms, such as irritation in the throat, persistent cough, difficulty clearing mucus, shortness of breath, wheezing, and others, were regarded as signs of respiratory dysbiosis. The use of probiotics was initiated.
Conclusions: The study established the irrational use of third- and fourth-generation cephalosporins as first-line antibacterial treatment. Symptoms of intestinal discomfort and manifestations of mucociliary respiratory tract dysfunction should be regarded as gut-lung axis phenomena of dysbiosis.

KEY WORDS: community-acquired pneumonia, antibiotic treatment, microbiota, children

Wiad Lek. 2025;78(6):982-986. doi: 10.36740/WLek/207348 DOI

INTRODUCTION

Community-acquired pneumonia (CAP) among children is a global health problem worldwide and one of the leading causes of hospitalization and mortality [1, 2]. Over the past 20 years, there has been a substantial decrease in the incidence of childhood pneumonia and pneumonia-associated complications [3]. New vaccines against Haemophilus influenzae type b and Streptococcus pneumoniae have contributed to decreases in complicated pneumonia cases and have reduced mortality [4]. Unnecessary hospitalization also represents a significant and potentially avoidable burden on the child, their family, and the healthcare system. Indications for hospitalization of a child with CAP differ significantly depending on the country, region, and hospital. Even after evaluating the prognostic severity of the disease and regional differences in the structure of hospital establishments, the criteria for hospitalization remain inconsistent between outpatient and inpatient institutions. Nevertheless, CAP is still among the leading causes of outpatient visits and hospital admissions [5].

The etiology of CAP in the pediatric population is variable and changes according to factors such as age, disease severity, and place of residence. A high percentage of healthy children are colonized by S. pneumoniae, H. influenzae, or infected by various viruses. Numerous studies have shown that clinical, laboratory, and radiological criteria cannot reliably differentiate between bacterial and viral etiologies in children with CAP [6, 7]. Therefore, treatment decisions should be based on the expected pathogens according to the child's epidemiology and age. However, mixed bacterial-viral and viral infections are common, which complicates pathogen detection and effective treatment. The "gold standard" for determining pneumonia etiology is the detection of respiratory pathogens in specimens taken directly from the lungs via bronchoalveolar lavage, pleural fluid sampling, lung biopsy, or aspiration [8]. However, because these methods are invasive and require anesthesia in children, they are rarely performed in clinical practice [9].

The managing of etiological pneumonia treatment remains a challenge nowadays because the empiric antibiotic therapy is the first step after hospitalization and could be sometimes law effective. S. pneumoniae is the most common cause of CAP in Europe, but underestimation of its sensitivity to widely use antimicrobial medication and use of high and long-lasting treatment

leads to inappropriate results, which exacerbates the problem of resistance to antibiotics [10, 11]. As some cases of CAP in children could be viral, not every patient with non-severe CAP and without risk factors needs to be treated with high and long dose of antibiotics [12, 13]. The optimal duration of antibiotic treatment of children even with known bacterial CAP still remains unclear. Y. Gao et al. (2023) show that shorter-duration, compared with longer-duration antibiotics use, do not appreciably increase mortality and probably have little or no impact on the need for change in antibiotics [14]. This approach will also help reduce side effects, costs, and the development of microbial resistance.

Longer duration of antibiotics treatment influence normal intestinal microbiota with development of different level dysbiosis. Host-microbiota interaction plays fundamental roles in the homeostasis of mucosal immunity [15, 16]. Dysbiosis of intestinal microbiota has various immune changes and many multifactorial diseases. Many years have been considered that the lungs a sterile organ because microbiological culture techniques had shown negative results [17]. Improvement of culture-dependent and independent techniques has facilitated understanding of lung microbiota that not only exists in healthy lung but also play great role in immune responses under both physiological and pathological conditions. Understanding dysbiosis of the respiratory microbiome and altered mucous immunity in patients with different illness holds great promise to develop targeted host-directed immunotherapy to reduce ineffective treatment, to improve patient outcomes [18]. It is now widely accepted that exist a bi-directional gut-lung axis with connections of the intestinal and pulmonary microbiota and that modulation of both microbiota exist in health as in pathological status. Isolated dysbiosis of the respiratory tract occurs when the natural microbial balance of the upper or lower airways is disrupted, often due to antibiotic use, environmental factors, or underlying conditions [19]. This imbalance can increase susceptibility to infections, activate inflammation, alter mucociliary clearance, and cause other respiratory issues.

Chinese investigators D. Yang et al. (2020) discuss the causal roles of pulmonary dysbiosis in disease settings and suggest that the interaction between lung microbiota and the host is critical for establishing immune homeostasis in the lungs [20]. However, what constitutes a "healthy" microbiota remains a topic of active debate. Some authors hypothesize that the use of specific bacterial strains as "probiotics" could have positive effects on host immunity and/or protection against pathogens, potentially benefiting both the treatment of intestinal disorders and pulmonary diseases [21].

AIM

The study aimed to analyze the features of antibacterial treatment in children, hospitalized for acute community acquired pneumonia and potential dysbiosis influence.

MATERIALS AND METHODS

The work analyzed medical records of 51 children in age from 2 to 13 years that were in children clinical hospital with mild or moderate CAP. In patients were studied clinical symptoms, severity of course, structure and duration of basic treatment measures, their cost, signs of dysbiosis. Statistical analysis performed by means of Statistica programs (version 5.11, StatSoft Inc.) with calculating mean (M) and its standard error (m). Multivariate cluster analysis was used to analyze the relationship between clinical signs and peculiarities of treatment. A p-value <0,05 was considered as statistically significant.

The study was conducted in accordance with the principles of the World Medical Association`s Declaration of Helsinki «Ethical Principles for Medical Research Involving Human Subjects». Informed consent to participate was obtained from all those included in the study (parents of children or their guardians), which emphasizes the absence of invasive interventions. The study protocol was discussed and approved at a meeting of the Biomedical Ethics Committee of Bukovinian State Medical University.

RESULTS

The duration of hospital treatment was, on average, 13.3±0.62 days, with subsequent outpatient treatment and rehabilitation. Antibiotics, antipyretics, mucolytics, and, in some cases, antihistamines and corticosteroids were used in the treatment. In 28 cases (54.9%), hospitalization lasted from 14 to 30 days. In these patients, after 5-7 days of illness, body temperature was normal or subfebrile, with low levels of intoxication and only slight fatigue or general weakness.

According to clinical recommendations, Amoxicillin should be the starting antibiotic for the treatment of CAP in previously healthy children. However, in our study, it was used in only one child (Fig. 1). The first line of antibacterial treatment was primarily based on third- and fourth-generation cephalosporins. The most expensive medication in the treatment was antibiotics, while the least expensive were the antipyretics. Given the community-acquired nature of the process, the initial use of cephalosporins was irrational and significantly increased the cost of treatment. The total average cost per case was 2346.9±145.7 UAH (51.2±3.2 EUR).

Starting from the end of the first week, signs of intestinal swelling, increased peristalsis, unstable defecation, and

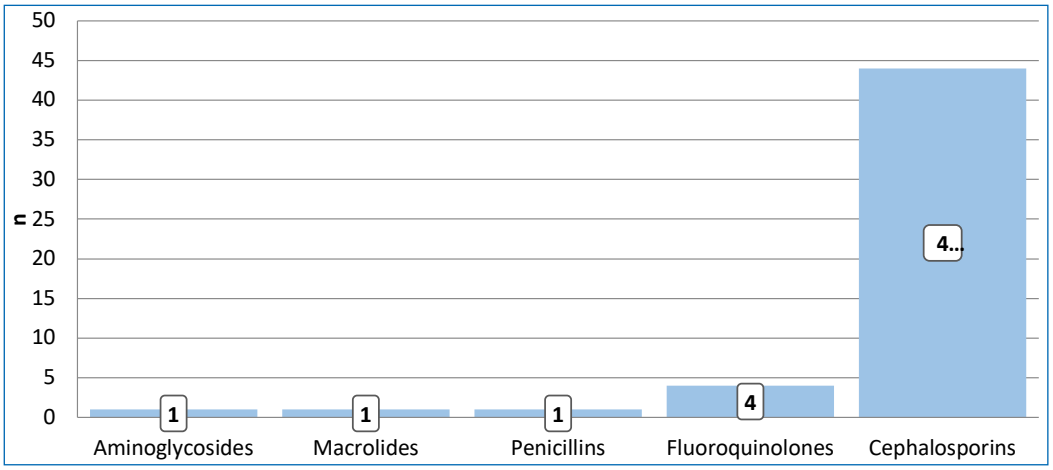

Fig. 1. The variants of first line antibacterial treatment (cases [n])

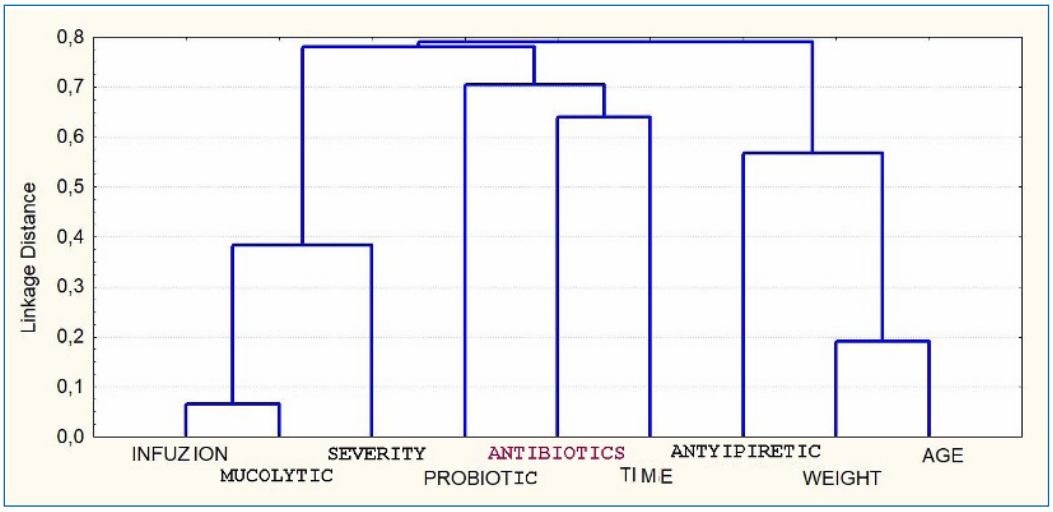

Fig. 2. Multivariate cluster analysis of the relationship between patients' indicators and treatment

other symptoms appeared. In all these cases, the symptoms were assessed as gut dysbiosis, and probiotics were prescribed. In this subgroup, some symptoms were noted, which we regarded as respiratory dysbiosis from the upper airways, such as frequent sore throat, persistent symptoms of chronic nasal congestion, postnasal drip, mild pharyngitis, and dryness or irritation in the throat. From the lower respiratory tract, symptoms mostly included persistent cough (dry or with minimal mucus secretion), difficulty clearing mucus, shortness of breath, or wheezing. These symptoms were assessed as dysbiosis of the respiratory tract, where the natural microbial balance of the upper or lower airways is disrupted. In all these cases, antibiotic use lasted more than two weeks, with a switch to another drug from the same group in the second line.

Multivariate cluster analysis of the relationship between clinical signs and treatment patterns revealed three distinct groups (Fig. 2). In the middle group, prolonged antibacterial treatment was associated with the use of probiotics. This suggests that prolonged use of antibiotics induces dysbiosis phenomena in the bi-directional gut-lung axis, linking the intestinal and pulmonary clinical symptoms.

DISCUSSION

There are a lot of last days investigations which show a high effectiveness of short course of antibiotics use. A. Dinh et al. (2021) in double-blind, randomized, placebo-controlled, non-inferiority have compared 5 days versus 10 days and 3 versus 7 days of antibiotic treatment of children with CAP and reported that shorter duration was not inferior or even superior to longer duration use [22]. The similar result was shown by Canadian authors from McMaster University and University of Ottawa [23, 24]. Authors also indicated on absents symptoms of dysbiosis in short course treatment. Other data was presented by J. Bielicki et al. (2021) as results of a multicenter, randomized, blinded, placebo-controlled trial with Amoxicillin monotherapy comparing total daily dose and duration (3 or 7 days) for treatment of childhood CAP [25]. It was conducted in many hospitals in the UK and Ireland and in this investigation was noted that disease severity at enrollment was not significantly different among children from each clinical. In treatment analysis was showed noninferiority for lower dose and shorter duration (shorter vs longer). There was no significant association between dose or duration of amoxicillin and severity of cough symptoms. From the other side, patients hospitalized with

pneumonia often receive excess antibiotic therapy [26]. Excess antibiotic treatment was associated with patient-reported adverse events [19]. Intravenous antibiotics play a critical role in clinical care, particularly for severe bacterial pneumonia. However, the inability of antibiotics to reach target tissues causes serious side effects, including liver and kidney damage, intestinal dysbiosis, cause gastrointestinal infections. The gut microbiota plays a vital role in the development of protecting against severe course of respiratory diseases like pneumonia. It was demonstrated the existence of the gut-lung axis and the interaction between the gut and the lung, which is related to the better prognosis for patients. Most of these studies recommended probiotic supplementation of pneumonia treatment moreover, probiotics suppress severe immune responses and inhibit pathologic inflammatory conditions in the body via modulation of immune responses [17, 21, 27].

CONCLUSIONS

The study established that, despite existing guidelines for the management of CAP in children, there is an irrational use of third- and fourth-generation cephalosporins as first-line antibacterial treatment, which should not be initiated at the start of treatment. Regarding the indication for inpatient care, the length of stay and the duration of antibiotic treatment were excessively long. The risks of antimicrobial resistance in these cases are high, and it is advisable to use a shorter duration of antibiotics.

Symptoms of intestinal discomfort and manifestations of mucociliary respiratory tract function deterioration should be regarded as phenomena of dysbiosis within the gut-lung axis. Compared with research on gut microbiota, our understanding of lung microbiota is still limited, and a number of conceptual questions remain to be answered.

REFERENCES

1. Florin TA, Tancredi DJ, Ambroggio L et al. Predicting severe pneumonia in the emergency department: a global study of the Pediatric Emergency Research Networks (PERN)-study protocol. BMJ Open. 2020;10(12):e041093. doi: 10.1136/bmjopen-2020-041093. DOI
2. Chen L, Miao C, Chen Y et al. Age-specific risk factors of severe pneumonia among pediatric patients hospitalized with community-acquired pneumonia. Ital J Pediatr. 2021;47(1):100. doi: 10.1186/s13052-021-01042-3. DOI
3. Tannous R, Haddad RN, Torbey PH. Management of Community-Acquired Pneumonia in Pediatrics: Adherence to Clinical Guidelines. Front Pediatr. 2020;8:302. doi: 10.3389/fped.2020.00302. DOI
4. Carter A, Msemburi W, Sim SY et al. Modeling the impact of vaccination for the immunization Agenda 2030: Deaths averted due to vaccination against 14 pathogens in 194 countries from 2021 to 2030. Vaccine. 2024;42(1):S28-S37. doi: 10.1016/j.vaccine.2023.07.033. DOI
5. Borges J, Rosa MV, Fernandes RM et al. Hospital admissions in children with acute respiratory disease in Portugal. Pulmonology. 2019;25(2):122-125. doi: 10.1016/j.pulmoe.2018.12.004. DOI
6. Tagarro A, Moraleda C, Domínguez-Rodríguez S et al. A Tool to Distinguish Viral From Bacterial Pneumonia. Pediatr Infect Dis J. 2022;41(1):31-36. doi: 10.1097/INF.0000000000003340. DOI
7. Rankin DA, Peetluk LS, Deppen S et al. Diagnostic models predicting paediatric viral acute respiratory infections: a systematic review. BMJ Open. 2023;13(4):e067878. doi: 10.1136/bmjopen-2022-067878. DOI
8. Hogea SP, Tudorache E, Pescaru C et al. Bronchoalveolar lavage: role in the evaluation of pulmonary interstitial disease. Expert Rev Respir Med. 2020;14(11):1117-1130. doi: 10.1080/17476348.2020.1806063. DOI
9. Meyer Sauteur PM. Childhood community-acquired pneumonia. Eur J Pediatr. 2024;183(3):1129-1136. doi: 10.1007/s00431-023-05366-6. DOI
10. Albuhairi S, Farhan MA, Alanazi S et al. Antibiotic Prescribing Patterns for Hospitalized children with Community-Acquired Pneumonia in a Secondary Care Center. J Infect Public Health. 2021;14(8):1035-1041. doi: 10.1016/j.jiph.2021.05.018. DOI
11. Antoon JW, Nian H, Todd J et al. Guideline-Concordant Antibiotic Use in Children With Community-Acquired Pneumonia. Hosp Pediatr. 2025:e2024007994. doi: 10.1542/hpeds.2024-007994. DOI
12. Donà D, Brigadoi G, Grandinetti R et al. Treatment of mild to moderate community-acquired pneumonia in previously healthy children: an Italian intersociety consensus (SIPPS-SIP-SITIP-FIMP-SIAIP-SIMRI-FIMMG-SIMG). Ital J Pediatr. 2024;50(1):217. doi: 10.1186/s13052-024-01786-8. DOI
13. Nascimento-Carvalho CM. Community-acquired pneumonia among children: the latest evidence for an updated management. J Pediatr (Rio J). 2020;96(1):29-38. doi: 10.1016/j.jped.2019.08.003. DOI
14. Gao Y, Liu M, Yang K et al. Shorter Versus Longer-term Antibiotic Treatments for Community-Acquired Pneumonia in Children: A Meta-analysis. Pediatrics. 2023;151(6):e2022060097. doi: 10.1542/peds.2022-060097. DOI
15. Shah T, Baloch Z, Shah Z et al. The Intestinal Microbiota: Impacts of Antibiotics Therapy, Colonization Resistance, and Diseases. Int J Mol Sci. 2021;22(12):6597. doi: 10.3390/ijms22126597. DOI
16. Kwon J, Kong Y, Wade M et al. Gastrointestinal Microbiome Disruption and Antibiotic-Associated Diarrhea in Children Receiving Antibiotic Therapy for Community-Acquired Pneumonia. J Infect Dis. 2022;226(6):1109-1119. doi: 10.1093/infdis/jiac082. DOI

17. Zhou Y, Liu M, Liu K et al. Lung microbiota and potential treatment of respiratory diseases. Microb Pathog. 2023;181:106197. doi: 10.1016/j.micpath.2023.106197. DOI
18. Roquilly A, Torres A, Villadangos JA et al. Pathophysiological role of respiratory dysbiosis in hospital-acquired pneumonia. Lancet Respir Med. 2019;7(8):710-720. doi: 10.1016/S2213-2600(19)30140-7. DOI
19. Fu L, Huo S, Lin P et al. Precise antibiotic delivery to the lung infection microenvironment boosts the treatment of pneumonia with decreased gut dysbiosis. Acta Biomater. 2024;184:352-367. doi: 10.1016/j.actbio.2024.06.026. DOI
20. Yang D, Xing Y, Song X, Qian Y. The impact of lung microbiota dysbiosis on inflammation. Immunology. 2020;159(2):156-166. doi: 10.1111/imm.13139. DOI
21. Baldi S, Fabbrizzi A, Di Gloria L et al. First Exploration of the Altered Microbial Gut-Lung Axis in the Pathogenesis of Human Refractory Chronic Cough. Lung. 2024;202(2):107-118. doi: 10.1007/s00408-024-00681-7. DOI
22. Dinh A, Ropers J, Duran C et al. Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. Lancet. 2021;397(10280):1195-1203. doi: 10.1016/S0140-6736(21)00313-5. DOI
23. Singla S, Sih K, Goldman RD. Antibiotic treatment duration for community-acquired pneumonia in children. Can Fam Physician. 2023;69(6):400-402. doi: 10.46747/cfp.6906400. DOI
24. Pernica JM, Harman S, Kam AJ et al. Short-course antimicrobial therapy for pediatric community-acquired pneumonia: The SAFER Randomized Clinical Trial. JAMA Pediatr. 2021;175(5):475-482. doi: 10.1001/jamapediatrics.2020.6735. DOI
25. Bielicki JA, Stöhr W, Barratt S et al. Effect of Amoxicillin Dose and Treatment Duration on the Need for Antibiotic Re-treatment in Children With Community-Acquired Pneumonia: The CAP-IT Randomized Clinical Trial. JAMA. 2021;326(17):1713-1724. doi: 10.1001/jama.2021.17843. DOI
26. Vaughn VM, Flanders SA, Snyder A et al. Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia: A Multihospital Cohort Study. Ann Intern Med. 2019;171(3):153-163. doi: 10.7326/M18-3640. DOI
27. Nayebi A, Navashenaq JG, Soleimani D, Nachvak SM. Probiotic supplementation: A prospective approach in the treatment of COVID-19. Nutr Health. 2022;28(2):163-175. doi: 10.1177/02601060211049631. DOI

This research was carried out according to the research work of Bukovinian State Medical University for 2022-2026 on the theme of «Chronobiological and adaptation aspects and features of autonomic regulation in pathological conditions in children of different age groups» (state registration number 0122U002245).

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Oleksandr H. Buriak
Bukovinian State Medical University
2 Teatralna Square, 58002 Chernivtsi, Ukraine
e-mail: buriakoleksandr1983@gmail.com

ORCID AND CONTRIBUTIONSHIP
Oleksandr H. Buriak: 0000-0002-6621-7582 A B C D
Yurii M. Nechytailo: 0000-0003-3050-961X E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.02.2025
ACCEPTED: 01.06.2025

ORIGINAL ARTICLE

CONTENTS

Dispensing of medicines via vending machines

Ivan S. Demchenko, Alina O. Pletenetska
BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: to analyze the possibilities to implement dispensing of medicines via vending machines.

Materials and Methods: A systematic literature review was conducted using PubMed, Scopus, and Google Scholar databases. A SWOT analysis of dispensing medicines through vending machines was performed. Ukrainian legal framework and content analysis were used to assess feasibility, with an anonymous survey of 106 respondents aged 20 to 70 gathering opinions on installing vending machines for over-the-counter medications in public places.

Results: The study showed the following: 1) strengths were: convenience, access to medicines in remote areas; 2) weaknesses: limited number of medicines, lack of possibility to consult with a pharmacist, cost of vending machines; 3) opportunities: possibilities to use for prescribed medicines or for chronic diseases medication; 4) threats: exclusion of pharmaceutical professionals from the process of ensuring access to medicinal products, self-medication and danger of side effects. The 58 % of respondents supported vending machines, citing convenience, availability, and shorter pharmacy queues.

Conclusions: Dispensing medicines via vending machines presents a viable alternative to traditional methods. The main advantage is patient convenience, but attention must be given to mitigating risks from self-medication. Licensing terms should be established for business entities involved in vending machine operations, ideally those holding a retail license for medicinal products.

KEY WORDS: access to medicines; pharmaceutical regulation; pharmaceutical policy

Wiad Lek. 2025;78(6):987-992. doi: 10.36740/WLek/207353 DOI

INTRODUCTION

Access to medicines is a crucial aspect of public health. In recent years, various forms of increasing access to medicinal products have become widespread, such as dispensing medicines via vending machines. Vending machines are widely used for food, drinks, small necessities, and many other things. However, the use of vending machines in the pharmaceutical sphere is a challenging area [1, 2]. Medicines are distinct from other commercial goods in many ways: potential impact on health and life, potential misuse or dangerous side effects, the requirement for a prescription from healthcare professionals or pharmacist consultation, sensitive storage conditions (temperature, humidity, light protection), and others. Given these factors, dispensing medicines via vending machines is not widely used due to precautionary measures.

The idea of using vending machines for medicines and other medical products was notably accelerated by the COVID-19 pandemic [3], as both individuals and healthcare systems sought possibilities to reduce virus transmission risks, minimize contact, and increase convenience. This distribution form remained in demand even after the pandemic period.

Dispensing medicines via vending machines has potential from an access to medicines (specifically, physical accessibility) perspective [4]. It provides convenience, especially for: availability outside regular pharmacy hours; accessibility in remote areas; reducing waiting times; urgent, but not emergency, situations; and availability in places where many people are (airports, train stations, shopping malls, etc.). However, concerns regarding safety, regulatory compliance, and the scope of medicines available through this distribution form need to be addressed.

Legal regulations regarding the dispensing of medicines vary across European countries [1, 5], largely depending on the possibility to dispense medicinal products outside of pharmacies. However, legal regulation of such distribution forms as dispensing medicines via vending machines goes slightly beyond, raising the question of whether it is possible to dispense medicinal products in this way at all. In this regard, Ukraine's experience in implementing online trade in medicinal products, implementing "mobile pharmacy points," and the receiving medicines by mail pilot project may be valuable.

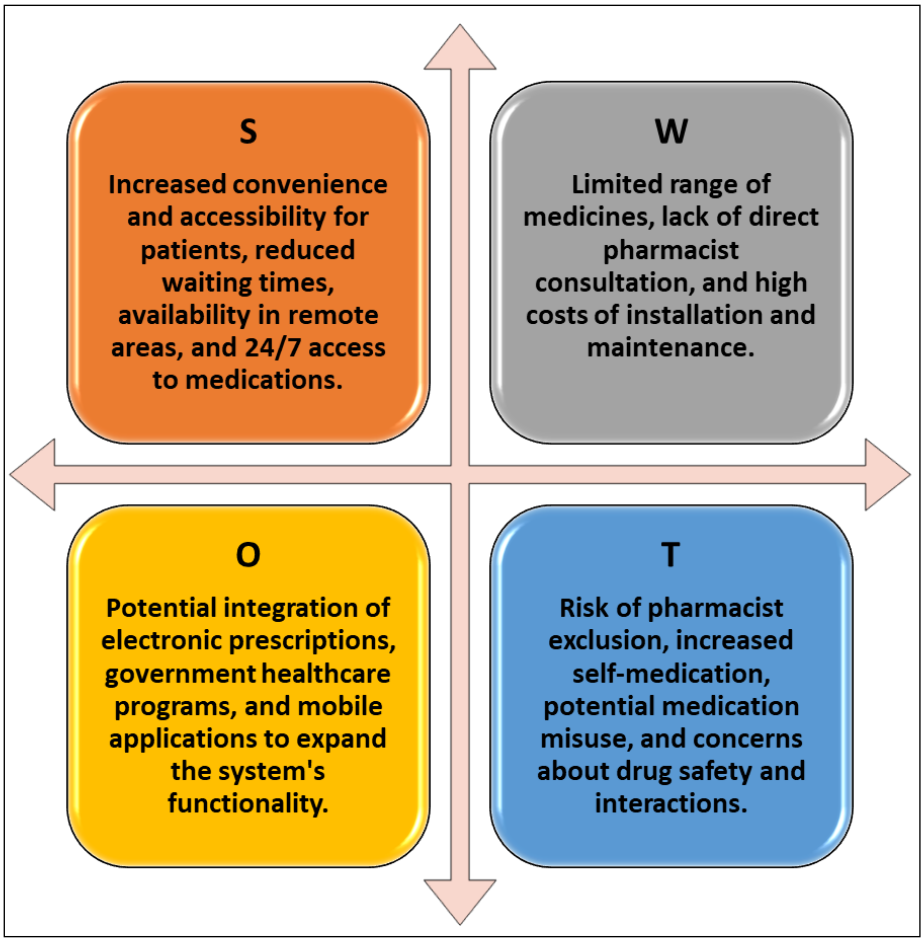

Fig. 1. SWOT analysis of automated medicine dispensing

AIM

The aim of the study was to analyze the possibilities of implementing the dispensing of medicines via vending machines. This article also considers the strengths, weaknesses, opportunities, and threats of this method of dispensing medicines.

MATERIALS AND METHODS

This study primarily relies on existing literature that reviews different aspects of dispensing medicines via vending machines. A systematic search was conducted using PubMed, Scopus, and Google Scholar databases. First, a SWOT analysis regarding the dispensing of medicines via vending machines is proposed. Then, based on the access to medicines approach and the Ukrainian legal framework, including content analysis as an example, the possible introduction of dispensing medicines via vending machines was analyzed. The study also employs the dialectical and hermeneutic methods and incorporates perspectives from scientific literature. Additionally, an anonymous survey of 106 respondents aged 20 to 70 was conducted to determine their opinions on installing over-the-counter medication dispensing machines in public places. The material was statistically processed, with percentages calculated.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that all norms of academic integrity and ethical standards of scientific activity were observed in the preparation of the article "Dispensing of medicines via vending machines." References to the works of other researchers have been made through proper citation in accordance with copyright legislation. The requirements of scientific citation ethics have been met. All study procedures were conducted in accordance with the ethical standards set by the Declaration of Helsinki. Participants were informed about the study's objectives and provided voluntary informed consent for participation. The survey was conducted anonymously to ensure confidentiality.

RESULTS

SWOT analysis regarding dispensing of medicines via vending machines. The SWOT analysis is conducted considering the positions and interests of the stakeholders, which include: state interests (including those

of regulatory bodies and authorities), pharmaceutical companies and pharmacies (including pharmacists, dispensers, and other pharmaceutical sector representatives), and patients (Fig. 1).

STRENGTHS – AS CURRENT FACTORS THAT COULD PROVIDE VARIOUS ADVANTAGES

Convenience for patients is driven by the need for more accessible and efficient ways to provide medicines.

In several countries, the number of pharmacies is regulated, with specific requirements established for their opening and operation. Some countries, including Ukraine, do not have such restrictions. It is quite common to have multiple pharmacies on the same street or even within the same building. From the perspective of a patient's ability to access medicinal products, this is very convenient. The use of vending machines for dispensing medicines would further expand the number of locations where patients can purchase medicines. Alongside this, non-prescription vending machines can increase patient satisfaction. For example, automated machines provide on-demand medicines and medical products at airports and train stations, reducing the need for queuing at hospitals or pharmacies, thereby increasing patient satisfaction [2].

Another aspect of convenience for patients is working hours. The number of pharmacies operating at night or on weekends and holidays is limited. The ability to use vending machines for dispensing medicines allows patients to access medications virtually at any time.

Additionally, using vending machines for dispensing medicines could reduce waiting time. Medicines can be purchased instantly without waiting in pharmacy lines.

Access to medicines in remote areas. Potentially, vending machines for dispensing medicines could be used in settlements where there are no stationary pharmacies.

WEAKNESSES – AS CURRENT FACTORS THAT COULD POTENTIALLY HAVE DISADVANTAGES AND POSSIBLE RISKS

Limited number of medicines. Vending machines could handle limited number of medicines. Thus, it could be used only for most frequently medicines. Any controlled substances must be excluded.

The ability to consult with a pharmacist. In many cases patients ask a pharmacist for some explanation therefore buy some medicines. At vending machines this option could be substituted with the possibility to make a phone call or by pressing a button to connect with an on-duty pharmacist.

Cost of vending machines. Vending machines by themselves are quite costly machines. For businesses, installing and maintaining such vending machines may not be cost-effective

OPPORTUNITIES – AS POSSIBILITIES TO GROW, IMPROVE PERFORMANCE AND GAIN BENEFITS

Vending machines could be used not only for most frequently used medicines, but also for prescribed medicines or for chronic diseases medication. For example, in Ukraine, state program "Affordable Medicines" is introduced, by which patients can receive medicines they need free of charge or with a partial co-payment. Currently, medicines under this government program can be obtained, including through an electronic prescription. The electronic prescription format consists of a 16-character alphanumeric code. Theoretically, a patient could enter this 16-digit code to receive the prescribed medication or make an additional payment using a payment terminal. Another option could be the use of a QR or barcode code, which would be scanned by the vending machine. Possibility to use different mobile applications also should be considered.

THREATS – AS FACTORS WHICH COULD NEGATIVELY IMPACT ON PROCESS OF DISPENSING MEDICINES VIA VENDING MACHINES

The key threat appears to be the potential exclusion of pharmaceutical professionals, particularly pharmacists, from the process of ensuring public access to medicinal products.

SELF-MEDICATION AND SIDE EFFECTS

An increase in the availability of non-prescription vending machines will likely lead to a rise in self-medication practices, building on existing trend [2]. Self-medication could take different forms: starting from misinterpretation of pain or other symptoms, leading to overdosing or misuse of medicines. This may lead to polypharmacy, situations where patients inadvertently acquire multiple medications that may interact adversely. It should be noted that there is research indicating that, on the contrary, the level of potential medical errors decreases [6].

As part of the study, a survey was conducted among 106 respondents aged 20 to 70 years to assess their attitudes toward the installation of vending machines for dispensing medications.

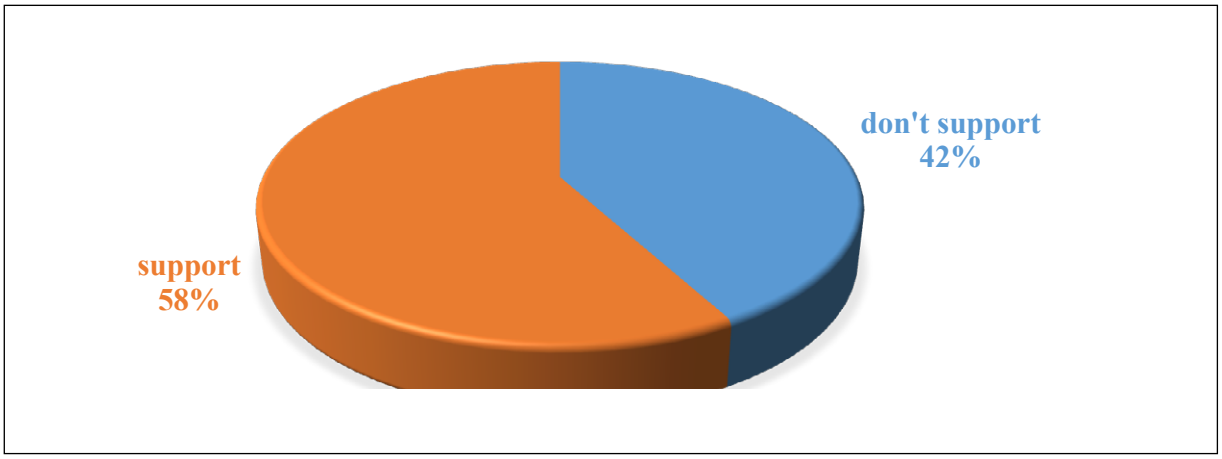

Fig. 2. Percentage distribution of respondents surveyed regarding the installation of over-the-counter medicine vending machines in public places

According to the survey, 68 % of respondents believe that the lack of 24-hour pharmacies is a problem, especially in times of war. 85 % of respondents said that they had at least once encountered a situation where a pharmacy was closed at night or on a day off.

Key survey results: 58 % of respondents (61 people) support the idea of installing pharmacy vending machines, highlighting their convenience, availability at any time, and reduction of queues in traditional pharmacies. 42% of respondents (45 people) were against it, expressing concerns about the lack of pharmaceutical consultation, potential misuse of medications, and the technical limitations of such machines (Fig. 2).

Among respondents aged 40 and older, 100 % supported the initiative to introduce pharmacy vending machines, citing the need for 24/7 access to medications and the convenience of purchasing them without waiting in line.

DISCUSSION

The concept of "access to medicines" is multifaceted and can be considered from various perspectives [4]. The concept of access to medicinal products encompasses issues of economic affordability, intellectual property protection, policy development, and ensuring the interests of vulnerable population groups, different patient access schemes, managed entry agreements, reimbursement issues, pricing policies, among others. Additionally, access to medicinal products includes the aspect of physical accessibility. Usually, physical accessibility refers to the availability and geographical accessibility of medicine for those who need them for rational use [7]. In the context of this study, the physical accessibility of medicines is viewed more as the ability to access medicines not only through traditional pharmacies.

In European countries it's a tendency towards the ability to dispense medicinal products not exclusively in pharmacies [5]. In the context of our study, it is useful to apply the following classification of non-pharmacy trade [1] in European countries, with certain remarks:

1) no non-pharmacy trade;

2) there is only a non-pharmacy trade in preparations with a low therapeutic effect (e.g., herbal medicines), or is under the supervision of a pharmacist or other person qualified in pharmaceutical sciences;

3) a non-pharmacy trade exists and is regulated by law and concerns selected active substances;

4) trade via non-pharmacy outlets.

The non-pharmacy outlets are defined as non-registered points of dispensing over the counter (OTC) medicines, for which there is no need to obtain a license for distribution and no need to fulfil inspection requirement for safe drug storage. The non-pharmacy outlets include supermarkets, petrol stations, drugstores, shops open to the public, and kiosks [1]. Obviously, if certain business entities are allowed to dispense medicines without a license, then, potentially, medicines could also be dispensed through vending machines. The presented classification primarily focuses on the location where medicines can be dispensed. However, in the context of dispensing medicines via vending machines, it is more appropriate to discuss the necessity of having or not having a relevant license for dispensing medicinal products.

In many European countries and in Ukraine, dispensing medicinal products is possible by business entities based on the appropriate license. The presence of a license indicates compliance with licensing conditions, which include, among other things: organizational requirements, requirements for premises, personnel requirements, and adherence to relevant good practices (namely – Good X Practice). When discussing vending machines, the question arises as to whether the accepted approach, based on the applicable licensing conditions, can be applied at all.

If we adhere to the position that the dispensing of medicines through vending machines remains subject to existing licensing conditions, the following questions arise regarding the organization of such activities:

1. **Which business entities could dispense medicines via vending machines**. Only business entities that hold a license for the retail trade of medicinal products (in other words, the operation of pharmacy establishments) should be allowed to engage in activities related to dispensing medicines through vending machines. The possibility of using vending machines can subsequently be revoked when there are concerns.

This essentially means that the ability to dispense medicines through vending machines, as well as the specific requirements for conducting such activities, must be enshrined in the relevant licensing conditions. For example, in Ukraine, obtaining a license for retail trade in medicinal products requires compliance with specific requirements. If a business entity wishes to manufacture medicines within a pharmacy, dispense medicines via electronic remote trade mechanisms, or use "mobile pharmacy points", each of these subcategories is subject to specific additional requirements.

It also means that licensing of dispensing medicines via vending machines should meet all licensing procedure requirements (including pre-inspection by recognized regulatory authority) and compliance requirements.

2. **Places, where business entities could install vending machines.** Nothing prevents a pharmacy from installing a vending machine inside its own premises. In Ukraine, some pharmacies from large pharmacy chains are already using such machines. Another option is installing vending machines outside the pharmacy premises. Vending machines can be placed in shopping centers, stores, gas stations, restaurants, educational institutions, residential complexes, etc. Essentially, the key requirement is that the location where the vending machine is installed ensures the proper storage conditions for the medicines inside. In this issue, they should be connected to the main electrical supply.

Information about the location of the vending machine must be entered into the relevant database, which records business entities authorized to conduct retail trade in medicinal products. This database should be administered by the relevant state authority authorized to oversee business activities in the field of retail trade in medicinal products.

Vending machines should be where they cannot be accessed by unauthorized persons including children [2]. Thus, according to the legislation of Ukraine, the dispensing of medicines to children under 14 years of age is prohibited. This means that when using vending machines, a mechanism for verifying the buyer's age must be implemented to prevent the sale of medicines to minors. Possible solutions could include identification through electronic documents or verification via a bank card with age restrictions.

3. **What medicines could be disposed via mending machines.** The authorized state bodies must establish a clear list of medicines that can be dispensed through vending machines. It could be every day medicines and associated items, including aspirin, paracetamol, ibuprofen, and indigestion and heartburn treatments readily available. Since these medicines are often compact and adequately wrapped, they can be distributed from small machines [2]. Furthermore, it should be restrictions on the quantity of these medicines that can be purchased at any one time from vending machines to avoid any potential harm.
4. **Requirement to consult pharmacist.** Pharmacist, who could be employed by business entities that hold a license for retail trade of medicinal products should be available to consult, on demand, remotely.

Automated medicine dispensing improves accessibility and convenience, especially in areas with limited pharmacy access or off-hours, enhancing healthcare delivery and aligning with goals of better medicine access and efficiency [8]. Additionally, alcohol-related impairment may affect medication purchases, especially in public areas like airports and entertainment districts. Proper regulations and buyer verification could help prevent such risks [9].

CONCLUSIONS

Dispensing medicines via vending machines is a viable alternative to "traditional" ways of dispensing medicine. Convenience for patients is the main strength of dispensing medicines via vending machines. However, there are also a number of potentially weak points and threats: exclusion of pharmaceutical professionals from the process of ensuring public access to medicinal products, self-medication, and the danger of side effects. Special attention should be given to minimizing risks associated with self-medication without professional guidance.

Preferably, business entities that hold a license for retail trade of medicinal products should be allowed to engage in activities related to dispensing medicines through vending machines. Licensing terms and conditions for dispensing medicines via vending machines should be established.

The results indicate significant interest in the implementation of pharmacy vending machines, particularly among older people. This suggests the potential for the future development of such a method of medication distribution, especially in regions with a lack of pharmacies or in high-traffic areas (airports, train stations, shopping centers, etc.).

REFERENCES

1. Oleszkiewicz P, Krysinski J, Religioni U, Merks P. Access to Medicines via Non-Pharmacy Outlets in European Countries – A Review of Regulations and the Influence on the Self-Medication Phenomenon. Healthcare. 2021;9(2):123—139. doi:10.3390/healthcare9020123. DOI
2. Jairoun AA, Al-Hemyari SS, Shahwan M et al. Access to non-prescription medicines via vending machines: key considerations to help transfer the self-care concept to the next generation while managing safety risks. Journal of Pharmaceutical Health Services Research. 2022;13(4):396–401. doi:10.1093/jphsr/rmac044.
3. Jairoun AA, Al-Hemyari SS, Abdulla NM et al. Acceptability and Willingness of UAE Residents to Use OTC Vending Machines to Deliver Self-Testing Kits for COVID-19 and the Implications. Journal of Multidisciplinary Healthcare. 2022;15:1759–1770. doi:10.2147/JMDH.S370441. DOI
4. Abbas N, Hasan SS, Curley L, Ud-Din Babar Z. Access to medicines - a systematic review of the literature. Research in Social and Administrative Pharmacy. 2020;16(9):1166 – 1176. doi:10.1016/j.sapharm.2019.12.009. DOI
5. López Vila ED, Buts C, Jegers M. A quantitative classification of OTC medicines regulations in 30 European countries: dispensing restrictions, distribution, pharmacy ownership, and pricing systems. Journal of Pharmaceutical Policy and Practice. 2023;16(1):19 – 30. doi:10.1186/s40545-023-00522-7. DOI
6. Sng Y, Ong CK, Lai YF. Approaches to outpatient pharmacy automation: a systematic review. European Journal of Hospital Pharmacy. 2019;26:157–162. doi:10.1136/ejhpharm-2017-001424. DOI
7. Afzali M, Khorasani E, Alvandi M et al. Providing a framework for assessment of the access to medicine. DARU Journal of Pharmaceutical Sciences. 2019;27(1):243–254. doi:10.1007/s40199-019-00268-1. DOI
8. Diachuk DD, Moroz GZ, Hidzynska IM, Kravchenko AM. Implementation of patient-centered care and medical care improvement: current state (review). Clinical and Preventive Medicine. 2023;1(23):67—77. doi:10.31612/2616-4868.1(23).2023.10. DOI
9. Mykhailychenko BV, Biliakov AM, Pletenetska AO. Features of the influence of low levels of alcohol intoxication on the functions of the human brain. Clinical and Preventive Medicine. 2025;1(1):52-8. doi:10.31612/2616-4868.1.2025.06. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Ivan S. Demchenko
Bogomolets National Medical University
5 Mechnikov st., 01133 Kyiv, Ukraine
e-mail: demchenko.ivan@gmail.com

ORCID AND CONTRIBUTIONSHIP

Ivan S. Demchenko: 0000-0001-8721-2775 A B C D E F
Alina O. Pletenetska: 0000-0002-7029-3377 B C D E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 25.01.2025
ACCEPTED: 29.05.2025

ORIGINAL ARTICLE

CONTENTS

The role of intraoperative debitometry in choosing the treatment strategy for patients with diabetes mellitus with stenotic-occlusive lesion of the tibial segment arteries

Sergii M. Didenko[1], Vitalii Y. Subbotin[1], Yurii M. Hupalo[2], Andrii V. Ratushniuk[3], Oleksandr M. Orlych[4], Oleksandr A. Sobko[4]

[1]CLINICAL HOSPITAL «FEOFANIYA» STATE ADMINISTRATIVE DEPARTMENT, KYIV, UKRAINE
[2]STATE INSTITUTION OF SCIENCE «CENTER OF INNOVATIVE HEALTHCARE TECHNOLOGIES» STATE ADMINISTRATIVE DEPARTMENT, KYIV, UKRAINE
[3]STATE INSTITUTION «NATIONAL SCIENTIFIC CENTER OF SURGERY AND TRANSPLANTATION NAMED AFTER O.O. SHALIMOV TO NATIONAL ACADEMY MEDICAL SCIENCES OF UKRAINE», KYIV, UKRAINE
[4]KYIV CITY CLINICAL HOSPITAL № 1, KYIV, UKRAINE

ABSTRACT

Aim: To improve the results of surgical treatment of patients with ischemic form of diabetic foot syndrome (IF DFS) with stenotic-occlusive lesion (SOL) of the tibial segment arteries by creating an algorithm of diagnostic and treatment tactics.

Materials and Methods: An analysis of the surgical treatment outcomes of 137 patients with type 2 diabetes mellitus (DM2) and IF DFS with SOL of the tibial segment arteries, critical limb ischemia, and ischemic foot necrosis was conducted.

Results: According to the obtained indicators of the popliteal artery debit after performing balloon angioplasty (BAP) of the tibial segment arteries, the patients were divided into three groups. All patients, depending on the degree of increase in the popliteal artery debit after BAP (group A – <1,5 times; 1,5-2 times; >2 times), transcutaneous oxygen pressure (TcPO2) and the option of revascularization according to the angiosomal concept, were assigned a certain number of points and compared with the quality and timing of wound healing in the groups. It is considered that the calculation of quantitative changes in the popliteal artery debit after performing BAP accurately determines the prospects for healing of foot wounds after necrotectomy in patients with IF DFS and can be a criterion for formulating further treatment tactics.

Conclusions: Measuring TcPO2 and determining the revascularization option based on the results of BAP allow the DM2 patients in groups A, B, and C to be assigned the appropriate number of points, the sum of which shows the prognosis for healing of foot wounds and the timing of using other methods of revascularization or performing amputation.

KEY WORDS: diabetes mellitus, balloon angioplasty, debitometry, necrectomy

Wiad Lek. 2025;78(6):993-999. doi: 10.36740/WLek/207355 DOI

INTRODUCTION

Diabetes mellitus remains one of the important problems of the healthcare system, and the prevalence of diabetes in different countries ranges from 1,5 to 6% and currently has a tendency to increase [1].

In people with diabetes for more than 20 years, the frequency of lower limb artery damage exceeds 80%. More than half of all non-traumatic lower limb amputations are performed in patients with diabetes, often repeatedly A feature of diabetic damage to the arterial bed is a multilevel stenotic-occlusive process in medium and small caliber arteries (popliteal, tibial and foot arteries) which leads to the development of chronic lower limb-threatening ischemia (CLLTI) [2]. The presence of CLLTI indicates an unfavorable prognosis, within a year after the manifestation of CLLTI, only 25% of patients recover, in 20% - symptoms persist; in 30% of patients the limb is amputated, and 25% - die [3].

In 2011, the International Working Group on the Diabetic Foot (IWGDF) adopted the following recommendation: "The goal of revascularization in these patients is to restore direct pulsatile blood flow to at least one artery in the foot, preferably the one supplying the anatomical site of the ulcer."This statement was the result of a number of studies that demonstrated the superiority of the angiosomal principle of revascularization [4].

AIM

The aim was to improve the results of surgical treatment of patients with ischemic form of diabetic foot (IF DFS) on the background of stenotic-occlusive lesions (SOL) of the tibial segment arteries by creating an algorithm of diagnostic and treatment tactics using intraoperative debitometry, microcirculation assessment using percutaneous measurement of transcutaneous oxygen pressure (TcPO2) in foot tissues and using the angiosomal concept.

MATERIALS AND METHODS

The results of surgical treatment of 137 patients with type 2 diabetes mellitus, with IF DFS on the background of SOL of the tibial arteries with threatening ischemia of the lower limb and ischemic genesis necrosis of the foot, who underwent treatment at the Center for Vascular Surgery of the Clinical Hospital «Feofaniya» State Administrative Department during 2014-2022 were analyzed. There were 86 men (62,8%), 51 women (37,2%). The age of the patients ranged from 58 to 78 years.

Inclusion criteria of patients in the study were:

1. Grade IV foot ischemia with the presence of necrotic tissue damage to the foot, which did not exclude the restoration of the supporting function of the limb;
2. SOL of the tibial segment arteries;
3. Patency of the superficial femoral vein (SFV), popliteal artery (PA), the presence of angiosome, or at least one passing artery of the foot.

Exclusion criteria were as follows:

1. Presence of acute coronary syndrome. Myocardial infarction, acute disruption of cerebral blood circulation within the last 6 months;
2. Predicted life expectancy up to 12 months;
3. Disseminated purulent-necrotic lesions of the foot, which required amputation;
4. Patients' unwillingness to perform the examination and treatment procedures.

All patients underwent ultrasound duplex scanning of the lower extremities arteries in the preoperative period using "Flex focus" made by "BK Medical" (Denmark). Angiography was performed by puncture of the SFV outfall under ultrasound control (Ukrainian Patent for Utility Model №. 114970) using "Euroampli ALIEN" angiographic system made by "EUROCOLUMBUS SRL" (Italy).

All 137 patients underwent enovascular interventions in the form of balloon angioplasty of the the lower leg segment arteries. The PA debit rate was measured using the following method: after installing a 6F introducer in the distal direction through the SFV outfall, a 0,035'' hydrophilic guidewire was passed into the PA, a 6F catheter was passed through it, and 20 ml of "Ultravist 370" contrast diluted with saline in a 1:1 ratio was injected into the catheter at a rate that excluded overflow of the SFV with contrast discharge into the deep femoral artery and branches of the common femoral artery. For X-ray control, the angiographic system "Euroampli ALIEN" made by "EUROCOLUMBUS SRL" (Italy) was used. The time during which all the contrast left the PA was determined and the PA debit was calculated for 1 minute.

After that, endovascular intervention was performed using the following technique: a hydrophilic J-shaped guidewire 0,035'' was inserted into the PA with support from a straight or J-shaped catheter 5F and led to the SOL zone. In the presence of SOL PA or tibioperoneal trunk (TPT), a hydrophilic guidewire 0,035'' was led beyond the SOL zone, and a dilation catheter with a balloon with a diameter of 3,5-5 mm was advanced through the affected area (depending on the diameter of the artery that was planned to be dilated). The balloon was inflated with a high-pressure syringe with a manometer, gradually increasing the pressure to 8-12 atm. Dilation was performed for 1-2 min with the introduction of 10 ml of a 1:200 heparin solution into the introducer and the balloon catheter channel. In the presence of residual stenoses in the balloon angioplasty (BAP) zone of more than 30%, the procedure was repeated 1-2 times until a satisfactory result was obtained.

The technique for performing the tibial and foot arteries BAP differed in that after passing the catheter with a 0,035'' guidewire into the PA, and entering the target tibial artery outfall, the 0,035'' hydrophilic guidewire was removed, and instead a 0,014'' straight guidewire was inserted through the catheter. A balloon dilation catheter with a 2,0-3,0 mm diameter and a 10-22 cm length was passed through the 0,014'' guidewire to the target tibial artery (depending on the artery diameter that was planned to be dilated and the length of the SOL zone), leaving the end of the guidewire 2-3 cm long free. Using the balloon catheter as a support for the guidewire, both were advanced simultaneously in the distal direction through the lesion area and BAP was performed according to the above technique.

In the foot, attempts were always made to restore the connection between the posterior and anterior tibial arteries by restoring patency of the external plantar artery, the deep plantar arch, and the deep plantar branch of the dorsalis pedis artery. After performing BAP, the balloon catheter and introducer were removed and manual compression was performed in the projection of the artery puncture for 30 minutes.

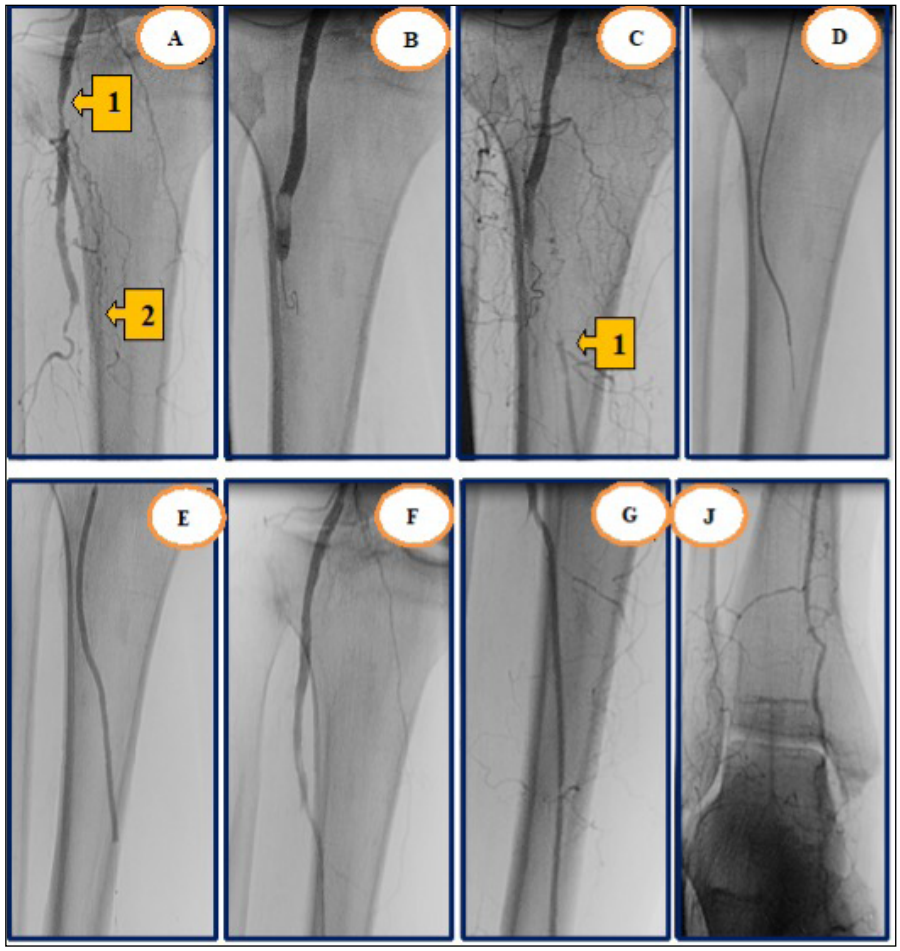

Fig. 1. Antegrade BAP of the arteries of the popliteal segment:
A – stenosis of the PA (1), occlusion of the branches of TPT (2);
B – PA BAP, 4,0 mm balloon;
C – restored patency of the PA, occlusion of the initial section of the posterior tibial artery (PTA) (1);
D – occlusion of the initial section of the PTA recanalized with a 0,035'' guidewire on a supporting catheter;
E – BAP of the initial section of the PTA, 2,5 mm balloon;
F, G, J – patency of the PTA restored up to its foot branches inclusive

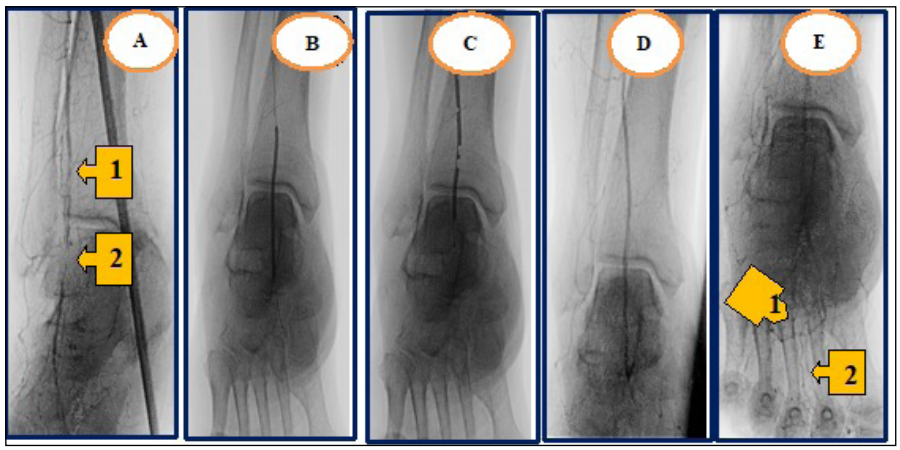

Fig. 2. BAP of the anterior tibial artery (ATA) and dorsalis pedis artery (DPA):
A – SOL of the distal third of ATA (1), the proximal third of DPA (2);
B, C – BAP of DPA and ATA;
D – restored patency of ATA and DPA;
E – contrasting of DPA branches: arcuate artery (1) and metatarsal arteries (2)

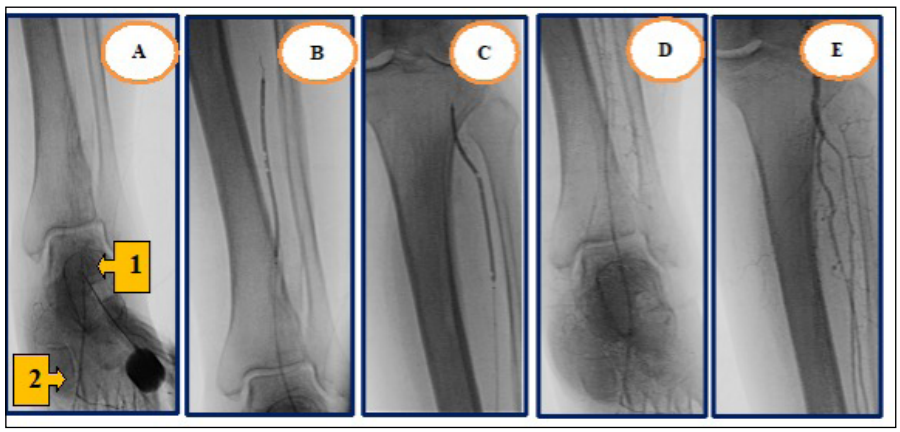

Fig. 3. Retrograde BAP of ATA:
A – retrograde puncture and contrast of the DPA (1) and arcuate artery (2);
B, C – retrograde BAP of the ATA;
D, E – restored patency of the ATA

If it was not possible to pass the guidewire in the tibial segment artery antegradely, retrograde puncture of the distal segment of the tibial artery in the lower third of the tibia or the corresponding foot artery was performed with a 22G needle and a microcatheter of the appropriate diameter was installed under ultrasound guidance. If percutaneous puncture was impossible, open surgical access to the target artery was performed. A straight 0,014'' guidewire was inserted through the microcatheter and a balloon dilation catheter with 2,0-2,5 mm diameter and 10-22 cm length was passed through it. The SOL zone was passed and BAP was performed according to the above method. BAP was considered successful if residual stenosis was <30%. If residual stenosis was >30%, dilation was repeated using a balloon catheter with a 0,5 mm larger diameter. If surgical access to the tibial or foot artery was performed, the introducer was removed after completed intervention, the hole in the artery was sutured with atraumatic Prolene 6-0 suture. The wound was sutured with drainage. An aseptic bandage was applied.

Angiograms of performing BAP of the popliteal-ankle-foot segment arteries are shown in Fig. 1, Fig. 2, Fig. 3.

Immediately after performing the BAP, the PA debit was determined using the above method, after which the introducer was removed, manual compression of the puncture area of the PA outfall was performed, and a compression bandage was applied for 1 day.

In all patients, 3 days after BAP, TcPO2 was measured using "TSM 4 Series" device, made by "Radiometer Copenhagen" (Denmark) near the necrotic lesion area, but in the area of viable tissues. Measurements were performed over an area with a uniform capillary bed without large arteries and veins, skin defects, and hair cover. Placing the electrode directly over the bone may lead to inaccurate results, especially if a change in body position causes the skin to be stretched by the protruding bone. Significant swelling in the examination area can also lead to inaccurate results.

During the examination, the patient was in a horizontal position, was in comfortable conditions and in a calm psycho-emotional state. Before the start of the examination, the electrode was calibrated with atmospheric air. The electrode was installed in a fixing ring on the skin. The cavity of the fixing ring was previously filled with 2-3 drops of electrolyte solution.

Three-five days after performing BAP, necrotectomy was performed on the foot within viable tissues, vacuum therapy methods were used, and a Tirsch or Reverden free split-cutaneous perforator flaps was transplanted.

The end point of the study was considered to be the healing of the foot wound after 1 and 3 months: complete, partial, or absent.

The study was carried out in accordance with the fundamental principles outlined in the Council of Europe Convention on Human Rights and Biomedicine, the Declaration of Helsinki adopted by the World Medical Association regarding ethical standards for medical research involving human participants, as well as current national legislation. The study protocol received approval from the local ethics committee, and written informed consent was obtained from all participants.

RESULTS

According to the obtained indicators of PA debit after performing BAP of the tibial segment arteries, patients were divided into three groups. Group A included 29 patients in whom PA debit after BAP of the tibial segment arteries increased up to 1,5 times. Group B included 44 patients in whom PA debit after BAP of the tibial segment arteries increased by 1,5–2 times. Group C included 64 patients in whom PA debit after BAP of the tibial segment arteries increased by more than 2 times. According to the degree of increase in PA debit after of the tibial segment arteries, patients in group A were assigned 0 points, group B – 1 point, group C – 2 points.

Three days after BAP, TcPO2 measurements were performed according to the above method. In group A, the TcPO2 index ranged from 0 to 20 mm Hg in 19 patients, from 20 to 40 mm Hg in 8 patients, and from 40 to 60 mm Hg in 2 patients. In group B, the TcPO2 index ranged from 0 to 20 mm Hg in 2 patients, from 20 to 40 mm Hg in 32 patients, and from 40 to 60 mm Hg in 10 patients. In group C, the TcPO2 index ranged from 0 to 20 mm Hg in 1 patient, from 20 to 40 mm Hg in 20 patients, and from 40 to 60 mm Hg in 43 patients. Patients with a TcPO2 index of 0–20 mm Hg were assigned 0 points, 20–40 mm Hg – 1 point, and 40–60 mm Hg – 2 points.

The analysis of the results of BAP was carried out according to the angiosomal concept. Restoration of blood supply to the necrotic area of the foot through the angiosomal artery - this option of revascularization was considered as direct (DR). Restoration of blood supply to the necrotic area of the foot not through the angiosomal artery, but through the artery that has the most developed anatomical connections with the angiosomal artery - collateral revascularization (CR). If no visible collateral branches to the necrotic area were found, this option of revascularization was considered as indirect (IR). In group A - the DR option was not performed in any patient; CR - 5 patients; IR - 24 patients. In group B - DR was performed in 16 patients; CR - 22

Table 1. Management of diabetes mellitus patients with SOL of the tibial segment arteries*

Group of patients	The increase of PA debit after BAP of the tibial segment arteries	Principles of management
A	<1,5 times	Bypass in the artery of the talocrural segment or amputation of the limb at the optimal level for further prosthetics
B	1,5–2 times	Treatment of foot wounds for 1-3 months, in the absence of at least partial healing of foot wounds - bypass in the artery of the talocrural segment or amputation of the limb at the optimal level for further prosthetics
C	>2 times	Treatment of foot wounds for up to 3 months, in the absence of at least partial healing of foot wounds – bypass surgery in the artery of the talocrural segment or amputation of the limb at the optimal level for further prosthetics

Note: * — in the absence of the possibility of determining TcPO2

patients; IR - 6 patients. In group C - DR was performed in 54 patients; CR - 8 patients; IR - 2 patients. If there was a DR variant, the patient was awarded 2 points; CR – 1 point; IR – 0 points.

In group A, 1 month after BAP and relevant foot operations, complete healing of foot wounds was not achieved in any patient, partial healing – 4 patients, no healing – 25 patients; after 3 months: complete healing of foot wounds in 1 patient, partial healing – 3 patients, no healing – 25 patients.

In group B, 1 month after BAP and relevant foot operations, complete healing of foot wounds occurred in 12 patients, partial healing – 15 patients, no healing – 17 patients; after 3 months: complete healing of foot wounds in 22 patients, partial healing – 12 patients, no healing – 10 patients.

In group C, 1 month after BAP and relevant foot surgeries, complete healing of foot wounds occurred in 45 patients, partial healing – 10 patients, no healing – 9 patients; after 3 months: 53 patients had complete healing of foot wounds, 6 patients had partial healing, and 5 patients had no healing.

An example of calculating the number of points scored by a random patient from group A: belonging to group A gives "0" points, TcPO2 within 20 – 40 mm Hg gives "1" point, the variant of BAP – CR gives "1" point. Thus, the sum of points = 2. The maximum sum of points for a patient from group A = 3. In total, all 29 patients from group A scored 17 points. The average number of points per 1 patient in group A = 17/29 = 0,59.

An example of calculating the number of points scored by a random patient from group B: belonging to group B gives a "1" point, TcPO2 within 40 – 60 mm Hg gives "2" points, the variant of BAP – CR gives a "1" point. Thus the sum of points = 4. The maximum sum of points for a patient from group B = 5. In total, all 44 patients from group B scored 150 points. The average number of points per 1 patient in group B = 150/44 = 3,41.

Here is an example of calculating the number of points scored by a random patient from group B: belonging to group C gives a "2" point, TcPO2 within 20 – 40 mm Hg gives "1" point, the variant of BAP – PR gives "2" points. Thus, the sum of the points = 5. The maximum sum of the points for a patient from group B = 6. In total, all 64 patients from group B scored 350 points. The average number of points per 1 patient in group B = 350/64 = 5,47.

The percentage of complete healing of foot wounds in group A was 0 % after 1 month and 3,5% after 3 months; in group B – 27,3% after 1 month and 50% after 3 months; in group C – 70,3% after 1 month and 82,8% after 3 months. Given this, we concluded: with a patient's score of «5-6» - the probability of healing of foot wounds is very high, in such patients it is advisable to focus on local wound treatment. With a score of «4» in the patient, the probability of healing of foot wounds is moderate. In such patients, it is advisable to focus on local wound treatment using more modern and expensive materials (adhesive bandages, sorbents, gel patches, polymer coatings, etc.) and the use of Prostaglandin E1, deproteinized hemoderivative of calf blood, alpha-lipoic acid, vitamin complexes, etc. With a score of «3» in the patient, the probability of healing of foot wounds is low. If such patients do not have at least partial healing of foot wounds after 1 month, it is necessary to consider the possibility of performing bypass surgery in the artery of the talocrural segment or amputation of the limb at the optimal level for further prosthetics. If the patient's score is «1-2», there is no chance of healing the foot wounds. In such patients, the question of the possibility of performing bypass surgery in the artery of the talocrural segment or amputation of the limb at the optimal level for further prosthetics should be immediately raised.

Considering the average number of points per patient in the selected groups: A – 0,59, B – 3,41, C – 5,47, we believe that the determination of quantitative changes in the PA debit after performing BAP sufficiently accurately determines the prospects for healing of foot wounds after necrotectomy in patients with diabetes mellitus

with grade IV foot ischemia and, in the absence of the possibility of determining TcPO2, may be a criterion for formulating the further tactics, being proposed in Table 1.

DISCUSSION

The concept of improving the quality of life dictates the need to preserve the supporting function of the lower limb in all possible ways when treating patients with IF DFS, since in the case of high amputation, numerous studies have proven a significant decrease in the quality of life [5, 6].

It should be noted that despite the widespread implementation of endovascular methods for the treatment of SOL of the lower limb arteries, a generally accepted algorithm for diagnostic and treatment tactics in patients with IF DFS with SOL of the tibial segment arteries still does not exist [7, 8].

The current literature has not yet fully addressed the issue of the informativeness of intraoperative debitometry, determination of TcPO2 in foot tissues, and the value of the angiosomal concept in making decisions about the tactics of endovascular revascularization [9-11]. The treatment of foot wounds after necrectomy in patients with IF DFS with SOL of the lower leg segment arteries after BAP is carried out without clear criteria for how long such treatment should last and when to switch to more radical treatment methods. This leads to an unjustified burden on budgetary and extra-budgetary sources of funding, because the cost-effectiveness of medical interventions is an important component of organizing the provision of medical care to patients with diabetes [12].

In this context, the issue of choosing the optimal method of limb revascularization in patients with diabetes mellitus and CLLTI due to damage to the arteries of the popliteal-ankle-foot segment remains relevant. Existing approaches require further improvement and clarification of indications for their use. In addition, the issue of choosing the optimal treatment tactics in patients with high surgical risk and in the absence of the technical possibility of performing revascularization remains insufficiently developed.

CONCLUSIONS

Measurement of TcPO2 and determination of the revascularization option (DR, CR and IR) based on the results of BAP allows to assign to patients of groups A, B and C the appropriate number of points, the sum of which shows the prognosis of healing of foot wounds and the timing of application of other methods of revascularization or amputation. The average number of points per patient in the selected groups: A – 0,59, B – 3,41, C – 5,47. The probability of healing of foot wounds: 5-6 points – high, 4 points – moderate, 3 points – low, less than 3 points – absent.

The division of patients into groups A, B and C, according to the increase in the PA debit after BAP of the tibial arteries, allows us to determine the tactics and timing of treatment of foot wounds in groups: A – there is almost no prospect of healing of foot wounds (1 month – 0 %, 3 months – 3,5 %), urgent bypass in the artery of the talocrural segment or amputation of the limb at the optimal level for further prosthetics is indicated; B - the prospects of healing of foot wounds are doubtful (1 month – 27,3 %, 3 months – 50,0 %), treatment of foot wounds is indicated within 1 month, in the absence of at least partial healing of foot wounds - bypass in the artery of talocrural segment or amputation; C – the prospects for healing of foot wounds are good (1 month – 70,3 %, 3 months – 82,8 %), treatment of foot wounds for up to 3 months is indicated, in the absence of at least partial healing of foot wounds - bypass surgery in the artery of the talocrural segment or amputation.

REFERENCES

1. Gerasymchuk PO, Fira DB, Pavlyshyn AV. Medyko-sotsialni ta ekonomichni pytannia v likuvanni khvorykh iz syndromom diabetychnoi stopy [Medical-social and economic issues in treatment of patients with diabetic foot syndrome]. Likars'ka sprava [Medical Affair]. 2020;3-4:42-48. doi: 10.31640/JVD.3-4.2020(7). (Ukrainian) DOI
2. Nikulnikov PI, Goodz IM, Orel YU, Ratushnyuk AV. Rekomendatsii z vedennia patsiientiv iz khronichnoiu ishemiieiu nyzhnikh kintsivok [Recommendations for the management of patients with chronic ischemia of the lower extremities]. Zdorovia Ukrainy [Health of Ukraine]. 2021;1(43):8-18. (Ukrainian)
3. Norgren L, Hiatt WR, Dormandy JA et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45:S5-67. doi: 10.1016/j.jvs.2006.12.037. DOI
4. Schaper NC, Andros G, Apelqvist J et al. Diagnosis and treatment of peripheral arterial disease in diabetic patients with a foot ulcer. A progress report of the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev. 2012;28(1):218-24. doi: 10.1002/dmrr.2255. DOI
5. Futuima YM, Bedenyuk AD, Kulbaba IY. Priorytetnist u vybori metodu khirurhichnoi korektsii kuksy pislia amputatsii dystalnoho viddilu stopy u khvorykh iz riznymy formamy syndromu diabetychnoi stopy [Priority in choosing the method of surgical stump correction after amputation of the distal foot in patients with different forms of diabetic foot syndrome]. Likarnyana khirurhiya. Zhurnal imeni L.YA. Koval'chuk. 2021;1:65-71. doi: 10.11603/2414-4533.2021.1.12025. (Ukrainian) DOI

6. Crane H, Boam G, Carradice D et al. Through-knee versus above-knee amputation for vascular and non-vascular major lower limb amputations. Cochrane Database Syst Rev. 2021;12(12):CD013839. doi: 10.1002/14651858.CD013839.pub2. DOI
7. Adams GL, Lichtenberg M, Wissgott C et al. Twenty-Four Month Results of Tack-Optimized Balloon Angioplasty Using the Tack Endovascular System in Below-the-Knee Arteries. J Endovasc Ther. 2023;30(3):393-400. doi: 10.1177/15266028221083462. DOI
8. Cai H, Dong J, Ye Y et al. Safety and Efficacy of Drug-Coated Balloon in the Treatment of Below-the-Knee Artery: A Meta-analysis. J Surg Res. 2022;278:303-316. doi: 10.1016/j.jss.2022.04.055. DOI
9. Alexandrescu VA, Brochier S, Schoenen S et al. Grades of Below-the-Ankle Arterial Occlusive Disease following the Angiosome Perfusion: A New Morphological Assessment and Correlations with the Inframalleolar GVG Stratification in CLTI Patients. Ann Vasc Surg. 2022;81:358-377. doi: 10.1016/j.avsg.2021.09.031. DOI
10. Didenko SM, Hupalo YM, Subbotin VY. Rezultaty khirurhichnoho likuvannia khvorykh iz tsukrovym diabetom ta khronichnoiu krytychnoiu ishemiieiu nyzhnoi kintsivky z urakhuvanniam danykh intraoperatsiinoi debitometrii [Results of surgical treatment in patients, suffering diabetes mellitus and chronic critical ischemia of lower extremity, taking into account the data of intraoperative debitometry]. The Ukrainian Journal of Clinical Surgery. 2020;87(5-6):36-40. doi: 10.26779/2522-1396.2020.5-6.36. (Ukrainian) DOI
11. Gupalo YM, Shapovalov DY, Shaprynskyi VV et al. Anhiosomna kontseptsiia pry revaskuliaryzatsii arterii homilky ta stopy u khvorykh iz tsukrovym diabetom [The angiosome concept in revascularization of the shin and foot arteries in patients with diabetes mellitus]. The Ukrainian Journal of Clinical Surgery. 2020;87(3-4):55-58. doi: 10.26779/2522-1396.2020.3-4.55. (Ukrainian) DOI
12. Tanasescu D, Moisin A, Fleaca R et al. Modern therapeutic options in diabetic foot ulcer. Journal of Mind and Medical Sciences. 2022;9(2):285-293. doi: 10.22543/2392-7674.1351. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Sergii M. Didenko
Clinical Hospital «Feofaniya» State Administrative Department
21 Zabolotnyi st., 03143 Kyiv, Ukraine
e-mail: hirurgdidenko@gmail.com

ORCID AND CONTRIBUTIONSHIP

Sergii M. Didenko: 0000-0002-3115-7524 C F
Vitalii Y. Subbotin: 0000-0002-1538-7004 A B
Yurii M. Hupalo: 0000-0002-4856-1398 D E
Andrii V. Ratushniuk: 0000-0003-0806-3973 D E
Oleksandr M. Orlych: 0000-0002-0538-9858 B E
Oleksandr A. Sobko: 0009-0009-1653-8984 A B

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 27.01.2025
ACCEPTED: 28.05.2025

ORIGINAL ARTICLE

CONTENTS

State of readiness for health behavior in the student youth

Larysa V. Harashchenko[1], Svitlana P. Palamar[1], Olena D. Litichenko,[1] Victorija V. Zhelanova[1], Liudmyla L. Nezhyva[1], Dana O. Sopova[1], Andrii O. Zhyltsov[1,2]

[1]BORYS GRINCHENKO KYIV METROPOLITAN UNIVERSITY, KYIV, UKRAINE

[2]MEDICAL CENTER «PALMYRA NARCOLOGICAL CLINIC», KYIV, UKRAINE

ABSTRACT

Aim: To analyze the state of readiness for health-promoting behavior among university students.

Materials and Methods: The methods of analysis of normative and scientific sources, systematic analysis and generalizations, the results of our own empirical research, questionnaire materials, and active modeling of the formation of a caring attitude towards health of modern youth were used. One hundred students of Preschool Education and Primary Education at the bachelor level of higher education took part in the survey.

Results: The results of the study allowed us to state that students of pedagogical specialties were aware of the importance of preserving and strengthening their own health (90%). 70% of respondents adhered to hygienic standards of living. 56% of respondents followed a diet. 25% of respondents formed the habit of doing physical exercises daily. 80% of respondents had bad habits, 78% tried to eliminate self-destructive habits from their own behavior. 15% of respondents were addicted to smoking. 100% of respondents used gadgets for studying and in other areas of life. 56% of respondents used mobile applications to lead a healthy lifestyle.

Conclusions: The results of the research work allow us to state that students of pedagogical specialties do not have fully formed health-preserving skills and abilities. The need and importance of engaging in physical culture, changing the daily routine, and eliminating self-destructive habits from their own behavior have not acquired personal meaning. In their process of implementing a system of values in life, the main component – the implementation of specific health-promoting actions and deeds in their own activities is unstable.

KEY WORDS: health-promoting behavior, health-preserving skills, educational process

Wiad Lek. 2025;78(6):1000-1006. doi: 10.36740/WLek/207356 DOI

INTRODUCTION

The current state of development of society puts forward new requirements for the development of higher education. Obtaining education in higher education involves not only ensuring the qualification competence of future specialists but also the personal growth of students. Important tasks in training future teachers include not only their study of the system of knowledge, professional skills, and abilities but also the formation of the teacher's personality with clear worldviews and values. Health itself is a high-quality and optimal prerequisite for the active life of every person. Therefore, we consider it an important task of higher education to ensure the continuity and comprehensiveness of educational and upbringing influence on the student's personality.

On the other hand, a responsible attitude towards one's own health is formed depending on the active life position of the individual. After all, in light of modern research in the fields of philosophy, medicine, psychology, and pedagogy, the focus is on the person whose foundation of life is health [1–4]. Any shortcomings in the process of forming a responsible attitude towards one's own health and activities related to its formation can lead to negative health trends [5–7].

The pandemic that the whole world has had to face has brought to the forefront a research area such as the formation of health-preserving behavior, which affects the lifestyle of different age and professional groups of the population. At the same time, solving this issue is related to the need to form healthy habits, primarily among young people, since it is during this age period that behavioral habits and skills necessary for life are formed, which affect the quality of health in the future. It is worth noting that the tendency to develop bad habits is partly formed during student years. Student life can be described as a kind of crisis stage, characterized by biological development and changes in social roles, as well as behavioral changes related to health. Studies by various scientists show that young people are prone to an unhealthy lifestyle (tobacco use, improper diet, increased stress, low physical activity, risky

sexual behavior, injuries and violence, etc.) [8- 13]. Such behavior not only affects overall health, but also affects the educational process, which can subsequently harm professional growth. Therefore, factors that negatively affect the formation of health-preserving behavior of students are insufficiently formed knowledge in this area and an unformed health-preserving environment of higher educational institutions [14]. The lifestyle of a modern young person can be characterized by such concepts and phenomena as: information overload, psychological stress, physical inactivity, overweight, chemical and non-chemical dependence, various food addictions, lack of high moral and ethical ideals, loss of purpose and meaning in life [15]. The problem, in our opinion, is that it is very difficult for the higher education system to balance the need to optimize activities to preserve the health of students, on the one hand, and increasing the intensification of the educational process to improve the quality and increase the level of formation of necessary competencies, on the other. Of course, the educational environment is gradually increasing the volume of preventive health programs and learning algorithms that minimize harm to students' health. But the negative factors here are both objective circumstances (for example, the introduction of distance learning due to the spread of coronavirus infection, the full-scale invasion of russian troops into the territory of Ukraine, the occupation of certain territories, the forced evacuation of residents and entire institutions, etc.), and subjective aspects, since students as a special demographic group are quite active, their requests are constantly changing, so it is necessary to develop new forms of work with them, which, of course, does not allow to significantly minimize the risks of health decline and increase the importance of factors forming health-preserving behavior for students.

AIM

The purpose of the study was to analyze the state of readiness for health-promoting behavior among young students.

MATERIALS AND METHODS

To update the didactic aspects of the problem, we used methods of analysis of normative and scientific sources, system analysis and generalisations, the results of our own empirical studies, questionnaire materials, and active modelling of students' health value formation. We conducted experiments using an empirical method of conducting scientific pedagogical research, namely the survey method. We chose a half-open type of survey (in addition to selecting an answer, respondents could also express their own point of view).

To process the results, we used the mathematical registration method, which allowed us to identify certain qualities in the analysed phenomena. To improve clarity and the convenience of further analysis of the findings, we used a graphical method of representing experimental data. We also used methods of hypothesis formulation, systemic analysis, and generalisation, which enabled us to draw conclusions in our research.

The study was conducted using the questionnaire method. One hundred students of Preschool Education and Primary Education at the bachelor level of higher education took part in the survey. These were students in their first and second years of full-time study, who had just begun studying academic disciplines from the professional block. Junior year students study the content component of the academic discipline "Humanities: Integrated Course", which involves systematising knowledge about the morphofunctional features of the human body, health and its factors, the hygienic foundations of education, disease prevention, and the active role of the individual in building their own trajectory towards a healthy lifestyle.

In the third year, students study academic disciplines such as "Health-Preserving Technologies in Preschool Education" and "Social, Health and Physical Education", with the aim of forming the professional competence of future teachers in preserving and strengthening the health of preschool and primary school children, and in ideologically rethinking the priority of the problem of health preservation.It is worth noting that a large part of students (70%) live in a dormitory or rent housing. That is, students plan all processes of daily life independently, make independent decisions to a certain extent, learn independence and responsibility, cooperate with teachers and peers, and adapt to new conditions of life, learning, and communication.

The purpose of the questionnaire is to obtain information regarding students' understanding of the need to take care of their own health, analyze their physical condition, the prerequisites for maintaining a healthy lifestyle, and the ability to make daily health decisions.

The questionnaire included the following open and closed questions:

1. Do you follow a sleep schedule? (What time do you fall asleep, what time do you wake up? Do you get enough sleep? Why?).
2. Do you change your daily routine because of the exam session? (What changes are happening in your daily routine?).
3. Do you have a habit of washing your hands? (How often do you wash your hands and why?).

4. Do you have a need and have you formed a habit of doing physical exercises daily?
5. What is your motivation to exercise?
6. Do you know any physical exercises that help you relieve your spine during prolonged sitting and relieve blood stagnation in the pelvic organs? How often do you perform them?
7. Do you follow a diet?
8. What foods do you prefer? (dairy products, meat, fish, fresh vegetables and fruits).
9. Does your behavior change during the epidemic, when the incidence of influenza and SARS increases? (taking vitamins, enriching your diet with fruits and vegetables, washing your hands, using a medical mask, clothing).
10. Do you practice eye hygiene? What do you do to relieve stress?
11. Do you practice good hearing hygiene? How long do you use headphones during the day? Do you think that using headphones negatively affects your hearing?
12. For what purpose do you use gadgets? (studying, games, communication, information, etc.).
13. How exactly do you use gadgets during learning activities? (explain).
14. How much time do you spend on gadgets and paper media (during a day or other period)?
15. Do you have any bad habits and what are they?
16. If you smoke, to what extent are you addicted to this habit?
17. Do you try to eliminate self-destructive habits from your own behavior (smoking, coffee, overeating, laziness, negative emotions, gadget addiction, inactivity, etc.)?
18. Do you use mobile applications to lead a healthy lifestyle? (specify which ones).

In this study, the authors adhered to the Ethical Principles for Medical Research Involving Human Subjects outlined in the World Medical Association's Declaration of Helsinki and current Ukrainian regulations. The study protocol was approved by the local ethics committee. Participation in the survey was voluntary and anonymous.

RESULTS

The results of the analysis of students' responses to the questionnaire were as follows. The vast majority of respondents (70%) answered the first question that they do not manage to follow the sleep schedule even with a great desire and there is not enough time for sleep.Generalized reasons for not following a sleep schedule are: studying (the need to perform a significant number of tasks); studying in two shifts; combining studying and working; communicating with peers; addiction to gadgets, etc. Only 30% of respondents affirmatively answered that they follow this regime or try to ensure healthy sleep. It should be noted that all students (100%) indicated disturbed sleep or insomnia due to the war in Ukraine, constant air raids, and missile and drone attacks from russia.

To the second question, 56% of respondents answered that preparing for exams does not fundamentally affect the routine of life processes. 44% of respondents indicated certain changes in their daily routine: going to bed later (preparing for the exam) and waking up earlier, emotional experiences, postponing various matters (personal, household) for later.

100% of respondents answered affirmatively to the third question. In most of the students' responses, we found fairly thorough explanations of the importance of frequent hand washing: taking care of your health, maintaining your own hygiene, adhering to health culture norms, and preventing diseases. Students also noted that they washed their hands more frequently and thoroughly during the COVID-19 pandemic.We must explain why we included this simple question in the questionnaire, because hand washing is a cultural and hygienic skill that is formed from early childhood. However, the experience of the authors of the article, conversations with students, and observations allow us to state that not everyone washes their hands thoroughly and correctly, although they are «convinced» of the correctness of performing this procedure. But it is precisely with this habit that the teacher demonstrates to children a daily practical example of caring for their own health and the health of others.

25% of respondents answered affirmatively to the fourth question. 75% of respondents do not have a habit of daily physical exercise. However, a significant number of them need and dream or plan to engage in physical education.

The students answered the fifth question as follows: 50% of respondents are convinced that physical exercises help to be beautiful, slim, contribute to physical perfection, and to receive aesthetic pleasure from a beautiful body shape.The importance of physical exercise for physical health and emotional relief was indicated by 40% of respondents. 10% of respondents noted that they are motivated by active recreation, good health, energy for the whole day, the desire to look and feel confident, become better and stronger, and have a flexible body.

To the sixth question 24% of students answered that they perform such exercises and that there is a need to perform physical exercises for this purpose. The majority of students (76%) indicated that they are not bothered by prolonged static sitting for now, and they do not have an urgent need to perform this type of exercise.

Although they noted that they change body position and take a dynamic break if necessary.

44% of respondents answered the seventh question of the proposed questionnaire that they do not follow a diet, 56% - follow a diet.

To the eighth question the answers were varied: 84% of respondents said they like fresh vegetables and fruits; 62% of respondents consume dairy products; 87% prefer meat; 53% like fish and seafood.

To the ninth question respondents answered that they take vitamins (44%), enrich their diet with fruits and vegetables (59%), wear masks, systematically wash their hands, avoid crowded places (65%), and dress warmer (71%). 12% of respondents do not take active measures to prevent viral diseases.

To the tenth question 56% of respondents answered affirmatively (they do eye exercises, use drops); 44% of respondents do not do special eye exercises.

To the eleventh question 60% of respondents indicated that they use headphones for a long time during the day, although they consider prolonged use of headphones harmful to hearing. 40% of respondents indicated that they observe hearing hygiene, that is, they rarely use headphones or try to spend as little time in headphones as possible, and they respond to mobile phone prompts about using the gadget with headphones for too long.

To the twelfth question 100% of respondents answered that gadgets are used everywhere: during educational activities (100%), to obtain various information (94%), for the game (43%), using gadgets to communicate with friends, relatives, and classmates (97%), for the work (6%), for watching movies, photos, videos, listening to music (20%).

To the thirteenth question, 100% of respondents answered that they use gadgets to view educational content. Students noted that such use of gadgets is effective and productive for optimizing educational activities.

To the fourteenth question, 80% of respondents answered that they spend significantly more time on gadgets during the day than on paper media.

To the fifteenth question, 20% of respondents answered that they had no bad habits, 80% of respondents had bad habits. The most common bad habits were addiction to smoking, coffee, gadgets, sweets, laziness, inactivity, nail biting, lip biting. One student (1%) thought that she perceived bad habits as a temporary need for the body when it wanted it.

The sixteenth question aimed to clarify students' answers to the previous question and specifically addressed young people's addiction to smoking. 15% of respondents answered affirmatively that they smoke. They noted that they smoke electronic cigarettes and do not consider them harmful to health. Sometimes they smoke to relieve stress.

The seventeenth question also concerned students' bad habits and was aimed at determining their readiness to eliminate self-destructive habits from their own behavior. 78% of respondents agree that smoking, coffee, overeating, laziness, negative emotions, gadget addiction, sedentary lifestyle, etc. are self-destructive habits. They are trying to think about it and take steps to reduce their dependence on these habits. 22% of respondents indicated that they do not plan to change their own lives because they are satisfied with them and that certain bad habits do not affect their physical and emotional state.

The following answers were received to the eighteenth question: 56% of respondents use mobile apps to lead a healthy lifestyle: «MindStrong Sport – training for the mind», Calorie counters «EatFit», «Calorie table», «FatSecret», «Water tracker» - water consumption control, «Step Counter – odograph, «WOWBODY», «Home Workout», - home workouts, «Flo Period & Pregnancy Tracker» - lunar cycle. 44% of respondents said they do not use it.

The summarized results of students' responses to the questionnaire are presented in the Table 1.

DISCUSSION

The results of the analysis of education seekers' responses, along with conversations with students, show that they understand the importance of health for a happy and active life. They recognise that the responsibility for their own health lies with the individual. They are aware of and acknowledge the significance of physical activity for maintaining a healthy lifestyle [1, 6]. They understand the importance of following a daily routine, ensuring proper nutrition and sleep, adhering to hygiene standards, and eliminating negative habits and desires from their lives as part of the health-preserving process [13]. Students in their first and second years have an understanding of the hygiene of organs and systems of the body, the importance of observing sanitary and hygienic norms concerning various life processes and learning. They have their own views on bad habits, their causes, and ways to eliminate them. It is important to note that students acknowledge that they make relatively little physical, intellectual, and emotional effort to engage in adequate health behaviours.

On the other hand, the results of the analysis of students' responses to the questionnaire lead us to believe that students are not active subjects of their own health-preserving activities. We record in them certain

Table 1. Summary table of students' responses to the questionnaire regarding readiness to be healthy

№	Question	Answers (%)	
1.	Maintaining a sleep schedule	Adhere (70%)	Do not comply (30%)
2.	Change of daily routine due to preparation for the exam session	Changes (56%)	No changes (44%)
3.	Hand washing habit	Formed (100%)	Not formed (none)
4.	The habit of doing physical exercise daily	Formed (25%)	Not formed (75%)
5.	Motivation for exercise	Beautiful body shape (50%) Health (40%) Active recreation (10%)	
6.	Carrying out exercises for unloading the spine	Doing exercises (24%)	Have no need (76%)
7.	Compliance with the diet	Adhere (56%)	Do not comply (44%)
8.	Preferred products	Dairy products (62%) Meat (88%) Fish (53%) Fresh vegetables and fruits (84%)	
9.	Behavioral changes during viral disease outbreaks	Take vitamins (44%) Enrich the diet with fruits and vegetables (59%) Wear masks, wash hands more often (65%) Dress warmer (71%) No changes (12%)	
10.	Eye hygiene	Adhere (56%)	Do not comply (44%)
11.	Hearing hygiene	Adhere (60%)	Do not comply (40%)
12.	Purpose of using gadgets	Study (100%) Searching for different information (94%) Games (43%) Communication (97%) Job (6%) Movies, music, videos, photos (20%)	
13.	Using gadgets during learning activities	Use (100%)	Do not use (none)
14.	The ratio of the use of gadgets and paper media	Gadgets (80%)	Paper media (20%)
15.	Presence of bad habits	Present (80%)	Absent (20%)
16.	Smoking addiction	Addicted (15%)	Have no dependencies (85%)
17.	Trying to eliminate self-destructive habits from one's own behavior	Are trying (78%)	Do not consider it necessary (22%)
18.	Using mobile apps to lead a healthy lifestyle	Use (56%)	Do not use (44%)

knowledge, understanding, ideas, desire, readiness for health-improving behavior. However, we do not consider the skills and habits of adequate health-promoting behavior among junior students to be sufficiently developed to speak of a conscious choice of such behavior in all aspects of life. The information and knowledge that students possess about the importance of making daily health decisions has not acquired the status of conviction and conscious actions to improve life through health formation. The above-mentioned position was particularly clearly confirmed by the students' responses regarding motivation to engage in physical exercise and the exclusion of self-destructive habits from their own behavior. A large number of students consider smoking, alcohol, drugs, coffee addiction, and gadget addiction to be bad habits. They don't think about the fact that self-destructive habits include laziness, overeating, negative emotions, negative thinking, a sedentary lifestyle, etc. The personal and motivational attitude towards the realization of physical abilities is not formed. There is awareness of the importance of physical exercise for health, but there is still no internal readiness to perform it systematically.

We are convinced that it is precisely through awareness during educational activities, communication with teachers, peers and different people, pedagogical practice, and leisure that students acquire knowledge, skills and abilities, and gain valuable life experience. Only health-preserving skills formed on the basis of a system of knowledge, awareness, ideas, understanding, and systematic practice will enable students to consciously use them in everyday life. So, we can claim that health behavior skills are formed through awareness of the importance of making health decisions, which

is related to the emotional and sensory sphere and, of course, volitional efforts.

PROSPECTS FOR FURTHER SCIENTIFIC RESEARCH

In the context of this issue, promising areas of further research are: the competence of a teacher at a higher education institution in the field of forming a culture of health for students; determining the motivation for students' readiness for health-preserving activities in a preschool educational institution as the basis for professional training; improvement of the working training program «Health-preserving technologies in preschool education»; development of the program of the selective educational discipline «Practicum of health support for students».

CONCLUSIONS

The results of the questionnaire analysis indicate that junior students of pedagogical specialties understand the importance of good health as a personal and social value. Students have certain knowledge, understanding, and general ideas about the need to lead a healthy lifestyle and adhere to the natural laws of human existence. However, there are not enough skills to convert this knowledge into the need, ability, and determination to be healthy and harmonious, to build balanced relationships with other people and the environment, to live and act in accordance with one's own health-promoting worldview and based on the assimilation of the cultural achievements of humanity or the nation. Junior students do not yet have an orientation towards the formation and preservation of health as an important personal and motivational need.

In fact, the individual himself must understand that knowledge, understanding, awareness and implementation into practice of daily health solutions are the key points on which the fullness of life will depend. Readiness for health-promoting behavior undoubtedly depends on each person's activity, level of aspirations, interests, needs, awareness, and responsibility.

REFERENCES

1. Palamar BI, Vaskivska HO, Palamar SP. Didactic aspects of cognition of human as a bio-psycho-socio-cultural personality. Wiad Lek. 2017;70(5):959-963.
2. Harashchenko L. Shliakhy vdoskonalennia fakhovoi pidhotovky maibutnikh vykhovateliv do zdoroviazberezhuvalnoi diialnosti. [Ways to Improve the Training of Future Educators to Health-Saving Activities]. Visnyk Luhans'koho natsional'noho universytetu imeni Tarasa Shevchenka. Pedahohichni nauky. 2020;7(338):195–201. doi: 10.12958/2227-2844-2019-1(324)-2-195-201. (Ukrainian) DOI
3. Vaskivska HO, Palamar SP, Kondratiuk SG et al. Psychodidactic determinants of the development of children of preschool age. Wiad Lek. 2018;71(6):1207-1214.
4. Okhrimenko IM, Pop OY, Hresa NV et al. Motivational and value-based attitude of law enforcement officers to motor activity as a factor of a healthy lifestyle. Wiad Lek, 2024;77(6):1224-1229. doi: 10.36740/WLek202406117. DOI
5. Petrovska T, Arnautova L, Palamar B et al. Korelyatsiya mizh pokaznykamy balansu nervovykh protsesiv z lokalizatsiyeyu kontrolyu u vysokokvalifikovanykh handbolistok. [Correlation between indicators of balance of nervous processes with localization of control in high skilled women handball players]. Klinichna ta profilaktychna medytsyna. 2023;4(26):96-103. doi: 10.31612/2616-4868.4(26).2023.14. (Ukrainian) DOI
6. Palamar B, Zhelanova V, Leontieva I et al. Vprovadzhennya sotsial'no-emotsiynoho navchannya v suchasnomu universyteti: vykhid za ramky akademichnoyi osvity. [Implementation of socio-emotional learning in the modern university: going beyond an academic education]. Klinichna ta profilaktychna medytsyna. 2024; 7(37): 95-102. doi:10.31612/2616-4868.7.2024.12. (Ukrainian) DOI
7. Palamar B, Gruzeva T, Palamar S et al. Ryzyk formuvannia syndromu emotsiinoho vyhorannia u studentiv z tochky zoru hromadskoho zdorovia. [Risk of emotional burnout syndrome in students from a public health perspective]. Klinichna ta profilaktychna medytsyna. 2020;3(12): 12-21. doi: 10.31612/2616-4868.3(13).2020.02. (Ukrainian) DOI
8. Lazurenko N. Social factors of spreading of tobacco smoking among college students. Revista San Gregorio. 2020. doi: 10.36097/rsan.v1i37.1290. DOI
9. Karadağ G, Bilgiç D, Öztürk N, Özdemir T. Relationship Between Nutritional Literacy and Healthy Life Skills of University Students. Eur J Education. 2025;60(1):e70019. doi: 10.1111/ejed.70019. DOI
10. Budnick S, Peters M, Dowthwaite JA. Cross-Sectional Analysis of College Students' Diet, Mental Health, and Hindrances to Healthy Lifestyles. Am J Lifestyle Med. 2025:15598276251315347. doi: 10.1177/15598276251315347. DOI
11. Marquès-Donoso A, Martínez-Hernández A, Revuelta P. University Students' Perceptions of Sustainability and Ecological Footprint in the Use of Digital Leisure. Education Sciences. 2025;15(1):21. doi: 10.3390/educsci15010021. DOI
12. Avram C, Nyulas V, Onisor D et al. Behavior and Lifestyle Among Students: The Influence of the University Environment. Nutrients. 2024;17(1):12. doi: 10.3390/nu17010012. DOI

13. Palamar SP, Harashchenko LV, Litichenko OD et al. The state of formation of a careful attitude towards health in the modern youth. Wiad Lek. 2024;77(11):2225-2231. doi: 10.36740/WLek/197101. DOI
14. Nosko M. Zdoroviazberezhuvalni tekhnolohii u fizychnomu vykhovanni [Health-preserving technologies in physical education: monograph]. Kyiv: SPD N.V. Chalchynska. 2014, p.300. (Ukrainian)
15. Zakalyak N. Analiz stanu zdorovia studentiv pedahohichnoho VNZ i poshuk shliakhiv yikh reabilitatsii [Analysis of the health status of students of a pedagogical university and search for ways of their rehabilitation]. In: Pedagogical technologies for forming a culture of personal health: materials of the 2nd All-Ukrainian Scientific and Practical Conference of Young Scientists and Students. Chernihiv: Chernihiv National Pedagogical University. 2015, p. 29–31. (Ukrainian)

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Svitlana P. Palamar
Borys Grinchenko Kyiv Metropolitan University
18/2 I. Shamo Blvd, 01601 Kyiv, Ukraine
e-mail: s.palamar@kubg.edu.ua

ORCID AND CONTRIBUTIONSHIP

Larysa V. Harashchenko: 0000-0002-7847-632X A B C D
Svitlana P. Palamar: 0000-0001-6123-241X A B C D
Olena D. Litichenko: 0000-0002-7004-3837 A B C D
Victorija V. Zhelanova: 0000-0001-9467-1080 A B D
Liudmyla L. Nezhyva: 0000-0001-9520-0694 D E F
Dana O. Sopova: 0000-0002-0814-6667 D E F
Andrii O. Zhyltsov: 0009-0007-7237-6196 D E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 17.02.2025
ACCEPTED: 25.05.2025

ORIGINAL ARTICLE

CONTENTS

Algorithm for predicting the clinical course and treatment effectiveness for patients with chronic myeloid leukemia using markers of metabolic intoxication

Ivanna M. Maikut-Zabrodska
SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: To develop a prognostic algorithm, taking into account the blood concentrations of medium-mass molecules (MMM), pyruvic acid (PA), and lactic acid (LA) as markers of metabolic intoxication (MI), in order to optimize the prediction of the clinical course and treatment effectiveness in patients with chronic myeloid leukemia (CML).

Materials and Methods: The study was conducted on 97 individuals (45 men, 52 women). The main group consisted of 77 patients with CML, aged (M ± m) 47.5 ± 1.4 years: 19 in stage I (chronic), 33 in stage II (acceleration), and 25 in stage III (blast crisis). The control group included 20 healthy individuals, aged 38.9 ± 1.3 years. A sequential Wald analysis, in a modified version with a 0.05 p-level threshold, was performed based on interim study results (levels of MMM, PA, and LA in blood, in addition to standard tests).

Results: The prediction algorithm aimed at identifying patients at high risk of CML progression and evaluating treatment effectiveness was developed, considering the MI markers. Reaching the predictive coefficient threshold sum is a criterion for determining the risk: if equal to or lower than "−19.8," the risk is high; if greater than "−19.8," but lower than "+19.8," the risk is uncertain; if equal to or greater than "+19.8," the risk is low.

Conclusions: The algorithm enables the stratification of patients with CML into risk groups. The incorporation of MMM, PA, and LA into the prognostic framework has the potential to enhance the predictive capacity of the model regarding clinical deterioration, treatment failure, etc.

KEY WORDS: chronic myeloid leukemia, peptides, lactates, pyruvates

Wiad Lek. 2025;78(6):1007-1013. doi: 10.36740/WLek/207357 DOI

INTRODUCTION

Recent epidemiological studies in Ukraine highlight the deterioration of health, particularly in the context of COVID-19 and war-related factors, unhealthy lifestyles, and insufficient access to personalized medical care, underscoring the urgency of individualized diagnostic and therapeutic strategies for vulnerable cohorts, including those with hematologic malignancies such as chronic myeloid leukemia (CML) [1–5]. It is one of the most common clonal myeloproliferative diseases, characterized by a specific genetic abnormality – the formation of the chimeric gene BCR-ABL due to the translocation t(9;22), which leads to the uncontrolled proliferation of myeloid cells [6]. Despite significant progress in the treatment of CML, particularly due to the introduction of tyrosine kinase inhibitors [7], the problem of assessing the state of metabolic processes that accompany the development and progression of the disease remains relevant [8].

In this context, the role of systemic metabolic disturbances, including so-called metabolic intoxication (MI), has attracted increasing attention. While markers such as medium-mass molecules (MMM), pyruvic acid (PA), and lactic acid (LA) are nonspecific and cannot be used for primary diagnosis by themselves, their potential as indicators of metabolic burden and predictors of therapy resistance or disease progression warrants investigation. These markers may reflect systemic metabolic stress secondary to leukemic proliferation and tumor-associated catabolic states and could serve as adjunctive parameters in the comprehensive assessment of disease dynamics. Recent studies, including our own preliminary observations, have suggested that quantitative changes in MMM, PA, and LA levels correlate with disease stage and hematologic response [9, 10], which implies a possible pathogenic role of MI in modulating leukemic cell behavior or host tolerance to therapy [11]. Therefore, a deeper understanding of these biochemical alterations may enhance individualized risk stratification and support therapeutic decision-making in already diagnosed CML cases.

In our previous stages of research and relevant pub-

lications, the following interim results were achieved [9, 10]. The study has enhanced the understanding of the diagnostic and prognostic value of plasma levels of MMM, PA, and LA (as well as a wide set of other biochemical markers) in patients with CML and identified early predictors of failure to respond to standard therapy. The correlation between MI markers and peripheral blood parameters at various stages of CML progression was assessed [9, 10]. Quantitative characteristics of MMM, PA, and LA fluctuations were established, confirming stage-dependent MI severity; specific changes in these markers at stage III were linked to the risk of febrile neutropenia [9, 10]. The research confirmed that MI intensity varies by disease stage, gender, age, and disease duration, justifying the correction of metabolic changes. It also demonstrated the diagnostic value of analyzing plasma and serum laboratory, morphological, and biochemical indicators [11].

The findings support using specific peripheral blood parameters to monitor metabolic status in CML patients and inform the development of screening tools.

AIM

The aim of the study was to develop a prognostic algorithm, taking into account the blood concentrations of medium-mass molecules, pyruvic acid, and lactic acid as markers of metabolic intoxication, in order to optimize the prediction of the clinical course and treatment effectiveness in patients with chronic myeloid leukemia.

MATERIALS AND METHODS

The study was a clinical prospective cohort comparative cross-sectional study involving 97 people: the main group consisted of 77 patients (mean [M] ± standard error of the mean [m]) (aged 47,5 ± 1,4 years, ranging 35–59 years; 35 men, 42 women) with CML (19 of them in stage I chronic, 33 in stage II acceleration, 25 in stage III blast crisis), the control group consisted of 20 practically healthy individuals (aged 38,9 ± 1,3 years, ranging 20–59 years; 10 men, 10 womn) as a references source for MMM, PA, LA values.

The following methods were used in the research: clinical (history taking, physical examination, instrumental), general laboratory (complete blood count with leukocyte formula, biochemical blood count, general urinalysis); special research methods (bone marrow puncture with myelogram calculation, cytochemical examination of red bone marrow and peripheral blood, immune phenotyping of blasts in red bone marrow and peripheral blood, lumbar puncture with biochemical examination of cerebrospinal fluid and morphological examination of centrifuged preparation); special biochemical studies (fluorometric, enzyme-linked immunosorbent assay); and statistical methods.

Quantitative indicators were evaluated based on the analysis of central tendency, variability, reliability of intergroup differences, and correlations, taking into account the nature of the data distribution. In the presence of a normal distribution, the arithmetic mean (M) and error of the mean (m) were calculated and expressed in the M ± m format. At the current stage of the study, the analysis of the distribution of clinical characteristics between groups was performed using a sequential Wald analysis in a modified version. To evaluate the prognostic significance of clinical signs, we determined the strength of influence (η^2, %) and informativeness (P, bits) according to the standard method. For all statistical calculations, the significance level was set at $p < 0.05$. All study data were stored and processed in a specialized database using Microsoft Excel (from the Microsoft 365 service; version 2503, build 18623.20178). StatSoft Statistica (version 12) and IBM SPSS Statistics (version 22.0) were used for statistical data processing.

The study was approved by the bioethics committee, as it complies with the basic principles of bioethics set forth in the Declaration of Helsinki of the World Medical Association, as well as national regulations. All patients involved in the study provided written informed consent to participate, which meets the ethical requirements for conducting research involving human subjects.

RESULTS

In order to use the previously published results of the MMM, PA, LA blood concentrations and other parameters study [9–11] for risk stratification based on clinical (anamnestic, physical), psychosocial and laboratory parameters, the parameters of their prognostic value and strength of influence were calculated using sequential Wald analysis in a modified version, which allowed to determine the diagnostic significance, prognostic value and strength of influence of individual factors on intergroup differences, as well as to calculate the corresponding prognostic coefficients.

The threshold value required to accept one of the two hypotheses was 19,8, which was determined according to the formula $(1-\alpha)/\beta$. In this calculation, the parameter α, which corresponds to the specified probability of a first-type error (incorrect failure to detect a threatening result), was set at a more stringent level of 0,01. The parameter β, which determines the probability of the second type of error (incorrect prediction of an unfavorable outcome), was chosen to be less stringent – 0,05.

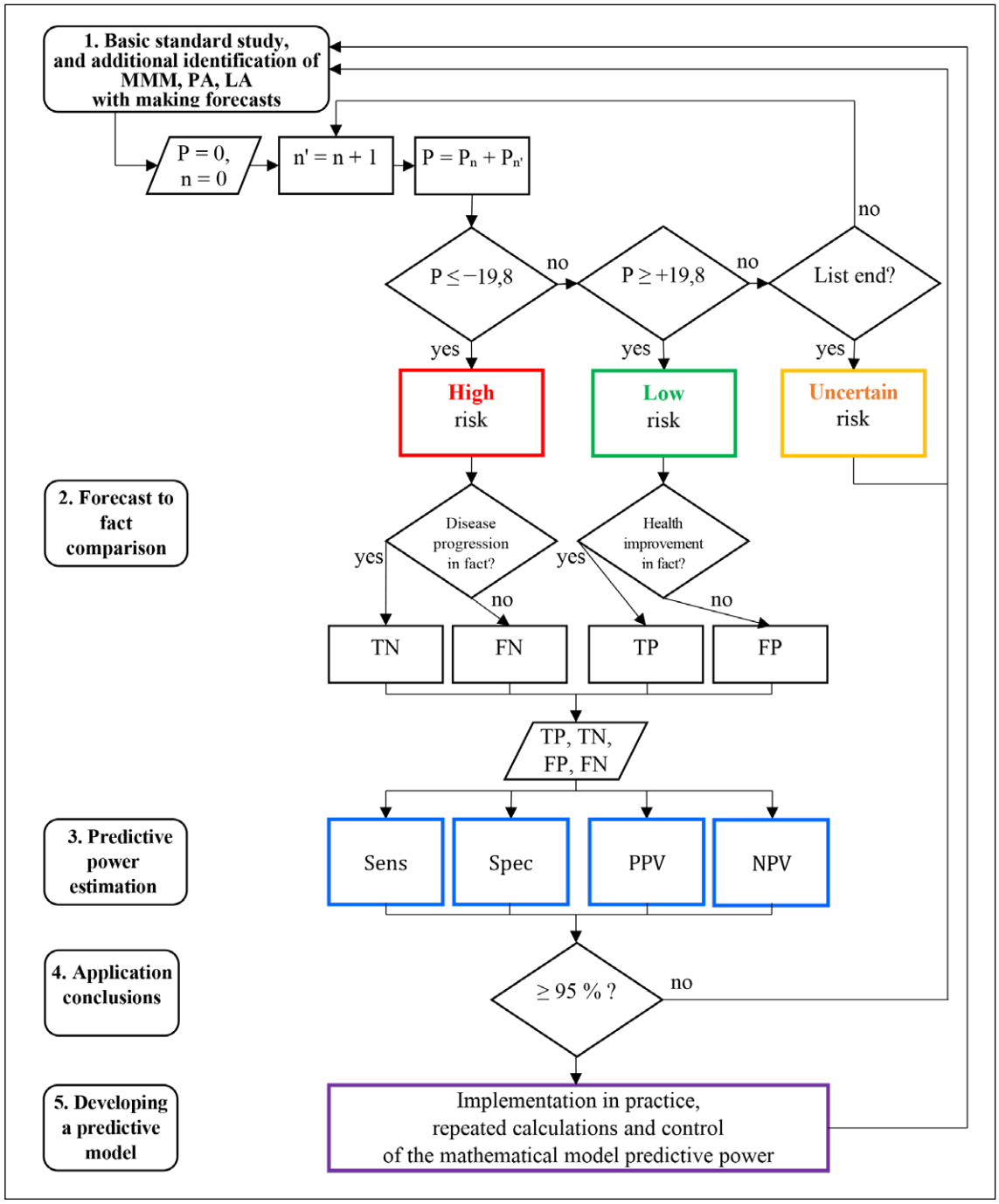

Fig. 1. Methodology for assessing the prognostic power and clinical effectiveness of a method (algorithm) for clinical course predicting in patients with chronic myeloid leukemia

Notes: MMM – medium-mass molecules; PA – pyruvic acid; LA – lactic acid; P – prognostic value of the indicator (pat); n – rank of the factor; TP – true positive results; TN – true negative results; FP – false positive results; FN – false negative results; Sens – sensitivity; Spec – specificity; PPV – positive predictive value; NPV – negative predictive value

Reaching the threshold sum of the predictive coefficients served as a criterion for determining the level of risk. If the calculated value was equal to or lower than −19,8, the risk was assessed as high. If the sum of the predictive coefficients is bigger than −19,8 but did not reach +19,8, the risk level was considered uncertain. If the sum of the predictive coefficients was equal to or greater than +19,8, the risk was classified as low.

An algorithm for predicting the effectiveness of treatment in patients with CML was developed. For each studied indicator, its presence or absence is determined, and the corresponding values of informativeness are added (Fig. 1).

The proposed algorithm aims to assess the individual risk of an adverse clinical course in patients with CML based on the set of indicators, including blood levels

of MMM, PA, and LA as markers of MI. While these indicators are not specific to CML diagnosis per se, they reflect the systemic metabolic burden and allow for supplementary stratification of patients' phenotypes, already diagnosed using validated hematological and molecular criteria. This stratification, in turn, contributes to personalized monitoring and therapeutic optimization.

Stage 1 (data initialization and risk score accumulation). The algorithm begins with a standard clinical-laboratory examination of the patient and additional determination of MMM, PA, and LA levels. This stage involves the calculation of a cumulative prognostic score P, which is initialized as zero (P=0, n=0, where n is the index of a prognostic feature). Each feature (e. g., elevated MMM or LA, reduced PA, etc.) is assigned a specific prognostic coefficient Pn based on its statistical informativeness (information value, P in bits). The score is updated iteratively: $P_{n'}=P_n+P_{n+1}$, where n' is the next index. This process continues until the threshold or all selected features are incorporated. Based on the cumulative score, risk stratification is performed:

- if $P \leq -19.8$, the clinical case is classified as "High risk", i. e., high probability of disease progression, suboptimal response to therapy, or metabolic decompensation, etc.;
- if $P \geq 19.8$, the clinical case is considered as "Low risk", indicating stable status and favorable therapeutic response likelihood, etc.;
- if $-19.8 < P < 19.8$, the risk is "Uncertain", warranting enhanced surveillance.

This stratification is not of diagnostic value but serves for dynamic prognostic assessment and therapeutic decision-making.

Stage 2 (forecast–reality comparison). Actual clinical outcomes (e. g., disease progression, remission, complications) are compared with the forecasted risk. Four possible outcomes are assessed:

- "true positive" (TP) – high-risk prediction confirmed by clinical deterioration;
- "true negative" (TN) – low-risk prediction confirmed by clinical stability or improvement;
- "false positive" (FP): high-risk prediction not confirmed (i. e., patient remained stable);
- "false negative" (FN): low-risk prediction contradicted by clinical worsening.

This stage is essential to evaluate the real-world performance of the risk algorithm and is repeated iteratively during follow-up.

Stage 3 (estimation of predictive power). Operational characteristics of the algorithm are calculated by represented standard formulas using the data from Stage 2:

- sensitivity – Sens=TP/(TP+FN) – ability to correctly predict deterioration;
- specificity – Spec=TN/(TN+FP) – ability to correctly identify patients with no adverse events;
- positive predictive value – PPV=TP/(TP+FP) – probability that a patient classified as high-risk actually deteriorates;
- negative predictive value – NPV=TN/(TN+FN) – probability that a patient classified as low-risk remains stable.

These indices quantify the diagnostic utility of prognostic modeling, complementing standard molecular monitoring.

Stage 4 (assessment of clinical applicability). If the calculated indices (particularly sensitivity and specificity) exceed 95 %, the model is deemed clinically applicable. If this threshold is not met, the model is recalibrated using larger datasets, refined variables, or adjusted thresholds. This iterative refinement is essential for increasing robustness and external validity.

Stage 5 (predictive model deployment and validation). The final stage entails the development and deployment of a predictive model for prospective use in clinical settings. It is applied to new patients with CML – those who were not included in the original dataset. This ensures validation on independent datasets and tests the generalizability of the approach.

In clinical terms, for any new patient with a verified diagnosis of CML, the levels of MMM, PA, and LA are entered into the algorithm. The resulting score stratifies the patient into one of three risk categories, thereby guiding the intensity of monitoring, consideration of therapy adjustment, or early intervention to prevent complications.

While cytogenetic and molecular tests (e. g., BCR-ABL1 quantification) remain the cornerstone of CML diagnosis and monitoring, they may not fully reflect the systemic metabolic stress or predict the likelihood of treatment-related intolerance and febrile complications. The inclusion of MI markers provides a supplementary layer of insight into the metabolic and functional status of the patient. This can be particularly useful in identifying subgroups (phenotypes) with latent metabolic decompensation despite optimal hematologic parameters; refining prognosis in elderly or comorbid patients who are prone to metabolic toxicity; detecting early metabolic shifts preceding clinical progression or treatment resistance.

To demonstrate the clinical utility of the proposed algorithm, we provide examples of its application in three representative patients with CML, whose biochemical profiles of metabolic intoxication markers – MMM, PA, and LA – were incorporated into prognostic modeling. These cases illustrate how the algorithm facilitates risk stratification and phenotypic pattern recognition beyond standard hematological parameters.

Patient A – "high-risk" profile (Stage III, "metabolic decompensation phenotype"). A 54-year-old male with blast crisis phase of CML presented with a markedly elevated plasma MMM concentration (1,75 conventional units (CU); reference range <1,2), increased LA (5,2 mmol/l), and significantly decreased PA (0,72 mmol/l). These findings corresponded to a cumulative prognostic coefficient (less than «–19,8»), classifying the patient as **high risk**. This metabolic pattern reflects a **catabolic intoxication phenotype**, characterized by systemic metabolic overload, tumor lysis, and impaired energy metabolism. The algorithm-guided assessment allowed timely intensification of supportive therapy and antifungal prophylaxis.

Patient B – "low-risk" profile (Stage I, "compensated metabolism phenotype"). A 41-year-old female in chronic phase exhibited only a marginal increase in MMM (1,32 CU), normal PA (1,12 mmol/l), and slightly elevated LA (2,4 mmol/l). The derived prognostic coefficient exceeded «+19,8», consistent with a **low-risk** category. The biochemical pattern indicated a **compensated phenotype**, with minimal metabolic dysregulation despite the underlying neoplastic process. This case supports the hypothesis that MI markers can provide early reassurance about therapeutic efficacy and metabolic stability in favorable responders.

Patient C – "uncertain risk" profile (Stage II, "transitional metabolic phenotype"). A 48-year-old male in acceleration phase showed moderate elevation of MMM (1,49 CU) and LA (3,6 mmol/l), with borderline PA (0,91 mmol/l). The cumulative score yielded between «–19,8» and «+19,8», placing the patient in the **uncertain risk** category. This case exemplifies a **transitional phenotype**, where MI markers signal subclinical instability. Based on algorithmic risk classification, intensified laboratory surveillance was implemented, which allowed early detection of resistance and transition to second-line therapy.

These representative cases illustrate how the integration of MI markers into the prognostic algorithm enables refined patient stratification into distinct risk and metabolic phenotypes, ranging from compensated to decompensated profiles. Each risk category informed therapeutic planning: "high-risk" cases prompted proactive supportive interventions; "low-risk" profiles allowed de-escalation of monitoring intensity; and "uncertain-risk" patients triggered closer dynamic reassessment.

In addition to conventional stratification models relying solely on cytogenetic and clinical data, this biochemical algorithm identifies subtle metabolic shifts that often precede clinical progression or therapy failure. Hence, the algorithm not only predicts outcome probability but also aids in tailoring the therapeutic landscape based on individual metabolic status.

Thus, in the context of modern clinical hematology, a prognostic algorithm has been developed that takes into account MI indicators, expands the possibilities of risk assessment, and increases the efficiency of predicting the health status of patients with CML, with possible patients' phenotypes distinguishing. This confirms the feasibility of its implementation in practical medicine for use in similar clinical situations.

DISCUSSION

One of the key aspects of the identified disorders is the relationship between the levels of metabolic markers and the effectiveness of therapy. According to the results obtained in our study, elevated levels of middle mass molecules correlate with reduced treatment efficacy in patients with advanced disease, which is confirmed by data on the prediction of therapeutic failure [10, 11]. These results indicate the need to include MI indicators in prognostic algorithms for assessing the effectiveness of therapy.

As noted by Y. Wang et al. (2024) [12], an improvement if MI parameters is observed in patients who respond well to treatment, while metabolism disorders accompany progressive tumor intoxication. Our results indicate the importance of taking this indicator into account in monitoring the effectiveness of treatment and predicting the complications [9, 11].

As previous studies have shown (J. M. Stempel et al., 2024) [13], older patients have a higher level of MI and a poorer response to treatment, which is consistent with our observations. In addition, special attention should be paid to the management of pregnant patients with CML, since, according to E. Chelysheva et al. (2024) [14], treatment during this period requires an individualized approach, taking into account possible metabolic changes.

Considerable attention in modern research is paid to the development of prognostic models to improve the accuracy of patient stratification. Predicting the effectiveness of treatment allows for the consideration of a wide range of factors and improves the accuracy of diagnosis (S. Bernardi et al., 2024) [15]. In our study, we proposed an algorithm that integrates laboratory indicators of MI into a risk assessment system.

Particular attention should be paid to achieving remission without therapy in patients with CML. As noted in the studies by H. Ureshino et al. (2024) [7] and D. Cattaneo et al. (2024) [16], repeated attempts to discontinue therapy can have positive results if patients are carefully selected and effective monitoring methods are

used. The results obtained in our study [9–11] indicate the importance of monitoring the levels of metabolic markers as predictors of the possibility of successful discontinuation of therapy, which is a promising area for further research.

Undoubtedly, the importance of an integrated approach to the diagnosis and treatment of CML, taking into account the level of MI, cannot be overstated. Expanding existing prognostic models to include MI markers could potentially increase the effectiveness of therapy and help timely identify patients at high risk of developing complications. The actual prognostic power of the algorithm for predicting the health status of patients suffering from CML, based on dynamic observation, requires further studies.

CONCLUSIONS

1. The proposed algorithm enables stratification of patients with CML into the risk groups of disease progression based on the cumulative prognostic coefficient derived from complex diagnostics, including metabolic markers.
2. The incorporation of MMM, PA, and LA into the prognostic framework has a potential of enhancing the predictive capacity of the model regarding clinical deterioration, treatment failure, or complications such as febrile neutropenia, etc.

Prospects for further research include evaluation of an actual prognostic power of the algorithm on the basis of dynamic observation with possible expanding the analysis of MI in patients with CML.

REFERENCES

1. Turova LO, Vezhnovets TA, Kantsypa VY. Analiz obiznanosti shchodo mozhlyvostey vprovadzhennya personalizovanoyi medytsyny sered likariv v Ukrayini: natsional'ne opytuvannya. [Analysis of awareness of the possibilities of implementing personalized medicine among doctors in Ukraine: national survey]. Klinichna ta profilaktychna medytsyna.. 2025;1:101–109. doi: 10.31612/2616-4868.1.2025.13. (Ukrainian) DOI
2. Lytvynova LA, Hrechyshkina NV, Donik OM et al. Okremi aspekty suchasnoho stanu zdorov'ya cholovichoho naselennya Ukrayiny. [Selected aspects of the current state of health of the male population of Ukraine]. Klinichna ta profilaktychna medytsyna.. 2023;8:118–125. doi: 10.31612/2616-4868.8.2023.14. (Ukrainian) DOI
3. Kostiukevych OM, Benkovska LK, Kravchenko AM et al. COVID-19 u patsiyentiv z miyeloproliferatyvnymy novoutvorennyamy: ryzyk tromboembolichnykh podiy ta suchasni varianty antytrombotychnoyi profilaktyky. [COVID-19 in patients with myeloproliferative neoplasms: The risk of thromboembolic events and current options for antithrombotic prophylaxis]. Klinichna ta profilaktychna medytsyna.. 2022;4:88–103. doi: 10.31612/2616-4868.4(22).2022.13. (Ukrainian) DOI
4. Paramonov VV, Dyagil IS. Kumulyatyvna zakhvoryuvanist' na limfoyidnyy ta miyeloyidnyy leykoz u riznykh rehionakh Cherkas'koyi oblasti u 2001 ta 2014 rokakh. [Cumulative incidence of lymphoid and myeloid leukemias in different regions of the Cherkassy Region in 2001 and 2014]. Klinichna ta profilaktychna medytsyna. 2021;2:48–56. doi: 10.31612/2616-4868.2(16).2021.06. (Ukrainian) DOI
5. Paramonov VV, Diagil IS. Kumulyatyvna zakhvoryuvanist' na hematolohichni novoutvorennya ta yiyi dynamika v riznykh rehionakh Cherkas'koyi oblasti u 1980, 1989, 2001 ta 2014 rokakh. [Cumulative incidence of hematological neoplasms and dynamic of this in different regions of the Cherkasy oblast in 1980, 1989, 2001 and 2014 years]. Klinichna ta profilaktychna medytsyna.. 2019;2:69–76. doi: 10.31612/2616-4868.2(8).2019.08. (Ukrainian) DOI
6. Shah NP, Bhatia R, Altman JK et al. Chronic Myeloid Leukemia, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2024;22(1):43–69. doi: 10.6004/jnccn.2024.0007. DOI
7. Ureshino H, Kamachi K, Kimura S. Second treatment-free remission attempt in patients with chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2024;24(4):e138–141. doi: 10.1016/j.clml.2023.12.011. DOI
8. Andorsky D, Kota V, Sweet K. Exploring treatment decision-making in chronic myeloid leukemia in chronic phase. Front Oncol. 2024;14:1369246. doi: 10.3389/fonc.2024.1369246. DOI
9. Maikut-Zabrodska I. Vmist molochnoi ta pirovynohhradnoi kyslot u plazmi krovi patsiyentiv iz khronichnoiu miieloidnou leikemiieiu. [Content of lactic and pyruvic acids in the blood plasma of patients with chronic myeloid leukemia]. Hematolohiia i perelyvannia krovi: Mizhvìdomchyi zbirnyk. 2023;42:164–173. doi: 10.33741/0435-1991.42.13. (Ukrainian) DOI
10. Maikut-Zabrodska I. Rezultaty doslidzhennia vmistu molekul serednoi masy u plazmi krovi patsiyentiv na riznykh stadiiakh prohresuvannia khronichnoi miieloidnoi leikemii. [Results of the study of medium-mass molecules content in blood plasma of patients at different stages of chronic myeloid leukemia progression]. Semeina medytsyna Yevropeiski praktyky. 2022;3(101):73–77. doi: 10.30841/2786-720X.3.2022.273920. (Ukrainian) DOI
11. Maikut-Zabrodska IM, Derpak YY, Vydyborets SV. Chronic mieloid leucemia: issues of pathogenesis, features of methabolic disorders, risk factors, prognostication of development. In: Entwiclung der soziokulturellen sphare und des gesundheitssystems in der modernen gesellschaft Monografische Reihe "Europaiche Wissenschaft". Karlsruhe: Scientific World – NetAkhat AV (Germany). 2021, p.86–100. doi: 10.21893/2709-2313.2021-07-05-011. DOI

12. Wang Y, Liang Z-J, Gale RP et al. Chronic myeloid leukaemia: Biology and therapy. Blood Rev. 2024;65:101196. doi: 10.1016/j.blre.2024.101196. DOI
13. Stempel JM, Shallis RM, Wong R, Podoltsev NA. Challenges in management of older patients with chronic myeloid leukemia. Leuk Lymphoma. 2024;65(9):1219–1232. doi: 10.1080/10428194.2024.2342559. DOI
14. Chelysheva E, Apperley J, Turkina A et al. Chronic myeloid leukemia diagnosed in pregnancy: management and outcome of 87 patients reported to the European LeukemiaNet international registry. Leukemia. 2024;38(4):788–795. doi: 10.1038/s41375-024-02183-0. DOI
15. Bernardi S, Vallati M, Gatta R. Artificial intelligence-based management of adult chronic myeloid leukemia: Where are we and where are we going? Cancers (Basel). 2024;16(5):848. doi: 10.3390/cancers16050848. DOI
16. Cattaneo D, Bucelli C, Bellani V. Treatment-free remission as a new goal in the management of chronic myeloid leukemia: Clinical and biological aspects. Hematol Oncol. 2024;42(5):e3309. doi: 10.1002/hon.3309. DOI

The research was conducted at the Department of Hematology and Transfusiology of the Shupyk National Healthcare University of Ukraine. The dissertation research is a fragment of the departmental research work topics:

1. *"Study of the regularities of formation and improvement of methods of diagnosis, treatment, chronic myeloproliferative, lymphoproliferative diseases and hematopoietic depression and optimization of their treatment and transfusion support" (state registration number 0115U002159, 2015–2019);*
2. *"The role of BCR-ABL1 gene mutations, chromosomal, molecular genetic disorders and immunogenetic parameters in the formation of approaches to optimizing targeted therapy of patients with chronic myeloid leukemia in the remote period after the Chernobyl accident" (state registration number 0116U003574, 2016–2020);*
3. *"Scientific and methodological support of standardization and personalization of medical and preventive and rehabilitation activities of a general practitioner - family doctor" (state registration number 0118U001145, 2018–2022);*
4. *"Scientific and methodological support of management of patients of all age groups with the most significant conditions and diseases at different levels of medical care" (state registration number 0123U105273, 2023–2027).*

CONFLICT OF INTEREST

The Author declare no conflict of interest

CORRESPONDING AUTHOR

Ivanna M. Maikut-Zabrodska
Shupyk National Healthcare University of Ukraine
9 Dorohozhytska St., 04112 Kyiv, Ukraine
e-mail: ivanna_zabrodska@ukr.net

ORCID AND CONTRIBUTIONSHIP

Ivanna M. Maikut-Zabrodska: 0000-0003-3945-3608 A B C D E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.02.2025
ACCEPTED: 22.05.2025

ORIGINAL ARTICLE

CONTENTS

The content of copper, iron and manganese in the saliva and blood of individuals with generalized periodontitis working in harmful industries

Zoryana B. Popovych, Volodymyr I. Sarapuk, Veronika Yu. Kateryniuk, Iryna Z. Chubiy, Iryna Z. Ostapyak, Natalia M. Pavelko, Oleksandra V. Bazalytska

IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

Aim: To investigate the content of Copper, Iron, and Manganese in the saliva and blood of patients affected by generalized periodontitis who have been working in harmful industries for an extended period.

Materials and Methods: The study enrolled 133 employees of the Burshtyn Thermal Power Plant (TPP). A comprehensive examination was conducted in 125 individuals with chronic generalized periodontitis of I and II degrees by clinical and biochemical methods. The study also enrolled 30 people not working at the Burshtyn TPP, examined with intact periodontium (controls). We investigated the content of Copper, Iron, and Manganese in biological materials using spectral analysis in 110 patients with chronic generalized periodontitis and 27 controls.

Results: The conducted examination indicated a disturbance in the content of Copper, Iron, and Manganese in the blood and mixed saliva of patients with generalized periodontitis who were employees of the Burshtyn TPP. We observed a decrease in the level of Manganese and Iron and an increase in Copper's content in patients with generalized periodontitis (vs. controls), which may indicate a violated metabolism of trace elements upon chronic exposure to small doses of heavy metal salts. The changes in the content of trace elements (particularly Copper and Manganese) were associated with the severity of the disease.

Conclusions: The changes in the level of particular trace elements in the saliva and blood of the examined individuals indicate their role in the development of generalized periodontitis.

KEY WORDS: periodontitis, trace elements, ecology, blood, saliva

Wiad Lek. 2025;78(6):1014-1018. doi: 10.36740/WLek/207358 DOI

INTRODUCTION

Over the period of the last few decades, the occurrence of dental diseases has been increasing. The latter is determined by many factors such as unfavorable ecology, deterioration of general health in adults and children, and worsening of living conditions due to the ongoing war. According to many observations, Ukraine is currently one of the most environmentally polluted countries in Europe and in the world due to the ongoing war. Environmental factors are considered one of the trigger factors which affect human health [1–7]. Therefore, studying the role of bad ecology regarding the occurrence and development of dental diseases remains relevant.

Numerous studies of the dento-maxillary system conducted in regions of intense technogenic pollution are gaining great importance; moreover, the question of allocating a special section — ecological dentistry — is being raised. In this aspect, the periodontium is regarded as an important informative structure that can be used in ecological monitoring.

Furthermore, the constant influence of man-made environmental pollution and psycho-emotional tension leads to disruption of adaptation processes and disease occurrence [2, 4, 5]. This problem is a part of extensive research directed towards early diagnosis of pre-pathological conditions, and justification of the principles and criteria concerning the real and maximum permissible load of adverse environmental factors on the population [8–10]. Such a system requires fundamental investigation, taking into account achievements in the field of medical and biological sciences in studying the mechanisms and patterns of the biological effects of the environment on the organism [10, 11].

In the process of the research, we examined children and adults from Burshtyn and surrounding villages (Ivano-Frankivsk region, Ukraine). There is a powerful thermal power plant here. According to the Ministry of Ecology and Natural Resources of Ukraine, by 2021 the Burshtyn Thermal Power Plant (TPP) ranked third in Ukraine in terms of emissions of pollutants into the atmosphere. About 965 thousand tons of waste were generated here during the year (pre-war period), of which about 158.6 thousand tons were emitted into the air. The Burshtyn TPP was repeatedly bombed during the war, as a result of which a large amount

of toxic substances found in slag ash dumps, as well as other toxic compounds, were released into the air.

The syndrome of environmentally induced lowered resistance leads to the development of disorders associated with the influence of eco-toxins and social factors, and causes elevated sensitivity of the body to adverse factors.

Copper is an element which is recommended for the assessment of human health in case of exposure to heavy metals [11]. This trace element enhances bone re-calcification, promotes the reversal of osteoporotic processes, and plays an important role in bone metabolism.

Cadmium ranks first in terms of toxicity among heavy metals and significantly affects both specific and nonspecific changes in the human body. We have already reported on the content of this trace element in our previous studies [6].

Iron is closely related to Cadmium. Its sufficient amount in food prevents the absorption of Cadmium. Iron also plays an important role in metabolic processes in areas of osteoporosis, in the formation of bone tissue, and has a positive effect on the formation of hydroxylapatites in the osteoid substance.

Manganese also has a protective effect. It is part of the active center in many enzymes, superoxide dismutase in particular, which are involved in protecting against peroxide radicals. Manganese affects the activity of phosphatases, which are involved in the metabolism of phosphorus-calcium compounds and influences the growth and maturation of cartilage and bone tissue.

We would like to report on the results regarding the content of trace elements (Copper, Iron, Manganese) in biological fluids — blood and mixed saliva — in people who have been employees of a thermal power plant for a long period of time and who live near this enterprise as well.

AIM

The aim of the research is to study the content of Copper, Iron**,** and Manganese in mixed saliva and blood in those affected with generalized periodontitis working in hazardous production for a long time.

MATERIALS AND METHODS

There were 163 people enrolled in this study, namely: 133 employees of the Burshtyn TPP and 30 people who do not work at the Burshtyn TPP. Among them were 109 men and 54 women aged from 20 to 49 years. One hundred and thirty-three employees of the Burshtyn TPP were diagnosed with generalized periodontitis of I and II degrees of severity, of whom 125 were diagnosed with chronic periodontitis and 8 were affected by acute periodontitis, which amounted to 93.98% and 6.02%, respectively.

A comprehensive examination was conducted in 125 patients with chronic generalized periodontitis of I and II degrees of severity (among them were 64 patients with generalized periodontitis of I degree and 61 with generalized periodontitis of II degree) using clinical (including periodontal pocket depth, Ramfjord Index [RI], and bleeding index by Mühlemann), biochemical, and radiological research methods; and there were also 30 people not working at the Burshtyn TPP examined with intact periodontium. The obtained results were recorded in the patients' outpatient charts. The examination consisted of complaints, and medical, social, and life history.

Biochemical studies were conducted at the Center for Bioelementology of Ivano-Frankivsk National Medical University (Head of the Department – Doctor of Biological Sciences, Professor G.M. Erstenyuk).

Quantitative determination of micro- and macro-elements (Iron, Copper, Manganese) in biological material was performed by the spectral method in 110 patients with generalized periodontitis and 27 people with intact periodontium. Biological fluids (blood and saliva) of patients were collected before breakfast, then dried at a temperature of 70–80°C. After drying, they were ashed in a muffle furnace at a temperature of 450–500°C.

Mineralization was carried out until the ash was free of coal impurities. Determination of Iron, Copper, and Manganese was carried out in ash solutions using an atomic absorption spectrophotometer C-115 "Saturn" in accordance with the requirements of the state standard and regulations.

All examinations were performed only with the voluntary written consent of the patients and in compliance with all bioethical norms, particularly the Declaration of Helsinki, and according to Ukrainian legislative and regulatory documents.

The data were analyzed using Statistica v. 14.0 (TIBCO Software Inc., USA) software. Quantitative variables were presented as mean ± standard error of the mean. We used the Student's t-test or ANOVA (with the Tukey's HSD post hoc test) for independent samples (to compare two or three independent groups of subjects, respectively). A p-value < 0.05 was considered statistically significant (considering the Bonferroni correction).

RESULTS

The data on the clinical characteristics of patients with chronic generalized periodontitis are presented in Table 1.

It was established that there was a significant increase in the depth of periodontal pockets in patients with generalized periodontitis of II degree by 25.16%, up to (3.83 ± 0.04) mm, while in patients with generalized periodontitis of I degree, this indicator was (3.06 ± 0.06) mm ($p < 0.001$).

The study of the RI also showed its notable increase depending on the severity of generalized periodontitis. The RI was (4.26 ± 0.14) points in the case of generalized periodontitis of I degree, increasing up to (4.63 ± 0.06) points in individuals with generalized periodontitis of II degree.

Table 1. Clinical characteristics of condition of periodontal tissues in patients with chronic generalized periodontitis

Indicators	Patients with chronic generalized periodontitis of I degree n=64	Patients with chronic generalized periodontitis of II degree n=61	p
Periodontal pocket depth, mm	3,06±0,06	3,83±0,04	<0,001
RI, points	4,26±0,14	4,63±0,07	<0,05
Bleeding index by Mühlemann, points	1,33±0,09	2,25±0,10	<0,001

Table 2. The content of trace elements in the blood and oral liquid of patients with generalized periodontitis and controls with intact periodontium

Indicators		People with intact periodontium n=27	Patients with chronic generalized periodontitis of I degree n=56	Patients with chronic generalized periodontitis of II degree n=54
Copper, mg% / raw sub.	Blood	0,17±0,01	0,19±0,01 p<0,01	0,22±0,01 p<0,001 p_1<0,001
	Oral liquid	17,19±0,92	20,34±0,99 p<0,05	21,43±0,96 p<0,05
Iron, mg% / raw sub.	Blood	79,68±2,93	67,70±2,96 p<0,05	63,75±3,00 p<0,001
	Oral liquid	0,79±0,03	0,67±0,03	0,59±0,04 p<0,05
Manganese, mcg% / raw sub.	Blood	3,90±0,06	3,45±0,06 p<0,001	3,00±0,06 p<0,001 p_1<0,001
	Oral liquid	0,03±0,002	0,02±0,002 p<0,05	0,01±0,003 p<0,001

Note: p – the significance of difference between the indicators of people with intact periodontium and patients with generalized periodontitis of I and II degrees, p1– the significance of difference between the indicators of patients with generalized periodontitis of I and II degrees

When studying the Mühlemann bleeding index, its growth was observed with the progression of the disease (see Table 1). In the group of patients with generalized periodontitis of I degree, this indicator was (1.33 ± 0.09) points, increasing by 69.17% to (2.25 ± 0.10) points in patients with generalized periodontitis of II degree ($p < 0.001$).

Thus, the study of the clinical condition of periodontal tissues in employees of the Burshtyn TPP suggests that there was a significant increase in all indicators in patients with generalized periodontitis as the pathological process in the periodontium progressed.

The results of our study, concerning the level of trace elements in the blood and oral fluid (mixed saliva) of Burshtyn TPP workers and controls (those not working at the Burshtyn TPP with intact periodontium), are illustrated in Table 2. The data obtained indicate a disruption of the trace element status, reflected in fluctuations of the statistical results. As can be seen from Table 2, the level of Copper, Iron, and Manganese in those diagnosed with generalized periodontitis is clearly associated with the severity of the disease.

In particular, there was an increase in Copper in the blood of patients with generalized periodontitis of degree I, with its level rising by 11.76% compared to (0.17 ± 0.01) mg%/raw sub. in subjects with intact periodontium ($p < 0.01$). In the case of generalized periodontitis of degree II, the concentration of Copper in the blood increased by 29.41%, reaching (0.22 ± 0.01) mg%/raw sub. ($p < 0.001$ vs. both periodontitis I degree and intact periodontium).

Similar changes were observed in the oral fluid (mixed saliva). The amount of Copper in the oral fluid of patients with generalized periodontitis of degree I was (20.34 ± 0.99) mg%/raw sub., and of degree II – (21.43 ± 0.96) mg%/raw sub., exceeding the corresponding indicator of people with intact periodontium (17.19 ± 0.92) mg%/raw sub. by 18.32% and 24.66%, respectively ($p < 0.05$ for both comparisons).

When studying the amount of Iron in patients with generalized periodontitis, it was found that its level decreased with the progression of the pathological process (see Table 2). If in the blood of patients with generalized periodontitis of degree I, its concentration decreased by 15.04%, then in patients with generalized periodontitis of degree II, it also declined by 20.00%, compared to the indicator in people with intact periodontium.

A significant reduction of Iron was detected in the oral fluid of patients with generalized periodontitis of degree II, down to (0.59 ± 0.04) mg%/raw sub., which differed from

the indicator in controls (0.79 ± 0.03) mg%/raw sub. by 25.32% ($p < 0.05$).

The study demonstrates that the amount of Manganese also decreased in patients with generalized periodontitis, namely: in the case of degree I, it lowered significantly by 11.54% in the blood and by 29.04% in the oral fluid; in the case of degree II, its level reduced by 33.33% in the blood and by 66.67% in the oral fluid (data compared with the corresponding indicators of individuals with intact periodontium). Additionally, the patients with generalized periodontitis of degree II demonstrated a lower level of Manganese, as opposed to those with degree I (Table 2).

Therefore, the results of the study show disturbances in the levels of Copper, Iron, and Manganese in the biological fluids of patients affected by generalized periodontitis, who have lived nearby and worked at the Burshtyn TPP for an extended period of time. There is a significant rise in Copper and a decline in Iron and Manganese levels in those affected by generalized periodontitis.

DISCUSSION

There are notable changes in the microelement spectrum found in the blood and mixed saliva of the examined patients, namely: a decreased amount of Manganese and Iron and an increased amount of Copper, which may indicate a disturbed metabolism of microelements under conditions of chronic exposure to small doses of heavy metal salts. Therefore, it can be concluded that the severity of generalized periodontitis is caused by changes in the content of trace elements that affect the permeability of cell membranes, the activity of enzymes responsible for compensatory mechanisms in tissues, including the periodontium. The latter is confirmed by the disordered microelement spectrum of blood and saliva in cases of worsening of the disease. The results of our studies are consistent with the studies of other scientists [12-15]. It has also been proved that the imbalance of microelements affects all organs and systems of the human body, causing various pathological conditions such as diabetes mellitus [13] and cardiovascular diseases [14]. The authors also indicate that Copper is an essential trace element for normal cell functioning; its deficiency has been reported to impair the function of vital copper-binding enzymes, while its excess can lead to cell death [13]. The precise and tight regulation of Copper homeostasis is summarized, and recent advances regarding the relationship between diabetes and plasma Copper are discussed.

The influence of heavy metals on the course of cancer has also been proven [9], as well as their effect on the development of Alzheimer's disease [15]. The authors admit that the disease is a complex multi-factorial disorder in which the convergence of polygenic, epigenetic, environmental, vascular, and metabolic factors tend to enhance susceptibility to the disease and shape its course. One of the cofactors converging with Alzheimer's disease is brain metal dysregulation.

There is a correlation reflected in the results of our study, which evidences the disturbances in Copper, Iron, and Manganese content in biological fluids of patients with generalized periodontitis working in poor environmental conditions.

CONCLUSIONS

The analysis of the gained results and the data of scientific research allow us to suggest that generalized periodontitis found in workers employed in hazardous production and living in adverse environmental conditions may be caused by technogenic microelementosis, which is characterized by an increased content of Copper in biological fluids and a decreased level of essential microelements (namely Iron and Manganese). The established changes in the microelement spectrum could lead to a disruption in the ratio of osteogenesis and osteolysis, decreased synthesis, and increased collagen breakdown, which weakens the mineralization of the organic matrix of periodontal bone tissue and enhances its resorption.

REFERENCES

1. Zasčiurinskienė E, Šidlauskas A, Kavaliauskienė A et al. Reliability and Validity of a Lithuanian Version of the Oral Health Impact Profile-A Study in Patients with Stage III-IV Periodontitis. Medicina (Kaunas). 2022;59(1):69. doi: 10.3390/medicina59010069. DOI
2. Asaduzzaman K, Khandaker MU, Binti Baharudin NA et al. Heavy metals in human teeth dentine: A bio-indicator of metals exposure and environmental pollution. Chemosphere. 2017;176:221-230. doi: 10.1016/j.chemosphere.2017.02.114. DOI
3. Scheiber I, Dringen R, Mercer JF. Copper: effects of deficiency and overload. Met Ions Life Sci. 2013;13:359-387. doi: 10.1007/978-94-007-7500-8_11. DOI
4. Aziz J, Rahman MT, Vaithilingam RD. Dysregulation of metallothionein and zinc aggravates periodontal diseases. J Trace Elem Med Biol. 2021;66:126754. doi: 10.1016/j.jtemb.2021.126754. DOI
5. Gil F, Hernández AF. Toxicological importance of human biomonitoring of metallic and metalloid elements in different biological samples. Food Chem Toxicol. 2015;80:287-297. doi: 10.1016/j.fct.2015.03.025. DOI
6. Popovych ZB, Rozhko MM, Ostapyak IZ et al. The content of zinc and cadmium in blood and oral fluid in generalized periodontitis in people exposed to adverse environmental factors. Wiad Lek. 2021;74(10):2407-2411. doi: 10.36740/WLek202110108. DOI

7. Popovych Z, Rozhko M, Ostapyak I, Oktysyuk Y. Biochemical indexes of mineral metabolism in patients from the polluted region affected by chronic periodontitis. Pharmacia. 2020;67(1):23-28. doi: 10.3897/PHARMACIA.67.E36150. DOI
8. Salehi S, Pouresmaieli M, Qarahasanlou AN. A sustainable way to prevent oral diseases caused by heavy metals with phytoremediation. Case Studies in Chemical and Environmental Engineering. 2025;11:101106. doi: 10.1016/j.cscee.2025.101106. DOI
9. Herman M, Jakubowska M, Piekoszewski W. Statistical analysis of the content of metals in blood serum and in the alternative material in head and neck carcinoma. Arabian Journal of Chemistry. 2024;17(3):105577. doi: 10.1016/j.arabjc.2023.105577. DOI
10. de Araújo EEN, Gueiros LA, Dos Santos Júnior JA et al. Teeth and alveolar bones as tracers of metals and radionuclides in inhabitants of a uranium region. Environ Res. 2024;259:119510. doi: 10.1016/j.envres.2024.119510. DOI
11. Bonham M, O'Connor JM, Hannigan BM, Strain JJ. The immune system as a physiological indicator of marginal copper status? Br J Nutr. 2002;87(5):393-403. doi: 10.1079/BJNBJN2002558. DOI
12. Rojas-Torres J, Quijón MEG, Henríquez-Vidal A et al. Permanent and decidua dentition as chronological biomarkers of heavy metal contamination: A review of the forensic literature. J Trace Elem Med Biol. 2024;84:127435. doi: 10.1016/j.jtemb.2024.127435. DOI
13. Chang W, Li P. Copper and Diabetes: Current Research and Prospect. Mol Nutr Food Res. 2023;67(23):e2300468. doi: 10.1002/mnfr.202300468. DOI
14. Saedi S, Tan Y, Watson SE et al. Potential pathogenic roles of ferroptosis and cuproptosis in cadmium-induced or exacerbated cardiovascular complications in individuals with diabetes. Front Endocrinol (Lausanne). 2024;15:1461171. doi: 10.3389/fendo.2024.1461171. DOI
15. Sensi SL, Granzotto A, Siotto M, Squitti R. Copper and Zinc Dysregulation in Alzheimer's Disease. Trends Pharmacol Sci. 2018;39(12):1049-1063. doi: 10.1016/j.tips.2018.10.001. DOI

The study was carried out within the framework of two researches: the research «Clinical effectiveness of complex treatment of diseases of hard dental tissues and periodontium in the population from ecologically bad regions», which was financed from the state budget of Ukraine (state registration number 0118U004144, implementation period 2018-2020); and the research «Complex morpho-functional study and substantiation of the use of modern technologies for the treatment and prevention of dental diseases», which is financed from the state budget of Ukraine (state registration number: 0121U109242, implementation period: 2021 – 2023).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Zoryana B. Popovych
Ivano-Frankivsk National Medical University
2 Galytska St., 76018 Ivano-Frankivsk, Ukraine
e-mail: zpopovych@ifnmu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Zoryana B. Popovych: 0000-0003-4472-3748 A D F
Volodymyr I. Sarapuk: 0000-0001-6986-7911 B C
Veronica Yu. Katerynyuk: 0000-0003-3256-3599 B E
Iryna Z. Chubij: 0009-0001-0826-5500 B C
Iryna Z.Ostapyak: 0000-0002-3042-7019 B C F
Natalia M. Pavelko: 0000-0002-5727-7399 B C
Oleksandra V. Bazalytska: 0009-0007-3842-6663 A B

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.02.2025
ACCEPTED: 26.05.2025

ORIGINAL ARTICLE

CONTENTS

Clinical and laboratory correlates of kidney function in multiple myeloma patients

Halyna R. Savuliak, Vladyslav O. Bardash, Tetiana A. Maksymets, Mykhaylo V. Perepelytsya, Zoryana M. Kit, Natalia V. Karpyshyn, Eugen Ya. Sklyarov

DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Aim: To investigate the relationships of kidney function with clinical and laboratory parameters in multiple myeloma (MM) patients**.**

Materials and Methods: A cross-sectional study involved 105 MM patients. Data included clinical manifestations and standard laboratory parameters. Kidney function was assessed via estimated glomerular filtration rate (eGFR), serum creatinine, urea, uric acid (UA), calcium (Ca), and albumin-to-creatinine ratio (ACR). The markers of MM activity and burden included M-protein, beta-2 microglobulin (β2m), albumin, hemoglobin (Hb), lactate dehydrogenase (LDH) and platelets (PLT). Rank biserial correlation assessed associations between symptoms and laboratory parameters. Rank-based canonical correlation analysis (RCCA) explored the multivariate relationship between six kidney function indicators and six MM-related markers.

Results: Common laboratory abnormalities included elevated β2m (90,5 %) and anemia (indicated by low Hb in 52,4 % of patients). Frequent symptoms included bone pain (71,4 %) and weakness (68,6 %). Symptoms like weakness/breathlessness correlated significantly with (β2m, M-protein) and renal impairment (creatinine, ACR, eGFR). RCCA identified one significant canonical correlation (R1=0,497; p=0,013), linking impaired renal function (characterized by low eGFR, high ACR, creatinine and urea) with a myeloma profile indicative of disease activity and burden (high β2m, low Hb, low albumin, and high M-protein).

Conclusions: The study confirms a significant multivariate association between a profile of impaired renal function and markers reflecting MM activity, hematopoietic suppression and systemic burden. These findings underscore the multifactorial nature of MM-related kidney injury and highlight the clinical utility of monitoring key laboratory markers (including eGFR, ACR, creatinine, β2m, Hb and albumin) alongside clinical evaluation for comprehensive assessment and management of MM patients.

KEY WORDS: multiple myeloma, chronic kidney disease, anemia

Wiad Lek. 2025;78(6):1019-1025. doi: 10.36740/WLek/207359 DOI

INTRODUCTION

Multiple myeloma (MM) is a malignant hematological disease characterized by the proliferation of plasma cells in the bone marrow and excessive production of monoclonal immunoglobulin – the M-protein [1]. MM is a multi-stage process that begins with the formation of a plasma cell clone, which subsequently undergoes malignant transformation, leading to the development of plasma cell myeloma – the final stage of the disease. The disease manifests as anemia, recurrent infections, osteolytic bone lesions, and hypercalcemia. One of the most frequent complications of this disease is kidney damage, which occurs in 20-50% of patients at initial presentation, and 10-13% of patients require dialysis at the time of diagnosis.

This significantly increases morbidity and mortality and limits treatment strategies [2, 3]. MM is associated with the highest rate of kidney damage among all cancer [4]. The mechanism of kidney damage in MM is multifactorial; however, the most common basis of "myeloma kidney" is the excessive excretion of free light chains that deposit in the distal and proximal tubules of nephrons. Another cause that leads to impaired renal function is hypercalcemia and hypercalciuria with subsequent hypovolemia, which leads to prerenal renal failure. Hyperuricemia and tumor lysis syndrome, amyloidosis, and microthrombotic lesions are also significant. In addition, nephrotoxic cytostatic drugs used in modern chemotherapy regimens, radiocontrast agents, and nonsteroidal anti-inflammatory drugs can lead to kidney dysfunction [5]. Additional risk factors for chronic kidney disease (CKD) in MM are the combined occurrences of hypertension and type 2 diabetes mellitus.

Despite the fact that this topic is well researched, it has not lost its relevance due to advances in understanding the pathogenesis of MM and CKD, as well as the development of new treatments for both nosologies. And the fact that CKD is one of the main causes of death in patients with MM further justifies the importance of timely intervention.

Table 1. Baseline characteristics of the study cohort (N=105)

Indicators	Median [Q1; Q3]	95 % CI
Body mass index (kg/m^2)	27,3 [24,5; 30,2]	[26,1; 28,3]
Systolic blood pressure (SBP, mm Hg)	135,0 [120,0; 145,0]	[130,0; 140,0]
Diastolic blood pressure (DBP, mm Hg)	90,0 [80,0; 95,0]	[85,0; 90,0]
Leukocytes (WBC, ×10^9/L)	4,9 [3,6; 6,4]	[4,4; 5,4]
Erythrocytes (RBC, ×10^{12}/L)	3,9 [3,6; 4,2]	[3,8; 4,0]
Hemoglobin (Hb, g/L)	126,0 [114,0; 135,0]	[121,0; 129,0]
Platelets (PLT, ×10^9/L)	196,0 [146,0; 241,0]	[177,0; 216,0]
Erythrocyte sedimentation rate (ESR, mm/h)	24,0 [12,0; 37,0]	[19,0; 28,0]
ALP (U/L)	74,0 [49,8; 92,8]	[61,6; 80,3]
ALT (U/L)	20,5 [15,5; 30,0]	[17,8; 24,3]
AST (U/L)	19,9 [16,0; 23,6]	[18,0; 20,9]
GGT (U/L)	35,0 [25,0; 44,0]	[32,0; 37,0]
Glucose (mmol/L)	5,5 [5,0; 6,0]	[5,3; 5,7]
Total protein (TP, g/L)	69,5 [63,8; 73,0]	[67,8; 70,7]
UA (μmol/L)	278,7 [216,7; 345,2]	[246,0; 308,3]
Ca (mmol/L)	2,36 [2,27; 2,48]	[2,29; 2,37]
Urea (mmol/L)	5,4 [4,3; 7,1]	[4,9; 5,9]
Creatinine (μmol/L)	80,1 [61,0; 95,4]	[73,1; 83,9]
eGFR (CKD-EPI, mL/min/1,73m^2)	85,0 [61,0; 101,0]	[77,0; 92,0]
β2m (mg/L)	3,7 [2,2; 6,1]	[3,0; 4,9]
Fibrinogen (g/L)	3,0 [2,1; 3,8]	[2,4; 3,2]
D-dimer (ng/mL)	320,0 [220,0; 580,0]	[250,0; 440,0]
Albumin (g/L)	40,8 [36,4; 43,8]	[38,6; 42,1]
M-protein (g/L)*	8,82 [4,9; 23,7]	[7,35; 18,7]
ACR (mg/g)	30,1 [5,6; 45,4]	[11,4; 34,1]
LDH	285,1 [246,0; 345,5]	[269; 310]
CRP (C-reactive protein)	6 [6; 6]	[6; 6]

Note: * — M-protein was detected in 35 out of 105 patients (33,3 % [95 % CI 24,6-43,3 %])

AIM

The aim of the study was to investigate the relationships of kidney function with clinical and laboratory parameters in MM patients.

MATERIALS AND METHODS

The study included 105 patients with MM who were undergoing treatment or observation at the State Institution "Institute of Pathology and Cell Therapy of the National Academy of Medical Sciences of Ukraine" (Lviv, Ukraine). The diagnosis of MM was made according to NCCN Clinical Practice Guidelines in Oncology, Version 2.2024 [6].

Inclusion criteria were: documented MM, age between 18 and 85 years, patient consent to participate in the study, and ability to cooperate adequately during the study process. Exclusion criteria were: patient refusal to participate, age <18 years, evidence of acute infectious processes of any etiology, pregnancy and lactation, decompensated heart failure and mental disorders.

The study was conducted in accordance with the Helsinki Declaration, the Convention for the Protection of Human Rights and Biomedicine, and the legislation of Ukraine, and was approved by the Ethics Committee of Scientific Research of the Danylo Halytskyi Lviv National Medical University: Protocol No. 1, dated January 23, 2023. All patients signed an informed consent form prior to the study.

The mean age of the subjects was 57,2±8,80 years (mean ± standard deviation [SD]). The cohort included 50 (47,6% [95% CI 38,3–57,1%]) women and 55 (52,4% [95% CI 42,9–61,7%]) men.

All patients underwent a thorough collection of complaints, medical history, and life history, as well as general clinical and laboratory examinations. These examinations included: a complete blood count, biochemical

Table 2. Association of clinical manifestations with laboratory and demographic parameters in MM patients (rank biserial correlation coefficient [r]; N=105)

Parameter	Weakness	Bone pain	Loss of body weight	Breath-lessness	Neuropa-thy	Infections	Diarrhea	Constipa-tion	Dyspep-sia
SBP	0,25*	0,15	0,40*	0,10	−0,04	−0,23	−0,09	−0,08	−0,29**
DBP	0,23*	0,16	0,06	0,09	0,04	−0,20	0,02	−0,18	−0,19
WBC	0,18	−0,02	0,37*	−0,04	−0,05	−0,13	0,18	−0,19	0,32**
RBC	−0,50***	−0,37**	−0,50**	−0,75***	0,13	0,05	−0,20	0,03	−0,02
Hb	−0,62***	−0,38**	−0,47**	−0,90***	0,16	0,05	−0,25*	−0,03	−0,13
PLT	−0,06	−0,22	−0,05	−0,43***	0,19	0,20	−0,00	−0,24	0,11
ESR	0,43***	0,36**	0,36*	0,44***	−0,09	−0,05	0,14	0,05	0,14
ALP	0,12	0,25*	0,61***	0,17	−0,21	−0,30*	0,12	−0,08	−0,13
ALT	−0,10	−0,19	0,03	−0,03	−0,23*	−0,24*	−0,10	−0,18	−0,07
AST	0,05	0,14	0,13	0,23	−0,24*	−0,27*	0,11	−0,21	−0,08
GGT	−0,09	−0,14	0,20	0,11	−0,05	−0,01	0,03	−0,11	−0,11
Glucose	−0,05	−0,06	0,04	−0,08	−0,03	−0,05	0,13	0,37*	−0,09
TP	0,03	0,11	0,32	0,04	−0,02	−0,21	−0,11	0,28	0,02
UA	0,16	0,05	0,31	0,27*	−0,03	−0,24*	0,16	−0,02	0,16
Urea	0,10	0,09	0,33	0,21	−0,26*	−0,15	0,07	−0,05	0,19
Creatinine	0,26*	0,06	0,31	0,39**	−0,13	−0,33**	0,08	0,15	0,17
eGFR	−0,30*	−0,15	−0,40*	−0,46***	0,19	0,31**	−0,12	−0,01	−0,22
β2m	0,39***	0,37**	0,43*	0,42***	−0,11	−0,25*	0,20	−0,07	0,03
Fibrinogen	0,16	0,09	0,10	−0,02	0,13	0,14	−0,09	0,04	−0,18
D−dimer	0,04	0,17	0,12	0,20	−0,05	−0,10	−0,09	0,03	−0,08
Albumin	0,00	−0,08	−0,10	−0,17	0,11	−0,14	−0,01	−0,14	−0,02
M−protein	0,44***	0,31**	0,47**	0,31**	−0,07	−0,31**	−0,11	−0,05	−0,01
ACR	0,29**	0,18	0,26	0,29*	−0,17	−0,29*	0,16	−0,05	0,33**

Note: * − $p < 0,05$; ** − $p < 0,01$; *** − $p < 0,001$

blood tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], lactate dehydrogenase [LDH], creatinine, urea, uric acid [UA], glucose, calcium [Ca], beta-2 microglobulin [β2m]), coagulation profile, blood protein electrophoresis, determination of immunoglobulin levels, and the determination of the albumin/creatinine ratio (ACR) in urine.

Hematological and biochemical blood tests, and coagulation profiles were performed using standard methods. Serum protein electrophoresis was performed on a Hellabio-Vitatron electrophoretic system (Greece). The assessment of albumin and creatinine excretion in urine was conducted using test strips from MICROLABBU-PLAN (Czech Republic). To assess renal function, the estimated glomerular filtration rate (eGFR) was calculated using an online calculator, employing the CKD-EPI formula (2021 modification) according to the KDIGO 2024 recommendations [7]. Baseline characteristics are presented in Table 1.

All statistical analyses were performed using R software, version 4.4.2.

Descriptive statistics were calculated for baseline patient characteristics. Continuous variables were assessed for normality using the Shapiro-Wilk test. Due to deviations from normality for most variables, continuous data were summarized and presented as median (1st Quartile [Q1]; 3rd Quartile [Q3]). The 95% confidence interval (CI) for the median was also calculated. Categorical variables, including the presence or absence of clinical manifestations, were described using absolute (n) and relative (%) frequencies. The 95 % CI for these proportions was computed using the Wilson score interval method.

Rank biserial correlation coefficient (r) was calculated to assess the pairwise association between clinical manifestations and baseline laboratory, demographic and disease markers.

To investigate the multivariate linear relationships between groups of variables, rank-based canonical correlation analysis (RCCA) was performed. One set comprised six kidney function indicators (eGFR, creatinine, ACR, urea, UA, and Ca). The second set comprised six indicators related to myeloma and its systemic effects

(M-protein, β2m, albumin, Hb, LDH, and PLT). The RCCA was conducted on patients with complete data for all variables included in the analysis. The overall significance of the model and the sequential significance of the canonical correlations were evaluated using Wilk's Lambda statistic with Rao's F-approximation. Canonical correlations and structure correlations (loadings) between the original variables and the derived canonical variates were examined for interpretation. For all statistical tests, a p-value < 0,05 was considered statistically significant.

RESULTS

Analysis of laboratory parameters in the studied cohort (N=105) revealed frequent abnormalities characteristic of MM. Among elevated parameters, increased β2m was observed in 95 (90,5% [95% CI 83,4–94,7 %]) patients, followed by a high ESR in 76 (72,4% [95% CI 63,2–80,0%]) patients, and elevated total protein levels in 18 (17,1% [95% CI 11,1–25,5%]) patients. Renal impairment (indicated by elevated creatinine) was detected in 21 (20,0% [95% CI 13,5–28,6%]) patients, and increased CRP was detected in 22 (21,0% [95% CI 14,3–29,7%]) patients. Hypercalcemia was noted in 15 (14,2% [95% CI 7,6–26,2%]) patients, while elevated UA in 11 (10,5% [95% CI 6,1–18,9%]) patients and elevated LDH in 9 (8,6%[95% CI 4,6–16,2%]) patients were less frequent.

Concurrently, the analysis showed significant rates of decreased parameters. Anemia was highly prevalent, with decreased Hb found in 55 (52,4% [95% CI 42,8–61,7%]) patients and reduced RBC observed in 52 (49,5% [95% CI 40,1–59,0%]) patients. Other cytopenias included thrombocytopenia, occurring in 44 (41,9% [95% CI 32,9–51,5%]) patients, and leukopenia in 36 (34,3% [95% CI 25,9–43,8%]) patients. Furthermore, prognostically significant hypoalbuminemia was detected in 35 (33,3% [95% CI 25,0–42,8%]) patients. Collectively, these findings highlight the typical patterns of paraproteinemia, hematopoietic suppression, renal involvement, and altered protein metabolism associated with MM in this patient group.

The frequency of major clinical manifestations of MM was evaluated in the cohort (N=105). The most common findings were bone pain, which was present in 75 (71,4% [95% CI 62,2–79,2%]) patients, and weakness, observed in 72 (68,6% [95% CI 59,2–76,7%] patients. Neuropathy occurred in 55 (52,4% [95% CI 42,9–61,7%]) patients. Dyspepsia was reported by 47 (44,8% [95% CI 35,6–54,3%]) patients. Frequent infections affected 42 (40,0% [95% CI 31,1–49,6%]) patients, followed by loss of body weight in 39 (37,1% [95% CI 28,5–46,7%]) patients, breathlessness in 32 (30,5% [95% CI 22,5–39,8%]) patients, diarrhea in 28 (26,7% [95% CI 19,1–35,8%]) patients, and constipation in 13 (12,4% [95% CI 7,4–20,0%]) patients.

Analysis using rank biserial correlation revealed significant associations between clinical manifestations and laboratory parameters in the studied cohort (Table 2). Notably, symptoms indicative of significant disease burden and systemic impact, such as weakness and particularly breathlessness, demonstrated strong positive correlations with markers of inflammation and tumor load (ESR, β2m, M-protein) and strong negative correlations with markers of anemia (Hb, RBC). The association between breathlessness and low Hb was exceptionally strong (r= –0,90; p<0,001). Furthermore, weakness, breathlessness, and loss of body weight were significantly associated with laboratory indicators of impaired renal function, including elevated creatinine and ACR, and reduced eGFR.

Regarding specific symptoms, bone pain showed significant positive correlations with markers potentially reflecting bone turnover and disease activity (ALP, ESR, β2m, M-protein). Similarly, loss of body weight correlated positively with ALP and other markers of disease activity/inflammation (ESR, β2m, M-protein), as well as with higher SBP and WBC.

In contrast, correlations for neuropathy were less pronounced, exhibiting only weak negative associations with ALT, AST, Urea, and GFR. Findings concerning infections were somewhat counter-intuitive, showing negative correlations with several disease markers (M-protein, β2m, creatinine, ACR) while positively correlating with eGFR, suggesting a need for further investigation. Gastrointestinal symptoms generally exhibited fewer significant associations; constipation was weakly linked to higher glucose levels, whereas dyspepsia showed moderate correlations with higher WBC and ACR, and lower SBP. Gastrointestinal symptoms and manifestations of neuropathy are most often side effects of chemotherapeutic agents, rather than direct signs of MM or kidney damage.

Further analysis was conducted to comprehensively evaluate the relationships between MM markers and impaired renal function using a non-parametric approach. RCCA was performed on the ranks of the six kidney function indicators (eGFR, creatinine, ACR, urea, UA, Ca) and six indicators related to myeloma and its systemic effects (M-protein, β2m, albumin, Hb, LDH, PLT). The analysis yielded six pairs of canonical variates.

The overall relationship between the two sets of ranked variables was statistically significant according to the Wilk's Lambda criterion (Wilk's Lambda = 0,554; F (36; 411,2) = 1,642; p = 0,013). Further testing

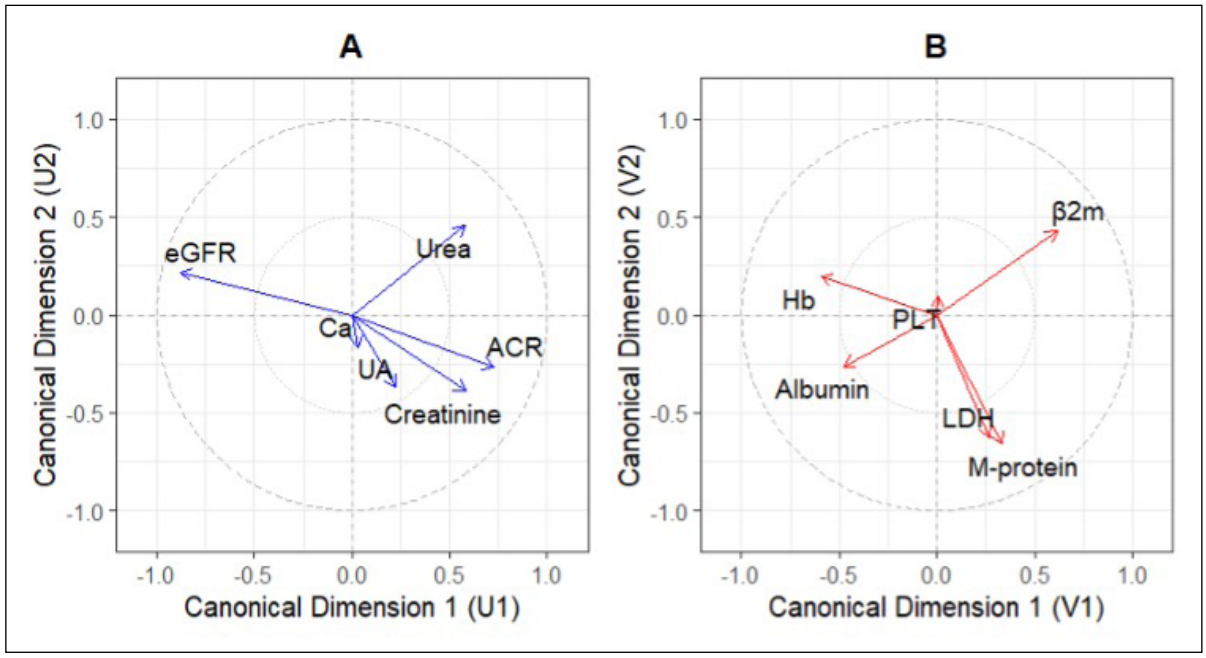

Fig. 1. Structure correlations from RCCA: kidney function indicators (A) and indicators related to myeloma and its systemic effects (B)

revealed that only the first canonical correlation (R1 = 0,497) was statistically significant. Subsequent canonical correlations were not statistically significant (R2 = 0,383, p = 0,228; R3 = 0,262, p = 0,566; R4-R6 were also non-significant).

Interpretation focused on the structure correlations (canonical loadings) for the first significant canonical dimension. The first canonical variate for the ranked kidney set (U1) was primarily characterized by a strong negative loading for eGFR (–0,88) and strong positive loadings for ACR (0,73), creatinine (0,58), and urea (0,58). UA exhibited a weak positive loading (0,22), while Ca showed a negligible loading (0,03) on U1. The corresponding canonical variate for the ranked myeloma set (V1) demonstrated strong positive loading for β2m (0,62) and strong negative loading for Hb (–0,59). Moderate negative loading was observed for albumin (–0,48) and moderate positive loading for M-protein (0,34). LDH displayed weak positive loading (0,27), whereas PLT had a negligible loading (0,01) on V1. (Fig. 1).

DISCUSSION

The most frequent symptoms in patients with MM are asthenia and bone pain, anemia, susceptibility to infections, hypercalcemia, and nephrotic syndrome, which is consistent with our results [8].

Most of the correlations we obtained in our study are weak or moderate, indicating the complex and multifactorial nature of MM. The presence of statistically significant correlations may indicate potential relationships between these parameters, which may be useful for understanding the pathophysiology of the disease and the clinical evaluation of patients.

It is traditionally believed that the presence of CKD at the time of MM diagnosis is a prognostically unfavourable factor that affects overall survival, treatment response, the risk of complications, and the quality of life of patients [9, 10].

The multifactorial nature of the relationship between MM and CKD, which includes numerous biomarkers of both nosologies, requires the use of complex analytical approaches. RCCA is one such multivariate method specifically designed to assess nonparametric relationships between two sets of variables.

The result of RCCA statistically compacts a set of known risk factors, such as low eGFR, low Hb, low albumin, high urea, high creatinine, and elevated ACR, into a single significant correlation dimension.

This reinforces the idea of the interconnectedness of CKD, anemia, increased β2m and hypoalbuminemia as a central characteristic of progressive MM, which is consistent with the results of regression models that identify these markers as prognostic factors.

RCCA does not identify independent predictors but captures a clinically significant and prognostically relevant pattern of target organ damage associated with MM. A similar study was conducted by W. Wei et al. [11] where they retrospectively investigated the relationship between clinicopathological characteristics and the frequency of kidney damage, response, and survival of patients with MM.

In particular, they found that secreted monoclonal immunoglobulin type IgG, free light chain κ/λ in serum,

elevated serum Ca, elevated urea, elevated UA, and ISS stage III were closely associated with kidney damage. Elevated LDH and CKD stage (G4-G5) were independent adverse factors influencing the overall survival of patients with MM and kidney damage. In addition, this study provided a model for predicting treatment response and kidney damage using 5 clinical signs, including Ca, MM stage, pre-treatment creatinine level, age, and sex [11].

The use of new biomarkers of acute kidney injury (NGAL, cystatin C, TIMP-2, IGFBP7) for earlier detection of kidney damage in patients with MM is being actively investigated. Kidney biopsy is becoming increasingly important for determining the type of kidney damage and prognosis, especially in cases of atypical clinical presentation or unexplained cause of kidney damage [12].

The shift in the diagnostic and research approach from a single marker to a cluster analysis of biomarkers, which will reflect the complex relationships in pathogenetic links, will allow for better prediction of the course and response to treatment, and thus improve therapeutic strategies.

STUDY LIMITATIONS

Despite its findings, this study has several limitations. Firstly, the cross-sectional design restricts the ability to establish causality between MM markers and renal function changes over time. Secondly, being a single-center study with 105 participants, the generalizability of results to broader MM populations may be limited. Thirdly, the analysis relied on standard laboratory markers, excluding newer kidney injury biomarkers, kidney biopsy data, detailed treatment histories, and molecular characteristics, which could provide deeper insights.

Future directions. Prospective longitudinal studies are needed to track the temporal relationship between MM progression, treatment, and CKD development, clarifying causal links. Larger, multi-center studies would enhance statistical power and generalizability. Incorporating novel kidney biomarkers (e.g., NGAL, Cystatin C) and systematically correlating findings with kidney biopsy results (when available) could improve early detection and pathogenetic understanding. Investigating the specific impact of different MM therapies on renal outcomes is crucial. Finally, employing advanced statistical methods, including machine learning, may uncover complex interactions and improve predictive modeling for CKD in MM patients.

CONCLUSIONS

Multivariate analysis using rank-based canonical correlation identified a statistically significant relationship between a profile of impaired renal function (primarily characterized by low eGFR, high ACR, high creatinine, and high urea) and a profile indicative of myeloma activity and burden (including high β2m, low Hb, low albumin, and high M-protein). This finding statistically reinforces the strong interplay between key disease processes, particularly myeloma activity, hematopoietic suppression, and renal involvement.

These results emphasize the multifactorial pathophysiology of MM and underscore the importance of integrating both clinical symptoms and a range of laboratory markers for comprehensive patient assessment. Monitoring parameters related to renal function (eGFR, ACR, creatinine), anemia, and disease burden (β2m, M-protein), alongside clinical evaluation, is essential for understanding disease status and may help inform management strategies for patients with MM.

REFERENCES

1. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(5):548–567. doi:10.1002/ajh.25791. DOI
2. Kundu S, Jha SB, Rivera AP et al. Multiple myeloma and renal failure: mechanisms, diagnosis, and management. Cureus. 2022;14(2):e22585. doi:10.7759/cureus.22585. DOI
3. Zhang Y, Pan J, Kang H et al. Prognosis of concurrent renal impairment at diagnosis of multiple myeloma: a systematic review. Ann Med. 2024;56(1):2380301. doi:10.1080/07853890.2024.2380301. DOI
4. Bridoux F, Leung N, Nasr SH et al. Kidney disease in multiple myeloma. Presse Med. 2025;54(1):104264. doi:10.1016/j.lpm.2024.104264. DOI
5. Menè P, Stoppacciaro A, Lai S, Festuccia F. Light chain cast nephropathy in multiple myeloma: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis. 2022;15:173–183. doi:10.2147/IJNRD.S280179. DOI
6. Kumar SK, Callander NS, Adekola K et al. Multiple myeloma, version 2.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2023;21(12):1281–1301. doi: 10.6004/jnccn.2023.0061. DOI
7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4):S117–S314. doi: 10.1016/j.kint.2023.10.018. DOI
8. Ștefan G, Cinca S, Chiriac C et al. Multiple myeloma and kidney impairment at diagnosis: a nephrological perspective from an Eastern European country. Medicina (Kaunas). 2023;59(7):1326. doi:10.3390/medicina59071326. DOI

9. Khan R, Apewokin S, Grazziutti M et al. Renal insufficiency retains adverse prognostic implications despite renal function improvement following Total Therapy for newly diagnosed multiple myeloma. Leukemia. 2015;29(5):1195–1201. doi:10.1038/leu.2015.15. DOI
10. Sharma R, Jain A, Jandial A et al. Lack of renal recovery predicts poor survival in patients of multiple myeloma with renal impairment. Clin Lymphoma Myeloma Leuk. 2022;22(8):626–634. doi: 10.1016/j.clml.2022.04.013. DOI
11. Wei W, Shi H, Chen H et al. Clinicopathologic predictors of renal response and survival in newly diagnosed multiple myeloma with renal injury: a retrospective study. Clin Exp Med. 2025;25(1):48. doi:10.1007/s10238-025-01571-9. DOI
12. Woziwodzka K, Vesole DH, Małyszko J et al. New markers of renal failure in multiple myeloma and monoclonal gammopathies. J Clin Med. 2020;9(6):1652. doi: 10.3390/jcm9061652. DOI

*The study was performed as a fragment of the complex scientific project of the Department of Therapy No. 1, Medical Diagnostics, Hematology and Transfusiology, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University «Features of Pathogenesis, Diagnosis, and Treatment of Diseases of the Cardiovascular, Digestive, Endocrine, and Respiratory Systems in Clinical and Experimental Settings» (state registration number 0120U*002142; term: 2020-2024).

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Vladyslav O. Bardash
Danylo Halytsky Lviv National Medical University
69 Pekarska St., 79010 Lviv, Ukraine
e-mail: bardashvlad123@gmail.com

ORCID AND CONTRIBUTIONSHIP
Halyna R. Savuliak: 0000-0002-8835-3147 A B D
Vladyslav O. Bardash: 0009-0005-8193-4941 C D
Tetiana A. Maksymets: 0000-0003-2659-1083 E F
Mykhaylo V. Perepelytsya: 0000-0002-7298-9271 E
Zoryana M. Kit: 0000-0001-6151-5583 B
Natalia V. Karpyshyn: 0000-0002-9539-3198 D
Eugen Ya. Sklyarov: 0000-0001-9037-0969 E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 20.02.2025
ACCEPTED: 01.06.2025

ORIGINAL ARTICLE

CONTENTS

Conflicts of interest in healthcare: Legal problems and prospects of improvement

Oleksandr M. Shevchuk[1], Olga O. Rzhevska[2, 3], Anastasiia Ye. Myroshnikova[4], Oleksandr A. Smiyukha[5], Oleksandr V. Lysodyed[1]

[1]YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE
[2]V. N. KARAZIN KHARKIV NATIONAL UNIVERSITY, KHARKIV, UKRAINE
[3]KYIV MEDICAL UNIVERSITY, KYIV, UKRAINE
[4]SOLEO LLC, DNIPRO, UKRAINE
[5]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

Aim: To study the problems of the legal regulation of conflicts of interest in the healthcare field in Ukraine and to propose directions for improving national legislation.

Materials and Methods: The methods of theoretical analysis, system-analytical, and comparative-legal methods provided us with the opportunity to characterise the features of the legal regulation of preventing conflicts of interest in the area under study.

Results: It is proposed to amend anti-corruption medical legislation on issues of conflict of interest in the healthcare sector. In particular, the need to introduce into legislative circulation the category and its interpretation of "conflict of interest in the healthcare sector" and "imaginary conflict of interest in the healthcare sector" is indicated. It is also proposed to introduce, at the legislative level, both oral and written forms of notification of conflict of interest, and to separately determine the procedure for electronic notification in this area. Additionally, a special register of notifications of conflict of interest in the area under study should be created.

Conclusions: An unresolved conflict of interest in the healthcare sector may indirectly limit the exercise of a person's right to healthcare and may also lead to the commission of a corruption offence in the healthcare sector. The above indicates an urgent need to improve its legal regulation.

KEY WORDS: healthcare sector, human rights, legal regulation

Wiad Lek. 2025;78(6):1026-1032. doi: 10.36740/WLek/207360 DOI

INTRODUCTION

According to the data from the population survey on the level of corruption, provided in the Anti-Corruption Strategy of Ukraine for 2021–2025, the healthcare sector has been identified as the highest priority area for combating corruption (38%) [1]. The same priority area for combating corruption is indicated in the Anti-Corruption Programme of the Ministry of Health of Ukraine for 2018–2020 [2]. In the State Anti-Corruption Programme for 2023–2025, the healthcare sector is also included among the priority areas for preventing corruption (clause 2.7). It was determined that shortcomings in the legislation limit the possibilities of minimising corruption by preventing and resolving conflicts of interest (clause 1.3), and that insufficiently transparent procedures for selecting personnel for healthcare institutions, along with the dishonesty of medical workers, remain pressing problems (clause 2.7.4) [3].

However, in practice, several problematic issues of legal regulation concerning conflicts of interest in the healthcare sector arise. Among them, it should be noted that certain elements of the legal mechanism for preventing conflicts of interest in the healthcare sector are normatively enshrined, but they are fragmented, not interconnected, and contain shortcomings and gaps in legislative regulation. As a result, there is an increase in the number of offences related to corruption in the healthcare sector. All of the above determines the relevance of the chosen topic of the article.

AIM

This scientific work aims to study the problems and identify shortcomings in the legal regulation of conflicts of interest in the healthcare sector in Ukraine, to analyse the controversial issues raised by scholars, and

to propose directions for improving national legislation, taking into account foreign experience.

MATERIALS AND METHODS

The methodological basis of the study is a set of methods and techniques of scientific inquiry. In particular, the following methods were used: formal-dogmatic, systemic, semantic, epistemological and axiological, sociological, comparative-legal, statistical, as well as systemic and structural analysis.

The complexity of the study is ensured by a systemic approach, which made it possible to consider and analyse the problems of conflicts of interest in medical legal relations in the unity of their content, essence, and legal form. The use of scientific methods contributes to achieving the objectives of the article, substantiating the conclusions of the study, and proposing solutions for optimising legislation on the prevention of conflicts of interest in the healthcare sector of Ukraine, taking into account foreign experience.

RESULTS

To address the challenges of legal regulation and the prevention of conflicts of interest in the healthcare sector in Ukraine, it is necessary to amend the legislation within systemic, organisational, and institutional contexts. It should be noted that there are several components of a conflict of interest in the healthcare sector, which are summarised in Table 1 [4].

Let us consider some of them. One of the problems of legal regulation of conflicts of interest in the medical field is that the function of resolving conflicts of interest in the healthcare sector should be assigned to the authorized unit, according to the regulation on the Authorized Unit (Person) for the Prevention and Detection of Corruption [5]. However, in most healthcare institutions, conflict of interest prevention is carried out by appointing an authorized person rather than creating an authorized unit. In addition, under such conditions, the functions of the authorized person are, in most cases, assigned to legal advisers, economists, or deputy heads of healthcare institutions, which contradicts the norms of the standard regulation [5] and the Law of Ukraine "On the Prevention of Corruption" [4]. However, given the above legislative provisions, authorized persons in healthcare institutions must perform exclusively anti-corruption functions, including preventing conflicts of interest, and assigning other duties to them is illegal. To eliminate this deficiency, it is necessary to provide for the mandatory creation of separate bodies in the research area with the involvement of public organizations, including international ones.

In the provisions of the special anti-corruption law [4], there is a discrepancy between the deadlines for reporting a conflict of interest and for its independent resolution, and it does not establish the form and procedure for reporting a conflict of interest [3]. To mitigate the above-mentioned problems, it is advisable to report a conflict of interest in the healthcare sector (real or potential) in writing or electronically, with registration in the existing record-keeping system.

One of the tools for preventing conflicts of interest in the healthcare sector may be the creation of special registers of conflicts of interest. In particular, in some foreign countries, each specific case of a conflict of interest must be recorded in a special register [6, 7]. Thus, the Law of the Republic of Moldova "On the Declaration of Assets and Personal Interests" of 17 June 2016, № 133, introduced appropriate registers in the state organization of Moldova for registering reports of conflicts of interest. It should be noted that the legislation of Moldova does not establish requirements for maintaining such registers in electronic form. In this country, they are decentralized and are maintained in each separate organization, and for certain categories of officials, a centralized register of notifications has been created, which is maintained by the anti-corruption organization of Moldova (the National Anti-Corruption Authority). Such registers should contain information on: (1) the number and date of submission of the declaration of conflict of interest, (2) the subject of the submission and their position, (3) the number of pages in the declaration, and (4) the measures taken to resolve the conflict of interest [8]. This experience can be used in national legislation on the prevention and resolution of conflicts of interest, including in the healthcare sector. There is similar experience in French legislation [9].

We believe that the national system of legislation on preventing conflicts of interest in the healthcare sector should provide for a centralized "Unified Register of Notifications of Conflicts of Interest in the Healthcare Sector," the administration of which should be entrusted to the National Agency for the Prevention of Corruption of Ukraine. The National Agency for the Prevention of Corruption of Ukraine, when administering the "Unified Register of Notifications of Conflicts of Interest in the Healthcare Sector," must determine: (1) the form of an application for an electronic notification of a conflict of interest, (2) the procedure for submitting a notification of a conflict of interest in the healthcare sector, (3) the measures

Table 1. The components of a conflict of interest in the healthcare sector

Component Number	Description
1	Private interest
2	Discretionary official or representative functions (including professional duties of a public officer and their function as a manager)
3	The existence of a conflict between private interest and authority

Table 2. Sections of the draft resolution of the Cabinet of Ministers of Ukraine "Procedure for organizing measures to prevent and resolve conflicts of interest in the bodies of the Ministry of Health of Ukraine"

№	Title of the section	№	Title of the section
I	General provisions	VII	Resolution of a conflict of interest in connection with employees joining commissions (committees, boards, etc.) in the management bodies of the Ministry of Health
II	Subjects of measures to prevent, resolve, and identify conflicts of interest in the management bodies of the Ministry of Health	VIII	Prevention of conflict of interest due to the presence of enterprises or corporate rights in the management bodies of the Ministry of Health
III	Responsibilities of employees in the management bodies of the Ministry of Health	IX	Restrictions on the joint work of close persons in the management bodies of the Ministry of Health in conditions of conflict of interest
IV	Measures to resolve conflicts of interest in the management bodies of the Ministry of Health	X	Restrictions on receiving gifts related to a conflict of interest in the management bodies of the Ministry of Health
V	Procedure for submitting a notification of the existence of a conflict of interest and its resolution in the management bodies of the Ministry of Health	XI	Procedure for recording information on the presence of a conflict of interest in the management bodies of the Ministry of Health
VI	Peculiarities of applying measures for external resolution of a conflict of interest in the management bodies of the Ministry of Health	XII	Responsibility for the violation of legislative requirements regarding the prevention and resolution of conflicts of interest in the management bodies of the Ministry of Health

used to resolve a conflict of interest in the activities of officials of public organizations in the healthcare sector, etc. Officials of legal entities under public law in the healthcare sector who have a conflict of interest and who are obliged to make a notification under the provisions of the special anti-corruption law [4] have the right to submit a notification of a conflict of interest to this register.

One of the problems of legal regulation in preventing conflicts of interest in the healthcare sector is the requirement for filing declarations by healthcare officials or service personnel in accordance with anti-corruption legislation. Thus, these persons are not subject to the obligation to file declarations and other financial control measures (except for heads of healthcare institutions of central, regional, district, and city significance).

However, Part 5 of Article 45 of the special anti-corruption law [4] does not explicitly exclude from the list of persons who may submit declarations the officials of healthcare institutions, including enterprises that provide medical services to the population based on an appropriate license and the professional activities of medical (pharmaceutical) workers (paragraph 3 of part 1 of Article 3) [10]. According to the organizational and legal form, healthcare institutions can be established and operate as municipal non-profit enterprises or municipal institutions, and their managers can be persons appointed to the position by the authorized executive office of the healthcare institution on a competitive basis by concluding a contract with them (Article 16) [10]. Therefore, officials of municipal non-profit enterprises established as a result of the reform of healthcare institutions (except for heads of healthcare institutions at the central, regional, district, and city levels) are not subject to the special anti-corruption law [4] in terms of the obligation to declare. However, in our opinion, they should be.

In Article 23 of the special anti-corruption law of Ukraine, public associations, their members or authorized representatives, as well as individual citizens, have the right to report a real or potential conflict of interest [4], including in the field of healthcare. For more effective implementation of the norm of this Law and increasing the effectiveness of preventing conflicts of interest in healthcare, it is advisable to provide for a notification on the website of the Ministry of Health of Ukraine about non-compliance with the requirements for the prevention and resolution of conflicts of interest in healthcare. This can be

done based on the already developed Information and Analytical System "Submission and Registration of Reports of Possible Corruption of the Ministry of Health of Ukraine," supplemented with an additional option. Note that such a system was created to stimulate the transfer of reports of corruption by creating internal and external channels for the provision of information and ensuring the protection of individuals (whistleblowers) who, in good faith, report corruption offenses from harassment and prosecution. The development of such a system is caused by the need to improve procedures related to receiving, recording, and reviewing reports of violations of anti-corruption legislation in the Ministry of Health of Ukraine [11].

The Ministry of Health of Ukraine, together with the State Enterprise «Electronic Health,» has implemented the Information and Analytical System «Submission and Registration of Reports of Possible Corruption of the Ministry of Health of Ukraine» [11]. Thus, the official website of the Ministry of Health of Ukraine has already posted a link «Report corruption» to provide the opportunity to submit notifications of facts of corruption or corruption-related offenses by electronic communication (according to the appropriate form) or by telephone [11]. Also, on the website of the National Police of Ukraine, such an opportunity to prevent a conflict of interest by reporting cases of non-compliance with the requirements for preventing a conflict of interest has already been tested in practice.

To improve risk-based mechanisms for detecting conflicts of interest in the healthcare sector, it is advisable to provide in the legislation for the automated detection of risks of conflicts of interest in the activities of officials belonging to legal entities under public law in the healthcare sector, the administration of which would be carried out by the National Agency for the Prevention of Corruption of Ukraine. In this case, the experience of legal support in Romania should be taken into account, where, since 2017, the IT system "Prevent" has been operating, which is used for the automated detection of risks of conflicts of interest in the field of public procurement carried out in Romania with EU funds [8]. The IT system "Prevent" acts as a prior verification mechanism, investigating potential conflicts of interest in the electronic public procurement system of Romania. Over three years, the Prevent IT system in Romania has reviewed over 50,000 procurement procedures and 260,000 contracts, and has issued warnings regarding 123 potential conflicts of interest. As a result, the number of cases of undisclosed conflicts of interest has decreased by 52% over the three years studied [12].

In addition, to form a unified approach to compliance with the rules for preventing conflicts of interest in the area under study, it is advisable to adopt a resolution of the Cabinet of Ministers of Ukraine titled "Procedure for Organizing Measures to Prevent and Resolve Conflicts of Interest in the Bodies of the Ministry of Health of Ukraine" (Table 2).

DISCUSSION

The lack of proof of the existence of a contradiction between private interest and official authority of a conflict of interest in the medical legal relations is decisive for administrative courts in Ukraine and therefore creates additional obstacles to bringing individuals to administrative responsibility for offenses related to corruption [3]. Scientists consider of conflict of interest in the medical legal relations from two perspectives. The first is as a component of preventing corruption in the medical legal relations [13, 14]. Protection of patients' rights in courts [15] as well as conflict of interest in judicial bodies [16]. Some foreign scientists consider conflict of interest in clinical practice, in particular, M. Eccles [17], J. Bindslev [18], G. Guyatt [19], and S. Norris [20]. It is worth noting the separate works of J. Neuman on the financial aspects of conflicts of interest among commission members in Canada and the USA who develop clinical practice guidelines, emphasizing their prevalence and the lack of public disclosure in most cases [21]. For example, M. Rodwin, studying conflicts of interest in healthcare in the USA, France, and Japan, notes that they are very widespread in these countries. Doctors hide or distort information about their diagnoses while having the interests of pharmaceutical and insurance companies. Such actions by doctors undermine public trust in them, as well as in the entire healthcare system, the effectiveness of the use of medicines, and threaten the development of medicine [22]. There is no single scientific position in the legal literature on the definition of types of conflict of interest; in particular, there is no consensus when defining its content. In particular, C. Muth understands "conflict of interest" as a situation in which a person risks acting biasedly due to personal interests [23]. A similar point of view is held by domestic researchers [24]. As is known, anti-corruption legislation contains an interpretation of two types of conflict of interest: potential and real [4]. The category of conflict of interest is distinguished in the field of healthcare [10], but its interpretation of content is not provided. To eliminate this deficiency in medical anti-corruption legislation, it is necessary to introduce the term "conflict of interest" into Article 1 of the basic medical law of Ukraine.

And also to supplement the section of this law with a new Article 78-2 entitled "Prevention and settlement of conflict of interest" [10]. There is no single scientific opinion on establishing the types of conflict of interest [24]. There are 3 types of conflict of interest situations in scientific works, in addition to those provided for in the legislation, namely "prospective", as well as "retrospective" and "imaginary conflict of interest"In our opinion, in the area under study it is necessary to foresee a "perceived conflict of interest in the field of health care" [25]. This type of conflict of interest is provided for by international standards and OECD recommendations [8]. In Canada, this type of conflict of interest prevention is provided for in the health care sector [26]. The lack of a definition of this term indicates that national anti-corruption medical legislation [4, 10] does not meet international standards in the area under study.

CONCLUSIONS

Legal methods for resolving conflicts of interest in the healthcare sector should be provided for in special medical legislation at the legislative level. This is due to the need to increase the effectiveness of measures to prevent the corrupt behavior of medical professionals, as well as the significant harmful consequences for the protection of human rights in the healthcare sector. In our opinion, the category of "perceived conflict of interest in the field of healthcare" should be provided for in Article 1 of the Law of Ukraine "Fundamentals of the Legislation of Ukraine on Healthcare". Thus, the term "perceived conflict of interest in the healthcare sector" should be understood as a situation in which the private interests of persons exercising their official or representative powers in the healthcare sector, their managerial decisions, may improperly influence the performance of their official duties, despite its actual absence.

REFERENCES

1. Zakon Ukrainy vid 20.06.2022 № 2322-IX «Pro zasady derzhavnoi antykoruptsiinoi polityky na 2021-2025 roky». [On the principles of state anti-corruption policy for 2021–2025: Law of Ukraine dated 20.06.2022, No. 2322-IX]. https://zakon.rada.gov.ua/laws/show/2322-20?lang=en#Text [Accessed 01 August 2024] (Ukrainian)
2. Nakaz Ministerstva okhorony zdorovia Ukrainy vid 21.11.2018 № 2156 "Pro zatverdzhennia Antykoruptsiinoi prohramy Ministerstva okhorony zdorovia Ukrainy na 2018 - 2020 rr.". [The Order of the Ministry of Health of Ukraine dated 21 November 2018, No. 2156]. https://moz.gov.ua/uploads/5/28864-dn_2156_21_11_2018_dod.pdf [Accessed 01 August 2024] (Ukrainian)
3. Postanova Kabinetu Ministriv Ukrainy vid 4 bereznia 2023 roku №220 "Pro zatverdzhennia Derzhavnoi antykoruptsiinoi prohramy na 2023–2025 roky". [On Approval of the State Anti-Corruption Program for 2023–2025: Resolution of the Cabinet of Ministers of Ukraine dated 04 March 2023, No. 220]. https://zakon.rada.gov.ua/laws/show/220-2023-%D0%BF#Text [Accessed 01 August 2024] (Ukrainian)
4. Zakon Ukrainy "Pro zapobihannia koruptsii" № 1700-VII vid 14.10.2014. [On the prevention of corruption: Law of Ukraine of 14 November 2014 №. 1700-VII] https://zakon.rada.gov.ua/laws/show/1700-18#Text [Accessed 01 August 2024] (Ukrainian)
5. Nakaz Natsionalnoho ahentstva z pytan zapobihannia koruptsii vid 27.05.2021 № 277/21 "Pro zatverdzhennia Typovoho polozhennia pro upovnovazhenyi pidrozdil (upovnovazhenu osobu) z pytan zapobihannia ta vyiavlennia koruptsii". [Model regulation on the authorized unit (authorized person) for the prevention and detection of corruption: Order of the National Agency on Corruption Prevention dated 27 May 2021, No. 277/21]. https://nazk.gov.ua/uk/documents/nakaz-vid-27-07-2021-277-21-pro-zatverdzhennya-typovogo-polozhennya-pro-upovnovazhenyj-pidrozdil-upovnovazhenu-osobu-z-pytan-zapobigannya-ta-vyyavlennya-koruptsiyi/ [Accessed 01 August 2024] (Ukrainian)
6. Moos K. Vnutrishnii zvit pro antykoruptsiini zakhody v Yevropi: Sfery diialnosti, dosvid, instrumenty. [Internal report on anti-corruption measures in Europe: areas of activity, experience, tools. Ukraine-EU civil society platform]. Brussels; 2016. https://www.eesc.europa.eu/sites/default/files/resources/docs/reportcorruption_ukr.pdf [Accessed 25 August 2024] (Ukrainian)
7. Health Code of the Republic of Tajikistan. https://ampeid.org/documents/tajikistan/health-code-of-the-republic-of-tajikistan/ [Accessed 27 August 2024]
8. Marchuk A. Polityka monitorynhu konfliktu interesiv u publichnomu sektori. [Policy of monitoring conflict of interest in the public sector]. https://kse.ua/wp-content/uploads/2020/06/Marchuk-A.-Politika-monitoringu-konfliktu-interesiv-u-publichnomu-sektori-converted.pdf [Accessed 11 August 2024] (Ukrainian)
9. Act No. 2013-907 dated 11 October 2013 on transparency in public life. Official Journal of the French Republic No. 0238 dated 12 October 2013. https://www.hatvp.fr/wordpress/wp-content/uploads/2018/01/Act-no.-2013-907-dated-11-October-2013-on-transparency-in-public-life.pdf [Accessed 19 August 2024]
10. Zakon Ukrainy «Osnovy Zakonodavstva Ukrainy pro Okhoronu Zdorovia» № 2801-XII vid 19.11.1992. [Fundamentals of Ukrainian legislation on health care: Law of Ukraine dated 19 November 1992. No. 2801-XII] https://zakon.rada.gov.ua/laws/show/2801-12#Text [Accessed 19 August 2024] (Ukrainian)

11. Natsionalne ahentstvo iz zapobihannya koruptsiyi. Natsionalna dopovid shchodo realizatsiyi zasad antykoruptsiynoyi polityky u 2020 rotsi. [National Agency for the Prevention of Corruption. National report on the implementation of the principles of anti-corruption policy in 2020]. https://nazk.gov.ua/wp-content/uploads/2021/06/NAZK_Nats.dopovid_15_06.pdf [Accessed 15 September 2024] (Ukrainian)
12. Anti-Fraud Knowledge Centre, Prevent System Romania. https://antifraud-knowledge-centre.ec.europa.eu/library-good-practices-and-case-studies/good-practices/prevent-system_en [Accessed 07 August 2024]
13. Shevchuk O, Yarova A. Prevention and settlement of conflicts of interest in health care of Ukraine as an administrative legal institute. Juridical Tribune. 2022;12(3):387–398. doi: 10.24818/TBJ/2022/12/3.05. DOI
14. Shevchuk O, Milash V, Goncharenko G et al. Conflicts of interest in the healthcare sector: legal aspects. Wiadomosci lekarskie, 2023;76(10):2283–2287. doi:10.36740/WLek202310123a. DOI
15. Shevchuk O, Matyukhina N, Davydenko S et al. Forensic examination in cases on the protection of human rights in the sphere of healthcare in Ukraine: legal issues. Juridical Tribune. 2022;12(4):552–565. doi: 10.24818/TBJ/2022/12/4.08. DOI
16. Shevchuk O, Matyukhina N, Babaieva O et al. Conflict of interest in the activities of judges in Ukraine and the European Union: a comparative legal study. Juridical Tribune - Tribuna Juridica. 2023;13(2):262–282. doi:10.24818/TBJ/2023/13/2.06. DOI
17. Eccles MP, Grimshaw JM, Shekelle P et al. Developing clinical practice guidelines: target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest. Implement Sci. 2012;7:60. doi: 10.1186/1748-5908-7-60. DOI
18. Bindslev JB, Schroll J, Gotzsche PC et al. Underreporting of conflicts of interest in clinical practice guidelines: cross-sectional study. BMC Med Ethics. 2013;14(1):19. doi: 10.1186/1472-6939-14-19. DOI
19. Guyatt G, Akl EA, Hirsh J et al. The vexing problem of guidelines and conflict of interest: a potential solution. Annals of Internal Medicine. 2010;152(11):738–741. doi: 10.7326/0003-4819-152-11-201006010-00254. DOI
20. Norris SL, Holmer HK, Ogden LA, Burda BU. Conflict of interest in clinical practice guideline development: a systematic review. PLoS One. 2011;6(10):e25153. doi: 10.1371/journal.pone.0025153. DOI
21. Neuman J, Korenstein D, Ross JS, Keyhani S. Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in Canada and United States: cross sectional study. BMJ. 2011;343:d5621. doi: 10.1136/bmj.d5621. DOI
22. Rodwin M. Conflicts of Interest and the Future of Medicine: The United States, France, and Japan (March 18, 2011). In: Suffolk University Law School Research Paper No. 11-16. Oxford University Press; 2011. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1789751# [Accessed 10 October 2024]
23. Muth CC. Conflict of Interest in Medicine. Journal of the American Medical Association. 2017;317(17):1812. doi: 10.1001/jama.2017.4044. DOI
24. Lishchyshyna OM, Melnyk YeO. Konflikt interesiv pry rozrobtsi medyko-tekhnolohichnykh dokumentiv. [Conflict of interests in the development of medical and technological documents]. Ukrainian Medical Journal. 2014;1(99)I/II:92–94. https://api.umj.com.ua/wp/wp-content/uploads/2014/02/4207.pdf [Accessed 10 October 2024] (Ukrainian)
25. Vasylevska TE. Konflikt interesiv na derzhavniy sluzhbi: etychni aspekty. Naukovo-informatsiynyy visnyk [Conflict of interest in civil service: Ethical aspects]. Naukovo-informatsiynyy byuleten' Akademiyi natsional'noyi bezpeky. 2014;1:106–120. http://irbis-nbuv.gov.ua/cgi-bin/irbis_nbuv/cgiirbis_64.exe?C21COM=2&I21DBN=UJRN&P21DBN=UJRN&IMAGE_FILE_DOWNLOAD=1&Image_file_name=PDF/nivanb_2014_1_9.pdf [Accessed 10 October 2024] (Ukrainian)
26. Chapter 7: Conflicts of Interest. In: Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2. 2022. https://ethics.gc.ca/eng/tcps2-eptc2_2022_chapter7-chapitre7.html [Accessed 05 September 2024]

The work is a fragment of comprehensive target program of the Department of Administrative Law and Administrative Activities, Yaroslav Mudryi National Law University "Constitutional and legal problems of ensuring the rule of law in the functioning of the mechanism of public power in Ukraine" (№ state registration 0111U000966; deadline: 2022-2025).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Oleksandr M. Shevchuk

Yaroslav Mudryi National Law University,
77 Hryhorii Skovoroda St.,, 61024 Kharkiv, Ukraine
e-mail: oleksandr-shevchuk@ukr.net

ORCID AND CONTRIBUTIONSHIP
Oleksandr M. Shevchuk: 0000-0003-4864-7316 B D
Olga O. Rzhevska: 0000-0002-6410-7769 A E
Anastasia E. Myroshnikova: 0000-0003-1799-8092 C D
Oleksandr A. Smiyukha: 0000-0002-8085-203X F
Oleksandr V. Lysodyed: 0000-0003-0648-829X C

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.12.2024
ACCEPTED: 18.05.2025

ORIGINAL ARTICLE

CONTENTS

Age-related characteristics of patients' satisfaction with medical care provided by general practitioners – family doctors

Vira Yu. Vozniuk, Tetiana A. Vezhnovets
BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: to investigate the age-related characteristics of patients' satisfaction with the quality and accessibility of primary health care provided by general practitioners-family doctors (GPs) in Kyiv.

Materials and Methods: A survey of 510 patients assessed satisfaction with the accessibility and quality of medical care provided by GPs using a 5-point Likert scale (4 and 5 points were considered as positive responses to the questions [«satisfaction»]; 1-3 – as negative [«dissatisfaction»]; and 0 – as undecided ones).

Results: The study demonstrated the significant trends in the opposite responses to certain survey questions across the different respondents` age groups. In particular, we revealed the advancing age-related (from <30 to >60 years group) trends toward satisfaction rate decrease with respect to the organization of an appointment with one`s GP, and satisfaction rate increase – regarding the availability of obtaining prescriptions for medicines. Patient dissatisfaction with the quality of medical care provided by GPs was influenced by three factors: appointment organization, accessibility of referrals to specialists, and the doctor's attitude toward the patient (AUC for logistic regression model: 0,965 [95 % CI: 0,946-0,979]).

Conclusions: The presence of age-related features of patients` satisfaction with the quality of medical care has been established, which should be taken into account when planning measures to improve the management of medical care quality in healthcare facilities. The key factors influencing the level of patients` dissatisfaction with the quality of primary healthcare were the organization of appointment scheduling, the availability of referrals to specialists, and the attitude of the GP towards the patient during the appointment.

KEY WORDS: general practitioner, patient satisfaction, primary care

Wiad Lek. 2025;78(6):1033-1038. doi: 10.36740/WLek/207361 DOI

INTRODUCTION

Primary health care (PHC) centres are the first point of contact between patients and the health system [1, 2]. PHC plays a key role in the sustainability of healthcare, providing a comprehensive range of services, from prevention to treatment and rehabilitation [3].

The World Health Organization emphasises the importance of the doctor-patient relationship in delivering quality healthcare [4]. A key component of quality healthcare is patient satisfaction, particularly with the primary care physician—general practitioners/family doctors—who are the first point of contact with the health service [5, 6].

Patient satisfaction is an important factor in determining the success of a healthcare facility [7]. Health systems based on primary health care have demonstrated effectiveness in reducing morbidity, mortality, and promoting equitable patient access to healthcare worldwide [8].

Patient satisfaction is also a significant indicator for evaluating health systems and predicting health outcomes [9]. Patient opinions and satisfaction with the services provided are essential for assessing service quality [10]. Satisfaction can be influenced by ethnic, regional, and socio-demographic differences, as well as age-related characteristics, which are determined by disparities in service quality and communication between the patient and doctor [5].

Thus, the issue of studying patient satisfaction with the quality of medical care, taking into account age differences, is highly relevant.

AIM

The aim of the study was to investigate the age-related characteristics of patients' satisfaction with the quality and accessibility of primary healthcare provided by general practitioners – family doctors (GPs).

MATERIALS AND METHODS

A survey of 510 patients was conducted using a questionnaire to study their satisfaction with the availability and quality of medical care provided by general prac-

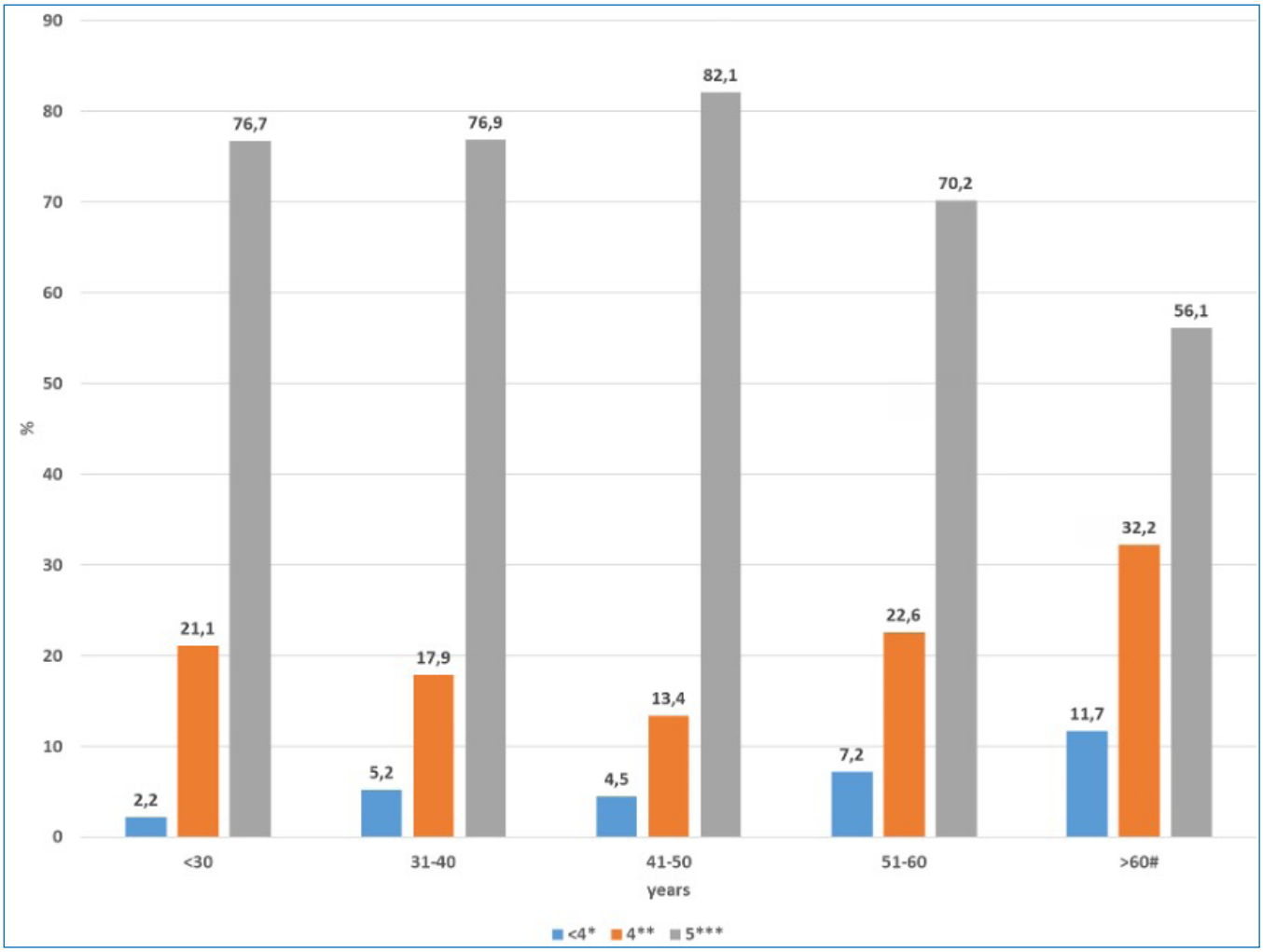

Fig. 1. The frequency of answers to the question № 1 (<4, 4 and 5 scores) in different age groups. * – p_{trend} = 0,003; ** – p_{trend} = 0,011; *** – p_{trend} <0,001; # – including 1 patient with 0 score, being conventionally assigned to the «<4» group

titioners-family doctors in primary care centers in Kyiv. The questionnaire was developed at the Department of Health Care Management of the Bogomolets National Medical University and contained 8 questions, including questions about the assessment of the organization of an appointment with GP, the quality of medical care provided, the possibility of obtaining necessary laboratory and diagnostic tests, the possibility of receiving referrals to narrow specialists and inpatient treatment, the availability of obtaining prescriptions for medications, and the doctor's attitude during the appointment.

The distribution of survey participants by age is as follows: under 30 years old — 90 (17,7 %) people, aged 31-40 years old — 78 (15,3 %) people, aged 41-50 years old — 112 (22,0 %) people, aged 51-60 years old — 84 (16,4 %) people, over 60 years old — 146 (28,6 %) people. The enrolled sample included 186 (36,5 %) males and 324 (63,5 %) females.

To assess the results of the survey, a Likert scale was used, in which patients rated the degree of their agreement or disagreement with each statement, from "very bad" to "very good" on a 5-point scale. Scores of 4 and 5 were considered positive responses to the question, 1-3 points were considered negative responses to the question, and 0 points were considered as undecided.

Statistical data analysis was conducted by the use of MedCalc v. 23.1.7 (MedCalc Software Ltd., Belgium). The frequency of certain patients` responses to the proposed questions across the studied age groups was analyzed by the $\chi^2$ test for trend. The uni- and multivariate logistic regression analysis was used to study the factors influencing the patients` assessment of the quality of medical care. To assess the degree of influence of each factor in the logistic regression model, the odds ratio (OR) and its 95% CI (confidence interval) were calculated. Receiver operating characteristic curve (ROC) analysis was used to assess the quality of the logistic regression model (with the calculation of area under curve [AUC] with 95 % CI). A p-value <0,05 was considered statistically significant.

COMPLIANCE WITH ETHICAL STANDARDS

The study was conducted in accordance with the principles of the World Medical Association's Helsinki

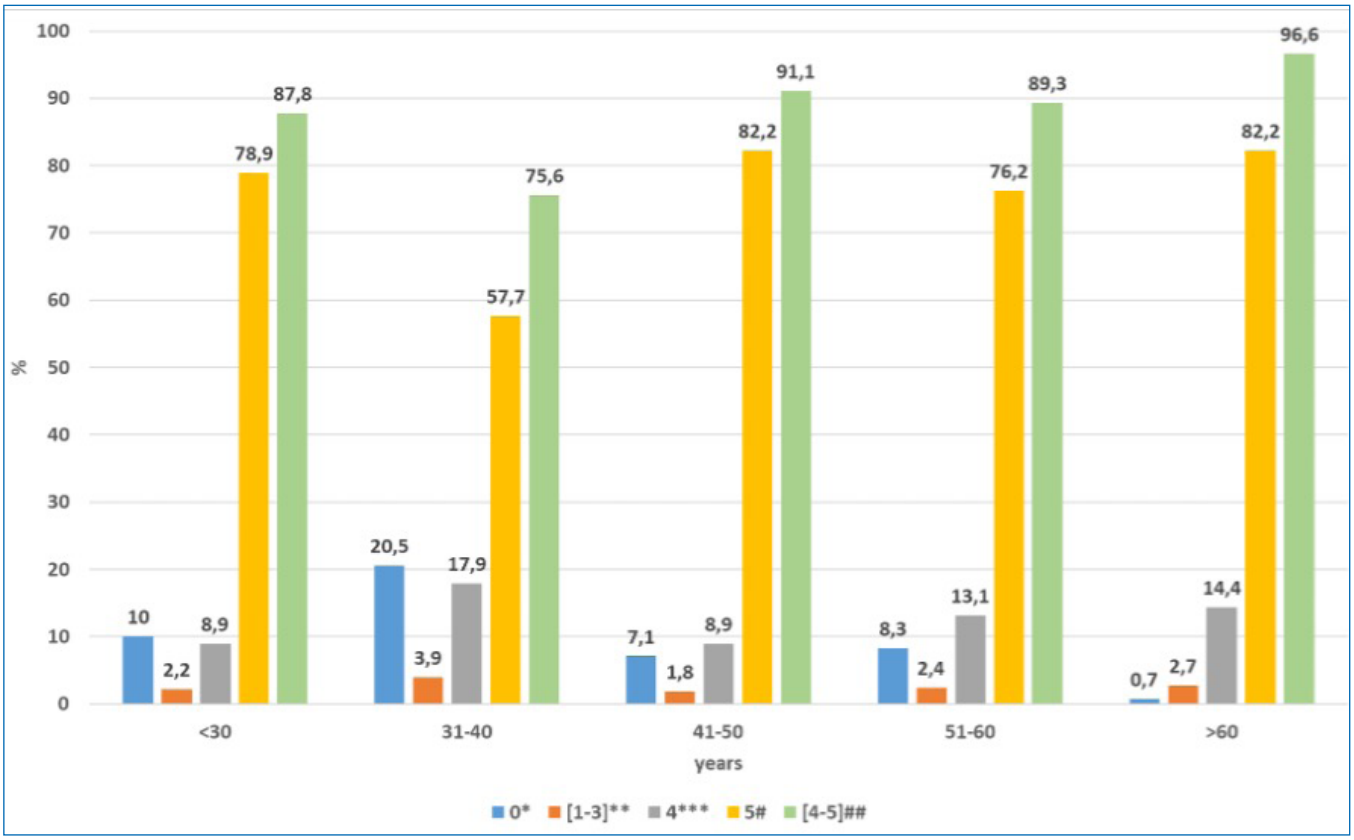

Fig. 2. The frequency of answers to the question № 7 (0, [1-3], 4, 5 and [4-5] scores) in different age groups. * – p_{trend} <0,001; ** – p_{trend} = 1,000; *** – p_{trend} = 0,452; # – p_{trend} = 0,058; ## – p_{trend} <0,001

Declaration, «Ethical Principles for Medical Research Involving Human Subjects» (2000). The survey was carried out with respect for confidentiality and anonymity, and all collected data were entered into the database in a de-identified form for further analysis.

RESULTS

The study data analysis demonstrated the significant trends in the positive and negative responses to the proposed questions, related to the certain aspects of patients` satisfaction with the quality and availability of medical care provided by GPs, across the different age groups of respondents.

Particularly, the data regarding the answers to the question № 1 («How would you rate the organization of an appointment with your GP?») on the assessment of the organization of an appointment with a GP revealed the significant trends in the frequency of responses of respondents of different age. The vast majority of patients positively assessed the organization of an appointment with their GP. In particular, the share of those satisfied with the organization of an appointment in the group under 30 years of age is 97,8% (4 and 5 points), of which 76,7% rated it with the maximum score (5 points). In the group over 60 years of age, the share of those satisfied is 88,3%, of which 56,1% rated it with the maximum score. In the group aged 31-40 years, the share of those satisfied is 94,8%, in the group aged 41-50 years – 95,5%. It is worth noting that in the group of respondents over 60 years of age, only 56,1% gave the maximum score, which is the lowest indicator among all age groups (Fig. 1).

At the same time, the results of the study of respondents' answers to question № 2 («Evaluate the quality of medical care provided to you by a doctor») did not reveal a significant trend regarding the frequency of the negative responses across different age groups. Importantly, the share of those satisfied with the availability of medical care by a doctor ranged from 96,4% in the 51-60 age group to 98,6% in the over-60 age group. In the under-30 age group, this figure was 97,8%, in the 31-40 age group – 97,4%, and in the 41-50 age group – 98,2% (p_{trend} = 0,747).

The respondents' answers to the question № 3 («How would you rate the availability of obtaining the necessary laboratory tests from your GP») were mostly satisfactory. In the group of patients under 30 years of age, the proportion of satisfied patients was 93,4%, in the group of 31-40 years of age – 89,7%, in the group of 41-50 years of age – 92,8%, in the group of 51-60 years of age – 92,9%, and in the group over 60 years of age – 87,7% (p_{trend} = 0,228). Among respondents

Table 1. The factors affecting the risk of negative assessment of the quality of medical care for question № 2 «Evaluate the quality of medical care provided to you by a doctor» (univariate analysis)

Factor (question score)	β ± m	p	OR (95 % CI)
№ 1 «Would you rate the organization of an appointment with your GP?»	–0,81±0,26	0,002	0,44 (0,27-0,74)
№ 3 «Assess the availability of necessary laboratory tests from your GP»	–0,57±0,20	0,005	0,57 (0,38-0,84)
№ 4 «Assess your availability for diagnostic examinations (ECG, ultrasound, X-ray)»	–0,56±0,19	0,003	0,57 (0,39-0,83)
№ 5 «Assess your availability for referrals to specialist doctors»	–0,98±0,21	<0,001	0,38 (0,25-0,56)
№ 6 «Assess your availability for receiving a referral for inpatient treatment»	–0,19±0,14	0,178	0,83 (0,63-1,09)
№ 7 «Assess the availability of prescriptions for medications»	–0,26±0,15	0,081	0,77 (0,57-1,03)
№ 8 «Rate the doctor's attitude towards you during the appointment»	–2,65±0,55	<0,001	0,07 (0,02-0,21)

Note: β – β-coefficient; m – standard error; OR – odds ratio; CI – confidence interval

Table 2. The factors affecting the risk of negative assessment of the quality of medical care for question № 2 «Evaluate the quality of medical care provided to you by a doctor» (multivariate analysis)*

Factor (question score)	β ± m	p	OR (95 % CI)
№ 1 «Would you rate the organization of an appointment with your GP?»	–0,92±0,45	0,040	0,40 (0,17-0,96)
№ 5 «Assess your availability for referrals to specialist doctors»	–1,14±0,35	0,001	0,32 (0,16-0,63)
№ 8 «Rate the doctor's attitude towards you during the appointment»	–2,48±0,60	<0,001	0,08 (0,03-0,27)

Note: AUC 0,965 (95% CI: 0,946 – 0,979)

over 60 years of age, the proportion of dissatisfied patients with the availability of obtaining laboratory tests was 11,6%, while among patients under 30 years of age – 4,4%.

When studying the respondents' answers to question 7 («How would you rate the availability of obtaining prescriptions for medicines»), it was found that the most satisfied group is patients over 60 years of age, of whom 96,6% were satisfied. Among patients aged 31-40, the proportion of satisfied patients is 75,6%, among patients under 30 – 87,8%, in the group of 41-50 – 91,1%, and in the group of 51-60 – 89,3%. It is noteworthy that 10% of respondents under 30 and 20,5% of respondents aged 31-40 could not assess the accessibility of obtaining prescriptions, while among respondents over 60 this proportion is only 0,7% (Fig. 2).

In addition, no significant trends were found for the frequency of responses` to the question № 4 «Evaluate the availability for you of diagnostic examinations (ECG, ultrasound, X-ray)», question № 5 «Evaluate the availability for you of referrals to specialist doctors», question № 6 «Evaluate the availability for you of referrals for inpatient treatment», and question № 8 «Evaluate the attitude of the doctor towards you during the appointment».

To determine the strength and direction of the influence of factor characteristics on patients' dissatisfaction with the availability and quality of medical care provided by primary care physicians in primary care centers in Kyiv, we used the method of constructing and analyzing of the logistic regression models (uni- and multivariate analysis). We assessed the impact on the result of the answer to question № 2, which concerned the assessment of the quality and availability of medical care, based on the answers to questions № 1, №№ 3-8 of the questionnaire.

Initially, the univariate analysis was conducted to assess the impact of each individual characteristic (answers to questions № 1, №№ 3-8) on the risk of dissatisfaction with the quality of medical care provided by a primary care physician.

The univariate analysis revealed the presence of a significant negative relationship between the responses to the questions № 1, №№ 3-5, № 8 and the risk of negative assessment of the quality of medical care (according to the question № 2) (Table 1).

According to respondents' answers (multivariable analysis), the quality of medical care is influenced by the following factors: organization of an appointment with a GP (question № 1), availability for a patient of referrals to specialist doctors (question № 5) and the doctor's attitude towards the patient during the appointment (question № 8) (Table 2).

The quality assessment of the logistic regression model (ROC analysis) is that the AUC 0,965 (95% CI: 0,946 – 0,979), which indicates an excellent relationship with the three-factor model of predicting the risk of a negative assessment of the level of satisfaction with the quality of medical care by GPs.

DISCUSSION

Globally, primary health care is becoming increasingly important in meeting the needs of patients and the population [8,11]. However, it is difficult to identify a single factor that is directly related to low or high levels of patient satisfaction with health services. A number of factors can influence patient satisfaction, including age, gender, socioeconomic status, health status, appointment conditions, treatment, and waiting times [12, 13]. Health systems are constantly changing and improving, so it is important to assess patient satisfaction outcomes to ensure the effective functioning of the health system and improve the quality of health care delivery [13]. The assessment of the quality of health care services depends largely on patient satisfaction and is an important indicator in assessing the health system and predicting health outcomes [5, 10].

Timely access to primary health care enhances patient satisfaction and the overall quality of medical care provided [14]. Patient satisfaction with medical services is a critical factor for the success of healthcare institutions [13]. According to our study, the majority of patients rated the organization of an appointment with their GP positively. In the group of respondents under 30 years of age, 97.8% were satisfied, with 76.7% giving the maximum score. Among patients over 60 years of age, 88.3% were satisfied, with 56.1% rating it the highest. Satisfaction in the 31-40 and 41-50 age groups was 94.8% and 95.5%, respectively. Notably, only 56.1% of respondents over 60 years old gave the maximum score, the lowest rate among all age groups.

Laboratory test results have an important impact on patient care, as they influence doctors' decisions about prescribing medications and monitoring and treating the vast majority of conditions [14]. Respondents' responses regarding the availability of necessary laboratory tests from their GP were mostly satisfactory. Among respondents over 60 years of age, the proportion of those dissatisfied with the availability of laboratory tests was 11,6%, compared with 4,4% among patients under 30 years of age. This suggests that older patients may face greater difficulties in accessing laboratory tests, which may affect the quality of their healthcare.

Many patients who present to GPs with chronic diseases and comorbidities are elderly [11, 12]. Our study found that the group most satisfied with the availability of prescriptions from a GP for chronic diseases were patients over 60 years of age (96.6%). It is noteworthy that 10% of respondents under 30 years of age and 20,5% of respondents aged 31-40 years were unable to assess the accessibility of obtaining prescriptions. This may be due to the fact that respondents in these groups are less likely to encounter the need to obtain prescriptions.

Based on the multivariate logistic analysis after stepwise inclusion/exclusion of variables into the predictive model for the risk of dissatisfaction with the quality of medical care, three factors were included in the model: the organization of the appointment, the availability of referrals to specialist doctors, and the doctor's attitude towards the patient.

It was established that the more satisfied the patients` were with the quality of appointment organization, the availability of referrals to specialists, and the doctor's attitude during the appointment, the less likely they were to be dissatisfied with the quality of medical care. This emphasizes the importance not only of the doctor's medical skills but also the organizational aspects of the healthcare facility's operations, including the accessibility of referrals to specialists, which can significantly improve the overall patient satisfaction with medical services. Based on these data, healthcare institutions can more effectively allocate resources to improve patient satisfaction [14]. Implementing changes based on this feedback is crucial for the modernization of the healthcare system and achieving optimal patient satisfaction [13].

CONCLUSIONS

The presence of age-related features of the formation of patient satisfaction with the quality of medical care has been established, which must be taken into account when planning measures to improve the management of the quality of medical care in health care facilities. The key factors that influence the level of patient dissatisfaction with the quality of primary healthcare are the organization of appointment scheduling, the availability of referrals to specialists, and the attitude of the GP towards the patient during the appointment.

REFERENCES

1. Almusawi MA, Radwan N, Mahmoud N et al. Analysis of patients' complaints in primary healthcare centres through the Mawid app in Riyadh, Saudi Arabia: a cross-sectional study. Malaysian Family Physician. 2023;18:17. doi: 10.51866/oa.72. DOI
2. Vozniuk VY, Vezhnovets TA. Modeli prohnozuvannya ryzyku nevdovolennya sered likariv zahal'noyi praktyky ta simeynykh likariv, yaki pratsyuyut' u tsentrakh pervynnoyi medychnoyi dopomohy. [Models for predicting the risk of dissatisfaction among general practitioners and family doctors working in primary healthcare centers]. Klinichna ta profilaktychna medytsyna. 2023;7:94—102. doi: 10.31612/2616-4868.7.2023.13. (Ukrainian) DOI

3. Alharbi A, Aljuaid M. Patients and health professionals' perceptions of primary health care services in Saudi Arabia: A scoping review. International Journal of General Medicine. 2024;17:1155–1170. doi: 10.2147/IJGM.S442892. DOI
4. Setlhare V, Madiba S. Doctor Attributes That Patients Desire during Consultation: The Perspectives of Doctors and Patients in Primary Health Care in Botswana. Healthcare (Basel). 2023;11(6):840. doi: 10.3390/healthcare11060840. DOI
5. Hayek S, Derhy S, Smith ML et al. Patient satisfaction with primary care physician performance in a multicultural population. Israel Journal of Health Policy Research. 2020;9(1):13. doi: 10.1186/s13584-020-00372-7. DOI
6. Vezhnovets YI, Yashchenko YB. Doslidzhennya ryzyku bat'kivs'koho nevdovolennya yakistyu medychnoyi dopomohy dityam iz zakhvoryuvannyamy dykhal'nykh shlyakhiv. [Research on the risk of parental dissatisfaction with the quality of medical care for children with respiratory diseases]. Klinichna ta profilaktychna medytsyna. 2023;7:74–80. doi: 10.31612/2616-4868.7.2023.10. (Ukrainian) DOI
7. Almass A, Aljohani HM, Alhaqbani RM et al. Patient satisfaction with quality of care at the Kingdom of Saudi Arabia. Cureus. 2022;14(12):e32102. doi: 10.7759/cureus.32102. DOI
8. Vezhnovets TA, Vozniuk VY. Rehional'nyy analiz zabezpechennya simeynymy likaryamy-terapevtamy v Ukrayini za period z 2008 po 2020 rik. [Regional analysis of the provision of general practitioners-family doctors in Ukraine during the period from 2008 to 2020]. Zdorov'ya natsiyi. 2023;1(71):10–18. doi: 10.32782/2077-6594/2023.1/02. (Ukrainian) DOI
9. Farooqi W, Abukaram TM, Alsulaiman T et al. Assessment of patient satisfaction regarding clinic visits in Riyadh, Kingdom of Saudi Arabia: A cross-sectional study. Cureus. 2024;16(8):e65958. doi: 10.7759/cureus.65958. DOI
10. Alhenaidi A, Al Nadabi W, Al-Haqan A, Kelender H. Patient satisfaction of primary care services in Gulf Cooperation Council countries: A scoping review. Journal of General and Family Medicine. 2023;24(5):279–287. doi: 10.1002/jgf2.640. DOI
11. Alharbi AK, Alhutayrashi AA, Alosaimi AN et al. Patient satisfaction and comprehension of physician and pharmacist prescription in Saudi Arabia: A cross-sectional study. Cureus. 2022;14(7):e27324. doi: 10.7759/cureus.27324. DOI
12. El-Kholy AA, Abdelaal K, Alqhtani H et al. Publics' perceptions of community pharmacists and satisfaction with pharmacy services in Al-Madinah City, Saudi Arabia: A cross-sectional study. Medicina. 2022;58(3):432. doi: 10.3390/medicina58030432. DOI
13. Ferreira DC, Vieira I, Pedro MI et al. Patient satisfaction with healthcare services and the techniques used for its assessment: A systematic literature review and a bibliometric analysis. Healthcare. 2023;11(5):639. doi: 10.3390/healthcare11050639. DOI
14. Zare S, Meidani Z, Shirdeli M et al. Laboratory test ordering in inpatient hospitals: A systematic review on the effects and features of clinical decision support systems. BMC Medical Informatics and Decision Making. 2021;21:20. doi: 10.1186/s12911-020-01384-8. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Vira Yu. Vozniuk
Bogomolets National Medical University
13 Shevchenko Blvd., Kyiv 01601, Ukraine
e-mail: Vera_Vozniuk@ukr.net

ORCID AND CONTRIBUTIONSHIP

Tatiana A. Vezhnovets: 0000-0003-1156-8614 A B E F
Vira Yu. Vozniuk: 0009-0003-4864-6329 C D E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 09.01.2025
ACCEPTED: 02.06.2025

ORIGINAL ARTICLE

CONTENTS

Clinical correlates of lower extremity arterial calcification in peripheral artery disease patients with concomitant stable coronary artery disease

Sviatoslav Y. Denysov[1, 2], Yuriy M. Hupalo[1], Vasyl V. Lazoryshynets[3]

[1]STATE INSTITUTION OF SCIENCE «CENTER OF INNOVATIVE HEALTHCARE TECHNOLOGIES» STATE ADMINISTRATIVE DEPARTMENT, KYIV, UKRAINE

[2]CLINICAL HOSPITAL «FEOFANIYA» STATE ADMINISTRATIVE DEPARTMENT, KYIV, UKRAINE

[3]NATIONAL AMOSOV INSTITUTE OF CARDIO-VASCULAR SURGERY AFFILIATED TO NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: To evaluate the associations of lower extremity arterial calcification (LEAC) with clinical profile of peripheral artery disease (PAD) patients with concomitant stable coronary artery disease (SCAD).

Materials and Methods: The cross-sectional study enrolled and analyzed clinical and instrumental data from 110 lower extremity PAD (chronic limb-threatening ischemia) patients (mean age [mean ± standard deviation] 71±8 years; 77 [70 %] males and 33 [30 %] females) with concomitant SCAD, underwent endovascular treatment during the period 2021-2025. LEAC was evaluated by CT-angiography with the assessment of Agatson calcium score (CS). The enrolled sample was subdivided into group 1 (CS <1000 units [n=60]) and group 2 (CS ≥1000 units [very extensive LEAC; n=50]).

Results: Group 2 (vs. group 1) was characterized by higher prevalence of atherosclerotic risk factors, namely smoking, overweight/obesity, and the cases of family history of cardiovascular diseases. Hypertension and diabetes mellitus tended to be more prevalent in group 2, as opposed to group 1. In addition, patients with CS ≥1000 units (vs. <1000) presented more frequently with atrial fibrillation/flutter, heart failure stage C, previous acute cerebrovascular event and the most advanced Rutherford stage 6.

Conclusions: The PAD patients with concomitant SCAD and very extensive LEAC demonstrated more severe PAD and higher comorbidity burden, as compared to their counterparts with less calcified lower extremity arteries. The obtained data substantiate the integrated approach to be implemented in the management of such polyvascular patients, particularly by the use of LEAC as a potential predictor of adverse cardiovascular events.

KEY WORDS: arteries, diabetes mellitus, calcification, endovascular treatment

Wiad Lek. 2025;78(6):1039-1046. doi: 10.36740/WLek/207362 DOI

INTRODUCTION

According to the literature, the prevalence of lower extremity (LE) peripheral artery disease (PAD) varies depending on a country's level of economic development: from 28,7% in low-income countries to 13,1% in high-income countries [1, 2]. LE PAD is recognised as an independent predictor of increased cardiovascular risk and significantly affects patients' quality of life and life expectancy [3, 4].

In the presence of PAD, coronary artery involvement is detected in 62–65% of cases, cerebrovascular involvement in 32,3% of patients, and the risk of cardiovascular mortality is markedly increased. Overall cardiovascular morbidity in such patients rises sixfold [5, 6].

Mortality among patients with LE PAD is 16,1 ± 2,1%, which significantly exceeds the rate observed in patients without PAD or cardiovascular pathology, where it is 4,1 ± 0,3% [7]. According to data from the US National Health and Nutrition Examination Survey, which included over 9,000 patients with LE PAD, the prevalence of cardiovascular pathology (myocardial infarction [MI], ischemic stroke, heart failure [HF]) exceeded 33% [8].

Over the past decade, treatment strategies for chronic lower limb ischemia have shifted from traditional surgical vascular interventions towards modern endovascular techniques [9, 10]. At the same time, the clinical criteria for selecting invasive strategies have also evolved: in particular, endovascular intervention is increasingly being applied in patients with intermittent claudication, even in the absence of critical ischemia [11].

Despite the widespread adoption of endovascular technologies in clinical practice, there is no unified

Table 1. The age and sex distribution of the enrolled sample of PAD patients with concomitant SCAD

Sex	n	%	Age intervals, years							
			41 – 50		51 – 60		61 – 70		≥71	
			N	%	N	%	N	%	N	%
Males	77	70	2	2,6*	10	13,0*	26	33,8*	39	50,6*
Females	33	30	0	0**	2	6,1**	10	30,3**	21	63,6**
Total	110	100	2	1,8	12	10,9	36	32,7	60	54,6

Note: * – among males; ** – among females

interpretation of the absolute and relative contraindications to their use. Among the clinically significant limitations are the presence of advanced atherosclerosis, acute arterial thrombosis, complete arterial occlusion, eccentric stenosis, and multiple vascular lesions [12]. Meanwhile, recent studies suggest that the outcomes of endovascular procedures may vary depending on the degree of lower extremity arterial calcification (LEAC) [13].

Numerous studies have confirmed that LE PAD is associated with atherosclerotic involvement of other vascular territories, including the coronary artery bed in patients with coronary artery disease (CAD), leading to reduced life expectancy, significant deterioration in quality of life, and an increased risk of patient disability [13–15]. This highlights the need for comprehensive diagnostic evaluation and the implementation of a multidisciplinary approach to the management of patients with polyvascular disease, particularly through thorough investigation of predictors of adverse outcomes. In this context, the study of associations between LEAC and the clinical profile of PAD patients with concomitant CAD is of both scientific and practical interest [13, 14, 16].

AIM

The aim of the study was to evaluate the associations of LEAC with the clinical profile of PAD patients with concomitant stable CAD (SCAD).

MATERIALS AND METHODS

The cross-sectional single-center study analyzed the clinical and instrumental data from 110 LE PAD patients with concomitant SCAD, underwent endovascular treatment in the Clinical Hospital «Feofaniya» State Administrative Department (Kyiv, Ukraine) during the period 2021-2025.

The age of the enrolled patients ranged from 47 to 84 years, with a mean ± standard deviation of 71 ± 8 years. The majority of patients were male (n = 77 [70,0%]), and more than half of the participants were over 70 years of age (Table 1).

The profile of the cardiovascular risk factors among the enrolled patients was as follows: smoking – 73 (66,4 %) cases, body mass index (BMI) – 52 (47,3 %), total serum cholesterol ≥5,2 mmol/l – 97 (88,2 %), hypertension – 96 (87,3 %), family history of cardiovascular disease – 50 (45,5 %), and diabetes mellitus (DM) – 98 (89,1 %).

Verification of SCAD was performed in accordance with established guidelines [17]. Twenty-nine patients (26,4%) presented with stable angina of CCS class III–IV. A history of myocardial infarction (MI) was identified in 34 (30,9%) patients, atrial fibrillation/atrial flutter (AF/AFl) in 30 (27,3%), heart failure (HF) stage C in 35 (31,8%), and previous acute cerebrovascular event (ACVE) in 22 (20,0%). Chronic kidney disease (CKD) of stage 3–4 (according to the KDIGO guideline [18]) was diagnosed in 21 (19,1%) patients, brachiocephalic atherosclerosis in 60 (54,6%), and chronic lung disease in 31 (28,2%) cases. Baseline statin therapy was received by 76 (69,1%) patients.

LE PAD was verified according to the widely accepted guidelines [3, 4, 19]. All 110 enrolled PAD patients presented with a chronic limb-threatening ischemia (CLTI) pattern, specifically with rest pain and trophic changes of the lower extremities. According to the Rutherford classification of chronic limb ischemia [20], stage 5 was identified in 98 (87,3%) patients and stage 6 in 14 (12,7%).

All 110 patients underwent computed tomography (CT) angiography of the lower extremity arteries with the calculation of the calcium score by the Agatson method (LEAC) [13, 21].

Considering the literature on the impact of the degree of vascular calcification on the outcomes of endovascular intervention [13], the sample of patients with PAD and concomitant SCAD was divided into two groups based on the degree of LEAC (by Agatson calcium score). Group 1 (n = 60) consisted of patients with a lower extremity calcium Agatson score of <1000 units (mild calcification) according to CT angiography (mean score: 460,1 ± 215,96 units). Group 2 (n = 50) included patients with a lower extremity calcium Agatson score of ≥1000 units (extensive calcification) (mean score: 2774,3 ± 1483,21 units).

The statistical data analysis was performed using Statistica v. 14.0 (TIBCO Software Inc., USA), IBM SPSS Statistics v. 27.0 (Armonk, NY: IBM Corp., USA), MedCalc v. 23.1.7 (MedCalc Software Ltd., Belgium) and MedStat v. 5.2. Quantitative variables were presented as mean ± standard deviation, and qualitative variables as absolute and relative (%) frequency (with a 95% confidence interval [CI], as required). To compare continuous variables between two unrelated samples, we used the Student's t-test (if variances were equal) or Welch's t-test (if variances were unequal). To compare qualitative variables, we used the χ^2 test (with a subsequent z-test to compare specific categories [ranks] of qualitative rank variables) and Fisher's exact test (for 2 × 2 tables). A two-tailed p-value < 0.05 was considered statistically significant.

ETHICS

The study was conducted in accordance with the principles of bioethics outlined in the Helsinki Declaration "Ethical Principles for Medical Research Involving Human Subjects," the "Declaration on Universal Norms on Bioethics" (UNESCO), and in compliance with current legislation of Ukraine. The study protocol was approved by the local ethics committee. All patients signed informed consent.

RESULTS

The data presented in Table 1 indicate an increase in the proportion of female patients among the older age groups, which is due to gender-specific features of CAD progression [6, 17]. The mean age of the female participants in this study was higher than that of the male participants (74 ± 8 vs. 69 ± 8 years, respectively; p < 0,001). In the oldest age group (≥81 years), women were six times more frequent than men: 39,4% (13/33) vs. 6,5% (5/77), respectively (p < 0,001). According to existing data, men suffer from CAD twice as often as women, but in patients with DM and aged >70 years, the incidence of CAD is similar in both sexes [6, 17, 22].

The distribution of patients in the study groups with varying degrees of lower extremity arterial calcification by age and sex is presented in Table 2.

Although patients aged 51-60 years were more frequent in group 1, and those aged 61-70 years were more frequent in group 2, no statistically significant differences in mean age were found between the study groups. At the same time, the comparison groups were comparable in terms of sex (Table 1). This provides grounds to suggest that the differences identified later are not related to the gender distribution of patients in each of the study groups.

Table 3 summarizes the data on the frequency of detection of individual risk factors for atherosclerosis in the study groups.

In the course of the study, we found that a higher percentage of smokers, individuals with overweight and/or obesity, hypertension (at the trend level), a family history of cardiovascular diseases, and DM (at the trend level) were observed in patients of group 2 compared to their percentage in patients of group 1 (Table 2). These findings align with general beliefs regarding the contribution of traditional atherosclerosis risk factors to the development of vascular calcification [23]. At the same time, the data regarding the frequency of a family history of cardiovascular diseases in the study groups may indirectly indicate the role of genetic factors in the development of vascular calcification [24].

When analyzing the risk factors for atherosclerosis among patients of the mentioned groups, attention is also drawn to the high frequency of patients with elevated serum cholesterol levels, which may be related to individual characteristics of lipid-lowering drug use. In group 1, 40 patients (66,7%) were receiving lipid-lowering therapy, while in group 2, 36 patients (72,0%) were receiving it (p=0,679). This fact may be associated with both insufficient statin therapy intensity and suboptimal patient adherence to treatment in both study groups. At the same time, assessing the effectiveness of hypolipidemic therapy is not advisable, as statin treatment leads to increased calcification of plaques, which can be considered part of their stabilization. Thus, the increase in the calcium index against the background of hypolipidemic therapy is more likely to be associated with the stabilization of atherosclerotic plaques rather than indicating the ineffectiveness of therapeutic treatment [25, 26].

At the next stage, we deemed it appropriate to examine the clinical picture of the study groups of patients with different degrees of lower extremity arterial calcification (Table 4).

Analysis of the data in Table 4 indicates a higher frequency of stage 5 according to Rutherford among patients of group 2 compared to those in group 1, which may clinically reflect differences in the prevalence of atherosclerotic processes in the studied groups.

At the same time, it is noteworthy that in group 2, patients with AF/AFl and HF stage C were more frequent compared to group 1 (Table 4). Additionally, the frequency of past myocardial infarction (MI) cases was quantitatively, though not significantly, higher in group 2. These findings may indirectly suggest more significant changes in myocardial functional state and hemodynamics in patients with extreme degrees of lower extremity arterial calcification. The latter creates

Table 2. Baseline demographic characteristics of PAD patients with concomitant SCAD in the studied groups

Parameters		Group 1 (LLCA <1000 Agatson units) N=60	Group 2 (LLCA ≥1000 Agatson units) N=50	p
Age, years		70 ± 9*	72 ± 6**	0,168
Age intervals, years, n (%)	41-50	2 (3,3)	0	0,012
	51-60^z	10 (16,7)	2 (4,0)	
	61-70^z	13 (21,7)	23 (46,0)	
	≥71	35 (58,3)	25 (50,0)	
Sex, n (%)	Males	42 (70,0)	35 (70,0)	1,000
	Females	18 (30,0)	15 (30,0)	

Note: * – age range: 47-84 years; ** – age range: 57-81 years; z – statistically significant difference by z-test (at p<0,05)

Table 3. The specific risk factors for atherosclerosis in PAD patients with concomitant SCAD in the studied groups

Parameters	Group 1 (LLCA <1000 Agatson units) N=60	Group 2 (LLCA ≥1000 Agatson units) N=50	p
Smoking, n (%)	32 (53,3)	41 (82,0)	0,002
BMI ≥25,0 kg/m^2, n (%)	18 (30,0)	37 (74,0)	<0,001
Total cholesterol ≥5,2 mmol/l, n (%)	51 (85,0)	46 (92,0)	0,375
Hypertension, n (%)	49 (81,7)	47 (94,0)	0,083
Family history, n (%)	21 (35,0)	29 (58,0)	0,021
DM, n (%)	50 (83,3)	48 (96,0)	0,062

Table 4. Baseline clinical presentation of PAD patients with concomitant SCAD in the studied groups

Parameters		Group 1 (LLCA <1000 Agatson units) N=60	Group 2 (LLCA ≥1000 Agatson units) N=50	p
Stable angina CCS class III-IV, n (%)		18 (30,0)	11 (22,0)	0,390
AF/AFl, n (%)		10 (16,7)	20 (40,0)	0,009
Previous MI, n (%)		15 (25,0)	19 (38,0)	0,153
HF stage C, n (%)		14 (23,3)	21 (42,0)	0,042
Rutherford stage, n (%)	5	60 (100)	36 (72,0)	<0,001
	6	0*	14 (18,0)**	

Note: * – 95 % CI [0-3,2 %]; ** – 95 % CI [16,3-41,5 %]

Table 5. Certain baseline comorbidities in PAD patients with concomitant SCAD in the studied groups

Parameters	Group 1 (LLCA <1000 Agatson units) N=60	Group 2 (LLCA ≥1000 Agatson units) N=50	p
CKD of stage 3-4, n (%)	9 (15,0)	12 (24,0)	0,330
Previous ACVE, n (%)	7 (11,7)	15 (30,0)	0,030
Brachiocephalic atherosclerosis, n (%)	30 (50,0)	30 (60,0)	0,339
Lung diseases, n (%)	13 (21,7)	18 (36,0)	0,136

a basis for a comprehensive approach to diagnosing (determining natriuretic peptide levels in blood serum, performing transthoracic echocardiography, and coronary angiography) and treating such patients [3, 4, 17]. At the same time, the high frequency of past MI in both study groups may indicate that the calcium score is a powerful predictor of cardiovascular events, particularly MI, in patients with multifocal atherosclerosis [13, 14, 21].

Data on other comorbid conditions among the patients in the studied groups are presented in Table 5.

When analyzing the comorbidities in the studied groups, the slightly higher, though not statistically

significant, frequency of CKD stage 3-4 in patients of group 2 (Table 5) stands out. As is known, CKD can be an aggravating factor that complicates the disease course, affects the outcomes of endovascular treatment, and increases mortality in patients with PAD [27].

At the same time, previous ACVE cases were more frequently observed in group 2 compared to group 1. Additionally, the high frequency of brachiocephalic artery atherosclerosis in both groups may indicate the systemic nature of the damage and also supports the previously suggested hypothesis regarding the role of the genetic factor in the formation of vascular calcification [24]. Finally, the more frequent detection of lung pathology in patients of group 2 (quantitatively, though not significantly) may be positioned as an additional marker of their more pronounced comorbid burden (Table 5).

DISCUSSION

The results obtained indicate a significant association between the degree of LEAC and the severity of the clinical course of atherosclerotic damage in PAD patients with concomitant SCAD. It was found that an extreme degree of calcification (Agatston index >1000 units) is associated with a more frequent detection of higher stages of chronic lower limb ischemia according to the Rutherford classification (stage 6), as well as a higher prevalence of conditions such as AF/AFl, previous MI (numerically, but non-significantly), HF stage C, and previous ACVE. These data are consistent with literature reports emphasizing the role of vascular calcification as a predictor of more severe clinical course and unfavorable intervention outcomes [13, 14, 21]. Vascular calcification is considered an active, regulated process similar to osteogenesis, involving cells of the vascular wall, mediators of inflammation, oxidative stress, and factors regulating calcium-phosphate metabolism [28]. The presence of pronounced calcification impairs the biomechanical properties of the vessel wall, reduces arterial elasticity, complicates endovascular intervention, reduces the effectiveness of angioplasty, and is associated with a higher risk of restenosis and stent thrombosis [13, 21, 29].

The detected differences in the higher prevalence of traditional atherosclerosis risk factors, such as smoking, excess body weight/obesity, family history, hypertension, and DM, among patients with a high calcium index, suggest their potential cumulative role in the development and progression of vascular calcification. These observations are supported by the works of other authors who indicate the multifactorial nature of vascular calcification, particularly in patients with systemic atherosclerosis and CKD [29-31].

Special attention is drawn to the high level of calcification despite the use of lipid-lowering therapy. According to the literature, statins may contribute to an increase in the density and degree of calcification of atherosclerotic plaques, which is interpreted as a mechanism of their stabilization rather than an indication of treatment inefficacy [25, 26, 32]. This is consistent with our observations regarding the absence of a statistically significant relationship between the frequency of baseline statin therapy and the degree of LEAC.

The high frequency of brachiocephalic artery involvement in the studied patients, as well as frequent cases of a positive family history, suggest a genetic predisposition to systemic calcification. The role of hereditary factors, particularly mutations in genes encoding mineralization inhibitors (e.g., MGP, ENPP1, etc.), is actively being studied and warrants further attention [24, 33].

Thus, the results of our study are consistent with the data from the global literature regarding the clinical significance of vascular calcification in patients with multifocal atherosclerotic lesions, particularly in those with concomitant PAD and SCAD, while also confirming the need for comprehensive diagnostics that encompass not only the anatomical characteristics of the lesions but also comorbidities, myocardial functional status, renal function, and genetic predisposition.

FUTURE RESEARCH PERSPECTIVES

Further studies should focus on assessing the impact of the intensity and duration of lipid-lowering therapy on the dynamics of the calcium index and the stability of atherosclerotic plaques, incorporating biomarkers of inflammation, vascular wall remodeling, and plaque stabilization. It is also important to investigate the role of genetic factors and calcification markers (such as osteoprotegerin, matrix Gla-proteins, etc.) in predicting the risk of vascular calcification and cardiovascular events in this patient category [24, 33, 34].

An important direction is the development of risk stratification models that take into account the degree of vascular calcification along with traditional risk factors, for a personalized approach to planning endovascular treatment and secondary prevention in patients with systemic atherosclerosis.

CONSLUSIONS

The conducted analysis allowed us to establish that PAD (CLTI) patients with concomitant SCAD and an extreme degree of LEAC (Agatston index ≥1000 units) are characterized by worse clinical features compared to patients with pronounced but less significant calcification (Agatston index <1000 units). Specifically, they more frequently experienced arrhythmias (AF/AFl), HF

stage C, previous ACVE, and the most advanced Rutherford stage 6, indicating a more severe course of LE PAD and a greater burden of comorbidities in patients with an exceptionally high degree of LEAC.

In patients with an extreme degree of LEAC, traditional risk factors for atherosclerosis, in particular smoking, overweight/obesity, and a family history of cardiovascular diseases, were more commonly observed. This confirms the key role of these factors in the progression of vascular calcification. Despite the comparable frequency of baseline statin therapy in both studied groups, the frequency of elevated total serum cholesterol remained high in a significant proportion of patients, which may indicate insufficient intensity or low adherence to treatment. At the same time, the increase in the calcium index during lipid-lowering therapy may reflect the stabilization of atherosclerotic plaques rather than their ineffectiveness.

The results obtained highlight the importance of considering the degree of LEAC when planning endovascular interventions in PAD patients with concomitant SCAD, as a high calcium index is associated with worse clinical status, a greater burden of comorbidities, and the presence of multiple risk factors.

REFERENCES

1. Fowkes FG, Rudan D, Rudan I et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382(9901):1329-1340. doi: 10.1016/S0140-6736(13)61249-0. DOI
2. Song P, Rudan D, Zhu Y et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019;7(8):e1020-e1030. doi: 10.1016/S2214-109X(19)30255-4. DOI
3. Mazzolai L, Teixido-Tura G, Lanzi S et al. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. Eur Heart J. 2024;45(36):3538-3700. doi: 10.1093/eurheartj/ehae179. DOI
4. Gornik HL, Aronow HD, Goodney PP et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149(24):e1313-e1410. doi: 10.1161/CIR.0000000000001251. DOI
5. Houghton JSM, Saratzis AN, Sayers RD, Haunton VJ. New Horizons in Peripheral Artery Disease. Age Ageing. 2024;53(6):afae114. doi: 10.1093/ageing/afae114. DOI
6. Martin SS, Aday AW, Almarzooq ZI et al. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. Circulation. 2024;149(8):e347-e913. doi: 10.1161/CIR.0000000000001209. DOI
7. Aboyans V, Criqui MH, Denenberg JO et al. Risk factors for progression of peripheral arterial disease in large and small vessels. Circulation. 2006;113(22):2623-2629. doi: 10.1161/CIRCULATIONAHA.105.608679. DOI
8. Gutierrez JA, Scirica BM, Bonaca MP et al. Prevalence and Outcomes of Polyvascular (Coronary, Peripheral, or Cerebrovascular) Disease in Patients With Diabetes Mellitus (From the SAVOR-TIMI 53 Trial). Am J Cardiol. 2019;123(1):145-152. doi: 10.1016/j.amjcard.2018.09.014. DOI
9. Hupalo Y, Shapovalov D, Shaprynskyi V et al. Anhiosomna revaskuliaryzatsiia stopi u khvorykh na tsukrovyi diabet. [Angiosome revascularization of foot in patients with diabetes]. Naukovyy visnyk Uzhhorods'koho universytetu. Seriya «Medytsyna». 2020;1(61):30-33. doi: 10.24144/2415-8127.2020.61.30-33. (Ukrainian) DOI
10. Dybiak YM. Aktualni pytannia rekonstruktyvnoi khirurhii homilkovykh arterii (ohliad literatury). [Current issues of reconstructive surgery of the ankle arteries (literature review)]. Bukovyns'kyy medychnyy visnyk. 2014;18(3):192-195. (Ukrainian)
11. Creager MA, Belkin M, Bluth EI et al. 2012 ACCF/AHA/ACR/SCAI/SIR/STS/SVM/SVN/SVS key data elements and definitions for peripheral atherosclerotic vascular disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Peripheral Atherosclerotic Vascular Disease). Circulation. 2012;125(2):395-467. doi: 10.1161/CIR.0b013e31823299a1. DOI
12. Watson NW, Mosarla RC, Secemsky EA. Endovascular Interventions for Peripheral Artery Disease: A Contemporary Review. Curr Cardiol Rep. 2023;25(11):1611-1622. doi: 10.1007/s11886-023-01973-9. DOI
13. Dong Y, Liu Y, Cheng P et al. Lower limb arterial calcification and its clinical relevance with peripheral arterial disease. Front Cardiovasc Med. 2023;10:1271100. doi: 10.3389/fcvm.2023.1271100. DOI
14. Aday AW, Matsushita K. Epidemiology of Peripheral Artery Disease and Polyvascular Disease. Circ Res. 2021;128(12):1818-1832. doi: 10.1161/CIRCRESAHA.121.318535. DOI
15. Chowdhury MM, Makris GC, Tarkin JM et al. Lower limb arterial calcification (LLAC) scores in patients with symptomatic peripheral arterial disease are associated with increased cardiac mortality and morbidity. PLoS One. 2017;12(9):e0182952. doi: 10.1371/journal.pone.0182952. DOI
16. van't Klooster CC, Nathoe HM, Hjortnaes J et al. Multifocal cardiovascular calcification in patients with established cardiovascular disease; prevalence, risk factors, and relation with recurrent cardiovascular disease. Int J Cardiol Heart Vasc. 2020;27:100499. doi: 10.1016/j.ijcha.2020.100499. DOI

17. Vrints C, Andreotti F, Koskinas KC et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45(36):3415-3537. doi: 10.1093/eurheartj/ehae177. DOI
18. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4S):S117-S314. doi: 10.1016/j.kint.2023.10.018. DOI
19. Conte MS, Bradbury AW, Kolh P et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg. 2019;69(6S):3S-125S.e40. doi: 10.1016/j.jvs.2019.02.016. DOI
20. Hardman RL, Jazaeri O, Yi J et al. Overview of classification systems in peripheral artery disease. Semin Intervent Radiol. 2014;31(4):378-88. doi: 10.1055/s-0034-1393976. DOI
21. Lee S, Kalra K, Kashikar A et al. Evaluation of Lower Extremity Calcium Score as a Measure of Peripheral Arterial Disease Burden and Amputation Risk. Ann Vasc Surg. 2023;95:154-161. doi: 10.1016/j.avsg.2023.02.009. DOI
22. Kalyani RR, Lazo M, Ouyang P et al. Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults. Diabetes Care. 2014;37(3):830-838. doi: 10.2337/dc13-1755. DOI
23. Di Vito A, Donato A, Presta I et al. Extracellular Matrix in Calcific Aortic Valve Disease: Architecture, Dynamic and Perspectives. Int J Mol Sci. 2021;22(2):913. doi: 10.3390/ijms22020913. DOI
24. Mishra PP, Mishra BH, Lyytikäinen LP et al. Genetic risk score for coronary artery calcification and its predictive ability for coronary artery disease. Am J Prev Cardiol. 2024;20:100884. doi: 10.1016/j.ajpc.2024.100884. DOI
25. Colantonio LD, Hubbard D, Monda KL et al. Atherosclerotic Risk and Statin Use Among Patients With Peripheral Artery Disease. J Am Coll Cardiol. 2020;76(3):251-264. doi: 10.1016/j.jacc.2020.05.048. DOI
26. Lai R, Ju J, Lin Q, Xu H. Coronary Artery Calcification Under Statin Therapy and Its Effect on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2020;7:600497. doi: 10.3389/fcvm.2020.600497. DOI
27. Smilowitz NR, Bhandari N, Berger JS. Chronic kidney disease and outcomes of lower extremity revascularization for peripheral artery disease. Atherosclerosis. 2020;297:149-156. doi: 10.1016/j.atherosclerosis.2019.12.016. DOI
28. Dweck MR, Chow MW, Joshi NV et al. Coronary arterial 18F-sodium fluoride uptake: a novel marker of plaque biology. J Am Coll Cardiol. 2012;59(17):1539-48. doi: 10.1016/j.jacc.2011.12.037. DOI
29. Ortega MA, De Leon-Oliva D, Gimeno-Longas MJ et al. Vascular Calcification: Molecular Networking, Pathological Implications and Translational Opportunities. Biomolecules. 2024;14(3):275. doi: 10.3390/biom14030275. DOI
30. Qin Z, Yu L, Zhang Y et al. Coronary artery calcification and plaque stability: an optical coherence tomography study. Heliyon. 2023;9(12):e23191. doi: 10.1016/j.heliyon.2023.e23191. DOI
31. Chen S, Tang R, Liu B. Current Understanding of Cardiovascular Calcification in Patients with Chronic Kidney Disease. Int J Mol Sci. 2024;25(18):10225. doi: 10.3390/ijms251810225. DOI
32. Puri R, Libby P, Nissen SE et al. Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: insights from SATURN. Eur Heart J Cardiovasc Imaging. 2014;15(4):380-388. doi: 10.1093/ehjci/jet251. DOI
33. Zaker B, Ardalan M. Vascular calcification; Stony bridge between kidney and heart. J Cardiovasc Thorac Res. 2020;12(3):165-171. doi: 10.34172/jcvtr.2020.29. DOI
34. Bäck M, Aranyi T, Cancela ML et al. Endogenous Calcification Inhibitors in the Prevention of Vascular Calcification: A Consensus Statement From the COST Action EuroSoftCalcNet. Front Cardiovasc Med. 2019;5:196. doi: 10.3389/fcvm.2018.00196. DOI

The study was conducted as a fragment of the scientific projects of the Scientific Department of Minimally Invasive Surgery (State Institution of Science «Center of innovative healthcare technologies» State Administrative Department) «Optimization of surgical treatment of patients under a multimodal program of rapid recovery based on the improvement of operative interventions, in particular with the use of nanobiosensor technologies and their anesthetic support» (state registration number 0122U000233; term: 2022-2024) and «Optimization of approaches to providing specialized medical care for surgical patients using personalized anesthetic support» (state registration number 0125U000315; term: 2025-2029).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Sviatoslav Y. Denysov

Clinical Hospital «Feofaniya»

21 Academician Zabolotny St, 03143 Kyiv, Ukraine

e-mail: Denisovsu84@gmail.com

ORCID AND CONTRIBUTIONSHIP
Sviatoslav Y. Denysov: 0000-0002-3214-8208 A B C D
Yuriy M. Hupalo: 0000-0002-4856-1398 A E F
Vasyl V. Lazoryshynets: 0000-0002-1748-561X E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 07.01.2025
ACCEPTED: 30.05.2025

ORIGINAL ARTICLE

CONTENTS

Peculiarities of psycho-emotional and neurovegetative state in Ukrainian women who have experienced war-related stress and ways of its non-medicinal correction

Viktor S. Matsyshyn[1], Kostiantyn O. Apykhtin[1], Anatolii M. Kravchenko[1], Nataliia M. Ovodiuk[1], Illya A. Chaikovsky[2]

[1]STATE INSTITUTION OF SCIENCE «CENTER OF INNOVATIVE HEALTHCARE TECHNOLOGIES» STATE ADMINISTRATIVE DEPARTMENT, KYIV, UKRAINE
[2]V.M. GLUSHKOV INSTITUTE OF CYBERNETICS OF THE NATIONAL ACADEMY OF SCIENCES OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: To investigate the peculiarities of psycho-emotional and neurovegetative disorders in women exposed to war-related stress and to assess the possibilities of their correction by cognitive behavioural therapy (CBT) and Transcendental Meditation (TM).

Materials and Methods: The study involved 72 women, 35 of whom had experienced high-intensity stress and 37 of whom were in the control group. The psychoemotional state was assessed by the DASS-21 test and a screening test for post-traumatic stress disorder. The neurovegetative state was assessed by mathematical analysis of heart rate variability (HRV). The main group was divided into subgroups that received correction using CBT or TM.

Results: In the main group exposed to the stressors of war, a higher level of anxiety, depression, PTSD score, and neurovegetative imbalance (decreased total adaptation reserve [SDNN], decreased parasympathetic regulation activity [RMSSD], increased vegetative balance index [LF/HF], indicating a shift towards sympathicotonia) was found. After the correction, both subgroups (CBT and TM) showed a decrease in anxiety, depression and stress. TM showed a more pronounced corrective effect on neurovegetative regulation and some indicators of psycho-emotional state (anxiety) compared to CBT.

Conclusions: A war significantly affects the psycho-emotional and neurovegetative state of women. Both of the applied non-medicated methods (CBT and TM) showed a significant corrective effect. The results of the study confirm the positive effects of TM and indicate the feasibility of its use for psychological support of persons exposed to the stress factors of war.

KEY WORDS: women, post-traumatic stress disorder, autonomic dysfunction

Wiad Lek. 2025;78(6):1047-1053. doi: 10.36740/WLek/207363 DOI

INTRODUCTION

The war in Ukraine, which was started by Russia in 2014 and escalated into a full-scale war in 2022, has had a significant impact on the lives and health of civilians, including women. The hostilities and the consequences of the socio-humanitarian crisis are causing numerous physical, psychological and social problems among women living in the conflict zone or who have been forced to flee their homes. Studies show that the effects of war include a significant increase in stress, anxiety, depression and post-traumatic stress disorder (PTSD) among women [1-3].

From February to May 2024, the State Institution of Science «Center of innovative healthcare technologies» State Administrative Department (Kyiv, Ukraine), in partnership with the Ukrainian public organisation Impact Force, UN Women and information support from the Ministry of Digital Transformation of Ukraine and «Diia. Education», the ReSTART Mindset educational and health programme was developed and implemented for women veterans and women family members of veterans. The programme included an assessment of women's health by conducting a survey and examining ECG readings with mathematical analysis of heart rate variability (HRV) [4-8]. To correct the condition, both the well-known and recommended by international protocols method of cognitive behavioural therapy (CBT) [9-12], and the method that has shown its effectiveness in PTSD and other stress disorders, but requires further research, – Transcendental Meditation (TM) [13-15], – were used.

AIM

The aim of the study was to investigate the peculiarities of psycho-emotional and neurovegetative disorders in women exposed to war-related stress and to assess the potential for their correction through psychotherapy and meditation.

MATERIALS AND METHODS

The main group consisted of 35 women who had experienced high-intensity severe war-related stress, with an average age of (mean [M] ± standard error of the mean [m]) 40,7 ± 1,4 years. The main group included women in a state of stress-associated uncertainty, such as internally displaced women who fled their homes because of the hostilities and wives of military personnel who are experiencing a difficult emotional state due to anxiety about their loved ones; women veterans who have returned to civilian life after service or people who are adapting to society after military service; women who worked in difficult conditions, including those who were under occupation, in the shelling zone or near the contact line, as well as those who participated in the evacuation of civilians, demining, etc. The control group consisted of 37 women, whose average age was 40,1 ± 1,7 years, who did not participate in hostilities, were not under occupation, did not have deceased military relatives, i.e. did not experience the effects of extremely intense stress factors associated with the war.

Standardised questionnaires were used to study the psycho-emotional state: DASS-21 (anxiety, depression, stress) [16] and the PTSD screening test recommended by the Ministry of Health of Ukraine [17]. The neurovegetative state was assessed using the functional parameters of the Autonomous Nervous System (ANS). To assess the functional state of the ANS, the method of mathematical analysis of HRV was used, which was carried out on the basis of an ECG recorded in a sitting position, at rest, for three minutes, using an ECG recorder DiaCard 06000.1 (Solvaig, Kyiv) and the "Harmony" software and hardware complex [5] with the "Oracle" computing core [6].

HRV was studied according to international clinical standards of 1996 [7, 8]. Additionally, the Roman Baevsky stress index (SI) was used [8, 18-21]. The following HRV parameters were evaluated: heart rate (HR), the standard deviation of normal-to-normal intervals (SDNN), the root mean square of successive differences (RMSSD), SI and the ratio of low-frequency to high-frequency power (LF/HF).

At the first stage of the study, the psychoemotional and neurovegetative state of women in the main and control groups was compared. The second stage of the study examined the effect of two types of corrective measures – CBT and TM – on women in the main group. For this purpose, in accordance with the type of correction used, the main group of women was divided into two groups, TM (15 women, average age 41,7 ± 2,1 years) and CBT (20 women, average age 40,1 ± 2,0 years).

Statistical analysis was performed using IBM SPSS Statistics 26 (USA). Quantitative data were presented as M ± m and median (Me) with interquartile range (first [Q1] and third [Q3] quartiles). The study used parametric and non-parametric methods of statistical evaluation: Student's T-test for independent (T unpaired) and paired (T paired) samples; non-parametric criteria: Wilcoxon test for paired samples (W), Mann-Whitney test for independent samples (U). Differences between group means and medians were considered significant at a significance level of $p < 0,05$; and at the trend level – at $0,05 < p < 0,1$.

ETHICS

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Scientific and Practical Centre for Preventive and Clinical Medicine of the State Administration of Affairs (Protocol No.1 dated January 15, 2024). Written informed consent was obtained from all participants, and their personal data were anonymized to ensure confidentiality.

RESULTS

Women in the ReSTART Mindset task force reported complaints related to high levels of stress, emotional exhaustion, and difficulties in adapting to war-affected living conditions. The most frequent psycho-emotional complaints included persistent feelings of anxiety, fear, and depression; emotional instability and irritability; reduced motivation; apathy; and a sense of helplessness. Women in the main group also reported difficulties with concentration and decision-making.

Common somatic complaints included pain syndromes in the cervical and lumbar spine, headaches, muscle tension, and sleep disturbances such as difficulty falling asleep, light or fragmented sleep, and frequent awakenings. In addition, women in the main group experienced vegetative symptoms, including palpitations, blood pressure fluctuations, a sensation of a lump in the throat, shortness of breath, gastrointestinal disturbances, excessive sweating, and dizziness.

Among the social complaints, feelings of isolation and being misunderstood by others were prominent, as were difficulties in forming or maintaining social contacts, and conflicts within the family or workplace caused by a worsened emotional state.

Complaints related to stress adaptation were also notable, including a perceived inability to cope with current circumstances, increased emotional vulnerability even to minor events, fear of the future, and feelings of uncertainty.

The women in the main group often experienced post-traumatic symptoms, such as flashbacks or re-

Table 1. Comparison of the primary group at baseline with the control group

Indicator	Groups	M ± m	Me	Q1	Q3	p
Sum of DASS-21 test, scores	control	27,46 ± 1,50	29	26	34	p (T) > 0,1 p (U) > 0,1
	main	29,71 ± 2,01	29	20	38	
Depression level, points	control	10,08 ± 0,61	11	8,5	12	p (T) > 0,1 p (U) > 0,1
	main	10,43 ± 0,88	10	6	13	
Anxiety level, points	control	5,65 ± 0,49	6	2,5	8,5	p (T) = 0,047 p (U) = 0,061
	main	7,37 ± 0,69	7	4	11	
Level of subjectively experienced stress, points	control	11,73 ± 0,69	13	10	14	p (T) > 0,1 p(U) > 0,1
	main	11,91 ± 0,73	13	8	15	
Level of PTSD severity, points	control	2,97 ± 0,15	3	2	4	p (T) = 0,001 p(U) = 0,001
	main	4,09 ± 0,29	4	3	5	
HR, bpm	control	76,16 ± 1,41	75,00	71,00	82,50	p (T) = 0,05 p(U) = 0,05
	main	80,49 ± 1,66	79,00	74,00	88,00	
SDNN, ms	control	42,81 ± 2,04	41,00	32,50	51,00	p (T) < 0,001 p(U) < 0,001
	main	32,20 ± 1,56	30,00	26,00	40,00	
RMSSD, ms	control	29,32 ± 1,58	29,00	20,50	38,00	p (T) < 0,001 p(U) < 0,001
	main	20,89 ± 1,59	19,00	15,00	28,00	
SI, units	control	194 ± 18	174	115	242	p (T) = 0,001 p(U) < 0,001
	main	342 ± 36	272	212	435	
Vegetative balance (LF/HF)	control	1,97 ± 0,30	1,56	0,79	2,07	p (T) = 0,033 p(U) = 0,022
	main	3,12 ± 0,44	2,46	1,11	4,12	

Note: p(T) – the significance of the difference in mean values (paired t-test); p(U) – the significance of the difference in medians (Mann-Whitney U test)

peated memories of traumatic events, nightmares, hyper-arousal, difficulty relaxing and a sense of constant alertness.

At the first stage of the study, the main group was compared with the control group at baseline. The following was found (Table 1). In the main group, compared to the control group, there was an increased level of anxiety, a higher degree of PTSD severity, a higher level of cardiovascular functioning (as indicated by HR), a lower overall adaptive potential of neurohumoral regulation (as indicated by SDNN), lower activity of parasympathetic modulation (by the RMSSD index), a higher level of tension of regulatory systems (by SI), and a more pronounced shift of autonomic balance towards sympathicotonia (by LF/HF index).

At the second stage of the study, changes in the psychoemotional state and HRV in the dynamics were investigated in each of the groups (CBT and TM), and the reliability of changes in their mean group values (by Student's T-test for paired samples) and medians (by the nonparametric Wilcoxon signed rank test) was assessed.

The following was found when analysing the indicators of psycho-emotional state assessment (Table 2). After correction, in both groups, CBT and TM, there was a significant decrease in the total score on the DASS-21 test (in the TM group p = 0,001; in the CBT group p = 0,004). At the same time, in the TM group, the median of this score decreased significantly (p = 0,003) from 24 to 11 points, and in the CBT group, it decreased significantly (p = 0,006) from 34 to 14 points.

The median score of depression in the CBT group corresponded to severe depression, according to the DASS-21 test. And in the TM group, the median depression score corresponded to moderate depression. After correction, in both groups, CBT and TM, there was a significant decrease in both the mean group scores of depression (p = 0,001 and p = 0,006, respectively) and median scores (p = 0,002 and p = 0,004, respectively). In the TM group, the median depression score decreased from 9 to 3, which is normal. And in the CBT group - from 12 to 5, which also corresponds to the norm.

The median anxiety score in the TM group (7 points) corresponded to «moderate anxiety», and in the CBT group (9 points) – to «severe anxiety». After correction, a significant decrease in the mean group anxiety level was observed in the TM group (p = 0,002), and in the CBT group – its decrease at the level of the trend (p = 0,076). The median anxiety score in the TM group significantly (p = 0,004) decreased from 7 to 2, which corresponds to the norm, and in the CBT group it had a strong downward trend (p = 0,066), from 9 to 6 points, which corresponds to «mild anxiety».

Table 2. Indicators of psycho-emotional state in the dynamics after correction

Indicator	Group	State	M ± m	Me	Q1	Q3	p
Sum of points DASS-21	CBT	initial	32,7 ± 2,6	34,0	20,8	39,8	$p_{(T)} < 0,01$ $p_{(W)} < 0,01$
		after correction	19,6 ± 3,4	14,0	9,0	32,5	
	TM	initial	25,8 ± 2,9	24,0	15,0	31,0	$p_{(T)} < 0,01$ $p_{(W)} < 0,01$
		after correction	11,3 ± 2,5	11,0	4,0	16,0	
Depression, points	CBT	initial	11,9 ± 1,1	12,0	6,8	15,5	$p_{(T)} < 0,01$ $p_{(W)} < 0,01$
		after correction	6,8 ± 1,3	5,0	2,0	11,5	
	TM	initial	8,5 ± 1,3	9,0	5,0	12,0	$p_{(T)} < 0,01$ $p_{(W)} < 0,01$
		after correction	3,6 ± 0,8	3,0	1,0	5,0	
Anxiety, points	CBT	initial	8,1 ± 1,0	9,0	4,0	12,5	$0,05< p_{(T)}<0,1$ $0,05< p_{(W)}<0,1$
		after correction	6,0 ± 1,2	6,0	2,0	8,5	
	TM	initial	6,4 ± 0,8	7,0	3,0	9,0	$p_{(T)} < 0,01$ $p_{(W)} < 0,01$
		after correction	2,5 ± 0,9	2,0	0,0	2,0	
Stress, points	CBT	initial	12,7 ± 0,9	13,0	10,0	15,8	$p_{(T)} < 0,01$ $p_{(W)} < 0,01$
		after correction	6,8 ± 1,1	5,5	3,0	10,5	
	TM	initial	10,9 ± 1,1	12,0	7,0	14,0	$p_{(T)} < 0,01$ $p_{(W)} < 0,01$
		after correction	5,1 ± 1,0	5,0	1,0	8,0	
PTSD, points	CBT	initial	4,5 ± 0,4	4,5	3,0	6,0	$p_{(T)} < 0,01$ $p_{(W)} < 0,01$
		after correction	2,7 ± 0,5	2,0	1,0	5,0	
	TM	initial	3,5 ± 0,3	3,0	3,0	4,0	$p_{(T)} < 0,001$ $p_{(W)} < 0,01$
		after correction	1,3 ± 0,5	1,0	0,0	2,0	

Note: p(T) – the significance of the difference in mean values when using Student's T-test for paired samples; p(W) – the significance of the difference in medians when using the Wilcoxon signed rank test

The median stress scores in the TM group (12 points) and the CBT group (13 points) corresponded to «moderate stress», according to the DASS-21 test. After correction, in both groups, CBT and TM, there was a significant decrease in the mean group values of stress (p = 0,001 for both groups) and medians (p = 0,003 in the TM group; p = 0,004 in the CBT group). In the TM group, the median stress score decreased from 12 to 5 points, and in the CBT group – from 13 to 5,5 points, which corresponds to the norm.

The median value of the PTSD score at baseline in the TM group (3 points) corresponds to the norm, i.e., the absence of PTSD. In the CBT group, the median PTSD score at baseline, before correction, was 4,5 points, which corresponds to the probable presence of PTSD. After correction, in both groups, CBT and TM, there was a significant decrease in the mean group values of PTSD severity (p <0,001 and p = 0,006, respectively). In the TM group, the median PTSD score significantly (p = 0,003) decreased from 3 to 1 point, and in the CBT group, it significantly (p = 0,010) decreased from 4,5 to 2 points, which corresponds to the norm (absence of PTSD).

The analysis of HRV indicators revealed the following (Table 3). The HR in the TM group after the course of correction tended to decrease, according to the average group value (p = 0,088). In the CBT group, there was no significant change in HR after the course of correction.

After the course of correction, the mean group value of SDNN in the TM group increased significantly (p = 0,011); the median also increased significantly (p = 0,021), by 11 ms. While in the CBT group, after correction, an increase in the average group SDNN value was noted at the level of the trend (p = 0,08); the median significantly (p = 0,046) increased by 2,5 ms.

After the course of correction, the average group indices of RMSSD, SI, LF/HF autonomic balance and their medians in the CBT and TM groups did not change significantly.

DISCUSSION

According to the World Health Organization, nearly 10 million Ukrainians may suffer from mental health disorders such as depression or anxiety, of which nearly 4 million may have moderate or severe cases [3]. Women who are homeless, sanguine, with mild depression and mild/medium anxiety are more likely to develop PTSD [1].

Describing the peculiarities of the psychoemotional and neurovegetative state of Ukrainian women, it is worth noting that the control group of women, according to the average group values, was characterised by severe depression and a moderately pronounced level of stress, which is subjectively experienced by the individual. This may be due to the fact that

Table 3. HRV indicators in the dynamics after correction

Indicator	Group	State	M ± m	Me	Q1	Q3	p
HR, bpm	CBT	initial	82,15 ± 2,40	81,50	75,50	88,75	$p_{(T)} > 0,1$ $p_{(W)} > 0,1$
		after correction	80,65 ± 2,19	79,00	74,00	81,75	
	TM	initial	78,27 ± 2,15	77,00	72,00	86,00	$0,05< p_{(T)}<0,1$ $0,05< p_{(W)}<0,1$
		after correction	74,67 ± 1,49	74,00	70,00	77,00	
SDNN, ms	CBT	initial	31,95 ± 2,15	30,50	26,00	39,50	$0,05< p_{(T)}<0,1$ $p_{(W)} < 0,05$
		after correction	36,90 ± 2,67	33,00	28,25	47,00	
	TM	initial	32,53 ± 2,32	30,00	26,00	40,00	$p_{(T)} < 0,05$ $p_{(W)} < 0,05$
		after correction	41,13 ± 4,22	41,00	34,00	51,00	
RMSSD, ms	CBT	initial	20,45 ± 2,06	18,00	15,25	26,50	$p_{(T)} > 0,1$ $p_{(W)} > 0,1$
		after correction	22,70 ± 2,61	19,50	16,25	30,50	
	TM	initial	21,47 ± 2,56	20,00	14,00	29,00	$p_{(T)} > 0,1$ $p_{(W)} > 0,1$
		after correction	24,73 ± 2,98	26,00	16,00	29,00	
SI, units	CBT	initial	382 ± 55	375	226	457	$p_{(T)} > 0,1$ $p_{(W)} > 0,1$
		after correction	283 ± 40	218	144	353	
	TM	initial	287 ± 39	261	205	408	$p_{(T)} > 0,1$ $p_{(W)} > 0,1$
		after correction	289 ± 83	158	122	275	
Vegetative balance (LF/HF)	CBT	initial	3,38 ± 0,64	2,77	1,05	5,36	$p_{(T)} > 0,1$ $p_{(W)} > 0,1$
		after correction	3,35 ± 0,70	2,07	1,18	3,95	
	TM	initial	2,77 ± 0,59	2,46	1,42	3,19	$p_{(T)} > 0,1$ $p_{(W)} > 0,1$
		after correction	3,41 ± 0,62	2,46	1,44	6,17	

Note: p (T) – the significance of difference in mean values using Student's T-test for paired samples; p (W) – the significance of difference in medians when using the Wilcoxon signed rank test

they experience less intense, chronic stress, a constant sense of danger to themselves and their families when living in a country at war. These results provide grounds for the expediency of taking corrective measures and implementing corrective actions for this category of the Ukrainian population as well.

Assessing the differences between the main group of women exposed to severe high-intensity war-related stress and women in the control group, the following features can be noted: higher indicators of anxiety level, severity of PTSD, energy level of cardiovascular system functioning; lower indicators of the general adaptive reserve of neurohumoral regulation (according to the SDNN index), lower activity of parasympathetic modulation (according to the RMSSD index), higher level of tension of regulatory systems (according to SI), a more pronounced shift in the autonomic balance towards sympathicotonia (by the LF/HF autonomic balance index).

Given the experience of the American researchers [22], it would be ideal to investigate the initial state of autonomous nervous regulation of civilian and military Ukrainian women before the start of the war, to take into account the influence of the initial functional state of autonomic regulation on the likelihood of developing PTSD after exposure to a stressful factor.

The main effects of the correction were as follows: in both groups, TM and CBT, the overall adaptive potential of neurohumoral regulation increased; in both groups, the integral indicator of psycho-emotional state assessment improved (the total score of the DASS-21 test decreased), the level of depression decreased, the severity of subjective stress decreased (according to the «stress» indicator of the DASS-21 test), and the severity of PTSD decreased; the level of anxiety in the TM group decreased significantly, and in the CBT group decreased at the level of a trend. At the same time, after the course of correction in both groups, CBT and TM, there were no significant shifts in the activity of parasympathetic modulation (RMSSD), the level of tension of regulatory systems (SI), and no significant changes in the LF/HF autonomic balance.

Thus, the results of this study give grounds to recommend the methods of correction (CBT and TM) used by us for the implementation of psychological support programmes aimed at reducing psychoemotional stress and normalising ANS among the population affected by war.

PERSPECTIVES FOR FUTURE WORKS

Further research could be aimed at expanding the sample to increase the reliability of the results, analysing gender differences in the effects of meditation and CBT, and studying the long-term effects of these methods on psychoemotional and neurovegetative state. Of particular relevance is the study of the mechanisms of action of meditation using

neuroimaging and the comparison of its effectiveness with other therapeutic approaches. Of particular interest is the development of adapted support programmes, their economic feasibility and assessment of cultural acceptability for Ukrainian society. Research among military personnel in the combat zone and evaluation of changes in the quality of life of participants are commercial aspects for further study and implementation of the methods.

CONCLUSIONS

1. Our study showed that Ukrainian women have abnormalities in both indicators of psychoemotional state and neurovegetative regulation. These abnormalities were more pronounced in the group of women who had experienced stressful events of high significance, which caused them to have a pronounced subjective feeling of nervous and emotional stress and a generally mobilising sympathicotonic autonomic response, which led to the depletion of adaptive reserves.
2. The correctional measures, CBT and Transcendental Meditation, had a generally positive effect, which consisted of an increase in the overall adaptive potential of autonomic regulation and improvement of the psycho-emotional state.
3. A comparative evaluation of the effects of CBT and TM showed that TM has a more pronounced corrective effect on the functional state of the autonomic nervous system (increases the overall adaptive potential of neurohumoral regulation), improves the psychoemotional state, with a particularly good reduction in anxiety, and more effectively reduces the manifestations of PTSD. Based on our data, we can recommend a combination of CBT and TM techniques, with the expectation of potentiating their corrective and therapeutic effects.
4. Further, larger-scale research is needed to reveal the mechanisms of influence of the correctional tools (CBT and TM) used in our study.

REFERENCES

1. Oros MM. Vplyv viyny na lyudynu. Zminy psykhiky ta kharakteru v umovakh voyennoho stanu [The impact of war on a person. Psyche and character changes in martial law]. Ukrayins'kyy medychnyy zhurnal. 2023;2(154)III-IV:3-7. doi: 10.32471/umj.1680-3051.154.241952. (Ukrainian) DOI
2. Golovakha Ye, Makeiev S et al. Ukrayinske suspilstvo v umovakh viyny. 2022: Kolektyvna monohrafiya [Ukrainian society in wartime. 2022: Collective monograph]. Kyiv: Institute of Sociology of the National Academy of Sciences of Ukraine. 2022. https://i-soc.com.ua/assets/files/monitoring/maket-vijna...2022dlya-tipografiivse.pdf [Accessed 19 February 2025] (Ukrainian)
3. Gottbrath LW. The silent toll of war: Ukraine's growing mental health crisis. Axios. https://www.axios.com/2023/02/24/ukraine-war-mental-health-russia-invasion-children [Accessed 24 February 2025]
4. Matsyshyn VS, Kravchenko AM, Chaikovsky IA et al. Heart rate variability as an objective criterion for the psycho-emotional state of combatants. Wiad Lek. 2023;76(10):2212-2218. doi: 10.36740/WLek202310113. DOI
5. Sharypanov AV, Vyshnevskyy VV, Kalmykov VG, Kizub LA. Svidotstvo pro reyestratsiyu avtorskoho prava No. 98944. Komp'yuterna prohrama «Avtomatyzovana tekhnolohiya upravlinnya dykhannyam «Harmony» [Certificate of copyright registration No. 98944. Computer program «Automated breathing control technology «Harmony»]. https://sis.nipo.gov.ua/uk/search/detail/1758287/ [Accessed 11 February 2025] (Ukrainian)
6. Chaikovskyy IA, Frolov YuO, Vasylyev VE, Dordiyenko MO. Svidotstvo pro reyestratsiyu avtorskoho prava No. 47857. Komp'yuterna prohrama «Reyestratsiya ta analiz malokanal'nykh EKG syhnaliv» [Certificate of copyright registration No. 47857. Computer program «Registration and analysis of low-channel ECG signals»]. https://sis.nipo.gov.ua/uk/search/detail/1527245/ [Accessed 11 February 2025] (Ukrainian)
7. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation. 1996;93(5):1043–1065. doi: 10.1161/01.CIR.93.5.1043. DOI
8. Yabluchanskiy NI, Martynenko AV, Isayeva AS. Osnovy prakticheskogo primeneniya neinvazivnoy tekhnologii issledovaniya regulyatornykh sistem cheloveka [Fundamentals of practical application of non-invasive technology for studying human regulatory systems]. Kharkiv: Osnova; 2000. (Russian)
9. Bandelow B, Allgulander C, Baldwin DS et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – Version 3. Part II: OCD and PTSD. World J Biol Psychiatry. 2023;24(2):118–134. doi: 10.1080/15622975.2022.2086296. DOI
10. Karatzias T, Murphy P, Cloitre M et al. Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. Psychol Med. 2019;49(11):1761-1775. doi: 10.1017/S0033291719000436. DOI
11. Hoppen TH, Morina N. Psychological treatments for post-traumatic stress disorder in adults: a network meta-analysis. Psychol Med. 2021;51(8):1260–1270. doi: 10.1017/S0033291720000070. DOI
12. Lewis C, Roberts NP, Andrew M et al. Psychological therapies for post-traumatic stress disorder in adults: systematic review and meta-analysis. Eur J Psychotraumatol. 2020;11(1):1729633. doi: 10.1080/20008198.2020.1729633. DOI

13. Nidich SI, Mills PJ, Rainforth M et al. Non-trauma-focused meditation versus exposure therapy in veterans with post-traumatic stress disorder: a randomized controlled trial. Lancet Psychiatry. 2018;5(12):975–986. doi: 10.1016/S2215-0366(18)30384-5. DOI
14. Bellehsen M, Stoycheva V, Cohen BH, Nidich S. A pilot randomized controlled trial of Transcendental Meditation as treatment for posttraumatic stress disorder in veterans. J Trauma Stress. 2022;35(1):22–31. doi: 10.1002/jts.22665. DOI
15. VA/DOD Clinical Practice Guidelines. Management of Posttraumatic Stress Disorder and Acute Stress Disorder 2023. https://www.healthquality.va.gov/guidelines/mh/ptsd/ [Accessed 11 February 2025]
16. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales. 2nd Ed. Sydney: Psychology Foundation. 1995.
17. Nakaz Ministerstva okhorony zdorov'ya Ukrayiny 23.02.2016 121. Unifikovanyi klinichnyi protokol pervynnoi, vtorynnoi (spetsializovanoi) ta tretynnoi (vysokospetsializovanoi) medychnoyi dopomohy "Reaktsiya na vazhkyi stres ta rozlady adaptatsiyi. Posttravmatychnyi stresovyi rozlad". [Order of the Ministry of Health of Ukraine No. 121 dated February 23, 2016. Unified Clinical Protocol for Primary, Secondary (Specialized), and Tertiary (Highly Specialized) Medical Care "Response to Severe Stress and Adjustment Disorders. Post-Traumatic Stress Disorder."]. https://www.dec.gov.ua/wp-content/uploads/2019/11/2016_121_ykpmd_ptsr.pdf [Accessed 10 March 2024] (Ukrainian)
18. Baevsky RM, Bennett BS, Bungo MW et al. Adaptive responses of the cardiovascular system to prolonged spaceflight conditions: assessment with Holter monitoring. J Cardiovasc Diagn Proced. 1997;14(2):53-57.
19. Quendler E, Trieb K, Nimmerichter A. Validation of automated detection of physical and mental stress during work in a Hühnermobil 225. Ann Agric Environ Med. 2017;24(2):329–331. doi: 10.5604/12321966.1235183. DOI
20. Huizinga JD, Chen JH, Hussain A et al. Determining autonomic sympathetic tone and reactivity using Baevsky's stress index. Am J Physiol Regul Integr Comp Physiol. 2025;328(5):R562–577. doi: 10.1152/ajpregu.00243.2024. DOI
21. Khan MSI, Prasad R, Rabeh N et al. Baevsky's Stress Index as a Sensitive Indicator for Biofeedback Efficacy in Medical Students: a Pilot Study. Annu Int Conf IEEE Eng Med Biol Soc. 2024;2024:1–4. doi: 10.1109/EMBC53108.2024.10782708. DOI
22. Minassian A, Maihofer AX, Baker DG et al. Association of predeployment heart rate variability with risk of postdeployment posttraumatic stress disorder in active-duty Marines. JAMA Psychiatry. 2015;72(10):979–986. doi: 10.1001/jamapsychiatry.2015.0922. DOI

The NGO Impact Force contributed to the provision of diagnostic medical equipment and the information campaign of the ReSTART Mindset project, and had no influence on the research process or data interpretation.
The research was partially supported by the National Research Foundation of Ukraine,grant No. 2023.04/0094 "Development of technology for objective monitoring of functional capabilities and stress of military personnel based on miniature electrocardiographs and machine learning", which had no influence on the research process or data interpretation.

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Viktor S. Matsyshyn
State Institution of Science
«Center of innovative healthcare technologies»
5 Verkhnya St., 01014 Kyiv, Ukraine
e-mail: vmatsyshyn@gmail.com

ORCID AND CONTRIBUTIONSHIP
Viktor S. Matsyshyn: 0000-0003-4356-8758 A B C D F
Kostiantyn O. Apykhtin: 0000-0003-0840-2269 A B C D
Anatolii M. Kravchenko: 0000-0001-6863-0197 A D E F
Nataliia M. Ovodiuk: 0000-0002-1218-2417 B C D
Illya A. Chaikovsky: 0000-0002-4152-0331 C E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 12.02.2025
ACCEPTED: 02.06.2025

ORIGINAL ARTICLE

CONTENTS

Comparison of high-frequency techniques in ablation of great saphenous vein for varicose vein treatment

Roman V. Radysh[1, 2, 3], Vasyl V. Shaprynskyi[1]

[1]STATE INSTITUTION OF SCIENCE «CENTRE OF INNOVATIVE HEALTHCARE TECHNOLOGIES» STATE ADMINISTRATIVE DEPARTMENT, KYIV, UKRAINE

[2]LVIV REGIONAL CLINICAL HOSPITAL, LVIV, UKRAINE

[3]CLINIC FOR VASCULAR SURGERY AND PHLEBOLOGY «REVASCO», LVIV, UKRAINE

ABSTRACT

Aim: To evaluate the outcomes of patients who underwent two different high-frequency techniques of varicose vein endovenous ablation in the great saphenous vein (GSV) region (radiofrequency ablation [RFA] or high-frequency endovenous welding [HFEW]), and to find out the options to improve long-term results.

Materials and Methods: The retrospective study enrolled 120 patients with primary varicose veins in the GSV region with CEAP stages C2–C6, treated in two private centers and operated on by a single operator from 2019 to 2021. The enrolled sample was subdivided into RFA (VNUS ClosureFast [n=58]) and HFEW ("SVARMED", Ukraine [n=62]) groups. Primary (such as occlusion rates) and secondary outcomes (such as postoperative pain [by VAS scale], complications, and recurrence rates) were assessed at 7 days, and at 3, 6, and 12 months postprocedurally.

Results: Both RFA and HFEW techniques showed high occlusion rates at 12 months postoperatively (96% and 97%, respectively [p=1,000]). The adverse events and perioperative complication rates were low and comparable between the two studied groups. Recurrence of varicose veins at the 12-month follow-up was numerically, but non-significantly, higher in the RFA group compared to HFEW (total: 14% vs. 6%, respectively [p=0,230]; junction source: 10% vs. 3%, respectively [p=0,154]).

Conclusions: Ablation of the GSV in patients with varicose vein disease by RFA and HFEW showed comparable early and midterm results with high occlusion rates at 12 months postoperatively. Recurrences in the RFA group, being numerically higher compared to the HFEW group, were primarily caused by new reflux coming from the femoral junction. HFEW requires further research for technical improvement and widespread implementation in practice.

KEY WORDS: varicose vein, endovenous welding, radiofrequency ablation

Wiad Lek. 2025;78(6):1054-1058. doi: 10.36740/WLek/207364 DOI

INTRODUCTION

Chronic venous disease and varicose veins are a major problem in healthcare systems all over the world. According to various data, the disease is widespread and affects up to 40–90% of the population, with a higher predominance among women [1]. Chronic venous insufficiency has a major impact on social life, quality of life, and healthcare systems. Various symptoms, ranging from small cosmetic defects and discomfort to pain, swelling, and trophic changes, including venous ulcers, affect quality of life and could lead to potential complications such as thrombosis, bleeding, and temporary disability. In the last two decades, many different techniques, including endovenous laser coagulation, radiofrequency ablation (RFA), high-frequency endovenous welding (HFEW), foam sclero-obliteration, endovenous mechanochemical obliteration, and adhesive methods of vein closure (glue), were developed to treat varicose veins [2]. All of them are reliable, with high technical success and occlusion rates, as well as symptomatic regression and healing of venous ulcers. Although primary occlusion rates are high for all techniques, the chronic character of varicose vein disease and often complicated anatomy lead to mid- and long-term recurrences, which are a major problem [3].

AIM

The study aim was to evaluate the outcomes of the patients who underwent RFA and HFEW for the treatment of primary varicose veins in the great saphenous vein (GSV) region, and to find out the options to improve long-term results.

MATERIALS AND METHODS

The retrospective analysis was performed by assessing the data from 120 patients (mean age [mean ± stan-

dard deviation] 40±17 years; 39 [32,5 %] males and 81 [67,5 %] females), who underwent RFA or HFEW for treatment of varicose vein disease in GSV region, being enrolled in two private centers from 2019 to 2021. Inclusion criteria were as follows: patients with incompetent GSV with reflux more than 500 ms, GSV diameter less than 2 cm, CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classes C2-C6; patient age more than 18 years.

Exclusion criteria were applied to patients who underwent previous venous surgery, patients with recurrent varicose veins, with history of deep vein thrombosis (DVT) or superficial thrombophlebitis, with known intake of anticoagulation medication, with lower extremity infections and known thrombophilia, pregnancy, chronic peripheral arterial disease, lymphedema of lower limbs, history of narcotic addiction, and intravenous narcotic use, patients with chronic venous disease on both legs who underwent simultaneous procedure on GSVs bilaterally.

Among 120 patients, the distribution of CEAP stages was as follows: C2 – 40 (33,3 %); C3 – 54 (45,0 %); C4 – 15 (12,5 %); C5 – 8 (6,7 %); and C6 – 3 (2,5 %) cases. The enrolled sample was subdivided into two study groups: group 1 consisted of 58 (48,3 %) patients treated with RFA (VNUS ClosureFast); group 2 included 62 (51,7 %) patients treated with HFEW («SVARMED», Ukraine).

Preoperative diagnostics included analysis of typical symptoms of varicose vein disease, physical examination to assess the presence and spread of varicosities on the legs, as well as ultrasound (US) duplex scan to assess retrograde blood flow in the GSV. Those GSVs with retrograde blood flow of more than 500 ms in the standing position after manual compression of the calf were regarded as insufficient. Preoperative mapping of varicosities and reflux in- and outflow points, as well as puncture sites, was performed before the operation in the standing position. All the patients signed informed consent forms and were given chronic venous insufficiency questionnaires (CIVIQ-20) to fill out before the operation. The study included patients operated on by a single operator, a vascular surgeon experienced in endovenous procedures. Postoperative therapy included micronized flavonoid fraction medication for a month and nonsteroidal anti-inflammatory drugs for three days. Per protocol, an elastic compression bandage was applied directly after the procedure, as well as compression stockings for one day. Class II graduated elastic compression stockings were applied for three weeks. Procedures were performed in the reverse Trendelenburg position. Patients were operated on under local anesthesia with mild sedation in the supine or prone position. In most cases, the GSV was punctured 5–10 cm below the knee under US control, followed by introducer (5F or 9F, depending on the technique) insertion. The catheter was inserted and positioned according to the instruction for use recommendations (2.0 cm from the femoral junction for RFA, and just below the junction for HFEW [zero zone]). Catheter insertion was followed by US-guided application of tumescent anesthesia (cooled modified Klein's solution) along the vein.

Calf and thigh tributes were removed in the Varady technique through microincisions under local anesthesia as well. Perforators were not treated in the primary setting. Fourteen patients in both groups underwent additional sclerotherapy intraoperatively using 0.5% polidocanol for the treatment of telangiectasias. All patients were discharged home directly after the procedure with a recommendation of 30 to 60 minutes of intensive walking.

Postoperative controls were performed on the next day, in seven days, and at 3, 6, and 12 months postoperatively. During the check-ups, physical examination and duplex US were performed to assess occlusion rates of the GSV, rates of recanalization, and reflux.

Patients completed the CIVIQ-20 questionnaire and Visual Analogue Scale (VAS) to measure pain intensity at 3, 6, and 12 months postoperatively. The VAS consisted of a 10 cm line, with two endpoints representing 0 ("no pain") and 10 ("pain as bad as it could possibly be").

The data were analyzed using MedCalc v. 23.2.1 (MedCalc Software Ltd., Belgium). The continuous variables were presented as mean ± standard deviation. The qualitative variables were presented as absolute and relative (%) frequency. Two independent samples were compared using Student's t-test (for continuous variables), and $\chi 2$ or Fisher's exact tests (for qualitative variables). A p-value <0.05 was considered statistically significant.

ETHICS

The research was carried out in adherence to the core principles outlined in the Council of Europe Convention on Human Rights and Biomedicine, the Declaration of Helsinki by the World Medical Association on ethical guidelines for medical research involving human participants, and the relevant regulations of Ukraine. The study protocol received an approval from the local ethics committee. Considering the retrospective design of current study, the informed patient`s consent was not required.

RESULTS

The study groups were comparable in the majority of baseline characteristics, as presented in Table 1.

Table 1. Baseline characteristics of patients in the studied groups

Parameters			Group 1 N=58	Group 2 N=62	p
Age, years			38±17	41±18	0,368
Sex, n (%)	Men		17 (29)	22 (34)	0,560
	Women		41 (71)	40 (65)	
Treated veins diameter, mm			8±3	10±3	<0,001
CEAP stage, n (%)		C2	22 (38)	18 (29)	0,577
C3		23 (40)	31 (50)		
C4		6 (10)	9 (14)		
C5		5 (9)	3 (5)		
C6		2 (3)	1 (2)		

Table 2. The endpoints, adverse events and complications in the studied groups

Parameters	Group 1 N=58	Group 2 N=62	p
Adverse events and perioperative complications			
EHIT type 2, n (%)	0	3 (5)	0,245
Temporary paresthesia and hypoesthesia, n (%)	5 (9)	7 (11)	0,764
Induration and temporary pigmentation, n (%)	7 (12)	7 (11)	1,000
Postoperative pain (VAS score ≥3), n (%)	6 (10)	6 (10)	1,000
Bruising, n (%)	21 (36)	24 (39)	0,851
Primary endpoints (at 12-month follow-up)			
Partial recanalization, n (%)	2 (4)	2 (3)	1,000
Varicose vein recurrence in total, n (%)	8 (14)	4 (6)	0,230
Varicose vein recurrence, femoral perforator source, n (%)	2 (4)	2 (3)	1,000
Varicose vein recurrence, junction source, n (%)	6 (10)	2 (3)	0,154

Note: EHIT – endothermal heat-induced thrombosis

Although the treated vein diameter was larger in group 2, this was not significant with regard to clinical presentation but could potentially interfere with occlusion rates.

The mean procedure time was comparable in both groups: 46±13 vs. 48±15 in groups 1 and 2, respectively (p=0.453). All operations showed a 100% technical success rate with no operative complications. No postoperative surgical complications, such as skin burns, bleeding, pulmonary embolism, etc., were observed.

The data on patients` outcomes are presented in Table 2.

Forty-five patients presented with mild local bruising due to performed mini-phlebectomies: 21 (36%) and 24 (39%) in groups 1 and 2, respectively (p=0.851). Twelve patients reported postoperative pain with a VAS score ≥3, with no difference between groups (6 [10%] patients in both groups [p=1.000]). Twelve patients developed temporary paresthesia and hypoesthesia on the calf (5 [9%] and 7 [11%] in groups 1 and 2, respectively [p=0.764]), which disappeared during the first month of follow-up. Induration and temporary pigmentation along the epifascial thigh tributaries of GSV were noted in 7 patients in both groups (12% and 11%, respectively [p=1.000]).

No major thrombotic postoperative complications, including DVT or pulmonary embolism, were noticed in the study groups. Endothermal heat-induced thrombosis (EHIT) type 2 was observed in 3 patients (5%) in group 2 with no need for further treatment. No cases of study equipment failure were noticed. Occlusion rates of the GSV trunk as a primary endpoint were 100% in both groups up to 6 months of follow-up. The 12-month assessment showed partial recanalization in 2 (4%) and 2 (3%) in groups 1 and 2, respectively (p=1.000). We observed varicose vein recurrence in both groups at 12-month follow-up, including 4 cases of thigh perforator recurrence (2 [4%] and 2 [3%] patients in groups 1 and 2, respectively [p=1.000]), and 8 cases of junction recurrences (6 [10%] and 2 [3%] patients, respectively [p=0.154]). Overall, the RFA group demonstrated a numerically, but non-significantly, higher frequency of varicose vein recurrence events compared to the

HFEW group (8 [14%] vs. 4 [6%] patients, respectively [p=0.230]).

DISCUSSION

Minimally invasive percutaneous methods of treatment for varicose vein disease over the last 20 years have shown excellent results due to high trunk occlusion rates, low complication rates, a well-established safety profile, and low early recurrence rates. Therefore, they are considered the gold standard for varicose vein treatment, replacing open surgery, including high ligation and stripping [4]. In fact, many different thermal minimally invasive techniques have been developed in recent years, including endovenous laser ablation, RFA, HFEW, as well as non-thermal techniques, such as mechanochemical or cyanoacrylate ablation and sclerotherapy. According to available data and studies described in many publications comparing thermal and non-thermal techniques, in most cases, non-thermal techniques had slightly worse technical results in closing veins due to existing recanalization [5, 6]. Nevertheless, clinical results, patient satisfaction rates, and quality of life were at the same level as in patients treated with thermal methods [7]. Although GSV occlusion rates are taken as the primary endpoint of most studies, the most important issue is varicose vein recurrence and symptoms of chronic venous insufficiency in long-term follow-up [8].

Thermal ablation aims to achieve permanent vein lumen occlusion through thermal energy application on the wall, which can be effective depending on the amount of energy absorbed [9].

Endovenous RFA to treat the incompetent GSV (VNUS ClosureFast) is a catheter-based device that delivers optimal thermal energy via an electrode with a temperature feedback loop using a thermocouple, which allows it to be applied in a controlled manner. This ensures transmural heating of the vein wall, minimizing thermal spread to adjacent tissues. According to many studies, the satisfaction rate of RFA for GSV reaches 95%, and the frequency of DVT rarely exceeds 1% [10].

The HFEW technique («SVARMED», Ukraine) works through a bipolar configuration electrode with a diameter of up to 3 mm and a length of up to 5 cm. The operating cycle of the welding is performed at a voltage from 10 to 100 V and an AC frequency from 50 to 500 kHz, with modulation from 0.1 to 250 kHz and tissue resistance of 0.1 to 1000 Ohms. The cycle duration ranges from 5 to 12 seconds [11]. Resistance, instead of a temperature-based self-regulating principle, governs the exposure of the working electrode surface in the vein lumen, allowing dose- and time-independent heating of the vein wall. This could lead to better efficacy, convenience, and a better safety profile [12].

Our experience allows us to obtain comparative results with available series of studies. The sample size and the retrospective nature of the analysis could be potential limitations of our results. The same applies to the relatively low recurrence rate, which is insufficient for further analysis. Nevertheless, our results are acceptable and comparable with the presented series. A one-year follow-up, from our point of view, is not sufficient and may not reveal possible long-term results. Our data enable us to plan prospective studies to improve treatment outcomes.

CONCLUSIONS

High-frequency-based techniques, such as RFA and HFEW, are effective and reliable methods of varicose vein treatment in the GSV region. Although they show high occlusion rates and excellent early and midterm results, the late results (particularly recurrences) still remain an unresolved issue. The recurrences in the RFA group, being numerically but non-significantly higher compared to the HFEW group, were primarily caused by new reflux coming from the femoral junction. The modified HFEW technique, including the zero zone catheter positioning for endovenous crossectomy and adjunctive anterior accessory vein ablation in selected cases, could lead to better long-term results with fewer recurrences and needs further research.

REFERENCES

1. Marsden G, Perry M, Kelley K, Davies AH. Diagnosis and management of varicose veins in the legs: summary of NICE guidance. BMJ. 2013;347:f4279. doi: 10.1136/bmj.f4279. DOI
2. Siribumrungwong B, Wilasrusmee C, Orrapin S et al. Interventions for great saphenous vein reflux: network meta-analysis of randomized clinical trials. Br J Surg. 2021;108(3):244-255. doi: 10.1093/bjs/znaa101. DOI
3. Gloviczki P, Lawrence PF, Wasan SM et al. The 2022 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society clinical practice guidelines for the management of varicose veins of the lower extremities. Part I. Duplex Scanning and Treatment of Superficial Truncal Reflux: Endorsed by the Society for Vascular Medicine and the International Union of Phlebology. J Vasc Surg Venous Lymphat Disord. 2023;11(2):231-261.e6. doi: 10.1016/j.jvsv.2022.09.004. DOI

4. De Maeseneer MG, Kakkos SK, Aherne T et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. Eur J Vasc Endovasc Surg. 2022;63(2):184-267. doi: 10.1016/j.ejvs.2021.12.024. DOI
5. Shaprynskyi V, Shaprynskyi V, Semenenko N. Vykorystannia termichnykh ta netermichnykh metodyk khirurghichnoho likuvannia khvorykh iz pervynnym varykoznym rozshyrenniam ven nyzhnikh kintsivok stadii C2 [Termal and non-thermal methods of treatment of patients with primary varicose diseases of the lower limbs of stage C2]. Klinichna ta profilaktychna medytsyna. 2021;4(18):45-50. doi: 10.31612/2616-4868.4(18).2021.07. (Ukrainian) DOI
6. Ontario Health (Quality). Nonthermal Endovenous Procedures for Varicose Veins: A Health Technology Assessment. Ont Health Technol Assess Ser. 2021;21(8):1-188.
7. Ahmed H, Soliman M. Mechano-chemical endo-venous ablation of varicose veins with Flebogrif occlusion catheter. Med J Cairo Univ. 2019;87(9):3749-3754. doi: 10.21608/mjcu.2019.69943. DOI
8. Lane T, Bootun R, Dharmarajah B et al. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins - Final results of the Venefit versus Clarivein for varicose veins trial. Phlebology. 2017;32(2):89-98. doi: 10.1177/0268355516651026. DOI
9. Van den Bos RR, de Maeseneer MMG. Endovenous thermal ablation for varicose veins: Strengths and weaknesses. Phlebolymphology. 2012:19(4):163-169.
10. Togola B, Laurent B, Bengaly B et al. VNUS ClosureFAST Radiofrequency of the Great Saphenous Vein for Superficial Venous Insufficiency: Experience of the CH of Cholet in France. World Journal of Cardiovascular Surgery. 2021;11:43-50. doi: 10.4236/wjcs.2021.115007. DOI
11. Glagolieva A, Gerashchenko R, Kurmanskyi A et al. The efficiency of high-frequency endovenous welding for surgical treatment of acute ascending thrombophlebitis of the great saphenous vein. Health Prob Civil. 2020;14(2): 94-99. doi: 10.5114/hpc.2020.94100. DOI
12. Khodos VA, Melnychuk HO. Efektyvnist metodu endovenoznoho vysokochastotnoho elektrozvariuvannia v khirurhichnomu likuvanni khronichnykh zakhvioriuvan ven nyzhnikh kintsivok [The effectiveness of the endovenous high-frequency electric welding method in the surgical treatment of chronic venous diseases of the lower extremities]. Likars'ka sprava. 2024;2(1171):33–40. doi: 10.31640/LS-2024-2-04. DOI

The study was performed as a fragment of the Scientific Department of Minimally Invasive Surgery scientific project (State Institution of Science «Center of innovative healthcare technologies» State Administrative Department) «Optimization of approaches to providing specialized medical care for surgical patients using personalized anesthetic support» (state registration number 0125U000315; term: 2025-2029).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Roman V. Radysh
Centre of innovative healthcare technologies
5 Verkhnya St., Kyiv 01014, Ukraine
e-mail: roman.radysh@gmail.com

ORCID AND CONTRIBUTIONSHIP

Roman V. Radysh: 0009-0009-3694-4605 A B C D
Vasyl V. Shaprynskyi: 0000-0002-1437-7410 A B E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.01.2025
ACCEPTED: 22.05.2025

ORIGINAL ARTICLE

CONTENTS

Analysis of the impact of traumatic stress on the health of children and adolescents

Hanna O. Shlieienkova[1], Mykhailo M. Cherkashyn[1], Kostiantyn V. Voloshyn[1], Olga O. Rzhevska[1,2], Oksana M. Tsiura[1], Natalia S. Shevchenko[1]

[1]V.N. KARAZIN KHARKIV NATIONAL UNIVERSITY, KHARKIV, UKRAINE;

[2]PRIVATE INSTITUTION OF HIGHER EDUCATION «KYIV MEDICAL UNIVERSITY», KYIV, UKRAINE

ABSTRACT

Aim: To analyze the health status of children and adolescents depending on the severity of traumatic stress.

Materials and Methods: The study involved 105 children and adolescents (mean age [mean ± standard deviation] 11,3±2,7; 48 [45,7%] boys and 57 [54,3%] girls), who suffered to some extent from the Russian army's invasion of Ukraine. The respondents' mental and somatic states were assessed using the Child Traumatic Stress Scale – Pediatric Traumatic Stress Screening Tool (PTSST) and the Children's Somatic Symptoms Inventory (CSSI-24).

Results: According to the screening data on the PTSST, 42,9% of children presented with a moderate risk, and 40,0% with a high risk of developing post-traumatic stress reaction (PTSR) (83% in total). We revealed a trend towards an increase in the PTSST score with respect to the increase in the stress burden per participant. The PTSST score was comparable between children who remained in the fighting zone and those who left and live abroad. The CSSI-24 data suggested that 44,8% of children had somatic symptoms of high or moderate intensity. Gastrointestinal complaints were identified more often than others and had a pronounced degree of severity. A strong direct correlation was revealed between PTSST and CSSI-24 scores ($\rho=0,726$; $p<0,05$).

Conclusions: The mental state of children was characterized by the risk of developing PTSR in more than 80% of children. A strong direct correlation between the level of traumatic stress reaction and the severity of somatic complaints indicates a high risk of developing somatic diseases as a result of the stress experienced.

KEY WORDS: health status, traumatic stress, mental state

Wiad Lek. 2025;78(6):1059-1065. doi: 10.36740/WLek/207365 DOI

INTRODUCTION

After the invasion of Ukraine by Russian invaders, many families with children were forced to flee abroad or to relatively safe regions of Ukraine. More than 1.5 million children are among those who have left [1, 2]. Forced displacement puts adults and children at increased risk of somatic and mental disorders. Numerous international organizations are working to solve this problem, including the World Health Organization, which created the project «Health emergency in Ukraine and refugee-receiving and -hosting countries, stemming from the Russian Federation's aggression», which provides medical care to refugees in need [3]. At the same time, a large number of children and adolescents have remained and continue to live in the regions under constant attack and shelling by the occupiers.

The majority of the war-affected population has negative consequences from the impact of stress on mental health [4-6]. For example, according to German researchers, 45,0% of children who left Ukraine for Germany after the outbreak of war have clinically significant signs of post-traumatic stress reaction (PTSR) and need professional help [7-8]. In their publications, doctors from Israel point out that more than half of the children who were forced to move from the war zone have general mental health problems [9]. Among refugees who have moved to Poland, 73,0% of respondents have PTSR [10].

In addition, the current situation has a negative impact not only on the mental but also on the somatic health of children and adolescents [11-13]. It is known that stress has a negative impact on the functional state of many organs and systems, which, on the one hand, may be due to the direct influence of hormones and neurotransmitters on the function of a particular organ, and on the other hand, to changes that occur during PTSR [14, 15]. For example, according to some researchers, during PTSR, limbic instability and changes in the hypothalamic-pituitary-adrenal and sympathetic-adrenal medullary axes occur, which in turn affects neuroendocrine and immune functions and causes dysregulation of the autonomic nervous system [16].

These factors lead to complaints from the child's somatic state, which can be a manifestation of both a pure stress response and a manifestation of a functional or organic disease [17,18].

Given the continuing impact of stress on children and adolescents in Ukraine, there is a need for a detailed analysis of their mental and physical health.

AIM

The aim of the study was to analyze the health status of children and adolescents depending on the severity of traumatic stress.

MATERIALS AND METHODS

The multicenter study involved 105 children and adolescents aged 8 to 17 years (average age [mean ± standard deviation] 11,3 ± 2,7 years, of whom (relative frequency [%] ± standard error) 45,7 ± 4,9 % (n=48) were boys and 54,3 ± 4,9 % (n=57) were girls, who were affected to varying degrees by the Russian army's invasion of Ukraine.

We analyzed the social and demographic characteristics: city of residence of the child at the time of the research (the area where the shelling continues, a relatively safe region of Ukraine or the European Union [EU] countries); food and/or drinking water shortages experienced during the war; staying in a bomb shelter for more than three days; and prolonged separation from close family members (as well as the total number of influencing factors). At the time of the survey, 21,9 ± 4,0 % (23/105) lived in Ukraine in relatively safe regions; 30,5 ± 4,3 % (32/105) lived in regions of Ukraine where shelling continued; and 47,6 ± 4,9 % (50/105) lived in EU (Table 1).

To assess the mental status of the respondents, a screening for childhood traumatic stress was conducted using the Child Traumatic Stress Scale – Pediatric Traumatic Stress Screening Tool (PTSST), developed by researchers in Utah and widely used around the world [19]. This questionnaire allows us to assess the level of traumatic stress disorder in points. Thus, the total number of points in the range from 0 to 10 indicates a mild risk or no risk of PTSR, from 11 to 20 – a moderate risk, and ≥21 – a high risk of developing PTSR.

The CSSI-24 (Children's Somatic Symptoms Inventory) scale was used to assess somatic symptoms, which measures the severity of somatic symptoms experienced by children and adolescents. The CSSI-24 measures 24 common symptoms from 0 to 4 in a form that is easy for children or parents to use. According to clinical guidelines [20], the total CSSI-24 score should be interpreted as follows: <18 – low; 19-31 – moderate; and ≥32 – as high. In addition, the CSSI-24 scale, according to the authors' recommendations, allows the division of somatic complaints into four main groups: gastro-, cardio-, pain/weakness, and pseudo-neurological complaints [20].

In Ukraine, the survey was conducted in general schools after obtaining written consent from parents or guardians. In other countries (Great Britain, Germany), the survey was conducted in support centers for Ukrainian refugees.

The statistical data analysis was carried out by the use of Statistica v. 14.0 (TIBCO Software Inc., USA), IBM SPSS Statistics v. 27.0 (Armonk, NY: IBM Corp., USA) and EZR v. 1.68. Quantitative data were presented as M ± SD, where M – mean, SD – standard deviation; or Me (IQR), where Me – median, IQR – interquartile range (first and third quartiles). Qualitative data were presented as absolute and relative (%) frequency with a standard error. The quantitative characteristics of two independent samples were compared using the Mann-Whitney U test. The Kruskal-Wallis test was used to compare the quantitative characteristics of four independent samples, with the following a posterior comparison between the study groups using the Mann-Whitney U test (considering the Bonferroni correction). The correlation analysis was performed using Spearman's rank correlation coefficient (ρ). A p-value <0,05 was considered as statistically significant (considering the Bonferroni correction).

ETHICS

The authors adhered to the principles contained in the Declaration of Helsinki and its latest amendments. All the participants gave oral and written voluntary informed consent for examination, tests, treatment, operation, analgesia and data processing (up to 14 years of age, the consent was signed by parents, after 14 years of age – by children). The work with participants was prepared and carried out in accordance with the principles of bioethics. The permission to conduct the study and the study protocol were approved of by the bioethics committee of the V.N. Karazin Kharkiv National University.

RESULTS

According to the screening data on the Child Traumatic Stress Scale – Pediatric Traumatic Stress Screening Tool, the average PTSST score for the entire sample was 19 (14-22) points, of which 17,1±3,7 % (18/105) of children had a score of from 0 to 10 points, which corresponded to a mild degree of childhood traumatic

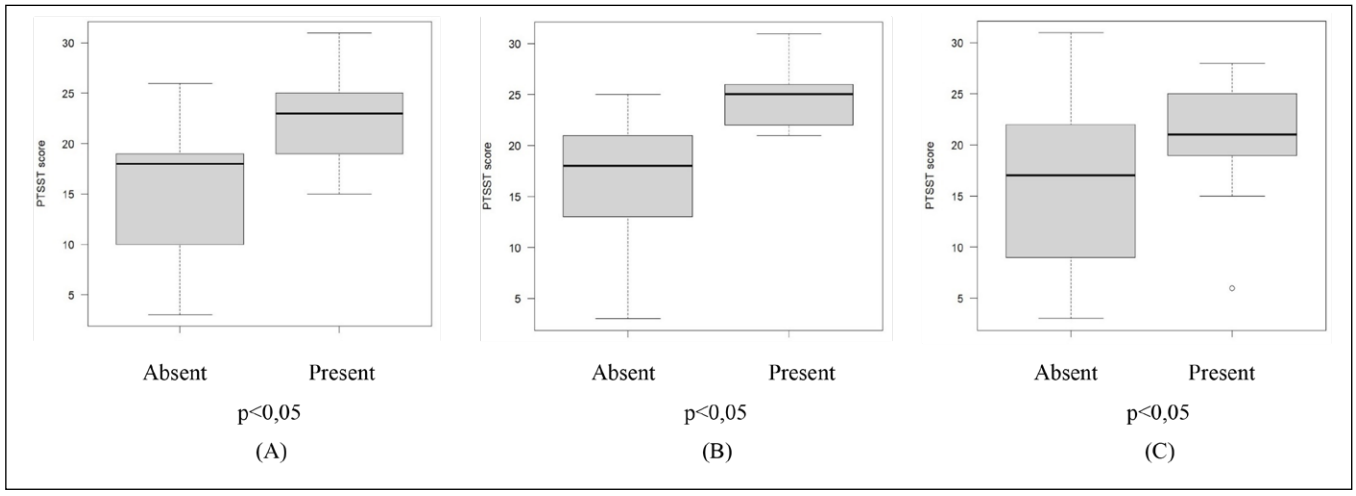

Fig. 1. The level of stress (by PTSST score) according to the presence of certain stressful factors among the enrolled children/adolescents (A – factor «Stayed in the bomb shelter for more than three days»; B – factor «Have experienced food and/or drinking water shortages»; C – factor «Witnessed the shelling and destruction of their hometown»; box-and-whisker plots)

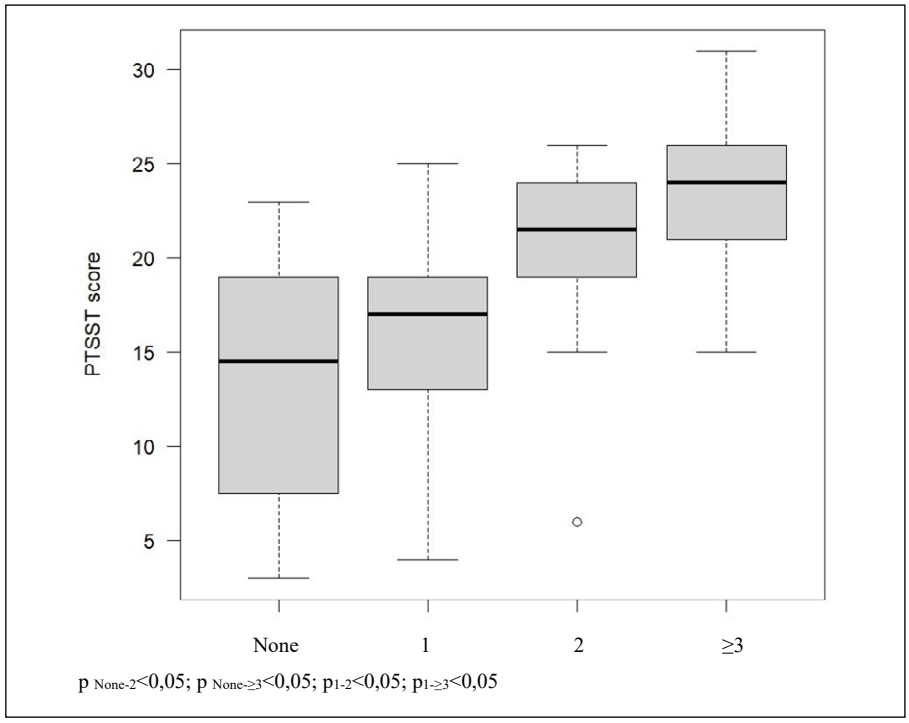

Fig. 2. The level of stress (by PTSST score) according to the number of stressful factors per participant (none, 1, 2 and ≥3; box-and-whisker plot). p_{None-2} – the significance of difference between «none» and «2» factors groups; $p_{None-\geq 3}$ – the significance of difference between «none» and «≥3» factors groups; p_{1-2} – the significance of difference between «1» and «2» factors groups; $p_{1-\geq 3}$ – the significance of difference between «1» and «≥3» factors groups. ρ = 0,633 (p<0,05 [n=105])

stress; 42,9 ± 4,8 % (45/105) from 11 to 20 points – an moderate degree of traumatic stress; 40,0 ± 4,8 % (42/105) above 21 points – a high degree of traumatic stress. Thus, more than 80 % of children were at risk of developing PTSR. In addition, boys and girls demonstrated the comparable PTSST score: 19 (13-22) vs. 19 (17-23), respectively (p=0,12).

When analyzing the relationship between the socio-demographic living conditions and traumatic stress indicators, we found that children who had been in the shelter for more than three days, who had experienced a shortage of food and/or drinking water, and those who witnessed the shelling and destruction of their hometown, had significantly higher levels of stress, as compared to their factor-free counterparts (Fig. 1). Moreover, we revealed a clear trend towards the rise of PTSST score with respect to the increase in the stressors burden per participant, indicating the growing need of psychological assistance at the background of stressful factors cumulation (Fig. 2).

When comparing PTSST score among children living in regions where shelling continues, children who have moved abroad, and children living in relatively safe regions of Ukraine, an interesting fact was revealed: the level of stress was almost the same for those who remained in the fighting zone and those who left and live abroad (19 [17-24] and 19 [15-23], respectively; p=0,96). At the same time, children living in relatively

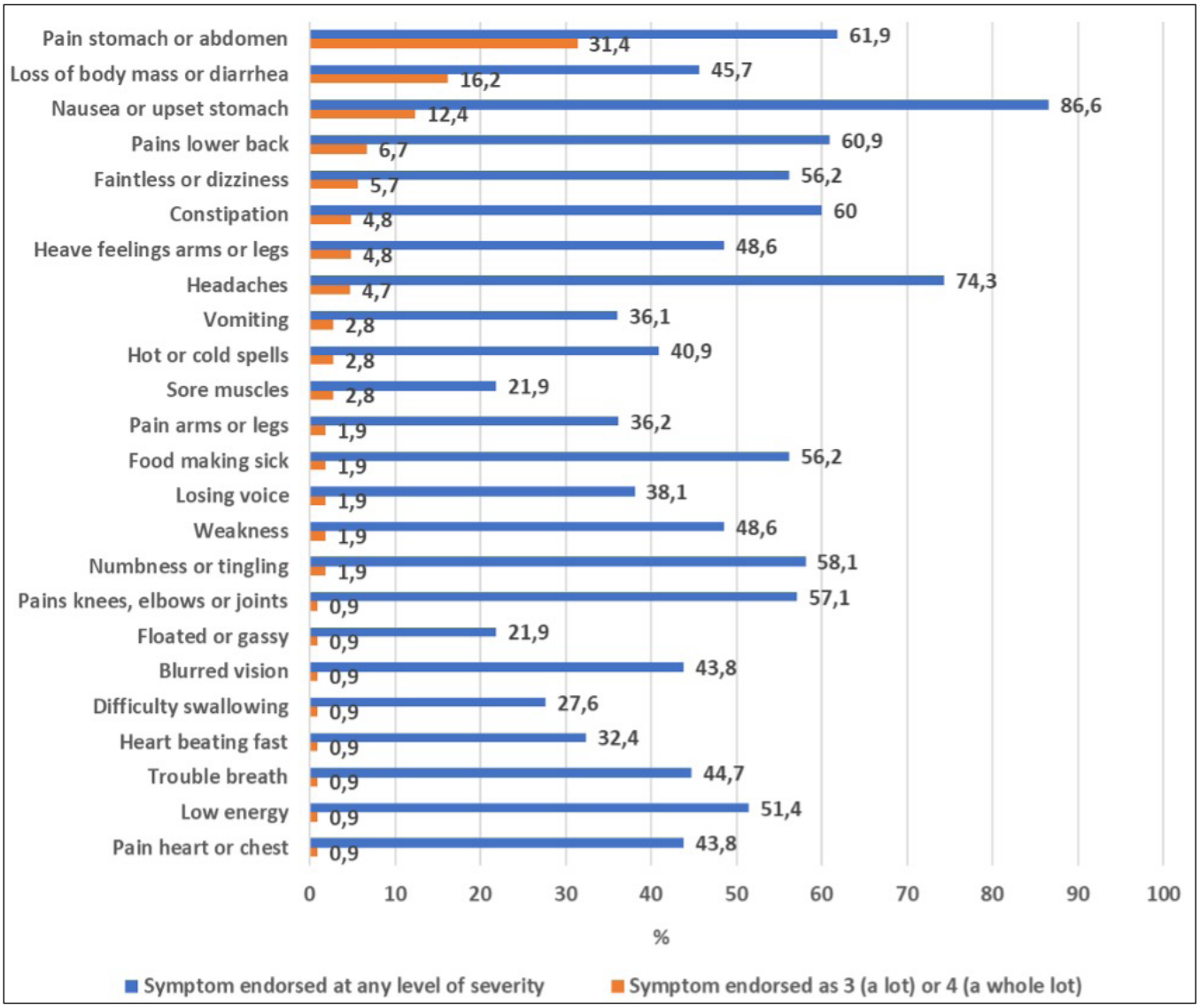

Fig. 3. The frequency of 24 CSSI-24 indicators at any level of severity, and with severity of 3-4 levels among the enrolled children (n=105)

Table 1. The social and demographic characteristics of the participants (n=105)

Parameters		n	% ± SE
Sex	Boys	48	45,7 ± 4,9
	Girls	57	54,3 ± 4,9
Have experienced food and/or drinking water shortages		18	17,1 ± 3,7
Stayed in the bomb shelter for more than three days		34	32,4 ± 4,6
Witnessed the shelling and destruction of their hometown		39	37,1 ± 4,7
Had a long separation from close family members		53	50,5 ± 4,9
The number of influencing factors per participant	None	28	26,7 ± 4,3
	1	30	28,6 ± 4,4
	2	30	28,6 ± 4,4
	3	14	13,3 ± 3,3
	4	3	2,8 ± 1,6
Living status	Reside in Ukraine in relatively safe regions	23	21,9 ± 4,0
	Reside in regions where shelling continues	32	30,5 ± 4,5
	After the outbreak of war left for the EU countries	50	47,6 ± 4,9

Note: SE – standard error

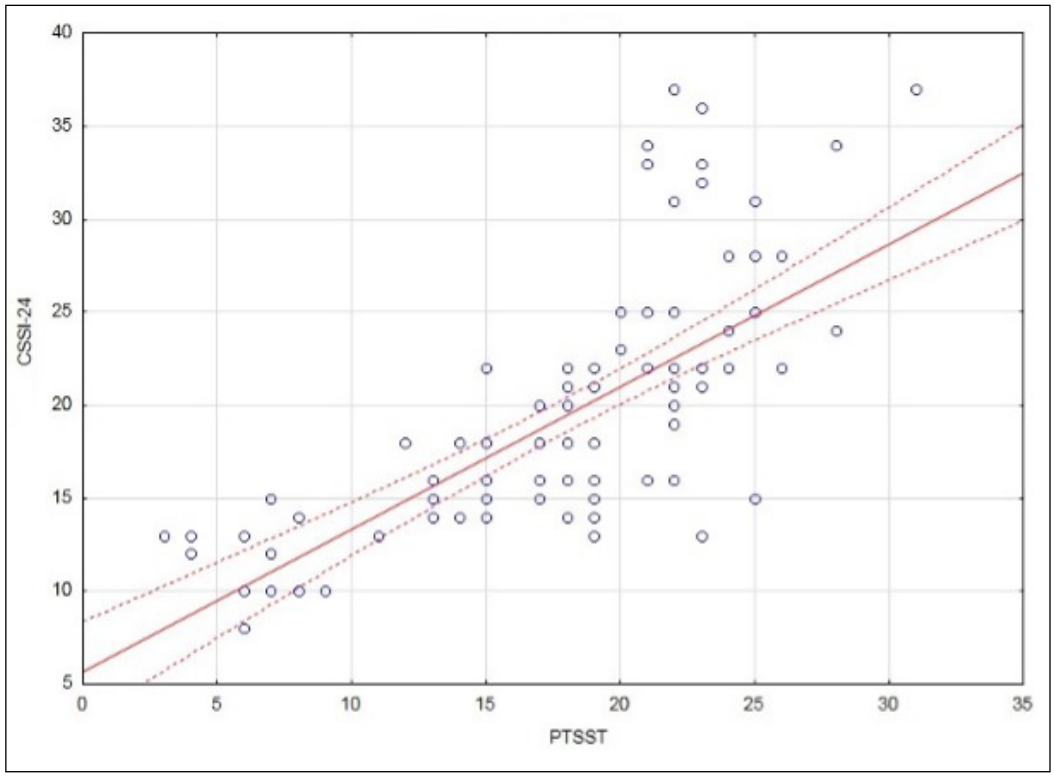

Fig. 4. The correlation between PTSST and CSSI-24 scores (dashed lines – 95 % confidence interval limits)

safe regions of Ukraine demonstrated significantly lower PTSST score (14 [8-19]) as compared to those living in regions with ongoing shelling ($p<0,05$), and a trend towards its lower value as opposed to those moving to EU countries ($p=0,06$).

So, the level of traumatic stress disorder was quite high both among children who went abroad due to the war and among children who did not leave their hometowns. This fact can be explained by the negative impact of forced migration, separation from loved ones and the difficulty of adapting to new conditions [3, 4].

The assessment of somatic symptoms using the CSSI-24 showed that most children had complaints of poor health. Thus, the mean value of the total CSSI-24 score for the entire sample was 20,0 ± 6,56. A high score (≥32) on the somatic symptoms assessment scale was reported by 19,1 ± 3,8 % (20/105) of respondents, a moderate (19-31) – 25,7 ± 4,3 % (27/105), and a low score (0-18) – 55,2 ± 4,9 % (58/105). There was no significant difference in the total CSSI-24 score between boys and girls. More detailed information on the presence and severity of each CSSI-24 indicator is provided in Fig. 3.

According to the results of the analysis, children noted gastrointestinal disorders more often than other somatic complaints during the questionnaire. Among the somatic complaints, pain in the stomach or abdomen, loss of body mass or diarrhea and nausea or upset stomach. Moreover, these complaints had a 3-4 degree of severity (Fig. 1). This fact can be explained by the existence of a close relationship between the functional state of the gastrointestinal tract and the psychological state. Thus, according to the literature, negative psychological states can affect immunity by changing the intestinal microbiome. The intestinal microbiota is important for human health, playing a specific role in the bidirectional communication between the gastrointestinal tract and the central nervous system. In turn, disturbances in the development of the intestinal microbiota can affect the state of the nervous system and potentially lead to adverse consequences for mental health [21].

In addition to the negative impact of stress on the intestinal microbiota, it is impossible to exclude the fact that changes in the usual diet and disturbances in the eating regimen affect the gastrointestinal tract of children who have suffered from military conflict.

The Spearman's correlation analysis revealed a direct strong correlation between PTSST and CSSI-24 scores ($\rho=0,726$; $p<0,05$ [n=105]) (Fig. 4).

Thus, children and adolescents with high scores on the PTSST scale had more numerous and severe somatic complaints, which can be explained both by the negative impact of pathophysiological mechanisms that are activated during stress on the somatic state of the child's body, and by the somatic manifestation of the stress reaction itself.

DISCUSSION

The analysis demonstrated that more than 80 % of the enrolled children and adolescents, who were af-

fected to some extent by the Russian army's invasion of Ukraine, had manifestations of traumatic stress reactions. The reaction of each child to stress is individual and depends on many factors, such as age, gender, economic status of the family, education of the parents, problems of integration into society in the country where the child is forced to live. According to many authors, the development of PTSR is due to many factors, namely negative "stressful experience", individual characteristics and adaptive capabilities of the child [2-3].

It is interesting to note that children, who were forced to leave their homes and went abroad, had almost the same level of PTSR as compared to children who remained in the regions with ongoing shelling. These observations coincide with the opinion of many authors about the negative impact on the mental state of internally displaced persons of such factors as difficult adaptation to a new environment, language barrier, lack of friends, disruption of the usual rhythm of life, limited circle of communication [7, 9, 10].

In addition, in the modern digital world, even children who left Ukraine at an early stage of the war and did not witness hostilities often continue to indirectly experience the conflict through extensive coverage in the media, social media, and communication with family members who remained in Ukraine.

According to the literature, traumatic stress reactions negatively affect the general health of children and adolescents and, if not treated in a timely manner, can lead to somatic diseases [11, 16, 17]. According to the results of our study, almost half of the children had moderate or pronounced somatic symptoms on the CSSI-24 scale.

A clear correlation has been established between the level of traumatic stress reaction and the severity of somatic complaints, which must be taken into account for the timely diagnosis and treatment of mental and somatic disorders.

CONCLUSIONS

1. A high risk of developing health disorders among children affected by the armed conflict in Ukraine has been identified. The mental condition of children was characterized by a risk of developing PTSR in 83 % of children, including a high degree of traumatic stress disorder in 40,0 % of respondents. The simultaneous influence of several negative factors on a child causes a cumulative effect and strengthens the manifestations of PTSR, which must be taken into account when developing tactics for providing psychological assistance to these children.
2. The analysis of the results of the PTSST scale showed a high level of traumatic stress reaction in children, regardless of their place of residence (staying in Ukraine in the regions of ongoing shelling or going abroad).
3. A strong direct correlation between the level of traumatic stress reaction and the severity of somatic complaints indicates a high risk of somatic diseases due to stress, which is the basis for additional medical examination of children at increased risk of developing PTSR.

REFERENCES

1. The Lancet Child Adolescent Health. Children: innocent victims of war in Ukraine. Lancet Child Adolesc Health. 2022;6(5):279. doi: 10.1016/S2352-4642(22)00102-X. DOI
2. Beyrer C. Assessing the Impact of Russia's Invasion of Ukraine on Health Services: Crimes of War. JAMA Health Forum. 2024;5(5):e240924. doi: 10.1001/jamahealthforum.2024.0924. DOI
3. Hodes M. Thinking about young refugees' mental health following the Russian invasion of Ukraine in 2022. Clin Child Psychol Psychiatry. 2023;28(1):3-14. doi: 10.1177/13591045221125639. DOI
4. Khailenko O, Bacon AM. Resilience, avoidant coping and post-traumatic stress symptoms among female Ukrainian refugees and internally displaced people. Int J Soc Psychiatry. 2024;70(6):1164-1174. doi: 10.1177/00207640241264662. DOI
5. Ben-Ezra M, Goodwin R, Leshem E et al. PTSD symptoms among civilians being displaced inside and outside the Ukraine during the 2022 Russian invasion. Psychiatry Res. 2023;320:115011. doi:10.1016/j.psychres.2022.115011. DOI
6. Johnson RJ, Antonaccio O, Botchkovar E et al. War trauma and PTSD in Ukraine's civilian population: comparing urban-dwelling to internally displaced persons. Soc Psychiatry Psychiatr Epidemiol. 2022;57(9):1807-1816. doi: 10.1007/s00127-021-02176-9 DOI
7. Bürgin D, Anagnostopoulos D, Board and Policy Division of ESCAP et al. Impact of war and forced displacement on children's mental health-multilevel, needs-oriented, and trauma-informed approaches. Eur Child Adolesc Psychiatry. 2022;31(6):845-853. doi: 10.1007/s00787-022-01974-z. DOI
8. Zasiekina L, Duchyminska T, Bifulco A et al. War trauma impacts in Ukrainian combat and civilian populations: Moral injury and associated mental health symptoms. Mil Psychol. 2024;36(5):555-566. doi: 10.1080/08995605.2023.2235256. DOI
9. Kapel Lev-Ari R, Aloni R, Ari AB. Children Fleeing War-Exploring the Mental Health of Refugee Children Arriving in Israel after the Ukraine 2022 Conflict. Child Abuse Negl. 2024;149:106608. doi: 10.1016/j.chiabu.2023.106608. DOI
10. Rizzi D, Ciuffo G, Sandoli G et al. Running Away from the War in Ukraine: The Impact on Mental Health of Internally Displaced Persons (IDPs) and Refugees in Transit in Poland. Int J Environ Res Public Health. 2022;19(24):16439. doi: 10.3390/ijerph192416439. DOI

11. Armitage R. War in Ukraine: the impacts on child health. Br J Gen Pract. 2022;72(719):272-273. doi: 10.3399/bjgp22X719621. DOI
12. Chudzicka-Czupała A, Hapon N, Chiang SK et al. Depression, anxiety and post-traumatic stress during the 2022 Russo-Ukrainian war, a comparison between populations in Poland, Ukraine, and Taiwan. Sci Rep. 2023;13(1):3602. doi: 10.1038/s41598-023-28729-3. DOI
13. Thabet AA, Abed Y, Vostanis P. Comorbidity of PTSD and depression among refugee children during war conflict. J Child Psychol Psychiatry. 2004;45(3):533-542. doi: 10.1111/j.1469-7610.2004.00243.x. DOI
14. Stone AL, Epstein I, Bruehl S et al. Twenty-year Outcomes of a Pediatric Chronic Abdominal Pain Cohort: Early Adulthood Health Status and Offspring Physical and Behavioral Health. J Pain. 2023;24(1):145-156. doi: 10.1016/j.jpain.2022.09.007. DOI
15. Lynch T, Davis SL, Johnson AH et al. Definitions, theories, and measurement of stress in children. J Pediatr Nurs. 2022;66:202-212. doi:10.1016/j.pedn.2022.07.008. DOI
16. Gupta MA. Review of somatic symptoms in post-traumatic stress disorder. Int Rev Psychiatry. 2013;25(1):86-99. doi:10.3109/09540261.2012.736367. DOI
17. Pinto RJ, Vieira de Castro M, Correia-Santos P et al. The mediating role of posttraumatic stress symptoms on somatization in adolescents: A two-wave longitudinal study. Psychol Trauma. 2023;15(1):S47-S54. doi: 10.1037/tra0001331. DOI
18. Lee RY, Oxford ML, Sonney J et al. The mediating role of anxiety/depression symptoms between adverse childhood experiences (ACEs) and somatic symptoms in adolescents. J Adolesc. 2022;94(2):133-147. doi: 10.1002/jad.12012. DOI
19. Keeshin B, Byrne K, Thorn B et al. Screening for Trauma in Pediatric Primary Care. Curr Psychiatry Rep. 2020;22(11):60. doi: 10.1007/s11920-020-01183-y. DOI
20. Walker LS, Beck JE, Garber J et al. Children's Somatization Inventory: psychometric properties of the revised form (CSI-24). J Pediatr Psychol. 2009;34(4):430-440. doi:10.1093/jpepsy/jsn093. DOI
21. Chang H, Perkins MH, Novaes LS et al. Stress-sensitive neural circuits change the gut microbiome via duodenal glands. Cell. 2024;187(19):5393-5412.e30. doi:10.1016/j.cell.2024.07.019. DOI

The work is a fragment of research work of the Department of pediatrics of V. N. Karazin Kharkiv National University "To investigate the features of the course of chronic diseases in adolescents in war and post-war conditions and to improve the system of their medical and psychological rehabilitation" (№ state registration 0119U102002; deadline: 2024-2026).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Hanna O. Shlieienkova

V.N. Karazin Kharkiv National University
52a Yuvileyny Ave., 61024 Kharkiv, Ukraine
e-mail: shleenkova@karazin.ua

ORCID AND CONTRIBUTIONSHIP

Hanna O. Shlieienkova: 0000-0001-9775-4324 A D
Oksana M. Tsiura: 0000-0001-8245-015X B
Natalia S. Shevchenko: 0000-0003-4407-6050 F
Kostiantyn V. Voloshyn: 0000-0001-8262-5159 C
Mykhailo M. Cherkashyn: 0009-0005-8163-5976 B
Olga O. Rzhevska: 0000-0002-6410-7769 E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 09.02.2025
ACCEPTED: 02.06.2025

ORIGINAL ARTICLE

CONTENTS

Prevalence and severity of depression in patients after cerebral stroke

Oleksandr M. Mishchenko[1], Maryna M. Mishchenko[2], Volodymyr I. Ponomaryov[1], Valeria V. Ponomaryova[1], Oleksandr O. Zlobin[1], Oleksandr M. Shevchenko[1], Tetyana V. Chastii[1]

[1]EDUCATIONAL AND SCIENTIFIC MEDICAL INSTITUTE OF THE NATIONAL TECHNICAL UNIVERSITY «KHARKIV POLYTECHNIC INSTITUTE», KHARKIV, UKRAINE

[2]KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

Aim: To analyze the prevalence and severity of depression in patients who suffered from cerebral stroke (CS).

Materials and Methods: A psychological study enrolled 300 patients after CS (main group [MG]: mean age [mean ± standard deviation] 56,7 ± 10,37 years; 134 [44,7%] males and 166 [55,3%] females) and 200 people without CS (control group [CG]: 57,2 ± 10,79 years; 64 [32,0%] males and 136 [68,0%] females). The levels of depression (LD) were assessed using the T.I. Balashova Depression Scale.

Results: The MG, as compared to the CG, demonstrated a higher depression score (52,6 ± 7,46 vs. 47,6 ± 6,88 points, respectively; $p < 0,001$) and had fewer patients without depression (35,7% vs. 68,0%, respectively; $p < 0,001$), as well as a higher frequency of mild depression (36,7% vs. 24,0%, respectively; $p = 0,003$) and subdepressive state (27,7% vs. 8,0%, respectively; $p < 0,001$). There were no significant associations between LD and factors such as age, sex, and dwelling in the MG. In contrast, CG males were more prevalent in the mild depression and subdepressive state categories compared to those free from depression. Also, mild depression in the CG was more frequently observed among urban dwellers than in the group without depression.

Conclusions: Patients who suffered from CS demonstrated a higher prevalence of more significant depressive disorders, namely mild depression and subdepression, compared to their CS-free counterparts.

KEY WORDS: cerebral stroke, depression, subdepressive state

Wiad Lek. 2025;78(6):1066-1070. doi: 10.36740/WLek/207366 DOI

INTRODUCTION

Many studies confirm that cerebral stroke (CS) is a global public health problem due to its significant medical and social consequences [1]. According to research, CS is a leading cause of morbidity, mortality, and disability in the global population [2–4], ranking third among the causes of death worldwide and accounting for more than 795 000 annual cases [5, 6]. CS is more common in low- and middle-income countries than in high-income countries [7]. More than 70% of deaths and 87% of disabilities caused by CS occur in low- and middle-income countries.

According to existing data, patients who have suffered a stroke experience motor, sensory, and communication deficits, as well as cognitive impairments [8], a low quality of life, and significant deterioration in both mental and physical health [9]. The consequences of these impairments primarily affect patients' social activity, provoking marked social isolation, which may lead to post-stroke depression and anxiety [10].

CS causes significant changes in a patient's socio-psychological orientation and personal psychological characteristics. This is directly determined by the nature of the pathology: a forced change in the individual's relationship with society, a substantial reduction in physical and social activity, the loss of numerous social contacts, and the disruption of the individual's social integration and environment. Such individuals often experience a form of "isolation" from their familiar social surroundings. These factors collectively provoke a transformation of the person's entire psychosocial sphere. As a result, various psychological disorders may develop, primarily characterised by depression, persistent low mood, anxiety, fears, obsessive focus on the illness, and worries about the future [11].

Thus, according to leading scientists, depressive manifestations are the most common mental symptoms that occur after CS and have negative consequences for the physical and mental health of affected individuals [11], which significantly reduces their quality of life [12].

Table 1. The demographic characteristics and levels of depression in the MG and CG according to the results of psychological testing

Parameters		MG N=300	CG N=200	p
Age, years		56,7±10,37	57,2±10,79	0,870
Sex, n (%)	Males	134 (44,7)	64 (32,0)	0,005
	Females	166 (55,3)	136 (68,0)	
Dwelling, n (%)	City	151 (50,3)	88 (44,0)	0,172
	Village	149 (49,7)	112 (56,0)	
Depression Scale, points		52,6±7,46	47,6±6,88	*<0,001*
LD, n (%)	Without depression$^{z/*}$	107 (35,7)	136 (68,0)	*<0,001*
	Mild depression$^{z/**}$	110 (36,7)	48 (24,0)	
	Subdepressive state$^{z/*}$	83 (27,7)	16 (8,0)	

Note: z – statistically significant difference by z-test (p<0,05); * – Fisher`s exact test: p<0,001; ** – Fisher`s exact test: p=0,003

Table 2. The demographic characteristics in the MG according to the results of psychological testing

Parameters		LD			p
		Without depression N=107	Mild depression N=110	Subdepressive state N=83	
Age, years, n (%)	<45	14 (13,1)	14 (12,7)	10 (12,0)	0,730
	46-55	26 (24,3)	36 (32,7)	25 (30,1)	
	≥56	67 (62,6)	60 (54,5)	48 (57,8)	
Sex, n (%)	Men	42 (39,3)	51 (46,4)	41 (49,4)	0,341
	Women	65 (60,7)	59 (53,6)	42 (50,6)	
Dwelling, n (%)	City	54 (50,5)	54 (49,1)	43 (51,8)	0,932
	Village	53 (49,5)	56 (50,9)	40 (48,2)	

Other researchers [13] have noted that depressive disorders are the most common and significantly burdensome complication following CS. It is known that post-stroke depression leads to a considerable impairment of patients' functional capabilities, cognitive abilities, and quality of life [11].

AIM

The aim of the study was to analyze the prevalence and severity of depression in patients suffered from CS.

MATERIALS AND METHODS

A single-centre cross-sectional study was conducted based on the results of a psychological assessment of 300 patients after CS (main group [MG]), who received rehabilitation services at the Clinical Sanatorium "Roshcha" of PJSC "Ukrprofozdorovnytsia", and 200 individuals without a history of CS (control group [CG]) in 2022–2023.

The MG included 134 (44,7%) males and 166 (55,3%) females, with a mean age (hereinafter – mean ± standard deviation) of 56,7 ± 10,37 years (n = 300). The CG included 64 (32,0%) males and 136 (68,0%) females, with a mean age of 57,2 ± 10,79 years (n = 200). There were 151 (50,3%) urban and 149 (49,7%) rural residents in the MG. In the CG, there were 88 (44,0%) urban and 112 (56,0%) rural residents.

The study fully complies with the fundamental bioethical principles set forth in the Council of Europe Convention on Human Rights and Biomedicine, the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, as well as in the relevant national regulations. The ethical protocol of this study was approved by the local ethics committee. Written informed consent was obtained from all study participants.

The inclusion criteria were as follows: reaching the age of 18 years, a history of CS (for MG), and consent to participate in the study. The exclusion criteria were: being underage (not reaching the age of 18), a history of CS (for CG), acute conditions, severe comorbidities, poor physical condition, pregnancy and lactation, alcoholism, and refusal to participate in the study.

The study of the levels of depression (LD) after CS was conducted using the Depression Scale by T.I. Balashova [12]. The results were evaluated as follows: up

Table 3. The demographic characteristics in the MG according to the results of psychological testing

Parameters		LD			p
		Without depression N=136	Mild depression N=48	Subdepressive state N=16	
Sex, n (%)	Men	12 (8,8)	42 (87,5)	10 (62,5)	p_{1-2}<0,001
	Women	124 (91,2)	6 (12,5)	6 (37,5)	p_{1-3}<0,001
Age, years, n (%)	<45	22 (16,2)	3 (6,3)	3 (18,8)	0,385
	46-55	35 (25,7)	17 (35,4)	5 (41,4)	
	≥56	79 (58,1)	28 (58,3)	8 (50,0)	
Dwelling, n (%)	City	50 (36,8)	31 (64,6)	7 (43,8)	p_{1-2}<0,001
	Village	86 (63,2)	17 (35,4)	9 (56,3)	

Note: p_{1-2} – statistically significant difference between the goups without depression and with mild depression; p_{1-3} – statistically significant difference between the goups without depression and with subdepressive state

to 50 points – a state without depression; from 50 to 59 points – mild depression of situational or neurotic genesis; from 60 to 69 points – subdepressive state or masked depression; more than 70 points – a real depressive state.

Statistical data analysis was performed using IBM SPSS Statistics v. 27.0 (Armonk, NY: IBM Corp., USA) and MedStat v. 5.2. Quantitative variables were presented as mean ± standard deviation, and qualitative ones as absolute and relative (%) frequency. To compare quantitative variables, we used the Mann-Whitney U-test. To compare qualitative variables, we used the χ^2 test (with post hoc Marascuilo-Liakh-Gurianov procedure for binary variables in three independent groups) and Fisher's exact test («2 × 2» tables). In the case of qualitative rank variables, and statistically significant differences between the study groups according to the χ^2 test, certain categories (ranks) were compared using the z-test. A 2-tailed p<0,05 was considered statistically significant.

RESULTS

The formed research groups were comparable in terms of age and residence. At the same time, females were more prevalent in CG (Table 1).

According to the data obtained from the Depression Scale by T.I. Balashova [12], a significant difference was observed between the studied groups both in terms of depression score and the prevalence of different LDs. In general, the MG demonstrated a higher depression score and was characterized by fewer patients without depression, as well as a higher frequency of mild depression and subdepressive state cases (Table 1).

There were no statistically significant associations between the degree of depression and such factors as age (under 45 years, 46-55 years and 56 years and over), sex and dwelling (Table 2).

At the same time, we revealed sex differences between the studied LDs in the CG. In particular, the group of people without depression was predominantly represented by females, who were more prevalent compared to the groups with mild depression and subdepressive state. In addition, males constituted the vast majority of cases in the mild depression group (Table 3).

Also, in the CG, a significant difference (in terms of indicators between the state of no depression and mild depression) in LD by place of residence was observed (Table 3). It was determined that the mild depression group was represented by urban residents to a greater extent than the group without depression. Correspondingly, freedom from depression was more frequently self-reported by rural dwellers, in contrast to people with mild depression.

DISCUSSION

Our data are fully consistent with similar studies conducted by other researchers. Thus, L. Liu et al. [11], based on the results of the literature data meta-analysis, determined that patients after a CS, which was accompanied by the development of early (within 3 months after the CS) depression, had a significant risk of maintaining this condition in the future. Quantitatively, two-thirds of patients had manifestations of depression within 1 year after CS. As a result, the researchers pointed out the need for continuous clinical monitoring of people with depression that developed after a CS.

Based on the results of a meta-analysis that included 77 studies on the prevalence of post-stroke depression, they determined that the overall prevalence of post-stroke depression was 27 % (95 % confidence interval [CI] 25-30 %) [11]. The prevalence of post-stroke depression was 24 % (95% CI 21-28 %) based on clinical interview and 29 % (95% CI 25-32 %) based on rating scales. The

study found that among patients who had a CS that was accompanied by the development of post-stroke depression within 3 months after the disease, 53 % (95 % CI 47-59 %) of patients had persistent depression, and 44 % (95 % CI 38-50 %) showed recovery. At the same time, the incidence of post-stroke depression in later periods (3 to 12 months) was 9 % (95 % CI 7-12 %). The cumulative incidence within 1 year after a CS was 38 % (95 % CI 33-43 %), the vast majority (71 % [95% CI 65-76 %]) of cases of post-stroke depression developed within 3 months after a stroke [11].

Other studies [14, 15] have also confirmed a significant prevalence of depression among patients after a stroke, in most cases determined by clinical interviewing [16].

In turn, C. Albus et al [17] confirmed that psychosocial factors such as low socioeconomic status, acute or chronic stress, depression or anxiety are significantly prevalent among cardiac patients and are associated with behavioral and biological risk factors that provoke an increased risk of cardiovascular disease (directly CS) and unfavorable disease outcome.

Thus, our results regarding the significant prevalence of post-stroke depressive manifestations were confirmed by other studies.

CONCLUSIONS

When determining the prevalence of depressive manifestations among patients after CS, a significantly higher prevalence of more severe depressive disorders was found compared to the CS-free controls. Patients who suffered from CS demonstrated a higher prevalence of mild depression and subdepression, in contrast to their CS-free counterparts.

REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990–2017: A Systematic Analysis for the Global Burden of Disease Study 2017. Lancet Lond. Engl. 2018;392:1789–1858. doi: 10.1016/S0140-6736(19)31047-5. DOI
2. Shuranova L, Vacková J, Rimárová K et al. Life after stroke and the key role of coordinated rehabilitation from the perspective of the stroke survivor families. Clinical and Preventive Medicine. 2024;6:44–50. doi: 10.31612/2616-4868.6.2024.06. DOI
3. Khan F, Chevidikunnan MF. Prevalence of Balance Impairment and Factors Associated with Balance among Patients with Stroke. A Cross Sectional Retrospective Case Control Study. Healthcare. 2021;9(3):320. doi: 10.3390/healthcare9030320. DOI
4. Hasan F, Gordon C, Wu D et al. Dynamic Prevalence of Sleep Disorders Following Stroke or Transient Ischemic Attack: Systematic Review and Meta-Analysis. Stroke. 2021;52(2):655–663. doi: 10.1161/STROKEAHA.120.029847. DOI
5. Zeng H, Chen J, Guo Y, Tan S. Prevalence and Risk Factors for Spasticity After Stroke: A Systematic Review and Meta-Analysis. Front Neurol. 2021;11:616097. doi: 10.3389/fneur.2020.616097. DOI
6. Virani S, Alonso A, Benjamin E et al. Heart disease and stroke statistics-2020 update: a report from the American heart association. Circulation. 2020;141:e139–596. doi: 10.1161/CIR.0000000000000746. DOI
7. Jones SP, Baqai K, Clegg A et al. Stroke in India: A systematic review of the incidence, prevalence, and case fatality. International Journal of Stroke. 2021;17(2):132–140. doi: 10.1177/17474930211027834. DOI
8. Kalashnikov VY, Stoyanov OM, Vastyanov RS et al. Otsinka stanu kohnityvnykh funktsii ta autorehuliatsii mozkovoho krovoobihu u patsiientiv z tserebrovaskuliarnoiu patolohiieiu na tli naslidkiv COVID-19. [Assessment of the status of cognitive functions and autoregulation of cerebral blood circulation in patients with cerebrovascular pathology against the consequences of COVID-19]. Klinichna ta profilaktychna medytsyna. 2024;6:58–63. doi: 10.31612/2616-4868.6.2024.08. (Ukrainian) DOI
9. Park J, Kim TH. The Effects of Balance and Gait Function on Quality of Life of Stroke Patients. NeuroRehabilitation. 2019;44:37–41. doi: 10.3233/NRE-182467. DOI
10. Mishchenko MM, Ognev VA, Mishchenko OM, Ponomaryov VI. Poshyrenist' tryvohy ta depresiyi u patsiyentiv pislya insul'tu holovnoho mozku. [Prevalence of anxiety and depression in patients after brain stroke]. Klinichna ta profilaktychna medytsyna. 2023;4:41-47. doi: 10.31612/2616-4868.4(26).2023.06. (Ukrainian) DOI
11. Liu L, Xu M, Marshall IJ et al. Prevalence and natural history of depression after stroke: A systematic review and meta-analysis of observational studies. PLoS Med. 2023;20(3):e1004200. doi: 10.1371/journal.pmed.1004200. DOI
12. Tangney JP, Baumeister RF, Boone AL. High Self-Control Predicts Good Adjustment, Less Pathology, Better Grades, and Interpersonal Success. Journal of Personality. 2004;72(2):271-324. doi: 10.1111/j.0022- 3506.2004.00263.x. DOI
13. Towfighi A, Ovbiagele B, El Husseini N et al. Poststroke Depression: A Scientific Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2017;48(2):e30–e43. doi: 10.1161/STR.0000000000000113. DOI
14. Uphoff EP, Newbould L, Walker I et al. A systematic review and meta-analysis of the prevalence of common mental disorders in people with non-communicable diseases in Bangladesh, India, and Pakistan. J Glob Health. 2019;9(2):020417. doi: 10.7189/jogh.09.020417. DOI

15. Dalvand S, Gheshlagh RG, Kurdi A. Prevalence of poststroke depression in iranian patients: A systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2018;14:3073–3080. doi: 10.2147/NDT.S184905. DOI
16. Mitchell AJ, Sheth B, Gill J et al. Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder. Gen Hosp Psychiatry. 2017;47:48–60. doi: 10.1016/j.genhosppsych.2017.04.001. DOI
17. Albus C, Waller C, Fritzsche K et al. Significance of psychosocial factors in cardiology: update 2018 : Position paper of the German Cardiac Society. Clin Res Cardiol. 2019;108(11):1175–1196. doi: 10.1007/s00392-019-01488-w. DOI

The work is a fragment of the research work of the Department of Public Health and Health Care Management of Kharkiv National Medical University of the Ministry of Health of Ukraine "Medical and Social Aspects of the Quality of Life of Young People with Overweight and Obesity" (State registration No. 0121U112044; term of implementation: 2023-2025).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Oleksandr M. Mishchenko
Kharkiv Polytechnic Institute
79 Hryhorii Skovoroda St, 61022, Kharkiv, Ukraine.
e-mail: alex_mischenko1976@ukr.net

ORCID AND CONTRIBUTIONSHIP

Oleksandr M. Mishchenko: 0000-0003-0043-2252 A B C D E F
Maryna M. Mishchenko: 0000-0002-4755-9384 A B C D E F
Volodymyr I. Ponomaryov: 0000-0003-2513-3187 D E F
Valeria V. Ponomaryova: 0000-0001-8623-0971 D E F
Oleksandr O. Zlobin: 0000-0002-8897-1017 D E F
Oleksandr M. Shevchenko: 0000-0002-1176-1687 D E F
Tetyana V. Chastii: 0000-0002-4745-5737 D E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 11.02.2025
ACCEPTED: 01.06.2025

ORIGINAL ARTICLE

CONTENTS

Adaptive educational technologies for overcoming the psycho-emotional barriers of higher education students in conditions of uncertainty

Lyudmyla L. Khoruzha[1], Mariia V. Bratko[1], Svitlana P. Palamar[1], Inna V. Leontieva[1], Marharyta K. Kozyr[1], Olena M. Tadeush[1], Maria V. Klepar[2]

[1]BORYS GRINCHENKO KYIV METROPOLITAN UNIVERSITY, KYIV, UKRAINE

[2]VASYL STEFANYK PRYKARPATTIA NATIONAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

Aim: To analyze the changes in the psycho-emotional state of participants in the educational process in Ukraine under wartime conditions and to identify effective educational technologies for overcoming psycho-emotional barriers.

Materials and Methods: The research applies both quantitative and qualitative analyses of data collected through surveys of 269 students and 100 faculty members at higher education institutions (totally, 369 respondents). The study is grounded in an interdisciplinary approach that combines psychological, pedagogical and sociological methods.

Results: The most common issues were anxiety, fear, and emotional exhaustion (222 individuals [60,2 %]). Problems with stress resilience were noted by 96 respondents (26,0 %), and traumatic wartime experiences were a challenge for 60 respondents (16,3 %). Feelings of physical danger were noted by 58 people (15,7 %). Misinformation and the information war were mentioned by 50 respondents (13,5 %). A total of 27 respondents (7,3 %) were forced to change their place of study, 12 (3,3 %) reported experiencing bullying, and 9 (2,4 %) reported discrimination based on origin or views. It has been found that the use of educational technologies such as trauma-informed approaches, coaching, mentoring, and mediation contributes to reducing stress levels and supporting psychological well-being.

Conclusions: In times of crisis, the educational process should focus not only on achieving academic outcomes but also on maintaining the psycho-emotional health of all participants. An integrated approach to learning, including adaptive educational technologies aimed at overcoming psycho-emotional barriers of higher education students, ensures the sustainability of the educational environment.

KEY WORDS: higher education, psycho-emotional barriers, educational technologies

Wiad Lek. 2025;78(6):1071-1077. doi: 10.36740/WLek/207367 DOI

INTRODUCTION

Modern education is significantly affected by global crises, including pandemics, armed conflicts, economic instability, and technological transformations. These factors create conditions of uncertainty that impact the psycho-emotional state of higher education students, complicate the learning process, and lower students' motivation and adaptability [1]. During the full-scale Russian invasion, the problems faced by participants in the educational process in Ukraine intensified, sometimes taking on threatening proportions [2].

One of the key strategies for overcoming psycho-emotional barriers is the implementation of adaptive educational technologies aimed at creating a safe learning environment, developing stress resilience, and increasing students' emotional intelligence. The use of coaching, mentoring, and mediation practices, as well as the principles of trauma-informed education and awareness-raising about mental health preservation and support, helps to minimize the impact of stressors and foster psychological flexibility among students.

AIM

The purpose of this article is to analyze and summarize modern educational technologies that support overcoming the psycho-emotional barriers of higher education students in uncertain conditions, taking into account the emotional needs of participants in the educational process as identified through the conducted survey.

MATERIALS AND METHODS

The main research tool was an online questionnaire, which included sections aimed at determining the level

of psycho-emotional stress, students' adaptation mechanisms, and the effectiveness of various educational technologies in overcoming psychological barriers. Participants in the survey included individuals from higher education institutions in major Ukrainian cities — Kyiv, Kharkiv, Lviv and Kherson — totaling 369 respondents, of whom 269 were students and 100 were faculty members, administrators, and support staff, categorized as other participants in the educational process.

ETHICS

The authors adhered to the Ethical Principles for Medical Research Involving Human Subjects outlined in the World Medical Association's Declaration of Helsinki and current Ukrainian regulations. The study protocol was approved by the local ethics committee. Participation in the survey was voluntary and anonymous.

RESULTS

A study conducted by the authors in autumn 2024 confirmed a significant deterioration in the psycho-emotional state of respondents from higher education institutions. The most common response to the question "How has your psycho-emotional state changed since the beginning of the full-scale invasion?" was "worsened," selected by 169 individuals (45,8 %). This indicates that nearly half of the respondents experienced negative changes in their psycho-emotional condition related to general stress and emotional strain. One in four survey participants (94 respondents [25,5 %]) chose "significantly worsened," confirming major psychological changes due to future uncertainty and increased stress factors. The response "hard to say" was selected by 73 respondents [19,8 %], suggesting that some participants may not be able to identify the impact of the war on their psycho-emotional state, possibly due to adaptation to conditions that have become familiar. The least common response was "no change," chosen by only 33 respondents (8,9 %). This indicates that only a small proportion of respondents did not feel any change in their emotional state, which may reflect psychological stability or an inability to perceive the effects of martial law. Overall, 71,3 % of respondents (the sum of "worsened" and "significantly worsened") reported a negative impact of the war on their psycho-emotional state, pointing to deep emotional distress in the educational environment under conditions of full-scale war.

Differences in responses between educators and students highlight varying levels of stress and adaptation, shaped by their roles and workload. Students more frequently experience uncertainty: 22,7 % selected "hard to say," indicating challenges in self-reflection. Educators and administrators emphasized a decline in emotional well-being (87 %), pointing to greater stress and responsibility. In a climate of uncertainty, the educational process cannot focus solely on academic outcomes. It is essential to support the psycho-emotional well-being of all participants. Education and, more specifically, the implementation of adaptive educational technologies should help overcome psycho-emotional barriers and preserve mental health. The integration of psychological support into the educational process not only enhances learning but also facilitates adaptation to change, ensuring resilience and comfort during wartime.

The identification of adaptive educational technologies that can effectively help overcome the psycho-emotional barriers of higher education students must be based on reliable empirical data. Therefore, let us analyze the results of the survey. Respondents' answers to the question "What psycho-emotional difficulties have you encountered at your educational institution during the war?" indicate a significant impact of the war on their well-being and the learning process (Fig. 1).

The most common issues were anxiety, fear, and emotional exhaustion (222 individuals [60,2 %]). A high level of stress was accompanied by uncertainty about the future (189 individuals [51,2 %]). A major challenge was the change in the learning format, which complicated adaptation for 150 respondents (40,7 %). A total of 102 people (27,6 %) faced difficulties due to a lack of resources (computers, internet access, educational materials), indicating limited access to education. Problems with stress resilience were noted by 96 respondents (26,0 %), financial difficulties by 86 (23,3 %), and traumatic wartime experiences were a challenge for 60 respondents (16,3 %). Feelings of physical danger were noted by 58 people (15,7 %). Misinformation and the information war were mentioned by 50 respondents (13,5 %), and conflicts in the educational environment by 41 (11,1 %). A total of 27 respondents (7,3 %) were forced to change their place of study, 12 (3,3 %) reported experiencing bullying, and 9 (2,4 %) reported discrimination based on origin or views.

A comparative analysis of the survey responses from students and other participants in the educational process revealed key differences in the perception of psycho-emotional difficulties during the war. The most widespread problems in both groups were anxiety, fear, and emotional exhaustion (62,8 % of students and 53 % of educators and administrators), as well as uncertainty about the future (47,6 % and 61 %, respectively). The

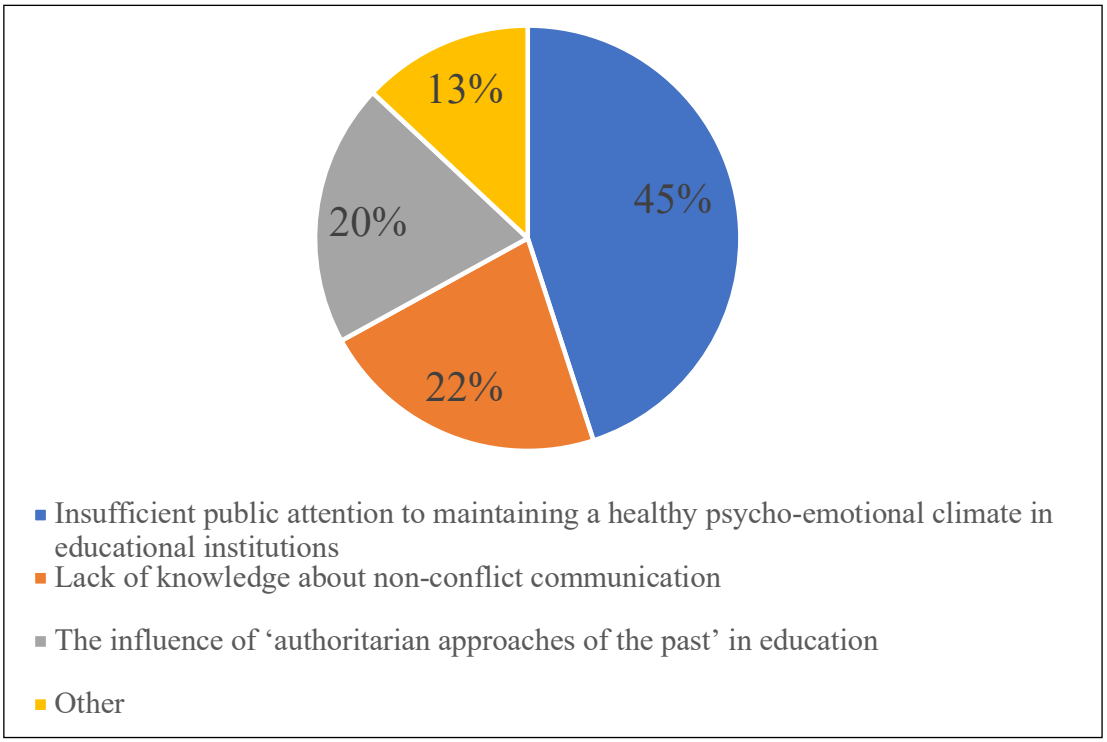

Fig. 1. The respondents' answers to the question «What psycho-emotional difficulties have you encountered at your educational institution during the war?» (%)

transition to online learning hindered adaptation for 36,8 % of students and 51 % of educators, indicating higher stress levels among adults due to the responsibility of organizing the learning process. Students were more likely to mention traumatic experiences, the impact of the information war, and bullying, while educators emphasized physical safety and anxiety about the future. Financial difficulties affected both groups almost equally. Discrimination based on ethnicity or political views was reported by few respondents, but more frequently mentioned by educators (4 % compared to 1,9 %).

High levels of stress and psycho-emotional tension among participants in the educational process affect their interaction, potentially causing conflicts and making conflict resolution more difficult. Survey participants noted that the most common approach was finding a compromise between conflicting parties, selected by 163 respondents (44,2 %). A significant portion (153 people [41,5 %]) also reported resolving conflicts through cooperation and joint problem-solving. However, some respondents indicated less constructive conflict resolution strategies. Specifically, 51 individuals (13,8 %) noted that conflicts remain unresolved, becoming "frozen conflicts." A total of 45 respondents (12,2 %) mentioned resolution through withdrawal of one of the parties, and 39 individuals (10,6 %) reported adapting to the conflict situation. The least common response was continued competition until one side wins, selected by only 15 respondents (4,1 %). Additionally, 40 respondents (10,8 %) noted other ways of resolving conflicts, which may include unique approaches or combinations of several methods. Overall, the results show that the vast majority of respondents (over 85 %) identified some mechanisms for resolving conflicts; however, a share of situations remains unresolved or is addressed through less optimal means.

A tense psycho-emotional environment in educational institutions is shaped by various factors, including both individual characteristics of participants and socio-economic conditions. The analysis of responses among educators allows us to identify the main causes of such an environment (Fig. 2).

The most frequently cited reason was a lack of societal attention to supporting a healthy psycho-emotional climate in educational institutions (45 %), indicating an overall underestimation of the impact of mental health on the quality of education. Other significant factors included a lack of knowledge about non-confrontational communication (22 %) and the continued influence of "authoritarian approaches from the past" in education, where the learning process is associated with punishment (20 %). A separate group of respondents (13 %) identified additional factors, with war and martial law being the dominant ones. Financial difficulties, national instability, increased administrative workload, and the declining social status of educators were also mentioned, all of which particularly affect the psychological climate in universities. The low level of psychological culture in society and insufficient attention to the emotional well-being of both students and educators further complicate the situation.

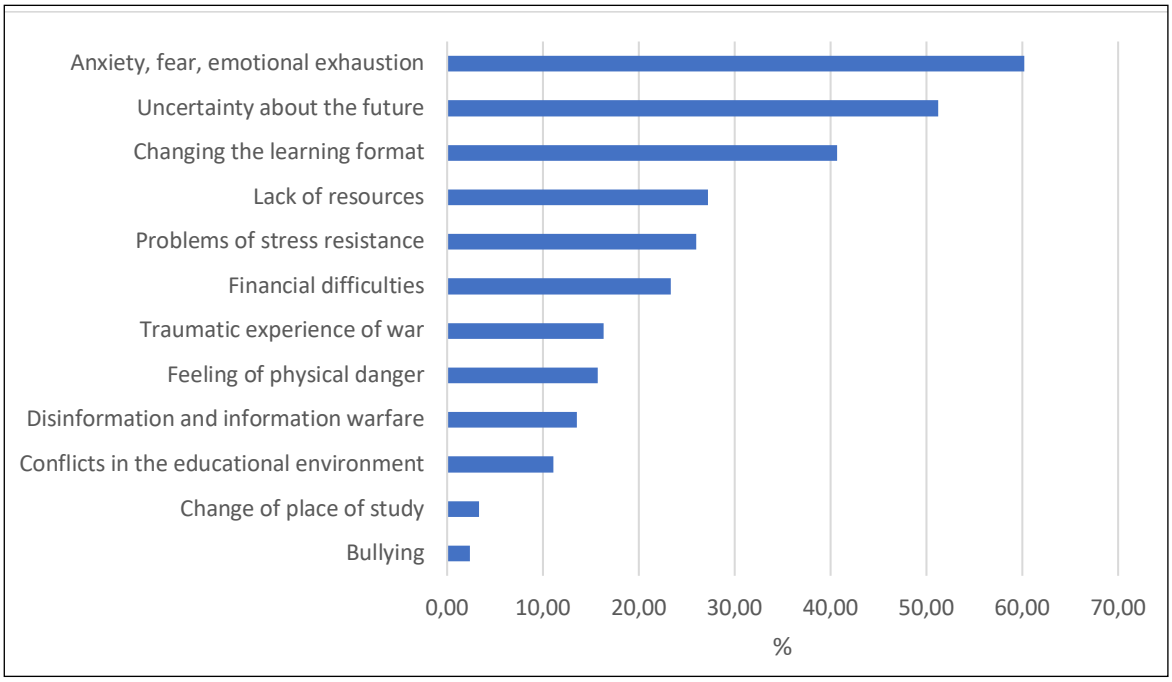

Fig. 2. The respondents' answers to the question «In your opinion, what is the MAIN cause of the tense psycho-emotional environment in Ukrainian higher education institutions?» (%)

Thus, the causes of psycho-emotional tension are multidimensional, encompassing both individual and systemic aspects. In addition to the war, sociocultural factors and the need to raise awareness about psychological well-being play a significant role. The results highlight the necessity of support measures, including psychological assistance, adaptation programs, and tools for overcoming psycho-emotional barriers. This calls for a comprehensive approach to reforming the educational environment, taking into account the psychological needs of all participants in the educational process.

DISCUSSION

In times of war, ensuring the psycho-emotional well-being of students becomes especially important. Modern educational technologies must not only support the learning process but also help overcome psycho-emotional barriers in crisis conditions. In this context, adaptive educational technologies are particularly effective as tools for adaptive learning. The adaptability of these technologies is reflected in various technological aspects: consideration of the nature of psycho-emotional issues, appropriate psychological and pedagogical support, selection of relevant content, defining individual learning trajectories, and reducing conflict potential.

One of the key technological approaches to addressing students' psycho-emotional well-being is trauma-informed education (TIE). Trauma-informed education acknowledges the effects of traumatic experiences on learners and ensures a safe and supportive learning environment. It is based on an understanding of how trauma influences learning, behavior, and mental health, and it involves the use of relevant pedagogical strategies. Its core principles include recognizing trauma and its impact on student development, learning, and behavior [3]; creating a safe environment that prevents re-traumatization and supports a sense of security [4]; building skills in self-regulation and resilience [5]; emphasizing interaction among educators, students, families, and other stakeholders [6]; and ensuring flexibility, adaptability, and personalization of the learning process to accommodate the needs of students with trauma experiences [7]. Practical aspects of implementing TIE include training educators to recognize the effects of trauma and respond appropriately [8], using methods of positive pedagogy to support students' mental well-being [9], and integrating TIE into higher education programs, especially in medical and social disciplines [10].

Coaching and mentoring, as adaptive educational technologies, play a significant role in overcoming the psycho-emotional challenges of students by supporting their adaptation, developing stress resilience, and improving emotional well-being. Mentoring is an effective tool for helping students adapt to the learning environment, fostering emotional stability, and building self-confidence [11]. Coaching and mentoring programs improve students' ability to self-regulate and

manage stress while developing adaptation and critical thinking skills, which are essential for academic and professional success. Mentorship programs significantly improve students' psychological well-being and reduce anxiety levels [12]. Interaction with educators helps students not only cope with stress but also find effective strategies for preventing it, which is particularly important under high academic pressure. Mentorship also contributes to academic achievement by helping students overcome challenges and stay motivated, fostering independence, problem-solving abilities, and sound decision-making [13].

Special attention should be given to partnership-based communication as one of the technologies for conflict resolution, which also plays a key role in creating a safe educational environment. In emotionally tense environments, conflicts may arise between participants in the educational process, requiring effective regulation mechanisms. Studies confirm that training students and educators in effective communication skills helps reduce the level of conflict in educational institutions [14]. Conflicts in educational settings are inevitable due to diverse opinions, cultural differences, and individual characteristics of students. However, proper conflict resolution strategies can significantly enhance the quality of interaction between students and educators [15].

Mediation is an effective technology for the constructive resolution of conflicts, involving a neutral third party to facilitate understanding between the conflicting sides. Research shows that the use of mediation in educational institutions significantly reduces levels of aggression, improves social interaction, and fosters a culture of peaceful cooperation [16]. The application of mediation in education enables: the development of constructive conflict-resolution skills among students; increased levels of trust and mutual understanding among participants in the educational process; reduction of stress and emotional tension within the educational environment; and the promotion of a culture of dialogue and non-violent communication. Studies show that students who undergo specialized training in communication and conflict management demonstrate higher levels of self-regulation and more effective strategies for resolving conflicts [17, 18]. Such programs include: role-playing and conflict situation simulations, where students learn to analyze problematic scenarios, find compromises, and practice resolution techniques in a safe setting, contributing to the development of active listening and empathy [19]; training in non-violent communication methods that help express feelings and needs without aggression, reducing conflict levels and improving mutual understanding [15, 20]; mediation programs that foster a culture of dialogue and peaceful dispute resolution, particularly through "peer-to-peer" initiatives; and emotional intelligence development programs that help individuals better understand their own experiences and manage impulsive reactions [21]. The implementation of these programs not only reduces conflict levels but also improves the overall atmosphere, academic performance, and contributes to the development of socially responsible individuals.

Studies show that educators with mediation and effective communication skills are more capable of fostering a healthy emotional climate [22]. Key strategies teachers can employ include creating an open and trusting atmosphere, using non-violent communication, and conducting communication training for students. The main benefits of mediation include transforming many conflict situations, developing responsibility and social competence, and strengthening trust among educational stakeholders. Students who participate in mediation programs develop better skills in constructive conflict resolution and exhibit lower levels of aggression and anxiety [23].

Another important area of focus is *raising students' awareness of mental health*. Research shows that targeted awareness campaigns and educational programs can significantly reduce the stigma surrounding mental disorders among students and increase their willingness to seek help [24]. Conducting awareness campaigns, webinars, and training sessions promotes a better understanding of stress coping mechanisms and adaptation to change — particularly relevant in conditions of high academic workload [25]. Including self-regulation and emotional literacy courses in academic programs is also an effective tool for supporting students' psychological resilience, with studies confirming positive changes in emotional well-being following such modules [26].

CONCLUSIONS

The results of the study confirmed that the psycho-emotional state of participants in the educational process in Ukraine has significantly deteriorated under wartime conditions. Most respondents reported elevated levels of stress, anxiety, emotional awareness, and uncertainty about the future. Educational technologies play a crucial role in overcoming psycho-emotional barriers by contributing to the creation of a safe learning environment and supporting the psychological well-being of students. The use of adaptive educational technologies — including trauma-informed approaches, coaching, mentoring, mediation, and others — helps to minimize the negative effects of stressors.

Awareness-raising campaigns focused on mental health can help reduce stigma and increase willingness to seek help. Therefore, in conditions of uncertainty, the educational process must focus not only on academic outcomes but also on preserving the psycho-emotional well-being of both students and educators.

There is a need to develop preventive methodologies and corresponding models for overcoming trauma and psycho-emotional barriers among all participants in the educational process, taking into account the multi-faceted nature of the core objectives of higher education.

REFERENCES

1. Palamar S, Harashchenko L, Litichenko O et al. The state of formation of a careful attitude towards health in the modern youth. Wiad Lek. 2024;77(11):2225-2231. doi: 10.36740/WLek/197101. DOI
2. Palamar B, Zhelanova V, Leontieva I et al. Vprovadzhennya sotsial'no-emotsiynoho navchannya v suchasnomu universyteti: vykhid za ramky akademichnoyi osvity. [Implementation of socio-emotional learning in the modern university: going beyond an academic education]. Klinichna ta profilaktychna medytsyna. 2024;(7):95-102. doi: 10.31612/2616-4868.7.2024.12. (Ukrainian) DOI
3. Goddard A, Jones R, Esposito D, Etcher L. Trauma-informed education in nursing: A concept analysis. J Nurs Educ. 2022;61(6):296–302. doi: 10.3928/01484834-20220404-15. DOI
4. Carello J, Butler L. Practicing what we teach: Trauma-informed educational practice. J Teach Soc Work. 2015;35:262–278. doi: 10.1080/08841233.2015.1030059. DOI
5. Julies Y. Trauma-informed practice as a component to improve student wellbeing. Set: Res Inf Teach. 2024. doi: 10.18296/set.1557. DOI
6. Wyatt Z, Hoban E, Macfarlane S. Trauma-informed education practice in Cambodia. Int J Asian Soc Sci. 2018;8:62–76. doi: 10.18488/journal.1.2018.82.62.76. DOI
7. Talabi P, Goldie C. Trauma informed educational strategies and recommendations for post-secondary health science programs. Inquiry@Queen's Undergrad Res Conf Proc. 2023;17(2). doi: 10.24908/iqurcp16699. DOI
8. Brown T, Fialkowski A, Elisseou S et al. Trauma-informed precepting: A novel curriculum for faculty development. Med Teach. 2024;1–6. doi:10.1080/0142159x.2024.2382858. DOI
9. Brunzell T. Trauma-aware practice and positive education. In: White M, Slemp G, Murray A, editors. Palgrave Handbook of Positive Education. Cham: Palgrave Macmillan. 2021, p. 125–140. doi: 10.1007/978-3-030-64537-3_8. DOI
10. Gao H, Chen P, Yao L. Trauma-informed practices in higher education: A comprehensive literature review (2015–2023). Int J High Educ. 2023;12(6):24820-24820. doi: 10.5430/ijhe.v12n6p149. DOI
11. Fletcher S. Mentoring in school: A handbook of good practice. London: Kogan Page. 2000.
12. Jones J, Smith H. A comparative study of formal coaching and mentoring programmes in higher education. Int J Mentor Coach Educ. 2022. doi: 10.1108/ijmce-03-2021-0054. DOI
13. Abiddin N. Mentoring and Coaching: The Roles and Practices. 2006. https://ssrn.com/abstract=962231 [Accessed 07 April 2025]
14. Ringgenberg A. Communication and conflict resolution in early childhood. 2016. https://api.semanticscholar.org/CorpusID:151835031 [Accessed 07 April 2025]
15. Sánchez M, Rea WRC. Mediación educativa como estrategia para la resolución de conflictos en el aula. [Educational mediation as a strategy for conflict resolution in the classroom]. Red Investig Educ. 2011;3(1):16–37. (Spanish)
16. Janeczko-Janicka M. Spotkanie przy mediacyjnym stole. Konteksty Pedagogiczne. [Meeting at the Mediation Table. Pedagogical Contexts]. Studia Edukacyjne. 2023;(68):89–106. doi: 10.14746/se.2023.68.7. (Polish) DOI
17. Agricola G. Designing Conflict Resolution Education: A Literature Review. 2010. https://studenttheses.uu.nl/handle/20.500.12932/4166 [Accessed 10 April 2025]
18. Arikawe O, Edwards-Fapohunda MO, Waite P. Strategies for student related crisis management in the learning environment in further education colleges in UK. Iconic Res Eng J. 2024;8(2):576–586. https://www.irejournals.com/formatedpaper/1706194.pdf [Accessed 10 April 2025]
19. Türnüklü A, Kaçmaz T, Turk F et al. Helping students resolve their conflicts through conflict resolution and peer mediation training. Procedia Soc Behav Sci. 2009;1:639–647. doi: 10.1016/j.sbspro.2009.01.113. DOI
20. Pirhadi Tavandashti R, Arefi M, Sajjadian I. Efficacy of nonviolent communication training based on Marshall Rosenberg theory on the empathy and life meaning in the students with the signs of violence. J Mod Psychol Res. 2024;19(73):194–203. doi: 10.22034/jmpr.2023.54836.5355. DOI
21. Goleman D, Cherniss C. Optimal leadership and emotional intelligence. Leader Leader. 2024;113:7–12. doi: 10.1002/ltl.20813. DOI
22. Lindsay P. Conflict resolution and peer mediation in public schools: What works? Confl Resolut Q. 1998;16:85–99. doi: 10.1002/crq.3890160109. DOI

23. García-Raga L, Grau R, López-Martín R. Mediation as a process for the management of conflict and the improvement of coexistence in educational centres: A study based on the perceptions of secondary school students. Procedia Soc Behav Sci. 2017;237:465–470. doi: 10.1016/j.sbspro.2017.02.091. DOI
24. Giroux D, Geiss E. Evaluating a student-led mental health awareness campaign. Psi Chi J Psychol Res. 2019;24(1):61–66. doi: 10.24839/2325-7342.JN24.1.61. DOI
25. Zhang J, Peng C, Chen C. Mental health and academic performance of college students: Knowledge in the field of mental health, self-control, and learning in college. Acta Psychol (Amst). 2024;248:104351. doi: 10.1016/j.actpsy.2024.104351. DOI
26. Leena A, Vinutha R, Jose M. Impact of a mental health awareness program on knowledge, attitude, and perceptions about mental health disorders among medical students. Natl J Physiol Pharm Pharmacol. 2022;12(11):1944–1944. doi: 10.5455/njppp.2022.12.03126202209042022. DOI

The research was carried out within the framework of the scientific topic of the Department of Education and Psychological and Pedagogical Sciences of Borys Grinchenko Kyiv Metropolitan University «Innovation in the Development of Higher Pedagogical Education in the Interdisciplinary Dimension» (state registration № 0121U000123; term: 2021-2026).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Svitlana P. Palamar
Faculty of Pedagogical Education
Borys Grinchenko Kyiv Metropolitan University
18/2 I. Shamo Blvd, 01601 Kyiv, Ukraine
e-mail: s.palamar@kubg.edu.ua

ORCID AND CONTRIBUTIONSHIP

Liudmyla L. Khoruzha: 0000-0003-4405-4847 A B C D E F
Mariia V. Bratko: 0000-0001-7162-2841 A B C D E F
Svitlana P. Palamar: 0000-0001-6123-241X A B C D E F
Inna V. Leontieva: 0000-0002-8084-1912 A B D
Marharyta K. Kozyr: 0000-0001-8402- 2589 A E
Olena M. Tadeush: 0000-0002-6373-4891 A E
Maria V. Klepar: 0000-0003-1671-3710 D E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 12.02.2025
ACCEPTED: 02.06.2025

ORIGINAL ARTICLE

CONTENTS

Protection of children's rights to access palliative medical services: Legal problems

Oleksandr M. Shevchuk[1], Anatolii M. Shevchuk[2], Olena O. Holovash[1], Oleksandr O. Mykhailenko[3], Arina O. Ivanytsia[2]

[1]YAROSLAV MUDRYI NATIONAL LAW UNIVERSITY, KHARKIV, UKRAINE
[2]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE
[3]PRINCE VOLODYMYR THE GREAT IAPM EDUCATIONAL AND RESEARCH INSTITUTE OF LAW, KYIV, UKRAINE

ABSTRACT

Aim: To identify legal issues in protecting children's rights to palliative care in Ukraine, to propose basic guarantees of their rights, and to note trends in foreign practice.

Materials and Methods: The study is based on its theoretical and empirical basis, the system of methods of scientific knowledge. The theoretical basis includes scientific articles, expert analysis of legislation and international organizations.

Results: The implementation of children's right to palliative care can be classified as universal and special. In the implementation of this right, children often face inadequate representation of their interests and shortcomings in the provision of medical services to them. As a result, the right of children to quality medical care when receiving palliative care, the right of children to receive palliative care at home, the right of the child to consent to receiving palliative care, the right of children to confidentiality and protection of personal data when receiving palliative care, and the right of children to privacy in this area are violated.

Conclusions: Accessibility of children's rights to palliative medical care is an important aspect of ensuring the implementation of one of the fundamental, inalienable human rights to life and health as the highest social values.

KEY WORDS: palliative medical services, children's rights, legal regulation

Wiad Lek. 2025;78(6):1078-1082. doi: 10.36740/WLek/207368 DOI

INTRODUCTION

Ukraine, having signed the Association Agreement between Ukraine and the EU in 2014, chose the European integration vector of its development, which provides for the gradual adaptation of norms, requirements, and approximation to European standards in the healthcare system through the implementation of its systemic reform [1]. The national healthcare systems of many countries around the world are facing new, more serious challenges that determine the quality of life of the population. One of these challenges is the constant increase in the number of incurable child patients who need palliative care. Thus, the Resolution of the Parliamentary Assembly of the Council of Europe of January 28, 2009, No. 1649 (paragraph 4), notes that an increasing number of social groups of the population (seriously ill, chronically ill, patients requiring individual care) at the final stages of their lives are unable to obtain proper legal protection of rights guaranteed by the state, to realize and satisfy their basic needs for medical care due to the significant costs of obtaining them. The Constitution of Ukraine, as a participant in international relations, provides for obligations to ensure the safety and quality of life of its citizens (Articles 3, 49), including the rights to health care and medical care. In particular, the protection of the rights of patients to medical care for incurable diseases [2], especially children. Children with incurable and debilitating diseases suffer from pain, but are often not provided with palliative care [3]. The number of such children-patients will grow, both in the world [4] and in Ukraine.

AIM

The aim of the study was to identify problems in the implementation of children's rights to palliative care in Ukraine, and on this basis to propose methods of legal provision of guarantees of such children's rights.

MATERIALS AND METHODS

The methodological basis of the study is a set of methods and techniques of scientific knowledge.

Table 1. The components of a children's right to palliative care

Component	Description
Medical	Children's right to symptomatic therapy, children›s right to prevention and treatment of chronic pain syndrome, children›s right to drug therapy, right to effective pain relief
Social	Children's right to provide social services of palliative care
Spiritual and psychological support	The right of children to spiritual and psychological support from their family and other caregivers

Table 2. The main ones principles of children's rights to palliative care

Component Number	Description
1	The principle of accessibility of palliative care for children
2	The principle of planning palliative care for children
3	The principle of continuity and continuity of palliative care for children
4	The principle of choosing a place of treatment when providing palliative care to children (with parental consent)
5	The principle of choosing the place of death when providing palliative care in children
6	The principle of ethical and humane treatment of the children-Patient and his family members, other persons caring for the children-Patient, 7 days a week

Table 3. The main violations of children's rights when receiving palliative care

Component Number	Description
1	Inaccessibility of palliative care (the vast majority of terminally ill children cannot receive it in the required volume)
2	Unavailability and insufficiency of medicinal narcotic drugs and other painkillers in the required quantities
3	Non-compliance of children's palliative care departments with international norms and standards for material and technical resources
4	Lack of qualified health workers for palliative care of children
5	Underfunding of the palliative care system for children from state sources
6	Children's representatives do not take their interests personally
7	Medical intervention on children under duress
8	Provision of unjustified medical care to children without appropriate indications

In particular, the following methods were used in the work: formal-dogmatic, systemic, semantic, epistemological and axiological, sociological, comparative-legal, statistical, systemic, and structural analysis. The comprehensiveness of the study of this article is ensured by a systematic approach, which made it possible to consider and analyze the problems of implementing children's rights to palliative care, in the unity of their content, essence, and legal form. The application of scientific methods allowed the authors to achieve the goal of the article, substantiate the conclusions of the study, and suggest ways to optimize legislation on the implementation of children's rights to palliative care

ETHICS

No animals or human subjects were used in this study.

RESULTS

Children's rights in the healthcare sector are divided into two groups. The first (universal) are inherent to both children and adults. The other group (specific) belongs only to children and is supported by guarantees of their legal status [5]. Among the latter category of children's rights are children's rights to palliative medical care [6-9]. National legislation provides for definitions of the category "palliative care" for all categories of patients. Thus, at the legislative level, it is stipulated that palliative care is a set of measures aimed at improving the quality of life of patients of all age categories and their family members who are faced with problems associated with life-threatening diseases. This complex involves measures to prevent and alleviate the patient's suffering through early identification and assessment of symptoms, pain relief, and overcoming other physical, psychosocial, and spiritual problems. (Article 35 – 4) [10].

Palliative care for children is divided into general and specialized palliative care. Palliative care for children (patients aged from birth to 18 years) is provided in accordance with the provisions of sections I - IV and paragraph 1 of section III of the Procedure for the Provision of Palliative Care [11]. When organizing the provision of palliative care to pediatric patients, preference is given

to organizational forms that allow for the provision of palliative care at home with the involvement of family members or legal representatives of the child, subject to the informed consent of such patients [11]. During the stay of a pediatric patient in a health care facility providing palliative care, the child's right to stay with family members is ensured [11]. Palliative care for children is provided in Ukraine at the expense of the state budget.

The right of children to palliative care is also provided for in international legislation. Thus, international legislation indicates that the right of children to treatment of illnesses and restoration of health (Article 24 of the Convention on the Rights of the Child) and directs political, civil, economic, social and cultural rights of children (who have not reached the age of 18 [12]). Children, including adolescents, have the same rights as adults: "the right to protect their own health to the extent that disease prevention and treatment allow, in order to achieve the highest possible level of health", which is reflected in the Declaration on Policy on Ensuring Patient Rights in Europe (paragraph 1.6, part 1) [13]; the right to treatment only subject to the patient's consent, which he has given voluntarily on the basis of relevant information (Article 5 of the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine) [14], the right to protection from torture, inhuman or degrading treatment or punishment (Article 3 of the Convention for the Protection of Human Rights and Fundamental Freedoms) [15] and others.

The main components of children's rights to palliative care are given below in Table 1 [7, 8, 11].

Palliative care for children is based on the same principles as palliative care for adults, but the principles under study also have their own specifics [16]. The main principles of implementing the right of children to palliative care are given below in Table 2 [4, 6, 11].

The main violations of the rights of minors who need palliative care have been identified in Table 3 [3, 7, 8, 17-19].

In the human rights framework, children's rights to receive and access palliative care are vital and must first be protected. This is due to the specific nature of the treatment, their vulnerability, the need for further protection and care and includes providing support to the child and his family. It should be noted that effective legal regulation of the implementation of children's right to palliative care should be aimed at improving their quality of life. Realization of this right for children also includes support for optimal child development, formal education, stimulation of development in order to enable the child at any age to live the best life.

DISCUSSION

There is no single approach to understanding the components of the implementation of children's right to access palliative care. The problematic issues are the application of both legal and ethical norms [6, 7], as well as the definition of a list of principles for the implementation of children's right to access palliative care. It should be noted that in 2002, the WHO first defined the definition of «palliative care for children». WHO experts understand this term as active, comprehensive care for the child's body, psyche and soul, as well as support for his family members [3]. However, there is still no unified scientific approach to the content of the legal construct "children's right to palliative care". In particular, other forms of palliative care are also distinguished in the legal literature, namely: "supportive care", "end-of-life care", "terminal care", "respite care" [2, 18, 20], however, some researchers point out the inappropriateness of distinguishing the above forms of palliative care.

The grounds for recognizing a child as a subject of legal relations for the provision of palliative medical care remain problematic. According to Article 3 of the special legislative act in the field of healthcare, the term "patient" is an individual who has sought medical assistance and/or who is provided with such assistance [10]. Regarding the subject of our research, it is necessary to take into account the legal status of minors and their right to receive palliative care. In particular, a minor is considered a child before reaching the age of fourteen, a minor is a child aged fourteen to eighteen (Part 2, Article 6) [21]. Based on the content of Article 284 of the Civil Code of Ukraine, a minor child has the right to be provided with medical care (Part 1), however, he or she cannot exercise this right independently [22]. In addition, we note that Article 43 of the special legislative act in the field of healthcare establishes that the use of methods of diagnosis, prevention and treatment of a minor child requires the consent of his legal representative [10]. That is, unlike a minor child, a minor child already has the right to independently exercise the right to palliative medical care. And he can exercise this right in two ways: to consent to medical care (Part 3); or to choose a doctor and methods of treatment in accordance with his recommendations (Part 2, Article 284) [22].

The child's rights to palliative care are ensured not only by the duties of medical workers, but also by the duties of their parents and legal representatives [23]. And violations of children's rights in this area are usually associated with improper representation of their interests by parents and legal representatives, and deficiencies in the provision of medical services [5,

23]. In particular, in the legal literature, some scholars express considerations regarding both lowering and increasing the age of a child for consenting to medical care. However, the provisions of the Convention on the Rights of the Child enshrine the obligation of States Parties to ensure that a child who is capable of forming his or her own views has the right to express those views freely in all matters affecting the child. This requirement of the Convention provides children with the opportunity to express their views freely and to have them taken into account in accordance with their age and level of maturity [12]. In our opinion, it is advisable to give a child the right to consent to the provision of palliative medical care from the age of 16. From this age, a child can make informed decisions when seeking medical attention and choose methods of treatment and medical care.

CONCLUSIONS

Accessibility of pre-palliative medical care for children is an important aspect of ensuring the implementation of one of the fundamental, inalienable human rights to life and health as the highest social values. This is recognized in United Nations conventions and protected by many international organizations. The representation and implementation of the right of children to effective access to palliative medical care is an important feature of a modern social, legal state and is a priority task of state policy in the field of health care of any democratic state. Given their age characteristics and limited capabilities, children are significantly limited in their ability to independently exercise their patient rights to palliative care. Therefore, children-patients who need palliative care should have additional guarantees of their rights protection. These rights of children can be classified as universal and special.

REFERENCES

1. Shevchuk O, Matyuknina N, Babaeva O et al. The human right to security in the implementation of the concept of the «right to health protection». Tribuna Juridica. 2021;11(3):535 -548. doi: 10.24818/TBJ/2021/11/3.08. DOI
2. Shevchuk O, Trofymenko V, Martynovskyi V et al. Realization of the human right to palliative care in Ukraine: problems and legal questions (review). Georgian Medical News. 2019;4(289):168 - 173.
3. Downing J, Randall D, Mcnamara-Goodger K et al. Children's palliative care and public health: position statement. BMC Palliat Care. 2025;24(1):89. doi: 10.1186/s12904-025-01653-1. DOI
4. Aidoo E, Rajapakse D. Overview of paediatric palliative care. BJA Educ. 2019;19(2):60-64. doi: 10.1016/j.bjae.2018.11.001. DOI
5. Pashkov V, Olefir A. Protection of children's rights in the health care: problems and legal issues. Wiad lek. 2017;70:1122-1132.
6. Garani-Papadatos T, Natsiavas P, Meyerheim M et al. Ethical Principles in Digital Palliative Care for Children: The MyPal Project and Experiences Made in Designing a Trustworthy Approach. Front Digit Health. 2022;730430. doi: 10.3389/fdgth.2022.730430. DOI
7. Rosengarten L, Davies B, Camara C. Law and ethics in palliative care of children and young people. Br J Nurs. 2021;30(3):154-155. doi: 10.12968/bjon.2021.30.3.154. DOI
8. Holder P, Coombes L, Chudleigh J et al. Barriers and facilitators influencing referral and access to palliative care for children and young people with life-limiting and life-threatening conditions: a scoping review of the evidence. Palliat Med. 2024;38(9):981-999. doi: 10.1177/02692163241271010. DOI
9. Gibson-Smith D, Jarvis SW, Fraser LK. Place of death of children and young adults with a life-limiting condition in England: a retrospective cohort study. Archives of Disease in Childhood. 2021;106: 780-785. doi: 10.1136/archdischild-2020-319700. DOI
10. Zakon Ukrainy «Osnovy Zakonodavstva Ukrainy pro Okhoronu Zdorovia» № 2801-XII vid 19.11.1992. [Fundamentals of Ukrainian legislation on health care: Law of Ukraine dated 19 November 1992. No. 2801-XII] https://zakon.rada.gov.ua/laws/show/2801-12#Text [Accessed 19 August 2024] (Ukrainian)
11. Nakaz Ministerstva okhorony zdorovia Ukrainy 04 chervnia 2020 roku № 1308 «Poriadok nadannia paliatyvnoi dopomohy» [Order of the Ministry of Health of Ukraine of June 4, 2020 No. 1308 «Procedure for Providing Palliative Care»] https://zakon.rada.gov.ua/laws/show/z0609-20#Text [Accessed 08 July 2024] (Ukrainian)
12. Convention on the Rights of the Child of 20 November 1989. https://www.ohchr.org/en/instruments-mechanisms/instruments/convention-rights-child [Accessed 10 July 2024]
13. Declaration on Policy for the Promotion of Patient Rights in Europe of 28 June 1994. https://www.activecitizenship.net/multimedia/files/charter-of-rights/the-forerunners-of-the-charter/The-Declaration-on-The-Promotion-of-Patients-Rights-in-Europe.pdf [Accessed 02 July 2024]
14. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine of 4 April 1997. https://rm.coe.int/168007cf98 [Accessed 03 July 2024]
15. Convention for the Protection of Human Rights and Fundamental Freedoms: Council of Europe Convention of 04.11.1950. https://zakon.rada.gov.ua/laws/show/995_004#Text [Accessed 09 September 2024]

16. Chelazzi C, Villa G, Lanini I, Romagnoli S et. all. The adult and pediatric palliative care: differences and shared issues. J Anesth Analg Crit Care. 2023;3(1):1. doi: 10.1186/s44158-023-00085-8. DOI
17. Radbruch L, Payne S. White Paper on standards and norms for hospice and palliative care in Europe: part 1. Palliative Medicine: The Research Journal of the EAPC. 2009;16(6);278-289.
18. Barros de Luca G, Zopunyan V, Burke-Shyne N et al. Palliative care and human rights in patient care: an Armenia case study. Public Health Rev. 2017;38:18. doi: 10.1186/s40985-017-0062-7. DOI
19. Pyke-Grimm KA, Fisher B, Haskamp A et al. Providing Palliative and Hospice Care to Children, Adolescents and Young Adults with Cancer. Semin Oncol Nurs. 2021;37(3):151166. doi: 10.1016/j.soncn.2021.151166. DOI
20. Meglič A, Lisec A. Paediatric Palliative Care in Clinical Practice: Ethical Issues in Advance Care Planning and End-of-Life Decisions. J Eval Clin Pract. 2025;31(3):e70094. doi: 10.1111/jep.70094. DOI
21. Zakon Ukrainy «Simeinyi kodeks Ukrainy» № 2947-III vid 10.01.2002 p. [Family Code of Ukraine: Law of Ukraine dated 10 January 2002 No. 2947-III] https://zakon.rada.gov.ua/laws/show/2947-14#Text [Accessed 02 August 2024] (Ukrainian)
22. Zakon Ukrainy «Tsyvilnyi kodeks Ukrainy» № 435-IV vid 16.01.2003 [Civil Code of Ukraine: Law of Ukraine dated dated 16 January 2003 № 435-IV] https://zakon.rada.gov.ua/laws/show/435-15#Text [Accessed 05 July 2024] (Ukrainian)
23. Fields D, Fraser LK, Taylor J et al. What does 'good' palliative care look like for children and young people? A qualitative study of parents' experiences and perspectives. Palliat Med. 2023;37(3):355-371. doi: 10.1177/02692163231154300. DOI

The work is a fragment of comprehensive target program of the Department of Administrative Law and Administrative Activities, Yaroslav Mudryi National Law University "Constitutional and legal problems of ensuring the rule of law in the functioning of the mechanism of public power in Ukraine" (№ state registration 0111U000966; deadline: 2022-2025).

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Oleksandr M. Shevchuk
Yaroslav Mudryi National Law University,
77 Hryhorii Skovoroda St., 61024 Kharkiv, Ukraine
e-mail: oleksandr-shevchuk@ukr.net

ORCID AND CONTRIBUTIONSHIP
Oleksandr M. Shevchuk: 0000-0003-4864-7316 B D
Anatolii M. Shevchuk: 0000-0001-9646-6312 A E
Olena O. Holovash: 0000-0003-0995-6570 C D
Oleksandr O. Mykhailenko: 0009-0007-2699-7901 F
Arina O. Ivanytsia: 0000-0002-4115-9638 C

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 22.11.2024
ACCEPTED: 19.05.2025

ORIGINAL ARTICLE

CONTENTS

Study on medical professionals' attitudes and awareness of multidisciplinary rehabilitation in pain syndromes

Lidiia V. Butska[1,2], Hanna B. Varina[3], Leonid V. Bondar[1], Olena A. Mialovytska[1]

[1]TARAS SHEVCHENKO NATIONAL UNIVERSITY OF KYIV, KYIV, UKRAINE

[2]INTERREGIONAL ACADEMY OF PERSONNEL MANAGEMENT, KYIV, UKRAINE

[3]BOGDAN KHMELNITSKY MELITOPOL STATE PEDAGOGICAL UNIVERSITY, ZAPORIZHZHIA, UKRAINE

ABSTRACT

Aim: To assess the awareness and training needs of healthcare professionals regarding the multidisciplinary rehabilitation of patients with pain syndromes and comorbid conditions resulting from war trauma.

Materials and Methods: The structured online survey of 120 people, including doctors, nurses, medical assistants, paramedics and senior students of medical universities in Kyiv and Zaporizhzhya (Ukraine). Before that, a targeted review of international (WHO, NICE, EULAR) and national guidelines on multidisciplinary rehabilitation was conducted. Based on this regulatory framework, the authors developed the «Multidisciplinary Rehabilitation Attitude and Readiness Questionnaire».

Results: Although 89% of respondents were familiar with the concept of multidisciplinary rehabilitation, only 17% demonstrated a comprehensive understanding. Most respondents (54%) reported only partial awareness and emphasized the need to improve teamwork skills and learn modern rehabilitation methods. Psychological support was recognized as essential by 58%, while 42% showed uncertainty or held misconceptions. Core rehabilitation components identified included pharmacological stabilization (65%), interdisciplinary collaboration (50%), and patient education (45%). However, elements such as empathy, active listening (25%), and social reintegration (15%) were undervalued. Only 23% of participants rated their competence in teamwork as sufficient, and nearly half (48%) assessed their preparedness as low. Priority areas for further education included trauma-informed care, psychological first aid, prevention of professional burnout, and the use of non-pharmacological methods such as electrotherapy and acupuncture.

Conclusions: Despite formal awareness of multidisciplinary rehabilitation, significant gaps exist in practical competencies. Expanding interdisciplinary training and emphasizing psychosocial components are critical to improving care for war-affected patients.

KEY WORDS: multidisciplinary rehabilitation, pain syndromes, psychological support

Wiad Lek. 2025;78(6):1083-1090. doi: 10.36740/WLek/207369 DOI

INTRODUCTION

The ongoing war in Ukraine has led to a significant increase in patients suffering from chronic pain syndromes accompanied by psychosomatic and emotional disorders. This clinical context requires an integrated multidisciplinary approach to treatment and rehabilitation. According to the Ministry of Health of Ukraine, 20–25% of individuals in combat zones require psychological first aid, and over 50% experience acute stress or psychosomatic symptoms [1].

The prevalence of chronic pain has notably risen among both civilians and military personnel, with up to 60% of wounded soldiers reporting persistent pain six months post-discharge, and more than 40% presenting comorbid psychological conditions. Furthermore, up to 50% of patients with somatic complaints exhibit signs of psychosomatic dysfunction [2]. The World Health Organization data indicate that 15–20% of hospitalised patients show symptoms of post-traumatic stress disorder (PTSD) or related psychological trauma, and as of 2023, over 80% of Ukrainians report high levels of stress due to the war [3].

Over the past decade, Ukraine has endured major upheavals that likely had a significant impact on the population's mental health. In 2014, following the Revolution of Dignity, Russia annexed Crimea and launched a military conflict in eastern Ukraine, leading to the displacement of around two million people. A study conducted on a representative sample of these internally displaced individuals revealed that 27,4% met the diagnostic criteria for PTSD, 20,6% for major depressive disorder, and 16,1% for generalised anxiety disorder. Additionally, 14,3% of men and 1,7% of women screened positive for alcohol use disorder [4].

Medical professionals increasingly encounter patients requiring not only pharmacological or physical care,

but also psychological support, behavioural correction, physical therapy, and social reintegration. However, the level of preparedness for such complex, team-based care remains uneven [4]. Estimates suggest that only 30–40% of healthcare workers possess basic knowledge of multidisciplinary rehabilitation, and fewer than 20% have received relevant training [5].

In this context, assessing healthcare professionals' awareness and attitudes towards multidisciplinary rehabilitation is essential for enhancing Ukraine's healthcare system during and after the war. Improving this approach is critical not only for effective treatment, but also for the long-term recovery and quality of life of affected patients.

AIM

The aim of the study was to evaluate the awareness, attitudes, and training needs of healthcare professionals and medical students regarding the multidisciplinary rehabilitation of pain syndromes associated with wartime comorbidities, and to identify key barriers and opportunities for improving interdisciplinary collaboration and psychological support in clinical practice.

MATERIALS AND METHODS

The development of the research instrument was informed by the analysis of international clinical guidelines (WHO, EULAR, NICE), national healthcare regulations of Ukraine, and current scientific literature on multidisciplinary rehabilitation, chronic pain, and psychosomatic disorders [1-6]. These sources highlighted the need for structured assessment of healthcare professionals' preparedness for interdisciplinary rehabilitation in the context of war-related comorbidities. Based on this foundation, the authors developed a structured survey tool – the «Multidisciplinary Rehabilitation Attitude and Readiness Questionnaire» – designed to evaluate the levels of awareness, clinical experience and professional training needs related to multidisciplinary approaches in managing pain syndromes.

The questionnaire consisted of four sections:

- Social and professional characteristics of the respondents;
- Awareness of the multidisciplinary approach in managing pain syndromes;
- Experience in interdisciplinary clinical teamwork;
- Perceived educational needs and qualification enhancement.

The study involved a total of 120 participants, comprising doctors, nurses, medical assistants, paramedics, and senior students from medical universities. The survey was conducted online. Data collection took place between December 2024 and February 2025. Participation was entirely voluntary and anonymous. The geographical distribution of the respondents included healthcare professionals and students from Zaporizhzhia and Kyiv. The survey was administered via Google Forms, and the sample characteristics – including age, professional background, and work experience – are presented in Fig. 1.

The representative sample consisted predominantly of respondents aged 36–45 years (45%). It is worth noting that among the respondents were also medical students under the age of 25 (20%). In terms of professional background, the respondents included doctors (18%), nurses (35%), medical assistants (14%), paramedics (13 %) and medical students (20%). The majority of respondents (42%) had more than 10 years of experience in the medical field, while 25% had 5–10 years of experience. About 13% had been working in the profession for 1–5 years, and only 20% were newcomers to the field, having worked in healthcare for less than a year

The study complied with international and national ethical standards. It adhered to the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, and Articles 43 and 45 of the Law of Ukraine "Fundamentals of Health Legislation". The study protocol was approved by the local ethics committee. All responses were provided voluntarily and anonymously (no personal data were collected).

RESULTS

One of the key objectives of the study was to determine the baseline level of awareness among healthcare professionals regarding the principles of multimodal (multidisciplinary) rehabilitation in the context of war-related patient care (Fig. 2).

When asked, "Are you familiar with the concept of a multimodal approach in rehabilitation?", the majority of respondents (n=107 [89%]) answered affirmatively. Only 13 respondents (11%) had not encountered this concept in their professional activities (Fig. 2). These results indicate that, at the current stage of development of the healthcare system in wartime conditions, active information and educational activities are being implemented to increase knowledge about the comprehensive approach to the rehabilitation of patients with combat injuries and pain syndromes.

Fig. 3 presents the distribution of the respondents' sample by their awareness of the principles and approaches to implementing a multidisciplinary approach in the rehabilitation of patients with comorbid conditions and pain syndromes caused by war.

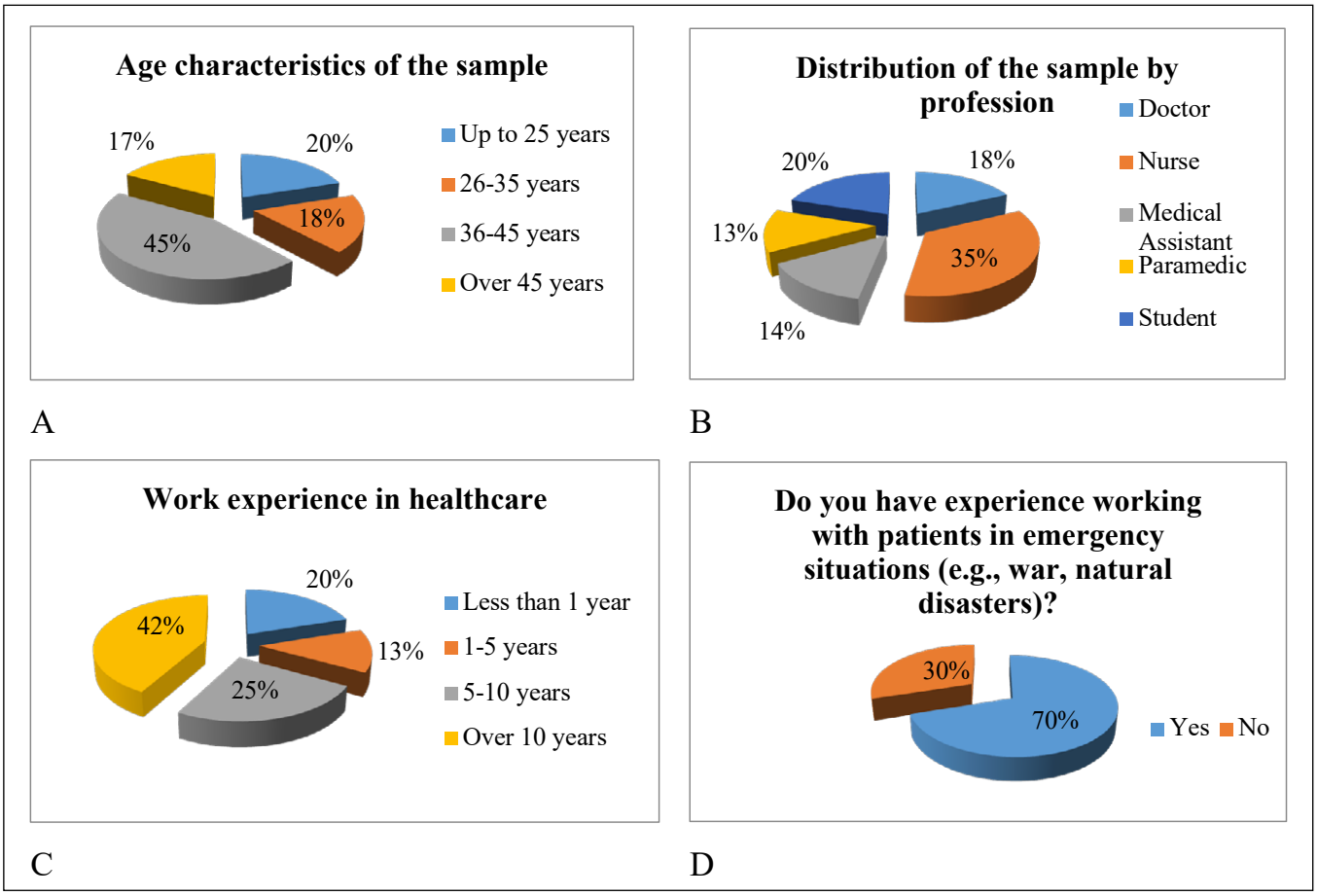

Fig. 1. The characteristics of the respondents` sample (n=120) by the following parameters: A – age distribution; B – distribution by profession; C – distribution by experience; D – distribution by experience in working with patients in emergency situations (data presented as percentages)

The majority of respondents (54%) have only a partial understanding of the approach and need more knowledge about its implementation, technologies, and collaboration among specialists. A smaller group (17%) is well-acquainted with the principles of the approach and can explain interdisciplinary collaboration methods. About 21% have heard of it but lack a clear understanding, while 8% are completely unfamiliar with the concept (Fig. 3). These results highlight a significant need to improve healthcare professionals' knowledge of the multidisciplinary approach in rehabilitation, particularly for patients affected by war, and to enhance their skills in teamwork, modern rehabilitation technologies, and inter-specialist interaction.

The data on the degree of understanding of psychological assistance and support in the implementation of the multidisciplinary approach in the rehabilitation of patients with comorbid conditions are summarized in. Fig. 4.

The survey results show that the majority of specialists – 70 (58%) – view psychological assistance in a multidisciplinary approach as initial psychological support for patients in crisis situations (trauma, stress, disaster). However, 20 respondents (17%) are unsure how to define psychological assistance, and another 20 (17%) equate it with emergency medical-psychological support for patients with mental disorders. Ten respondents (8%) define it as providing psychological and pharmacological help for mental disorders. Overall, 42 % of specialists require further clarification on the concept of psychological assistance, highlighting the need for an integrated training system to equip healthcare professionals with the skills to provide psychological support in clinical settings (Fig. 4).

The analysis of responses to the question «What are the key stages of the multidisciplinary approach in rehabilitation? » (Fig. 5) revealed that the majority of respondents – 78 (65%) – consider pharmacological therapy for stabilizing the patient's condition a key element of the rehabilitation process.

Half of the respondents – 60 (50%) – emphasised the importance of involving additional specialists (rehabilitologists, psychologists, physiotherapists) as essential. Fifty-four (45%) identified informational support for the patient, especially in cases of combat injuries and chronic pain, as important. Only 42 (35%) believed building a trusting relationship with the patient is a key aspect. Regarding psychological aspects, 30 respondents (25%)

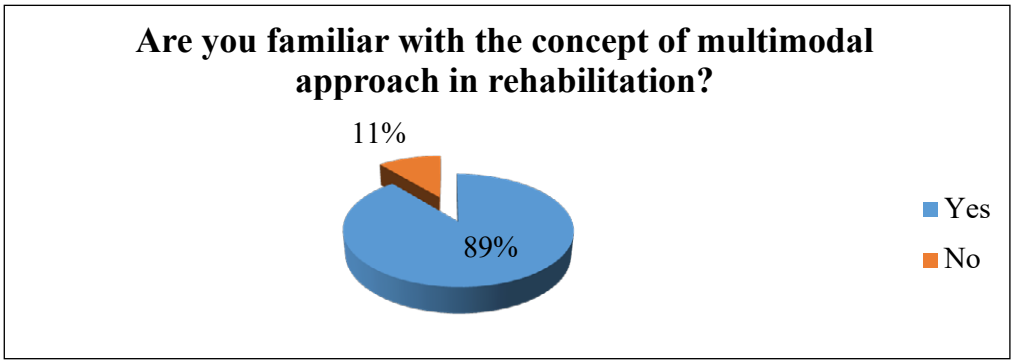

Fig. 2. The distribution (%) of the respondents` sample (n=120) by the awareness of the multimodal approach in rehabilitation

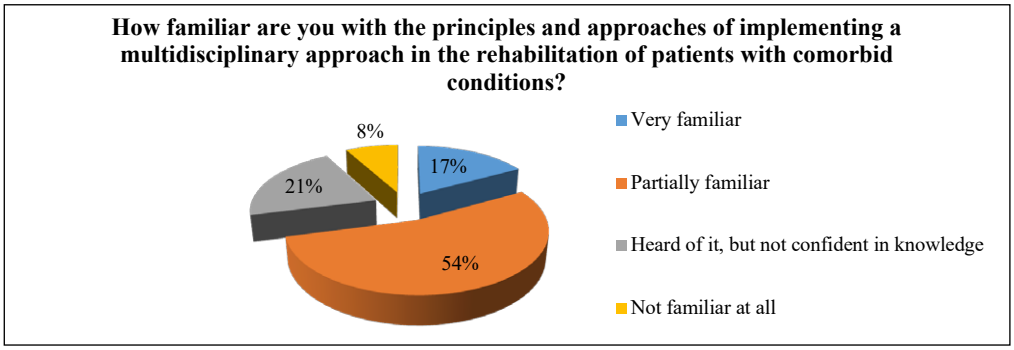

Fig. 3. The distribution (%) of the respondents` sample (n=120) by the awareness of the principles of implementing a multidisciplinary approach in the rehabilitation of patients with comorbid conditions and pain syndromes caused by war

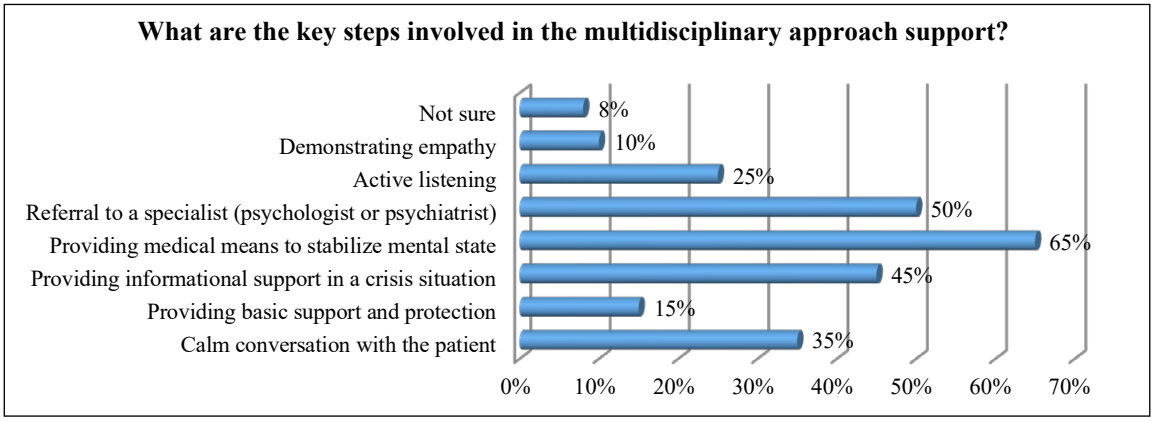

Fig. 4. The distribution (%) of the respondents` sample (n=120) by the degree of understanding of psychological assistance and support in the implementation of the multidisciplinary approach in the rehabilitation of patients with comorbid conditions

prioritised active listening, and 12 (10%) saw empathy as necessary. Only 18 (15%) highlighted social adaptation and restoring functional activity as crucial for overcoming combat injuries. Ten respondents (8%) struggled to identify the key aspects of the multidisciplinary approach, highlighting the need for further professional training to improve healthcare workers' knowledge of teamwork and rehabilitation strategies for patients with comorbid conditions and pain syndromes from war (Fig. 5).

The subjective evaluation of competence in multidisciplinary teamwork revealed that the majority of respondents – 58 (48%) – rated their skills as low, indicating insufficient preparation in comprehensive rehabilitation for patients with pain syndromes and comorbid conditions (Fig. 6).

Only 28 respondents (23%) felt competent for effective interdisciplinary collaboration, while 14 (12%) rated their skills as high. Fifteen individuals (13%) considered their preparation very low, which could hinder effective teamwork and patient rehabilitation. Only 5 specialists (4%) rated their competence as very high, having received specialised training in teamwork, rehabilitation technologies, and managing patients with combat injuries. Most respondents highlighted the need for supervision and intervision groups to improve training, share experiences, and analyse clinical cases. They also called for clear procedural protocols for team collaboration in rehabilitating patients with pain syndromes caused by war (Fig. 6).

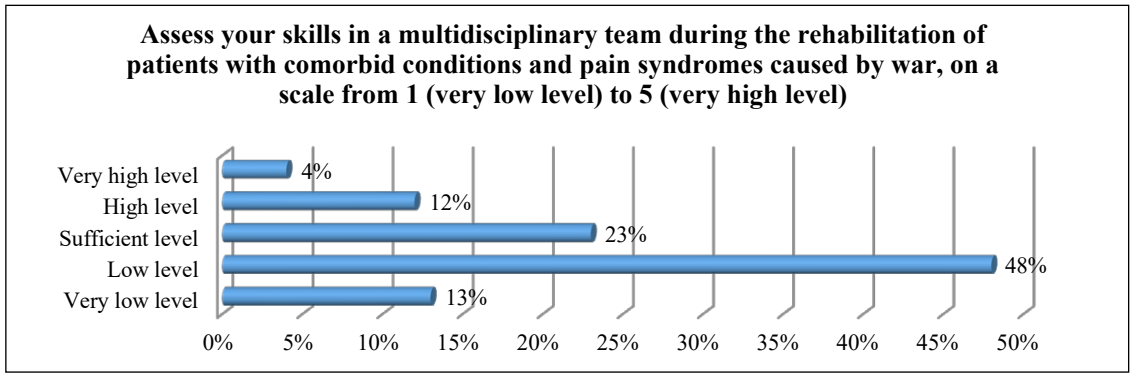

Fig. 5. The analysis of respondents' awareness regarding key concepts of implementing the multidisciplinary approach in the rehabilitation of patients with comorbid conditions and pain syndromes caused by war (data presented as percentages)

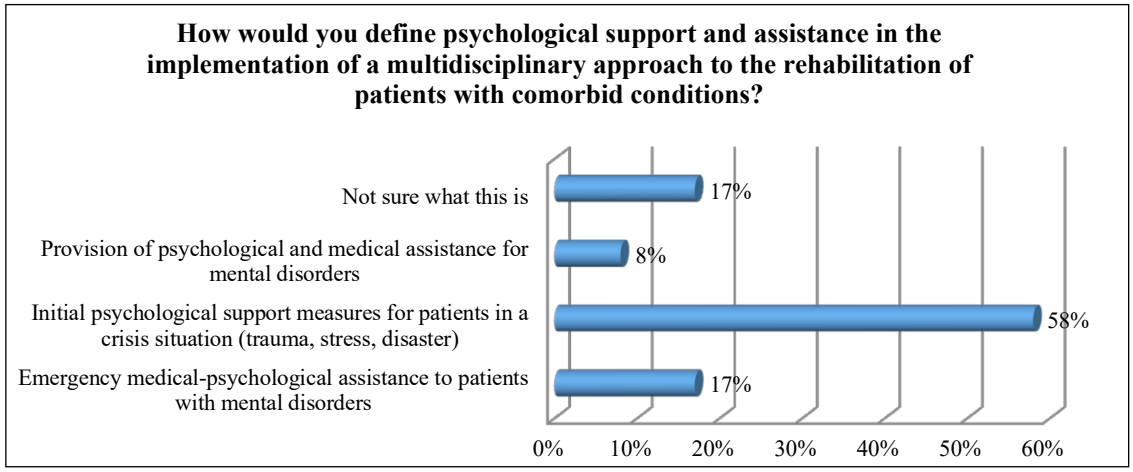

Fig. 6. The distribution (%) of the respondents` sample (n=120) by the self-assessment of healthcare workers' skills in multidisciplinary teamwork in the rehabilitation of patients with comorbid conditions and pain syndromes caused by war

DISCUSSION

Recent studies confirm the effectiveness of a multidisciplinary approach in the rehabilitation of patients with comorbid conditions and pain syndromes. Involvement of specialists from different fields significantly enhances treatment outcomes, improves patients' quality of life, and helps prevent pain chronification. According to A. Rogers and S. Farris [6], pain is a complex biopsychosocial phenomenon that requires a multimodal treatment strategy. The authors emphasize that an interdisciplinary perspective is essential for understanding how pain influences a patient's identity and emotional well-being.

Chronic pain encompasses not only physical but also neuroplastic, immune, endocrine, and psychosocial dimensions. PTSD, chronic stress, and depressive disorders contribute to sympathetic nervous system hyperactivity and elevate levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha) [7], which in turn lead to sensitization of the nervous system. These processes are associated with changes in the structure and function of the prefrontal cortex, hippocampus and limbic system, negatively affecting cognitive performance and emotional regulation, as noted by B. Key and D. Brown [8]. The progression of chronic pain is further complicated by shared pathophysiological mechanisms with other chronic conditions such as diabetes, cardiovascular disease, and depression. Social isolation, low levels of emotional support, and sleep disturbances intensify pain perception and increase the risk of chronification, as indicated by J. van Wyngaarden et al. [9]. Additionally, conditions such as fibromyalgia, neuropathic pain, and comorbid mental disorders create further challenges for effective treatment strategies [10-12].

A broad body of evidence supports the efficacy of a multimodal rehabilitation approach that integrates pharmacotherapy, physical activity, electropuncture, acupuncture [11, 13], cognitive-behavioral therapy and social support mechanisms [8, 9, 11]. For instance, Y. Ashar et al. [12] have demonstrated that psychological therapies significantly contribute to pain reduction and long-term recovery. Similarly, group therapy, patient education, and social rehabilitation programs reduce stress, foster reintegration, and enhance the overall effect of medical interventions [14]. In the context of combat-related injuries, multidisciplinary rehabilitation

assumes a critical role. Elevated stress levels among both patients and healthcare professionals necessitate comprehensive care models that address the emotional and psychological dimensions of trauma. L. Butska et al. [15] highlight the value of neuroimaging and internet-based interventions, while physical therapy methods – including acupuncture and electrotherapy – have also shown clinical effectiveness in post-traumatic rehabilitation. Collaborative treatment protocols and structured interdisciplinary training programs improve treatment efficiency and contribute to consistent recovery outcomes [16].

The findings of the current study, conducted among healthcare professionals in Zaporizhzhia and Kyiv, underscore the pressing need for widespread implementation of the multidisciplinary rehabilitation model for patients with war-related pain syndromes and comorbidities. The high level of general awareness among respondents (89 %) regarding the concept of multidisciplinary care reflects a positive shift in medical education, which now increasingly incorporates biopsychosocial models of pain management (J. van Wyngaarden et al. [9]; A. Lee et al. [16]). Nonetheless, a critical discrepancy was identified between declarative awareness and practical readiness: 79 % of respondents acknowledged lacking sufficient knowledge or confidence to function effectively within interdisciplinary teams. This finding aligns with the conclusions of L. Butska et al. [17] and Y. Ashar et al. [18], who emphasized that insufficient interdisciplinary training compromises the quality of care for patients with psychosomatic disorders.

Psychological support was identified as a crucial component of the rehabilitation process by 58 % of participants. This corresponds with data presented by B. Key and D. Brown [8], which demonstrate strong comorbidity between chronic pain and depression. These results also reinforce the necessity of integrating psychotherapeutic interventions as part of long-term rehabilitation strategies (F. Beissner et al. [14]). Moreover, Y. Ashar et al. [18] provide neurobiological evidence that prolonged pain can cause structural reorganization of brain areas responsible for emotion regulation, further justifying the inclusion of psychological support in standard protocols.

The key components of a multidisciplinary approach, as recognized by respondents — such as the involvement of psychologists, physiotherapists, physical and rehabilitation medicine specialists, as well as the application of non-pharmacological methods like electrotherapy, acupuncture, patient education, and social reintegration — correspond to best practices supported by international systematic reviews (S. Raja et al. [19]; L. Butska [15]). Respondents also highlighted priority areas for further training, particularly in crisis psychology, psychological first aid, burnout prevention, and trauma-informed care. These identified needs are in line with global recommendations for preparing healthcare workers to operate in disaster zones and military conflict environments (O. Kesiena et al. [20]; L. Butska et al. [17]). In summary, the data obtained in this study support the necessity of strengthening the competencies of healthcare professionals in interdisciplinary collaboration and complex rehabilitation techniques. This conclusion is consistent with modern healthcare approaches that recognize multidisciplinary interaction as a cornerstone of effective post-war recovery strategies [19].

The structured analysis of survey results made it possible to assess the readiness of healthcare professionals to implement a multidisciplinary rehabilitation model, identify typical challenges in interdisciplinary cooperation, evaluate the need for additional training, and propose recommendations for enhancing educational curricula and clinical practices. These findings serve as a foundation for further efforts to improve comprehensive care for patients suffering from chronic pain and psychosocial consequences of war.

CONCLUSIONS

The study revealed that while most healthcare professionals are familiar with the concept of multidisciplinary rehabilitation, a significant proportion lack a deep understanding of its principles and practical implementation. This gap reflects insufficient training in interdisciplinary collaboration and comprehensive patient care. Psychological support is recognized as important, yet often interpreted narrowly, underscoring the need for improved education in crisis psychology and trauma-informed practices. Furthermore, essential elements of patient-centered care – such as empathy, communication, and social reintegration - are undervalued compared to biomedical interventions. Self-assessments also point to low confidence in interdisciplinary teamwork, suggesting that structured educational programs, practical training, and clear protocols are urgently required. Strengthening these areas is crucial for improving the quality of rehabilitation services, particularly in the context of war-related health challenges.

REFERENCES

1. Martsenkovskyi D, Shevlin M, Ben-Ezra M et al. Mental health in Ukraine in 2023. Eur Psychiatry. 2024;67(1):e27. doi: 10.1192/j.eurpsy.2024.12. DOI
2. Goto R, Pinchuk I, Kolodezhny O et al. Mental health services in Ukraine during the early phases of the 2022 Russian invasion. Br J Psychiatry. 2023;222:82–87. doi: 10.1192/bjp.2022.210. DOI
3. World Health Organization. Ukraine – WHO special initiative for mental health. Geneva: WHO. 2021. https://www.who.int/publications/m/item/ukraine---who-special-initiative-for-mental-health [Accessed 19 February 2025]
4. Shevlin M, Hyland P, Vallières F et al. A comparison of DSM-5 and ICD-11 PTSD prevalence, comorbidity and disability: An analysis of the Ukrainian Internally Displaced Person's Mental Health Survey. Acta Psychiatr Scand. 2018;137(2):138–147. doi: 10.1111/acps.12840. DOI
5. Hyland P, Vallières F, Shevlin M et al. Psychological consequences of war in Ukraine: Assessing changes in mental health among Ukrainian parents. Psychol Med. 2023;53(15):7466-7468. doi: 10.1017/S0033291723000818. DOI
6. Rogers AH, Farris SG. A meta-analysis of the associations of elements of the fear-avoidance model of chronic pain with negative affect, depression, anxiety, pain-related disability and pain intensity. Eur J Pain. 2022;26(8):1611–1635. doi:10.1002/ejp.1994. DOI
7. Song Q, Zhang Z, Liang Y. Neuroplasticity in the transition from acute to chronic pain. Neurotherapeutics. 2024;21(6):e00464. doi: 10.1016/j.neurot.2024.e00464. DOI
8. Key B, Brown DJ. Neuroscientific underpinnings of psychosocial factors in chronic pain. Pain Med. 2025;26(5):290–291. doi:10.1093/pm/pnaf014. DOI
9. Van Wyngaarden JJ, Archer KR, Pennings JS et al. Psychosocial predictors of chronic pain 12 months after surgical fixation for lower extremity fracture: A prospective study. Phys Ther. 2022;102(10):pzac101. doi: 10.1093/ptj/pzac101. DOI
10. Harte N, Aaron RV, Bhattiprolu K et al. The association between anxiety and depression symptoms and pain and function in adolescents and young adults with chronic pain: A meta-analysis. J Psychosom Res. 2024;187:111945. doi:10.1016/j.jpsychores.2024.111945. DOI
11. Butska L. Clinical and physiological justification of the application of physical therapy as a component multidisciplinary approach in combatants after combat closed cranial brain injury (brain contusions). Multidisciplinary medicine and human health: Theoretical and methodological foundations of the innovative development of the health care system in the information society. Katowice: The University of Technology in Katowice Press; 2024, p. 24–46.
12. Ashar YK, Lumley MA, Perlis RH et al. Reattribution to mind-brain processes and recovery from chronic back pain: A secondary analysis of a randomized clinical trial. JAMA Netw Open. 2023;6(9):e2333846. doi: 10.1001/jamanetworkopen.2023.33846. DOI
13. Kong JT, Puetz C, Tian L et al. Effect of electroacupuncture vs sham treatment on change in pain severity among adults with chronic low back pain: A randomized clinical trial. JAMA Netw Open. 2020;3(10):e2022787. doi:10.1001/jamanetworkopen.2020.22787. DOI
14. Beissner F, Preibisch C, Schweizer-Arau A et al. Psychotherapy With Somatosensory Stimulation for Endometriosis-Associated Pain: The Role of the Anterior Hippocampus. Biol Psychiatry. 2018;84(10):734-742. doi: 10.1016/j.biopsych.2017.01.006. DOI
15. Butska L, Drevitska O. Lenha E. Application of the multilevel multidisciplinary approach at rehabilitation of the persons working in the conditions of high psychophysical loadings and suffering from pain syndromes. Role of science and education for sustainable development. Series of monographs. Faculty of Architecture, Civil Engineering and Applied Arts University of Technology, Katowice. Monograph 44. Katowice: Publishing House of University of Technology. 2021, p. 722—733.
16. Lee AC, Driban JB, Price LL et al. Responsiveness and Minimally Important Differences for 4 Patient-Reported Outcomes Measurement Information System Short Forms: Physical Function, Pain Interference, Depression, and Anxiety in Knee Osteoarthritis. J Pain. 2017;18(9):1096-1110. doi: 10.1016/j.jpain.2017.05.001. DOI
17. Butska LV, Chernyak VA, Drevitska OO et al. The role of university clinics in advancing higher medical education. Pol Merkur Lekarski. 2024;52(5):583-588. doi: 10.36740/Merkur202405116. DOI
18. Ashar YK, Gordon A, Schubiner H et al. Effect of Pain Reprocessing Therapy vs Placebo and Usual Care for Patients With Chronic Back Pain: A Randomized Clinical Trial. JAMA Psychiatry. 2022;79(1):13-23. doi: 10.1001/jamapsychiatry.2021.2669. DOI
19. Raja SN, Carr DB, Cohen M et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-1982. doi: 10.1097/j.pain.0000000000001939. DOI
20. Kesiena O, Atarere J, Benden M. The impact of multiple regions of pain and work-life balance among healthcare workers. Work. 2023;75(1):357-362. doi: 10.3233/WOR-211239. DOI

The preparation of the questionnaire and the conduction of the study were carried out independently and authentically, without external interference. The materials developed by the authors, as well as the conducted analysis, are being published for the first time. The authors are not aware of any similar studies conducted in Ukraine. *The research received no external funding.*

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Hanna B. Varina
Bogdan Khmelnitsky Melitopol State Pedagogical University
59 Naukove Mistechko St., 69000 Zaporizhzhia, Ukraine
e-mail: varina_hanna@mdpu.org.ua

ORCID AND CONTRIBUTIONSHIP
Lidiia V. Butska: 0000-0002-7928-0177 A B C D F
Hanna B. Varina: 0000-0002-0087-4264 B C D E
Leonid V. Bondar: 0000-0002-0039-7111 C E F
Olena A. Mialovytska: 0000-0002-5382-0032 C E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 15.01.2025
ACCEPTED: 29.05.2025

ORIGINAL ARTICLE

CONTENTS

Professional medical communication in war conditions: Gender aspect

Natalia V. Stuchynska[1], Nina P. Lytvynenko[1], Natalia M. Saveliuk[2], Nina A. Chernenko[1], Olena V. Sadovnycha[1], Iya P. Kaminska[1], Oksana M. Kikinezhdi[2]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

[2]TERNOPIL VOLODYMYR HNATIUK NATIONAL PEDAGOGICAL UNIVERSITY, TERNOPIL, UKRAINE

ABSTRACT

Aim: To investigate the features of professional medical communication in wartime through the prism of gender characteristics based on the analysis of authentic dialogues from clinical conversations.

Materials and Methods: Bibliosemantic, content, psychosemantic, and comparative analysis; empirical methods: observing the living language of doctors and patients, creating and typologising the collection of authentic doctor-patient dialogues. The authentic audio and video recordings of 232 doctor-patient dialogues were collected. After conducting an initial typology of the dialogues, four samples were created: «male» and «female doctors», «male» and «female patients». The dialogues were transcribed and subjected to content analysis using the «Textanz» software (v. 2.3).

Results: The psycholinguistic features of professional medical communication in each of the four studied samples were established. For example, male doctors have higher speech activity within their professional role (181 words vs. 138 for female doctors). Their speech is characterised by a predominance of verbs and rational structuring. In contrast, female doctors use nominative constructions with a predominance of nouns, pronouns, and adverbs more often, which indicates the objectification of symptoms and an empathic orientation. Female patients show higher speech activity, ask questions more often, and use more emotionally coloured vocabulary and modal words, which indicates increased anxiety.

Conclusions: The study confirms the presence of gender-based models of medical communication, which are exacerbated in wartime. The results of the study can be used in training on the development of communication skills of medical workers, in writing clinical protocols, as well as in psychological support for wounded and displaced persons.

KEY WORDS: psycholinguistics, communicative competence, medical education, war

Wiad Lek. 2025;78(6):1091-1097. doi: 10.36740/WLek/207370 DOI

INTRODUCTION

In the conditions of a full-scale war, the medical system of Ukraine is facing a huge load, which requires highly qualified medical workers, prompt medical intervention, and constructive professional communication. A significant increase in the number of patients with inclusion, numbness, chronic psychotraumatization, post-traumatic stress disorder, and other problems requires scientifically based styles of professional communication. Performing a physical examination, collecting anamnesis, diagnosing, providing medical care, and making decisions in various clinical situations requires a doctor to have developed psycholinguistic competence. The latter should include gender-specific features of professional communication, as they affect the style of communication, the level of trust and expectations, and help to preserve and improve the psychoemotional state of patients who have heightened sensitivity due to the circumstances caused by war [1-4].

Understanding gender aspects of communication helps doctors establish a constructive dialogue more quickly and interact more effectively with different population groups in wartime conditions (civilians, military, internally displaced persons, children, and the elderly), as women and men experience crisis situations differently and have different needs for proper medical care.

AIM

The aim of the study was to investigate the features of professional medical communication in wartime conditions through gender characteristics, based on the analysis of authentic medical dialogues within clinical communication.

MATERIALS AND METHODS

To achieve the goal, the following theoretical research methods were used: bibliosemantic, content, psychose-

mantic, and comparative analysis, differentiation, and generalization; empirical methods included observing the living language of doctors and patients in compliance with bioethical norms, creating a collection of doctor-patient dialogues, and typologizing experimental data by gender indicators. Finally, statistical processing was carried out using the «Textanz» special software (v. 2.3).

The empirical study involved direct observation of the style and structure of dialogues between a doctor and a patient in wartime conditions in Ukraine. During 2024, 232 doctor-patient dialogues were collected in the format of video and audio recordings within the context of a professional official reception procedure, in compliance with ethical, bioethical, and legal standards and with the voluntary consent of all participants. After conducting an initial typology to identify gender-specific features of professional medical communication in wartime conditions, 74 video and audio recordings were selected from the collection. These recordings were transcribed into texts and subjected to content analysis using the «Textanz» specialized computer program (v. 2.3). The texts were analyzed separately into four samples: "Male doctors" (sample 1), "Female doctors" (sample 2), "Male patients" (sample 3), and "Female patients" (sample 4).

RESULTS

The results obtained in first two gender-differentiated samples of male and female doctors are summarized in Table 1.

Let us analyze the results given in the Table 1. First of all, we state that a total of 7050 statistically significant words were recorded in sample 1 and 4828 – in sample 2. Thus, male doctors used 181 words in their communication on average, and female doctors – 138. Considering such results, we assume that the professional role position of a "doctor" encourages men to more actively verbally communicate than women. However, this assumption requires further research involving larger samples.

The most frequent (with a significant quantitative predominance) among the main parts of speech in both samples were pronouns (total number is 2698), which both male and female doctors use approximately equally (the relative frequency of significant pronouns in sample 1 and sample 2 was, respectively, 37,82% and 36,07%). Also, in both samples, the "You" category clearly dominates within pronouns (46,09% and 49,91% of the total number of statistically significant words recorded). This result is expected taking into account the role and task of the doctor in the "Doctor-Patient" system: an official appeal to the patient in order to clarify the state of his/her health and, if necessary, to discuss the diagnosis and treatment scheme.

The second most common main part of speech in terms of the total number of recorded words was the noun (1642). In the sample of female doctors, the noun is every fourth word among the statistically significant ones (25,87%); however, it is only every fifth (20,25%) in the sample of male doctors. Moreover, there are obvious differences between the samples in the composition of nouns within the leading category: it is "Diseases and their symptoms" for male doctors (19,58%), and "Examination, treatment and results" for the female ones (21,31%). In connection with such results, it can be argued that in communication with patients, the former are more focused on stating the fact of the disease and its manifestations, while the latter delve more into discussing the process of diagnosing the disease, the treatment process, and its predicted results.

The third most represented part of speech in both samples was the verb (1537 words). In sample 1, the dominant basic category was "To be" (39,09%); in sample 2, it was the "Communication and its components" category (30,44%). Therefore, male doctors are more likely to focus on stating the presence of certain facts (primarily, as noted above, the facts of diseases and their symptoms), while female doctors, on the other hand, try to ease their verbal communication with patients, particularly by using facilitating words (for example, they more often invite their patients to come in, pass by, or tell something, etc.).

Next, male doctors use verbs more frequently than nouns (21,73% and 20,25%, respectively), while female doctors use nouns more frequently (25,87% versus 20,29%). Therefore, in this context, it is somewhat more important for men to emphasize the effectiveness, influence, and/or dynamics of certain phenomena and events, while for women, naming, i.e., stating the relevant phenomena, is more important.

The fourth most common part of speech in terms of the number of occurrences in speech is the adverb (1121 words). Although the dominant category was "Temporality" (29,09% and 37,21%) in both samples, women use concepts from the corresponding category relatively more often and focus primarily on what is happening "now," while men are more involved in what should be or can be "later".

The adjective (141 words) turned out to be noticeably less numerous. In both samples, "neutral" adjectives are used more often in professional communication (42,65% and 47,95% respectively). In all probability, it illustrates the efforts of male and female doctors to remain emotionally neutral, since, on the one hand,

Table 1. The dominant categories and lexemes of different parts of speech within the male and female doctors samples

Part of speech (total word count)	«Male doctors» sample			«Female doctors» sample		
	Total	Basic category (absolute/ relative total count)	Basic lexemes	Total	Basic category (absolute/ relative total count)	Basic lexemes
I. Main parts of speech (7273)	**4262**	-	-	**3011**	-	-
Pronoun (2698)	1612 (37,82 %)	«You» (743/46,09 %)	«you», «your», «yours»	1086 (36,07%)	«You» (542/49,91 %)	«you», «your», «yours»
Noun (1642)	863 (20,25 %)	«Diseases and their symptoms» (169/19,58 %)	«pain», «disease, illness, disorder»	779 (25,87 %)	«Examination, treatment and results» (166/21,31 %)	«analyses, examination», «reffer-al», «treatment»
Verb (1537)	926 (21,73 %)	«Be» (362/39,09 %)	«be, continue», «will be», «was»	611 (20,29 %)	«Communi-cation and its components» (186 / 30,44 %)	«speak, tell», «understand»
Adverb (1121)	691 (16,21 %)	«Temporality» (201 / 29,09 %)	«afterwards, then», «now»	430 (14,28 %)	«Temporality» (160 / 37,21 %)	«now», «after-wards, then»
Adjective (141)	68 (1,60 %)	«Neutral» (29 / 42,65 %)	«such», «com-mon»	73 (2,42 %)	«Neutral» (35 / 47,95 %)	«common», «such»
Numeral (134)	102 (2,39 %)	–	«three», «four», «once, several times»	32 (1,06 %)	–	«once, several times», «three»
II. Function words (4605)	**2788**	**-**	**The most frequent part**	**1817**	**-**	**The most frequent part**
Conjunction (2003)	1169 (41,93 %)	–	«and» (234 / 20,02 %)	834 (45,90 %)	–	«and» (196 / 16,77 %)
Preposition (1591)	1062 (38,09 %)	–	«in» (408 / 38,42 %)	529 (29,16 %)	–	«in» (202 / 30,89 %)
Particle (603)	376 (13,49 %)	–	«no, not» (133 / 35,37 %)	227 (12,49 %)	–	«no, not» (75 / 33,04 %)
Interjection (277)	181 (4,10 %)	–	«please» (125 / 69,06 %)	96 (2,81 %)	–	«please» (51 / 53,13 %)
Parenthetical expression (17)	11 (0,39 %)	–	«for example» (only)	6 (0,33 %)	–	«for example» (only)

these specialists should not provoke the patient to possible affective "outbursts", and, on the other hand, they should prevent their own emotional "burnout".

The least frequent of all the recorded main parts of speech is the numeral (134 words). In this case, male doctors use numerals approximately twice as often as female doctors (2,39% and 1,06% respectively). Apparently, this is one of the indicators of a greater effort made by men to quantify reality related, in particular, to the sphere of human health, its disorders, and methods of recovery.

Let us briefly analyze the situation with function words. Generally, the dominant function part of speech (2003 words) was the conjunction. Its relative share is quite high in both samples (41,93% and 45,90%) with the predominance of an "and" conjunction, which indicates a significant semantic coherence of the speech of male and female doctors.

The second most commonly used function part of speech was the preposition (1591 words). Its relative rate is noticeably higher in the sample of male doctors while comparing to the sample of female doctors (38,09% vs 29,16%). Moreover, the dominant "in" preposition in both samples has also a higher frequency in the verbal communication of men (38,42% for sample 1 and 30,89% for sample 2). This indicates a clearer orientation of men as specialists to the definition and discussion and, in particular, to the localization of certain phenomena (symptoms of a disease, the location of a patient, etc.).

The particle turned out to be the third most common function word (603 words). In general, particles (as well

Table 2. The dominant categories and lexemes of different parts of speech in samples of male and female patients

Part of speech (total word count)	«Male patients» sample			«Female patients» sample		
	Total	Basic category (absolute/ relative total count)	Basic lexemes	Total	Basic category (absolute/ relative total count)	Basic lexemes
I. Main parts of speech (2949)	**1114**	-	-	**1835**	-	-
Pronoun (961)	407 (36,54 %)	«I» (201/49,39 %)	«I», «me», «my»	554 (30,19%)	«I» (291 / 52,53 %)	«I», «me», «my»
Adverb (702)	291 (26,12 %)	«Temporality» (91 / 31,27 %)	«sometimes», «afterwards, then»	411 (22,40 %)	«Temporality» (124 / 37,21 %)	«sometimes»,«now»
Verb (557)	207 (18,58 %)	«Be» (66 / 31,88 %)	«was»	350 (19,07 %)	«Be» (124 / 35,43 %)	«was»
Noun (533)	156 (14,00 %)	«Diseases and their symptoms» (43 / 27,56 %)	«pain», «problems»	377 (20,54 %)	«Temporality» (83 / 22,02 %)	«day», «years», «time»
Numeral (108)	37 (3,32 %)	–	«one», «first», «three»	71 (3,87 %)	–	«three», «two»
Adjective (88)	16 (1,44 %)	«Neutral» (only)	«such», «last»	72 (3,92 %)	«Neutral» (60 / 47,95 %)	«such», «last»
II. Function words (2444)	**1058**	**-**	**The most frequent part**	**1386**	**-**	**The most frequent part**
Conjunction (829)	369 (34,88 %)	–	«and» (122 / 33,06 %)	460 (33,19 %)	–	«and» (150 / 32,61 %)
Particle (756)	313 (29,58 %)	–	«no, not» (153 / 48,88 %)	443 (31,96 %)	–	«no, not» (201 / 45,37 %)
Preposition (723)	296 (27,98 %)	–	«in» (113 / 38,18 %)	427 (30,81 %)	–	«in» (158 / 37,00 %)
Exclamation (136)	80 (7,56 %)	–	«well» (57 / 71,25 %)	56 (4,04 %)	–	«well» (46 / 82,14 %)

as the dominant negative particles "no" and "not") are used by both male and female doctors to approximately the same extent (average particle rates are 13,49% and 12,49%, negative particles – 35,37% and 33,04% respectively).

Another part of function word analyzed was the exclamation (277 words found). Surprisingly, but in their professional communication, male doctors use exclamations approximately twice as often as female doctors (4,10% vs 2,81%). Moreover, male doctors also use the dominant expression of "please" more often (69,06% vs 53,13%). In this regard, we assume that in the field of relevant professional communication, men find it somewhat more difficult to hide their needs and expectations compared to women. However, a single "for example" parenthetical expression (17 words) was found at an approximately the same level in both samples (0,39% and 0,33%).

The results obtained in the following two samples (male patients and female patients) are summarized in Table 2.

As can be seen from Table 2, a total of 2172 statistically significant words were recorded in sample 3, and 3221 in sample 4. Thus, on average, male patients used 75 words in their communication, and female patients used 67. In our opinion, such a difference is not significant. The significantly lower average number of words used by male and female patients (compared to male and female doctors) can be explained by the distress experienced during an appointment with a specialist, where the words of the doctor often become more important than their own. Additionally, psychological defense mechanisms may also be triggered (in particular, repression, and as a result, an unwillingness to talk about certain matters).

DISCUSSION

First of all, it is worth noting that this study is a continuation of our previous scientific work [5-8]. In works [5, 6], in particular, we were able to establish and describe

psycholinguistic indicators of doctors' communication in wartime based on the analysis of doctor-patient dialogues. In general, professional communication of doctors in wartime is poorly researched, despite its undoubted relevance [1, 9, 10].

Based on the conducted content analysis of gender-specific features of professional medical interaction, it can be stated that male doctors use more words (181 versus 138 for female doctors), which indicates higher speech activity within the professional role. Their speech is characterized by a predominance of verbs and rational structuring. Female doctors more often use nominative constructions with a predominance of nouns, pronouns, and adverbs, which indicates the objectification of symptoms and an empathic orientation. Female patients show higher speech activity (135 words versus 89 for male patients), ask questions more often (62 % vs. 38 %), and use more emotionally colored vocabulary and modal words, which indicates increased anxiety.

The most frequent among the main parts of speech in samples 3 and 4, as well as in the samples of male and female doctors (1 and 2), were pronouns (total word count: 961). However, male patients use pronouns somewhat more often than female patients (the relative frequency of statistically significant pronouns in sample 3 and sample 4 is 36,54 % and 30,19 %, respectively). In other words, men are more inclined to personalize and, therefore, to specify communication, as well as to show an understanding of their own health problems and their causes. However, the dominant "I" lexeme is represented in both samples to approximately the same extent (49,39 % and 52,53 %).

In the samples of male and female doctors, the second most frequent part of speech was a noun, but in the samples of male and female patients, it was an adverb (702 words), which is a part of speech that expresses a sign of an action, state, or quality. The established fact testifies to the greater orientation of patients to expressing the corresponding signs of their own processes and states related to health, while doctors primarily name a phenomenon or fact.

In samples 3 and 4, the "Temporality" notion dominates within the specified part of speech (relative indicators are 31,27 % and 37,21 %, respectively). As it can be seen, women use the category of adverbs somewhat more often. In addition, it is more important for them what is happening "now" with their health, while for men – it is what will happen "later, then."

The third most numerous main part of speech is the verb (557 words). It is used by both male and female representatives of both samples to approximately the same extent (18,58 % vs 19,07 %). Moreover, the basic category "To be" was found to be dominant in both samples (31,88 % and 35,43 %). Interestingly, within this category, both male and female patients use the lexeme "was" most often, which means they talk about certain events or phenomena in the past tense. This can be associated with the mental operation of comparison as well as with nostalgia for a happier (pre-war) past.

Unlike in the first two samples, the noun became only the fourth most important part of speech in a generalized analysis of the results for all four samples. At the same time, while (as a part of speech) its relative importance is less than that of a verb for male patients, it is somewhat higher for female patients. Here is the relative frequency of nouns and verbs usage: 14,00 % and 18,58 % in the sample of male patients, and 20,54 % and 19,07 % – in the sample of female patients. Considering such indicators, it can be argued that for men, it is relatively more important not often to name certain of their symptoms, but to indicate what led to them or how the situation can be changed. We also note differences between the samples of male and female patients in the leading category of nouns: it is "Diseases and their symptoms" for men (27,56 %), and "Temporality" – for women (22,02 %). Accordingly, while men mention "pain" in this context more often, women talk more about "days" and "years". Thus, male patients are more focused on discussing the current symptoms of their diseases while female patients delve more into the time trajectories and prospects of the course of the diseases.

Unlike the samples of doctors, the numeral is not the least frequent among all the recorded main parts of speech (108 words) in the samples of patients. At the same time, representatives of both samples use numerals to approximately the same extent (3,32 % vs 3,87 %).

Instead, the adjective was the least significant in terms of its quantitative representation in both analyzed samples (88 words). Female patients use adjectives in their speech approximately three times more often than male patients (1,44 % vs 3,92 %). This indicates, in particular, the lower ability of women to hide their emotions in communication. Male patients use only neutral adjectives in their speech (100 %), while female patients use even less than a half (47,95 %). We consider this as a manifestation of men's reluctance to give negative or positive characteristics to their states and processes through their attempts to verbally maintain emotional neutrality.

Now, let us analyze the situation with the function words. Both in the samples of male and female doctors, the conjunction (829 words) became dominant again, and the relative frequency of its use was approximately the same in both patient samples (34,88 % and 33,19 %,

respectively). In the speech of patients, the "and" conjunction also prevails (33,06 % and 32,61 %).

In contrast to the recorded texts of verbal communication of doctors, the second most important functional part of speech was the particle (756 words). In all four samples, the negative particles "no" and "not" turned out to be significantly dominant ones (relative indicators in samples 3 and 4 are 48,88 % and 45,37 %, respectively). Next, male and female patients use negations in their speech more often than male and female doctors (the relative rates of negations in doctors' speech are 35,37 % and 33,04 %, respectively). However, any significant gender differences in all these speech contexts were not recorded.

The third most numerous function word was the preposition (723 words). The relative frequency of its use in speech by both men and women does not differ significantly (27,98% and 30,81%, respectively). Moreover, the dominant (in both samples) preposition "in" is also approximately equally found in both samples (sample 3 has 38,18%, sample 4 – 37,00%).

Another function part of speech that was found in the samples of patients is the exclamation (136 words). Similarly, with regard to the recorded situation with male and female doctors, it was also found in the samples of male and female patients that men use exclamations approximately twice as often as women (7,56% and 4,04%, respectively). In general, patients resort to exclamations about twice as often as the specialists to whom they apply for medical care. Moreover, while doctors mostly use the "please" expression, the patients use the "no" exclamation (71,25% and 82,14%). Therefore, during a doctor's appointment, patients express their experiences through individual exclamations with women doing this more often.

The results of our research complement the work of some scientists, in particular the work [8], in which attention is focused on the macro level of the political economy of health care and the role of women during armed conflict. For the first time, we turn to the micro level, i.e. to live medical communication that unfolds between a doctor and a patient. The study [4] analyzed gender and narrative in digital political communication during wartime, and our study was the pioneer to identify unique linguistic markers inherent in direct (face-to-face) professional interaction in the medical field under wartime conditions.

CONCLUSIONS

Based on the content analysis of dialogues, specific gender speech patterns were investigated and identified for the first time. They directly affect the quality, efficiency, and emotional background of medical care in wartime conditions.

The study confirms the presence of gender-based models of medical communication, which are exacerbated in wartime. The results of the study can be used in training on the development of communication skills for medical workers, in writing clinical protocols, as well as in psychological support for wounded and displaced persons. It is advisable to integrate the obtained data into educational programs for the training of future doctors to form their sensitivity to gender aspects of medical communication.

REFERENCES

1. Kuchyn IL, Stuchynska NV, Saveliuk NM et al. Investigation of psycholinguistic indicators of doctors' professional communication under war conditions in Ukraine. Med Pharm Educ Discourses. 2024;2:31–37. doi:10.32782/eddiscourses/2024-2-1. DOI
2. Kuchyn IL, Stuchynska NV, Saveliuk NM et al. Studying of psycholinguistic features of doctors' professional communication under war conditions. Wiad Lek. 2024;77(4):670–675. doi:10.36740/WLek202404109. DOI
3. Kuchyn IL, Vlasenko OM, Stuchynska NV et al. Physical health of students and digitalization of higher medical education: Risk factors. Wiad Lek. 2023;76(4):758-764. doi: 10.36740/WLek202304109. DOI
4. Pavliuc A. Gender and narrative in digital political communication during Russia's full-scale invasion of Ukraine. Media, War & Conflict. 2025;0(0):1-19. doi: 10.1177/17506352241309225. DOI
5. Koval LM. Psykholinhvistychnyi analiz tekstu yak intehratyvnyi metod suchasnoho movoznavstva [Psycholinguistic analysis of the textas an integrative method of modern linguistics]. Collections of scientific works of the professor-teaching staff of Vasyl Stus DonNU. 2021, p. 118–120. (Ukrainian)
6. Asanova A, Khaustova O. Typical difficult situations in doctor-patient interactions. Psychosomatic Medicine and General Practice. 2018;3(3):e0303125. doi: 10.26766/pmgp.v3i3.125. DOI
7. Blahun S, Stuchynska N, Lytvynenko N et al. The Communicative Competence of Future Healthcare Specialists in the Context of Pharmaceutical Market Transformation. Archives of Pharmacy Practice. 2022;13(1):74–81. doi: 10.51847/geyd1jzGpp. DOI
8. Meagher K, Attal B, Patel P. Exploring the role of gender and women in the political economy of health in armed conflict: a narrative review. Global Health. 2021;17:88. doi: 10.1186/s12992-021-00738-9. DOI

9. Chaban O, Khaustova O. Psykhichne zdorovia v period pandemii COVID-19 (osoblyvosti psykholohichnoi kryzy, tryvohy, strakhu ta tryvozhnykh rozladiv). [Mental health during the COVID-19 pandemic (features of psychological crisis, anxiety, fear and anxiety disorders)]. NeuroNews. 2020;3(114):26–36. https://neuronews.com.ua/uploads/issues/2020/3(114)/nn20_3_26-36.pdf [Accessed 30 January 2025] (Ukrainian)
10. Chaban O, Khaustova O. Medyko-psykholohichni naslidky dystresu viiny v Ukraini: shcho my ochikuiemo tas hcho potribno vrakhovuvaty pry nadanni medychnoi dopomohy? [Medical and psychological consequences of war distress in Ukraine: what we expect and what needsto be taken into account when providing medical care?]. Ukrayins'kyy medychnyy zhurnal. 2022;4:150. doi: 10.32471/umj.1680-3051.150.232297. (Ukrainian) DOI

The research was performed within the framework of a research topic «Ensuring the quality of computer science and physics and mathematics training of future healthcare professionals in the classroom and distance learning environment» (2024-2026, № state registration 0124U000724).

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Nataliia V. Stuchynska
Bogomolets National Medical University
34 Beresteiskyi Ave., 03680 Kyiv, Ukraine
e-mail: nvstuchynska@gmail.com

ORCID AND CONTRIBUTIONSHIP
Natalia V. Stuchynska: 0000-0002-5583-899X A B C D E F
Nina P. Lytvynenko: 0000-0002-6572-2392 A B C D E F
Natalia M. Saveliuk: 0000-0001-5246-9677 B C E
Nina A. Chernenko: 0000-0001-9438-433X A B E F
Olena V. Sadovnycha: 0000-0001-7031-7538 B C E
Iya P. Kaminska: 0000-0001-7156-0484 A B F
Oksana M. Kikinezhdi: 0000-0002-9240-279X B C E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 06.02.2025
ACCEPTED: 02.06.2025

ORIGINAL ARTICLE

CONTENTS

Effectiveness and safety of intravenous iron sucrose in correcting ferritin level for female patients with iron deficiency anemia

Maysam Riyadh Mohammed Hussein Alaasam[1], Raffat Hilal Abboodi[2], Hasanat Abdulrazzaq Bakir Aljabery[1]
[1]COLLEGE OF MEDICINE KUFA UNIVERSITY, KUFA, IRAQ
[2]ALNAJAF TEACHING HOSPITAL, ALNAJAF, IRAQ

ABSTRACT

Aim: The study aims to evaluate the effectiveness and safety of intravenous iron sucrose in correcting serum ferritin in female patients with iron deficiency anemia.
Materials and Methods: A prospective clinical study was conducted at Alsader Medical City in AlNajaf City/ Iraq. We enrolled 100 female patients with iron deficiency anemia, and hemoglobin less than 12 mg/dl. Two hundred mg of elemental iron was given twice weekly over 2.5 hours, and the patients were observed closely for any potential side effects. The main effectiveness endpoint gained from variation in serum ferritin and hemoglobin from baseline to end of the study. The safety evaluation includes recording any side effects developed either during or after intravenous administration.
Results: The mean of hemoglobin concentration at bassline was 8.05±0.891 mg/dl, and the mean of hemoglobin after one month of treatment was 11.234±1.232G/dl,($p < 0.0001$). There was an increase in serum ferritin concentration from the beginning of the study with 10.2±0.23ng/dl to 224.12±0.772 ng/dl, ($p<0.0001$) after 1 month of treatment. No one of the patients had any serious or lethal side effects.
Conclusions: Intravenous iron sucrose is an effective and safe option for the correction of serum ferritin in female patients with iron deficiency anemia.

KEY WORDS: Ferritin, intravenous iron sucrose, IDA

Wiad Lek. 2025;78(6):1098-1102. doi: 10.36740/WLek/203830 DOI

INTRODUCTION

Iron is important for almost all organisms and vital for growth and survival [1]. It plays a vital role in numerous biological activities, including DNA biosynthesis, transport of oxygen, and generation of cellular energy [2]. Most of the body's iron is used in erythrocytes to bind and transport oxygen [3]. Iron deficiency is the diminution of total-body iron, particularly of hepatocyte iron stores and macrophages. Because most of the body's iron is used for hemoglobin synthesis, anemia is the most apparent sign of iron deficiency [4]. WHO defines anemia as Hb <13 g/dL in adult males and Hb <12 g/dL in adult females [5]. Anemia affects quality of life and is associated with fatigue, impaired cognitive function, and decreased capacity for work [6, 7]. The major cause of iron deficiency is blood loss, especially during menstruation or due to bleeding from the gastrointestinal tract; the next most common reason is poor absorption [8]. Women have a higher incidence of iron deficiency [9].

Serum ferritin is the most dependable early test for diagnosing of iron deficiency anemia (IDA) [10]. Ferritin is present in most tissues as a cytosolic protein, and extracellular ferritin plays a role as an iron carrier to deliver iron to cells. A single ferritin molecule can sequester up to 4500 iron atoms, thus making it potentially a very effective iron delivery system [10]. In the treatment of IDA, oral iron supplements are an inexpensive and available effective option. There are many formulations of oral iron like iron salt example, ferrous sulfate, ferrous gluconate, and ferrous fumarate. Other public iron formulations include ferrous succinate, ferrous ascorbate, ferric citrate, carbonyl iron, liposomal iron, heme iron polypeptide, and polysaccharide iron complexes (PICs) [11]. The problem with oral iron is the long duration of treatment; it requires 3-6 months for serum ferritin to normalize. On the other hand, serum ferritin does not rise with the oral iron treatment of IDA until hemoglobin levels are normal and the initial elevation seen with a double dose is most likely due to the absorption of iron exceeding the utilization for erythropoiesis causing brief storage, that rapidly decreased as reflected by the rapid decrease in serum ferritin when iron stopped [12]. In addition, the response to oral iron is unpredictable,

most likely due to malabsorption of iron and poor compliance with medication [13]. Common adverse effects of oral iron include gastric upset, vomiting, diarrhea, constipation, metallic taste, and dark stool [14]. Intravenous iron can avoid all these problems, and it is a good alternative to oral iron. In addition to that, there are certain situations in which intravenous iron is considered as a first choice like cases of severe anemia, the need for rapid correction of iron before surgery [15], or in patients with IDA and congestive heart failure [16]. An important concern is the safety of the available formulation. Although most of the newer generations of intravenous iron show a good safety profile, its use has been limited to treating IDA in patients with renal impairment on hemodialysis [17].

Iron sucrose is one of the first intravenous iron preparations; it is one of the oldest therapeutic agents still widely used today. Without a doubt, it is the most frequently used intravenous iron preparation worldwide [18, 19]. Despite its safety, iron sucrose has many adverse effects including allergic reaction**s** (e.g. rash, pruritus, urticaria, flushing), gastrointestinal (e.g. diarrhea, nausea, and vomiting), systemic (e.g fever, tachycardia, headache, and hypotension), respiratory (e.g. wheezing or dyspnea) and serious side effects (e.g. cardiac arrest, death, anaphylactic reactions, and shock [20].

AIM

This study aims to evaluate the effectiveness and safety of intravenous iron sucrose in the correction of serum ferritin in female patients with iron deficiency anemia.

MATERIALS AND METHODS

A prospective clinical study was conducted at Alsader Medical City in AlNajaf / Iraq. The study was carried out from June 2017 to April 2023. We enrolled 100 female patients with iron deficiency anemia with hemoglobin less than 12 g/dl.

The cause of anemia is mostly due to menstruation and abnormal uterine bleeding. Patients with anemia due to causes other than iron deficiency, patients with hypersensitivity to iron, patients with acute inflammation, and pregnant women were excluded from the study.

The current study was conducted following the Declaration of Helsinki (as revised in 2013), and approved by an Ethics committee of the medical college/Kufa University.

The subjective of the study was explained to the patients in Arabic language, and informed consent was taken from all the participants. After careful history and examination of all participants, age, and weight were reordered. A specimen of whole blood was collected in ethylene diamine tetra acetic acid (EDTA) containing a Vacutainer tube (purple top) for complete blood count with reticulocyte count, RBC indices, and ESR measurement, before iron administration and four weeks later.

CBC analysis was performed using the Sysmex XN-550 hematology analyzer, while serum ferritin levels were measured using the Roche Cobas e 411 immunoassay analyzer.

To ensure the reliability of laboratory measurements, duplicate sample testing was performed on a subset of blood samples, and all hematology and immunoassay analyzers were calibrated daily using manufacturer-provided standards. Additionally, the intra-assay and inter-assay coefficient of variation (CV) was calculated for ferritin and hemoglobin measurements to assess reproducibility.

The iron dose is calculated according to Ganzoni Equation [21]**:**

Total iron deficit [mg] = body weight [kg] x (target Hb-actual Hb) [g/dl] x 2.4 + depot iron [mg].

The target hemoglobin is 12 g/dl.

Iron sucrose diluted in 0.9% NaCl solution, final concentration range is 1-2 mg of elemental iron/mL

Two hundred mg of elemental iron was given twice weekly over 2.5 hours, and the patients were observed closely for potential side effects.

All patients completed the study.

The main effectiveness endpoint gained from variation in serum ferritin and hemoglobin from baseline to end of the study.

The safety evaluation include**s** recording any side effect**s** developed either during or after intravenous administration.

The Statistical Package for the Social Sciences (SPSS) was used to analyze all data; data are presented as mean and standard deviation. A paired sample t-test was used to compare the latest and baseline ferritin concentrations.

RESULT

The mean age of the patient was 32.3±0.36 years, ranging between 16-55 years old. The mean BMI was 24.7±0.14 (Table 1).

The mean of hemoglobin concentration at bassline was 8.05±0.891 G/dl, and the mean of hemoglobin after one month of treatment was 11.234±1.232G/dl, ($p < 0.0001$). There was an increase in serum ferritin concentration from the beginning of the study with 10.2±0.23ng/dl, to 224.12±0.772 ng/dl, ($p<0.0001$) after 1 month of treatment (Table 2).

Table 1. Baseline characteristic of the study population

Parameters	mean±sd
Age, year	32.3±0.36
BMI	24.7±0.14
Hemoglobin, g/dl	8.05±0.891
Ferritin, ng/ml	10.2±0.23

The pretreatment mean of corpuscular hemoglobin (MCH) was 18.236 ±0.934 pg/cell, which increased to 29.48±1.350 pg/cell (p <0.0001) after 1 month. Likewise, there is an increase in mean corpuscular volume (MCV) from 64.124±0.12 fL to 75.56± 0.255 fL (p <0.0001). The mean corpuscular hemoglobin concentration (MCHC) increased from 23.54±0.14 pg/cell at the bassline to 30.25±0.654 pg/cell at the end of the end of the study (p <0.0001). The reticulocyte count mean before treatment was 0.468± 0.115% increased to 1.664± 0.224% (p <0.0001) post-treatment. RDW-CV change from 16.76±0.776% pretreatment to14.53±0.132% (p <0.0001) after 1 month of treatment. ESR mean was 27.9±0.13 mm/hr at the beginning of the study changed to 18.9±0.82 mm/hr (p <0.0001) at the end of it (Table 3).

Over the study period, only one patient developed hypotension. 10 patients had dizziness, 5 patients developed fatigue, 1 patient had vomiting and 7 patients had nausea. 2 patients had pruritus and 15 patients had burning at the injection site. No one of the patients had any serious or lethal side effects. Most of the side effects are related to methods of administration, rapid administration of the drug is the leading cause of the side effects, when we changed the duration and rate of administration, most of the side effects disappeared.

DISCUSSION

Serum ferritin is a useful and convenient test to assess the status of iron storage; Low serum ferritin is very specific for iron deficiency anemia [10]. The duration of serum ferritin correction is 3-6 months with oral iron therapy, which is one of the drawbacks of oral treatment. Poor adherence to oral iron leads to the ineffectiveness of the treatment in the correction of serum ferritin and the importance of an alternative measure [22].

Intravenous iron sucrose is cleared rapidly from the serum of the patient, with a terminal half-life of 5.3 ± 1.6 h and total body clearance of 1.23 ± 0.22 L/h (20.5 ± 3.7 mL/min) [23]. Following intravenous administration of iron sucrose into patients with anemia, the liver, spleen, and bone marrow rapidly take up iron. Most (97%) of injected iron is used for red blood cell (RBC) synthesis in these patients [24].

Previously, the use of intravenous iron sucrose was restricted to patients with chronic kidney disease on regular hemodialysis, nowadays many promising attempts to use intravenous iron sucrose in the treatment of IDA in patients without hemodialysis.

In this study, the average increase in hemoglobin was > 3 mg/dl after 4 weeks of treatment, which is consistent with other studies that found intravenous iron sucrose is effective in correcting hemoglobin in IDA [25, 26].

The important finding in this study is that Serum ferritin increased> 200ng/ml, after 4 weeks of treatment even before hemoglobin returns normal. There are few studies focused on the effect of intravenous iron on ferritin levels, Blunden RW, *et al*. found that serum ferritin peaks 7-9 days after intravenous iron dextran [27]. The results of the current study were similar to the results of other studies which show that serum ferritin increase with intravenous iron sucrose administration [28, 29].

The safety of iron sucrose was evaluated by the appearance of side effects during or after infusion. Our result found that most of the side effects during administration were due to the rate of administration and when we changed it, most of the side effects disap-

Table 2. Hemoglobin and serum ferritin before treatment and after 4 weeks of treatment

Parameters	Pretreatment level (mean±sd)	Post-treatment level (mean±sd)	P-value
Hemoglobin, g/dl	8.05±0.891	11.234±1.232	< 0.0001
Ferritin, ng/ml	10.2±0.23	224.12±0.772	< 0.0001

Table 3. RBC indices before treatment and after 4 weeks of treatment

Parameter	Pretreatment level (mean±sd)	Post-treatment level (mean±sd)	P-value
MCH pg/cell	18.236 ±0.934	29.48± 1.350	<0.0001
MCV Fl	64.124±0.12	75.56± 0.255	< 0.0001
MCHC pg/cell	23.54±0.14	30.25±0.654	<0.0001
Reticulocyte count %	0.468± 0.115	1.664± 0.224	<0.0001
RDW-CV%	16.76±0.776	14.53±0.132	<0.0001
ESR mm/hr	27.9±0.13	18.9±0.82	<0.0001

peared and the patients continued their doses without any side effects. Most of the side effects were minor, this finding is consistent with other studies that found iron sucrose is safe in the management of IDA [30].

CONCLUSIONS

Intravenous iron sucrose is an effective and safe option for the correction of serum ferritin in female patients with IDA.

REFERENCES

1. Macdougall IC, Comin-Colet J, Breymann C et al. Iron sucrose: A wealth of experience in treating iron deficiency. Adv Ther. 2020;37(5):1960–2002. doi: 10.1007/s12325-020-01323-z. DOI
2. Ning S, Zeller MP. Management of iron deficiency. Hematology Am Soc Hematol Educ Program. 2019;2019(1):315–322. doi: 10.1182/hematology.2019000034. DOI
3. Camaschella C. Iron deficiency. Blood. 2019;133(1):30–39. doi: 10.1182/blood-2018-05-815944. DOI
4. Lee S, Ryu KJ, Lee ES et al. Comparative efficacy and safety of intravenous ferric carboxymaltose and iron sucrose for the treatment of preoperative anemia in patients with menorrhagia: An open-label, multicenter, randomized study. J Obstet Gynaecol Res. 2019;45(4):858–864. doi: 10.1111/jog.13893. DOI
5. Jacob OM, Kant S, Haldar P et al. Intravenous iron sucrose and change in hemoglobin, ferritin, and oxidative stress markers among moderately anemic pregnant women. Indian J Public Health. 2020;64(1):11–16. doi: 10.4103/ijph.IJPH_464_18. DOI
6. Bhavi SB. Serum ferritin changes on administration of intravenous iron in iron deficiency anemia in pregnancy. Int J Clin Obstet Gynaecol. 2018;2(5):134–137.
7. De Franceschi L, Iolascon A, Taher A, Cappellini MD. Clinical management of iron deficiency anemia in adults: Systemic review on advances in diagnosis and treatment. Eur J Intern Med. 2017;42:16–23. doi: 10.1016/j.ejim.2017.04.018. DOI
8. Shuoyan N, Zeller MP. Recent advances in iron-deficiency anemia treatment. Hematology Am Soc Hematol Educ Program. 2021;2021(1):320–330.
9. Van Wyck DB, Spinowitz BS, Adhikarla R et al. Safety and efficacy of iron sucrose in sensitive patients. Am J Kidney Dis. 2020;75(3):88–97. doi: 10.1053/ajkd.2000.8276. DOI
10. Rodolfo D, Cançado P, Novis de Figueiredo P et al. Efficacy and safety of intravenous iron sucrose in adults with iron deficiency anemia. Rev Bras Hematol Hemoter. 2021;43(1):439–443. doi: 10.5581/1516-8484.20110119. DOI
12. Cançado RD, Muñoz M. Intravenous iron therapy: how far have we come? Rev Bras Hematol Hemoter. 2011;33(6):461–469. doi: 10.5581/1516-8484.20110123. Crielaard BJ, Lammers T, Rivella S. Targeting iron metabolism in drug discovery and delivery. Nat Rev Drug Discov. 2017;16(6). DOI
13. Munoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia. 2017;72(2):233–247. doi: 10.1111/anae.13773. DOI
14. Tolkien Z, Stecher L, Mander AP et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: A systematic review and meta-analysis. PLoS One. 2015;10(2):e0117383. doi: 10.1371/journal.pone.0117383. DOI
15. Ganz T. Systemic iron homeostasis. Physiol Rev. 2013;93(4):1721–1741. doi: 10.1152/physrev.00008.2013. DOI
16. DeLoughery TG. Iron deficiency anemia. Med Clin North Am. 2017;101(2):319–332. doi: 10.1016/j.mcna.2016.09.004. DOI
17. McLean E, Cogswell M, Egli I et al. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005. Public Health Nutr. 2009;12(4):444–454. doi: 10.1017/S1368980008002401. DOI
18. Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Dis. 2006;12(2):123–130. doi: 10.1097/01.MIB.0000196646.64615.db. DOI
19. Seid MH, Dahl NV, Lau G et al. Effect of ferumoxytol on quality of life in iron deficiency anemia from abnormal uterine bleeding. Obstet Gynecol. 2014;123(5):181S–182S. doi:10.1097/01.AOG.0000447200.43420.E9. DOI
20. Guyatt GH, Patterson C, Ali M et al. Diagnosis of iron-deficiency anemia in the elderly. Am J Med. 1990;88(3):205–209. doi: 10.1016/0002-9343(90)90143-2. DOI
21. Wheby MS. Effect of iron therapy on serum ferritin levels in iron-deficiency anemia. Blood. 1980;56(1):138–140.
22. Auerbach M, Ballard H, Glaspy J. Clinical update: Intravenous iron for anaemia. Lancet. 2007;369(9572):1502–1504. doi: 10.1016/S0140-6736(07)60689-8. DOI
23. Auerbach M, Ballard H. Clinical use of intravenous iron: Administration, efficacy, and safety. Hematology Am Soc Hematol Educ Program. 2010;2010(1):338–347. doi: 10.1182/asheducation-2010.1.338. DOI
24. Critchley J, Dundar Y. Adverse events associated with intravenous iron infusion: A systematic review. Transfus Altern Transfus Med. 2007;9(1):8–36. doi:10.1111/j.1778-428X.2007.00042.x. DOI
25. Lee S, Ryu KJ, Lee ES et al. Comparative efficacy and safety of intravenous ferric carboxymaltose and iron sucrose for the treatment of preoperative anemia in patients with menorrhagia: an open-label, multicenter, randomized study. J Obstet Gynaecol Res. 2019;45(4):858–

864. doi: 10.1111/jog.13893. DOI
26. Cançado RD, Figueiredo PON, Olivato MCA, Chiattone CS. Efficacy and safety of intravenous iron sucrose in treating adults with iron deficiency anemia. Rev Bras Hematol Hemoter. 2011;33(6):439–443. doi: 10.5581/1516-8484.20110119. DOI
27. Blunden RW, Lloyd JV, Rudzki Z, Kimber RJ. Changes in serum ferritin levels after intravenous iron. Ann Clin Biochem. 1981;18(4):215–217. doi: 10.1177/000456328101800405. DOI
28. Jacob OM, Kant S, Haldar P et al. Intravenous iron sucrose and change in hemoglobin, ferritin, and oxidative stress markers among moderately anemic pregnant women. Indian J Public Health. 2020;64(1):11–16. doi: 10.4103/ijph.IJPH_464_18. DOI
29. Van Wyck DB, Cavallo G, Spinowitz BS et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial. Am J Kidney Dis. 2000;36(1):88–97. doi: 10.1053/ajkd.2000.8276. DOI
30. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: establishing a safe dose. Am J Kidney Dis. 2001;38(5):988–991. doi: 10.1053/ajkd.2001.28587. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Maysam Riyadh Mohammed Hussein Alaasam
Kufa university
299G+HPX, Kufa St, Kufa, Najaf Governorate, Iraq
e-mail: maysam.alaasam@gmail.com

ORCID AND CONTRIBUTIONSHIP

Maysam Riyadh Mohammed Hussein Alaasam: 0000-0002-8888-8782 A B C D E F
Raffat Hilal Abboodi: 0009-0006-1640-3156 A C F
Hasanat Abdulrazzaq Bakir Aljabery: 0000-0002-7910-2725B C

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 05.02.2024
ACCEPTED: 08.05.2025

ORIGINAL ARTICLE

CONTENTS

Criteria of a smile in twins

Maryna A. Shundryk, Iryna Y. Marchenko, Iryna M. Tkachenko, Valeriy Y. Marchenko, Yaroslav Y. Vodoriz
POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

Aim: The purpose of the work was study of the influence of genetic and environmental factors on the formation of classic smile parameters.

Materials and Methods: Research was conducted on 12 people (6 pairs of (MZ) twins): 4 pairs of females and 2 pairs of males. The age of the patients was 17-28 years.

Results: In (MZ) twins, the criteria for an ideal smile coincide in 51.6% of cases, do not coincide in 26.6% of cases, there are no criteria in 21.8% of cases. Genetic factors have a significant influence on the morphological features of the teeth, because more than 50% of the parameters of an ideal smile in (MZ) twins are coincided.

Conclusions: Signs of external similarity in (MZ) twins, taking into account such morphological characteristics as the set of the eyes, the shape of the nose, lips and teeth are confirmed by photo documentation and biometric research methods. However, the ratio between lips, teeth and gums when forming a smile in (MZ) twins is the same in 51.6% of cases. Based on the results of this study, we cannot confirm the primary role of genetics in dental features such as the ideal smile criteria. Environmental factors (nature of nutrition, bad habits, sucking, tooth extraction, sleeping on the stomach, etc.) and traumas have a significant influence on the features of dental smile parameters.

KEY WORDS: monozygotic twins, criteria, smile, teeth, lips

Wiad Lek. 2025;78(6):1103-1110. doi: 10.36740/WLek/207371 DOI

INTRODUCTION

When people are happy, they smile. Among all variants of emotional expression on the human face, a smile functionally is the most positive but also the most complex option. However, not many people can boast of a naturally perfect smile. The attractiveness of a smile largely depends on the correct proportions and relationship of three elements: teeth, gums and lips.

Numerous studies indicate that the criteria for a smile are multifactorial in nature, and both genetic and environmental factors are involved in their formation.

Examining the state of dentition in twins, taking into account the influence of genetic and environmental factors, allows to determine the influence of these factors on many physical and behavioral features or anomalies [1-13]. This is possible because monozygotic twins are two independent organisms with absolutely identical genetic features, the difference between them can be explained by environmental factors [8, 13].

The idea of the twin method was formulated by F. Galton in 1865, but its final modification is associated with the name of H. Siemens. It was he who in 1924 justified the using of the twin method in genetics.

The character and a smile feature depend on the growth and development of the craniofacial complex, which is influenced by genetic and environmental factors and determines its morphological and functional features [11].

The results of scientific studies have shown a significant genetic influence on the length of the base of the skull, the body of the upper jaw and the length of the lower jaw. Environmental factors are mainly involved in determining the characteristics of the teeth (for example, the inclination of the incisors). Research on twins is a unique method of assessing the influence of genetic and environmental factors on personality formation [12]. (MZ) twins are the result of fertilization of one egg-cell, which at an early stage of embryogenesis is divided into two identical embryos. Each embryo has the same number and distribution of genes - the genotype, which is manifested by the same morphological features - the phenotype. Variations in (MZ) pairs are the result of the influence of various environmental factors, as well as the interaction of genetic and environmental factors. The model of (MZ) twins is used in dental practice, which makes it possible to study the differences in orofacial structures between (MZ) twins [2, 4, 6, 7].

Genetic modeling showed that additive genetic and unique environmental factors explained the variation in all measured occlusal characteristics to the best extent, except of width between mandibular canine. High heritability was observed for most intra-arch occlusal variables (0.61–0.85), including canine width and maxillary and mandibular molar width, dental arch depth and perimeter [10]. Environmental factors such as food, habits (sucking, etc.) and injuries strongly influence the characteristics of teeth [1, 5, 9, 14]. During the comparative analysis of bite anomalies in (MZ) and dizygotic (DZ) twins and determining the role of genetics and the environment, a high frequency of intrapair similarity of bite anomalies was determined (from 80 to 94%). The frequency of intrapair similarity in (MZ) twins was 100%, and in (DZ) twins - only 57%. This study found that environmental factors are responsible for a greater number of malocclusions.

Pairs of (MZ) twins show a higher level of correlation than pairs of (DZ) twins, which provides convincing evidence that genes play a significant role in the etiology of dental caries, periodontal diseases, and malocclusion [2,4]. The lack of data in the literature on the dynamics of the interaction of genetic and environmental factors in the formation of the main indicators of the ideal smile criteria made it necessary to carry out this study.

AIM

Clinical study of the influence of genetic and environmental factors on the formation of an ideal smile criteria.

MATERIALS AND METHODS

The research was conducted in 12 people: 6 pairs of (MZ) twins: 4 pairs of females and 2 pairs of males. The age of the patients was 17-28 years. Homozygosity of twins was confirmed by the coincidence of phenotypic traits, which are determined by numerous loci and have full penetrance under any external conditions. We noted signs of external similarity, taking into account morphological characteristics: color and shape of hair, eyebrows, color of the skin and iris of the eyes, cut of the eyes, shape of the nose, lips, outline and shape of the ears. A subjective examination of the patients was carried out, taking into account the place of birth and residence, transferred and concomitant diseases, psycho-emotional state of the twins, occupation and objective examination of the patients using photo documentation and biometric research methods.

Evaluation of patients' smiles was carried out according to the following parameters: 1. Parallelism of horizontal landmarks. 2. Smile line. 3. Gum level. 4. Vertical symmetry and the middle line. 5. "Golden ratio". 6. Proportions of teeth. 7. Interincisal angles. 8. Zenith of gingival contours. 9. Cutting edges position. 10. Interdental gingival papillae.

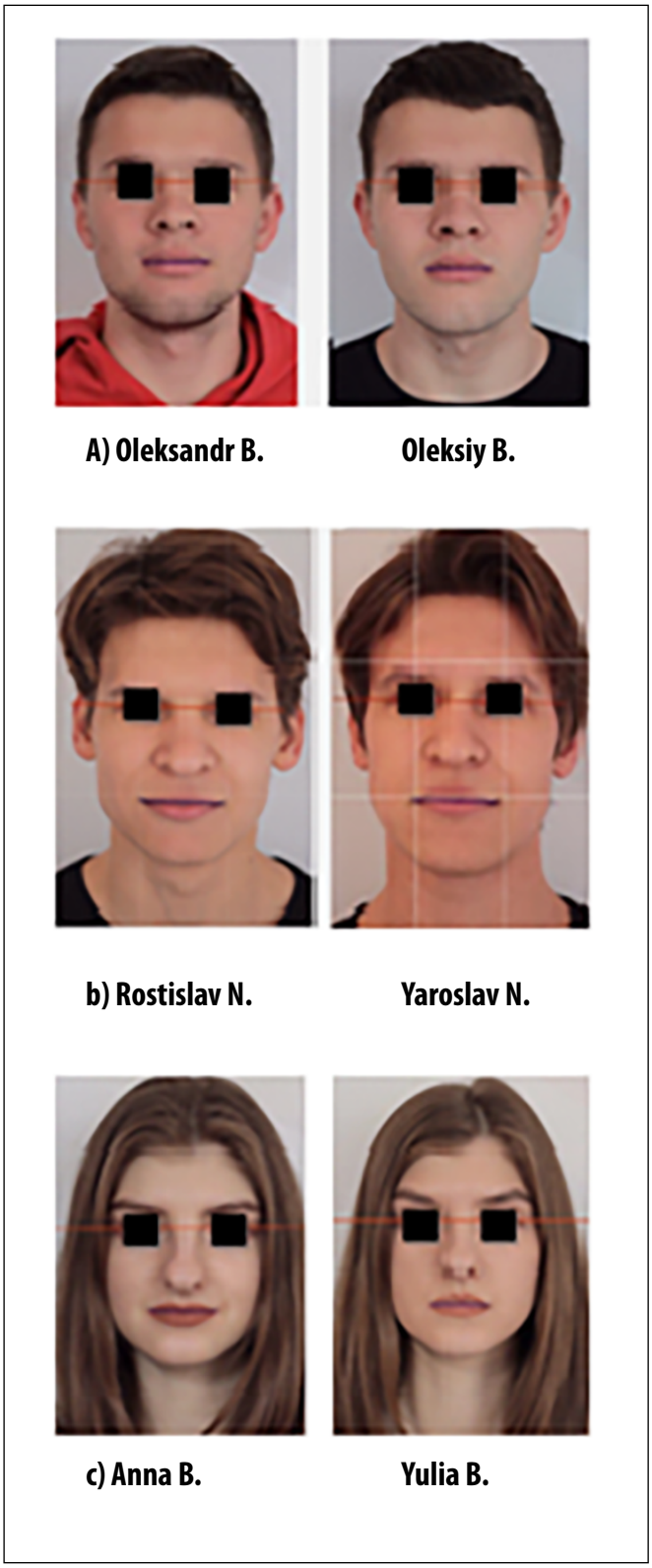

Fig. 1. Determination of the horizontal landmarks parallelism: a), b), c).

Fig. 2. Definition of the smile line: a), b), c).

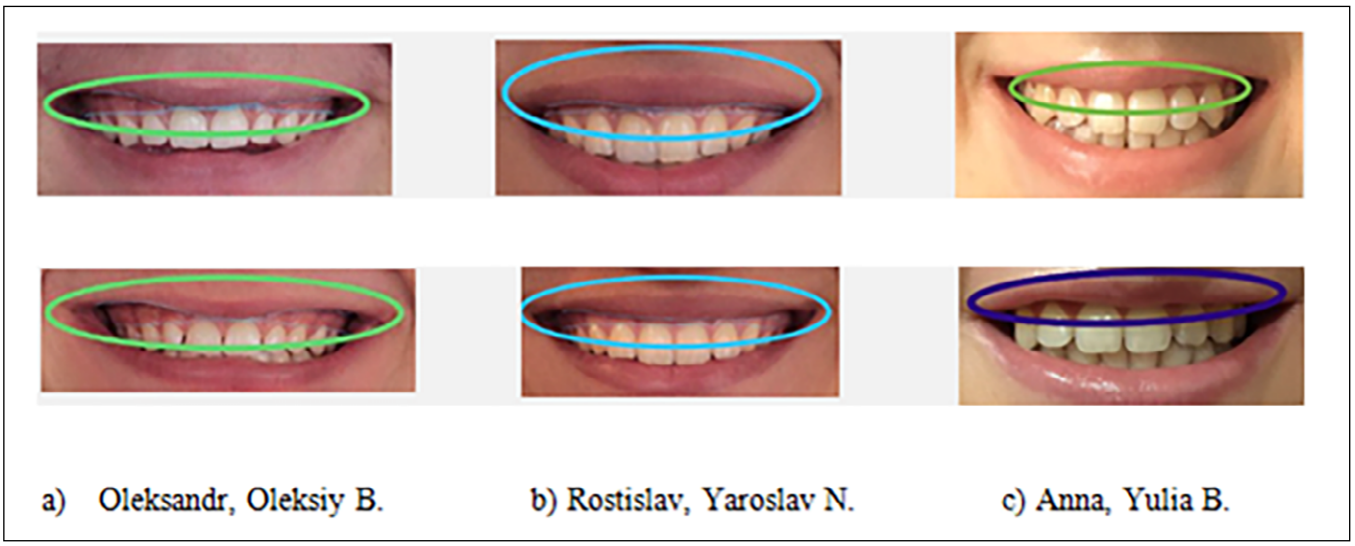

Fig. 3. Determination of the gum level criterion: a), b), c).

RESULTS

When studying the parallelism of horizontal landmarks, we determined the parallelism of imaginary lines: between the pupils and the line of the lips. Both of them should be parallel to the lines connecting the edges of the central incisors and the cutting tubercles of the canines.

Parallelism of horizontal landmarks is equally expressed in four pairs of monozygotic twins, does not coincide in one pair, and is not expressed in one pair (Fig. 1). The smile line runs along the cutting edges of the upper front teeth and should ideally repeat the curve of the upper edge of the lower lip, that is, be convex.

The smile line is equally expressed in three pairs of (MZ) twins, it does not coincide in one pair, it is not expressed in two pairs (Fig. 2). A smile looks attractive and more aesthetically pleasing if the line connecting the necks of the teeth repeats the line of the upper lip. At the same time, with a maximally open smile, only the gingival triangles between the teeth and a small strip of gums above them (no more than 2-3 mm wide) should be visible. The gingival level criterion is equally expressed in two pairs of (MZ) twins, does not coincide in two pairs, is not expressed in two pairs (Fig. 3).

To determine vertical symmetry and the middle line, we conventionally drew a line through the center of the face, which passes between the central incisors of the upper jaw and should coincide with the middle line of the face.

We determined the rule of the "golden proportion" by calculating the ratio of the width of the central incisors and canines to the width of the lateral incisor of the upper jaw in the projection on the frontal plane from the calculation - 0.618:1:1.618. This criterion is equally

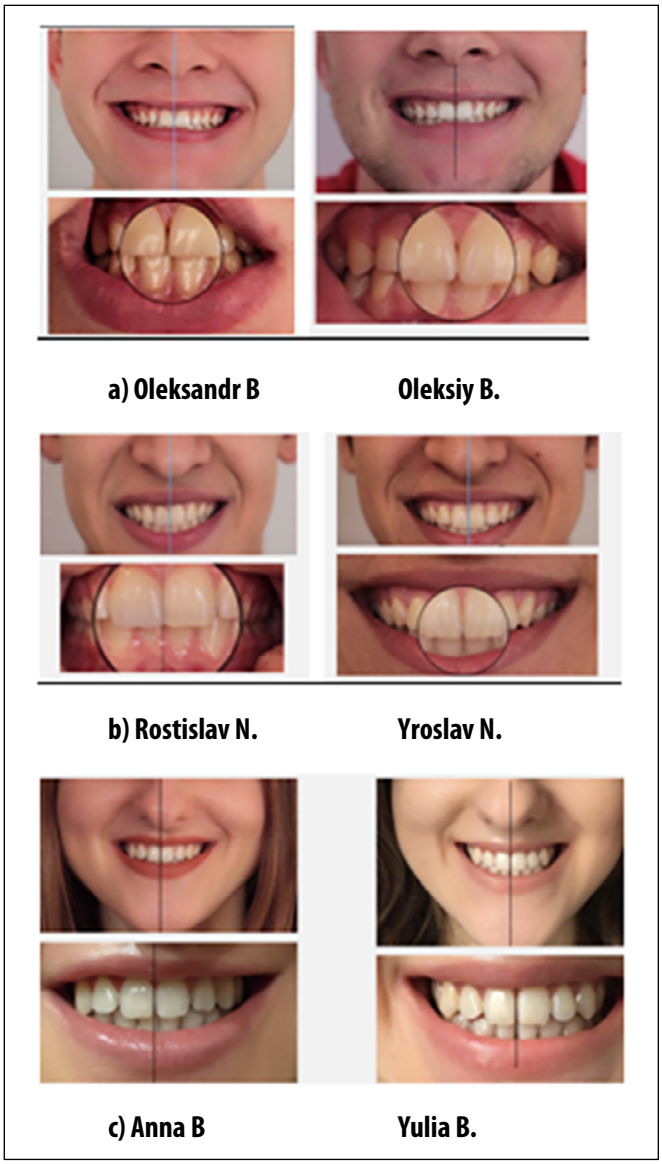

Fig. 4. Determination of vertical symmetry and the middle line of the face: a), b), c).

expressed in three pairs of (MZ) twins, does not coincide in one pair, is not expressed in two pairs (Fig. 5).

For the central incisors of the upper jaw, there is a rule according to which teeth with a ratio of tooth width to tooth length of approximately 0.7-0.8 to 1 look most harmonious (Fig. 6). This criterion is equally expressed in three pairs (MZ) of twins, does not coincide in two pairs, is not expressed in one pair of (MZ) twins. When determining the "interincisal angles" parameter, the gaps between the cutting edges of the front group of teeth were examined. These angles should gradually increase from the center to the periphery. In (MZ) female twins, the corners of the incisors are rounded, in (MZ) male twins, the corners of the incisors are straighter (Fig. 7).

The "interincisal angles" criterion is equally expressed in one pair of (MZ) twins (female), it does not coincide - in five pairs of twins.

To determine the zenith of the gingival contour, the most concave part of the gums around the neck of the tooth was evaluated. The level of zeniths near different teeth in the smile area should be at different levels. The central incisors and canines are approximately at the same level, the lateral incisors are somewhat lower than both. At the same time, it is important that the zeniths on symmetrical teeth are at the same level. This criterion is equally expressed in four pairs (MZ) of twins, does not coincide in one pair, is not expressed in one pair (Fig. 8).

To determine the position of the cutting edges, the teeth of the central group were evaluated. The cutting edges of the central group of teeth are located at different levels. This criterion is equally expressed in five pairs of (MZ) twins, not expressed in one pair (Fig. 9).

Assessment of the condition of gingival papillae was carried out by examination. In all patients, all gingival papillae have a healthy appearance - triangular shape with a sharp top, pink color, no swelling. Between the central incisors, the gingival papilla is the longest, and its length gradually decreases toward the periphery. This criterion is equally expressed in three pairs of (MZ) twins, does not coincide in one pair, is not expressed in two pairs (Fig. 10).

According to the obtained results, the maximum number of matches of ideal smile parameters in (MZ) twins concerns criterion 9 (position of cutting edges) - in five pairs and criterion 1 (parallelism of horizontal landmarks) - in four pairs. There are no matches in 5 pairs of (MZ) twins according to the 7th criterion (interincisal angles) (Fig. 11). Thus, in (MZ) twins, the smile criteria match in 51.6% of cases, do not match in 26.6% of cases, and are absent in 21.8% of cases. So, genetic factors have a significant influence on the morphological features of the teeth, more than 50% of the parameters of an ideal smile in twins are coincided (Fig.12).

DISCUSSION

Most of the monozygotic twins are alike. In general it is expected that the monozygotic twin pairs are the same within the congenital defects, chromosomal abnormalities and Mendelian disorders. However, more and more often non-compliances of monozygotic twin pairs are reported. It is quite a unique occurrence that two genetically identical individuals can exhibit a variety of phenotypes due to the impact of environmental factors and epigenetic variances.

One of the main methods of genetics for assessing the influence of genetics and the environment is the twin method. It is undeniable that genetic factors control the size and morphology of teeth, gums, and lips, which are components of a smile. Since MZ twins

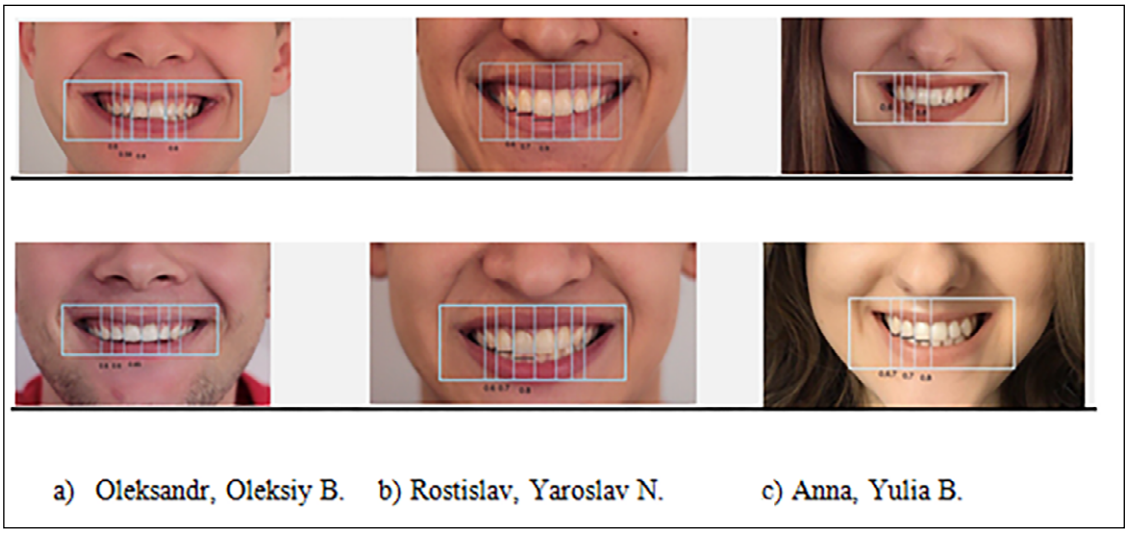

Fig. 5. Definition of the "golden ratio" rule: a), b), c).

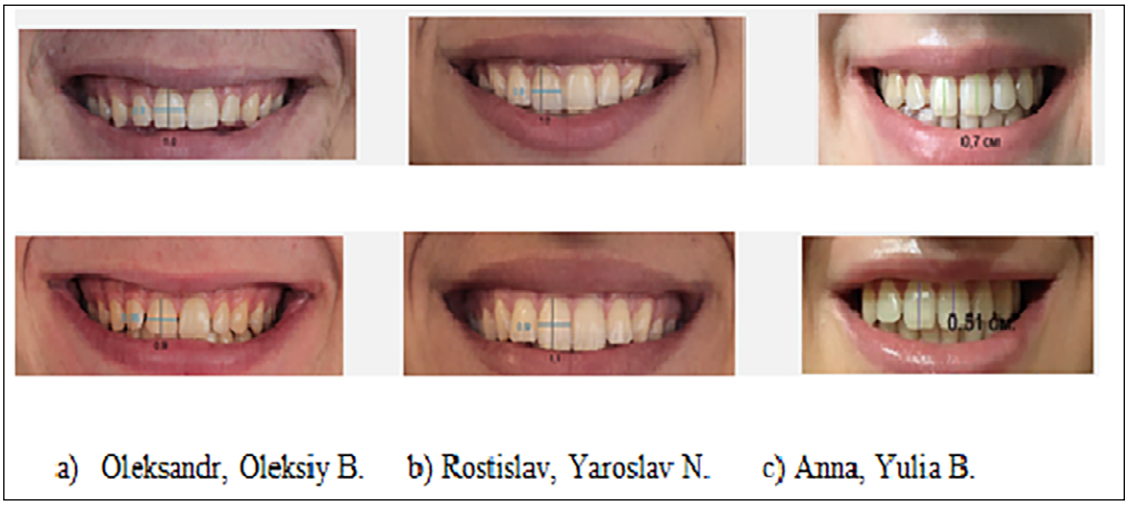

Fig. 6. Determination of tooth proportions: a), b), c).

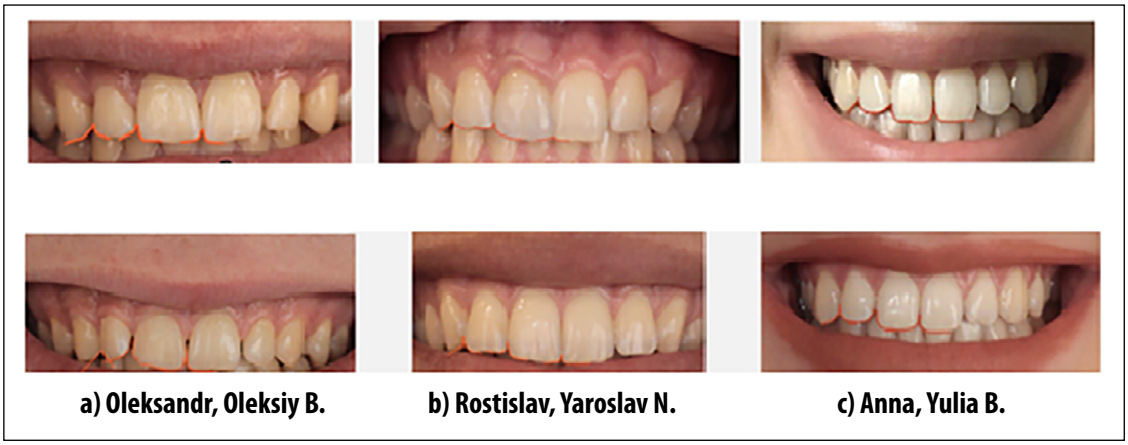

Fig. 7. Determination "intercutting angles" parameter: a), b), c).

have identical genetic material, the differences between them in determining smile criteria can be explained by environmental factors [2-4]. Environmental factors such as food, habits and injuries strongly influence the features of the teeth. The monozygotic (MZ) twin model is one particularly valuable method, given that examining the smile criteria of only one pair of MZ twins provides insight into the underlying causes of the observed variation. Scientific studies of monozygotic twins have proven a significant genetic influence on the length of the skull base, the body of the maxilla, and the length of the mandible, since an identical genotype (number

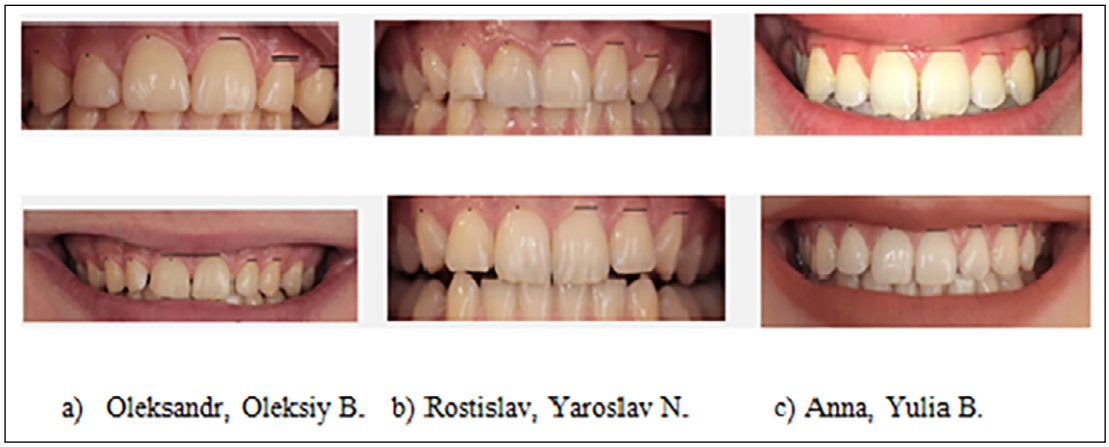

Fig. 8. Determination of the zenith of the gingival contour: a), b), c).

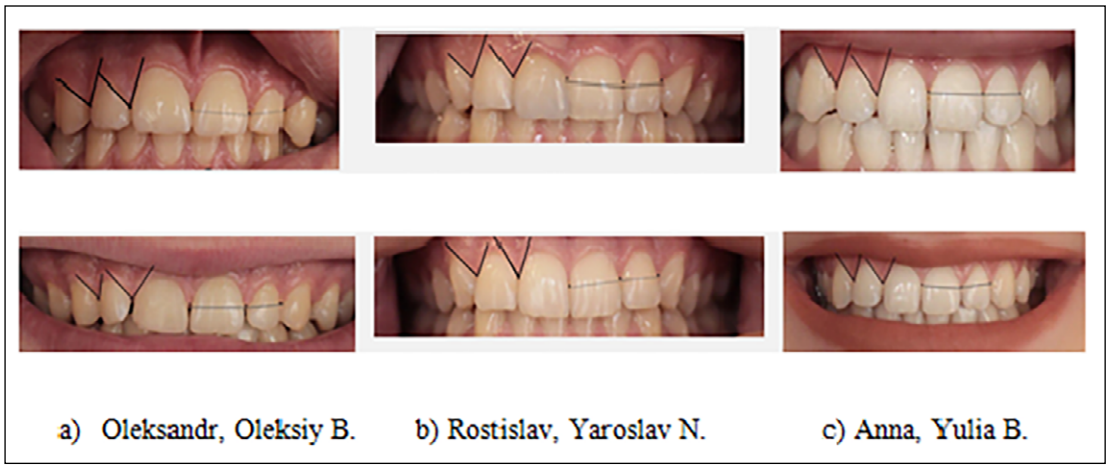

Fig. 9. Determination of the position of the cutting edges: a), b), c).

Fig. 10. Assessment of the condition of gingival papillae: a), b), c).

and distribution of genes) is manifested by the same morphological features - the phenotype. High heritability is characteristic of most intracranial occlusal ratios, including the width of the canine and the width of the maxillary and mandibular molars, the depth and perimeter of the dental arch [12]. The intrapair similarity of malocclusion anomalies in monozygotic twins reaches 100%, while in dizygotic pairs it is only 57%. Environmental factors such as nutrition, habits (sucking, etc.) and trauma strongly influence dental characteristics, such as incisor inclination, depth of incisal overlap, and are responsible for many physical and behavioral features or anomalies that lead to the formation of malocclusion.

CONCLUSIONS

Research on (MZ) twins is a unique method of assessing the influence of genetic and environmental factors on the formation and development of the cra-

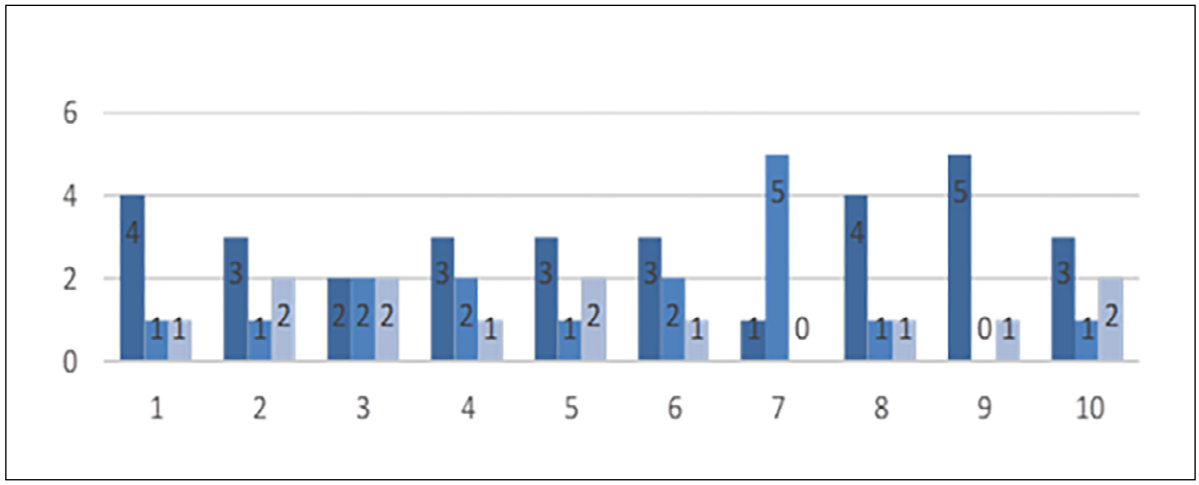

Fig. 11. The number of coincidences of smile criteria in (MZ) twins

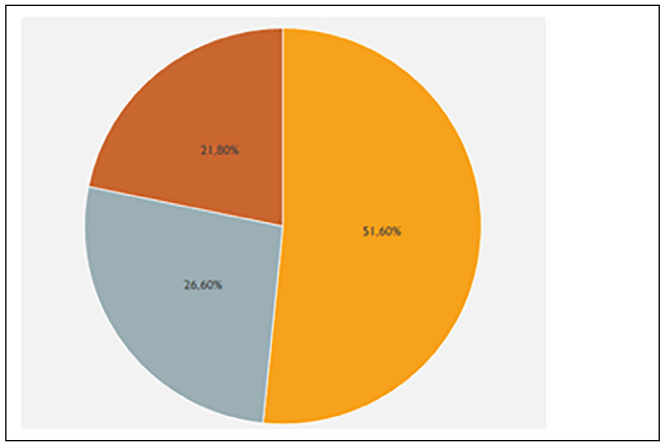

Fig. 12. The number of matches of ideal smile parameters in (MZ) twins (%).

niofacial complex. Signs of external similarity in (MZ) twins, taking into account morphological characteristics: the shape of the eyes, the shape of the nose, lips, and teeth, is confirmed by photo documentation and biometric research methods. However, the ratio between lips, teeth and gums when forming a smile in (MZ) twins is the same in 51.6% of cases. Based on the results of this study, we were unable to confirm a primary role of genetics in dental features such as criteria for a perfect smile. Environmental factors (nature of nutrition, bad habits, sucking, tooth extraction, sleeping on the stomach, etc.) and injuries have a significant influence on the features of dental smile parameters.

REFERENCES

1. Miazek W, Smala K, Piskórz M et al. The Differences in the dentition pattern in monozygotic twins based on panoramic examinations – case report on two pairs of twins. Journal of Education, Health and Sport. 2023;36(1):21-26. doi:10.12775/JEHS.2023.36.01.002. DOI
2. Burke PH. Intrapair facial differences in twins. Acta Genet Med Gemellol (Roma). 1989;38:37-47. doi:10.1017/s0001566000002816. DOI
3. Lundstrom A. Tooth morphology as a basis for distinguishing monozygotic and dizygotic twins. Am J Hum Genet. 1963;15(1):34-43.
4. Townsend G, Hughes T, Luciano M et al. Genetic and environmental influences on human dental variation: a critical evaluation of studies involving twins. Archives of Oral Biology. 2009;54(1):45-51. doi:10.1016/j.archoralbio.2008.06.009. DOI
5. Suzuki R, Ishige S, Koike H et al. Familial cherubism in monozygotic twins: A 9-year follow-up. Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology. 2022;34(5):587-592. doi:10.1016/j.ajoms.2022.02.009. DOI
6. Tiro A, Dzemidzic V, Salaga-Nefic S et al. Heritability of Craniofacial Characteristics in Twins - Cephalometric Study. Medical Archives. 2019;73(3):205-208. doi:10.5455/medarh.2019.73.205-208. DOI
7. Kawala B, Antoszewska J, Necka A. Genetics or environment? A twin-method study of malocclusions. World Journal of Orthodontics. 2007;8(4):405-410.
8. Hughes T, Thomas C, Richards L, Townsend G. A study of occlusal variation in the primary dentition of Australian twins and singletons. Archives of Oral Biology. 2001;46(9):857-864. doi:10.1016/s0003-9969(01)00026-7. DOI
9. Lin TH, Hughes T, Meade MJ. The genetic and environmental contributions to variation in the permanent dental arch form: a twin study. European Journal of Orthodontics. 2023;45(6):868-874. doi:10.1093/ejo/cjad054. DOI
10. Delfin LF, Shastri SM, Madan K. Assessment of the oral health status of monozygotic and dizygotic twins - a comparative study. Oral Health and Preventive Dentistry. 2012;10(2):135-139.
11. Townsend G, Richards L, Hughes T et al. Epigenetic influences may explain dental differences in monozygotic twin pairs. Australian Dental Journal. 2005;50(2):95-100. doi:10.1111/j.1834-7819.2005.tb00347.x. DOI

12. Sharma K. Sex differences in genetic determinants of craniofacial variations - a study based on twin kinships. Acta Genet Med Gemellol (Roma). 1998;47(1):31-41. doi:10.1017/s0001566000000350. DOI
13. Baydas B, Oktay H, Metin Dagsuyu I. The effect of heritability on Bolton tooth-size discrepancy. European Journal of Orthodontics. 2005;27(1):98-102. doi:10.1093/ejo/cjh088. DOI
14. Hughes TE, Townsend GC, Pinkerton SK et al. The teeth and faces of twins: providing insights into dentofacial development and oral health for practising oral health professionals. Australian Dental Journal. 2014;59(1):101-116. doi:10.1111/adj.12101. DOI
15. Perinetti G. Sta Tips Part IV: Selection, interpretation and reporting of the intraclass correlation coefficient. South European Journal of Orthodontics and Dentofacial Research. 2018;5(1):3-5. doi:10.5937/sejodr5-17434. DOI
16. Townsend GC, Richards L, Hughes T et al. The value of twins in dental research. Australian Dental Journal. 2003;48(2):82-88. doi:10.1111/j.1834-7819.2003.tb00014.x. DOI

This scientific work is a fragment of the initiative research of the Department Therapeutic Dentistry Propaedeutics of Poltava State Medical University "Substantiation of the choice of treatment methods of the oral cavity organs diseases depending on their morphofunctional features". State registration number 0124U004553. Deadline 01.2024-12.2029 and research project funded by the Ministry of Health of Ukraine from the state budget "Development of methods for treatment and prevention of pulmonary fibrosis by activation of PPAR-gamma receptors" State Registration No.0122U201686. Implementation period 01.2023-12.2025.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Maryna A. Shundryk
Poltava State Medical University
24 Shevchenko St., 36021 Poltava Ukraine
e-mail:shundrikliliya@gmail.com

ORCID AND CONTRIBUTIONSHIP

Maryna A. Shundryk: 0000-0003-3186-5923 A B
Iryna Y. Marchenko: 0000-0001- 7092-1786 C D
Iryna M. Tkachenko: 0000-0001-8243-8644 E F
Valeriy Y. Marchenko: 0009-0006-5697-5378 A D
Yaroslav Y. Vodoriz: 0000-0001-9388-1270 C F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 11.02.2025
ACCEPTED: 01.06.2025

ORIGINAL ARTICLE

CONTENTS

Experimental study of the adhesive capacity of resident and transient representatives of the oral cavity microflora to different base materials

Yurij Kushnir, Mykola Rozhko, Roman Kutsyk, Roksolana Verbovska, Bohdan Pelekhan, Svyatoslav Rozhko, Lesya Kurovets

IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

Aim: To compare the adhesive ability of resident and transient representatives of the oral cavity microflora to various base materials used for the manufacture of removable dentures.

Materials and Methods: The presented report is an experimental study in vitro. 3 types of base materials, namely Vertex, Breflex and Villacryl were used in order to evaluate the adhesive ability of microorganisms. Strains of opportunistic pathogens representing the facultative anaerobic transient microflora of the oral cavity were used for the research. After the cultures cultivation, the number of isolated colonies grown from the microbial cells that adhered to the material sample was counted.

Results: *Staphylococci* adhered to all tested samples of base materials very weakly. Adhesion of methicillin-sensitive *S. aureus* (to Villacryl was at the level of the control material, i.e. glass (adhesion indices constituted 0.58 and 0.64). It was significantly weaker in relation to Breflex (adhesion index was 0.47) and, especially, to Vertex (adhesion index was 0.39).

All materials demonstrated adhesion indices lower than glass for α-hemolytic streptococci and staphylococci. Adhesion indices of Breflex and Villacryl resin for *β-hemolytic streptococci* differed little from the corresponding values of glass.

Conclusions: All tested samples of base materials showed significant biological inertness: the adhesion indices of the vast majority of the tested microorganisms were lower than those of the control material. Oral *streptococci* showed the weakest adhesive ability to Villacryl (average values of adhesion indices 0.51 and 0.68 appropriately). *Staphylococci* and *Candida* yeast-like fungi showed a weak adhesive ability to the samples of base materials, especially to Vertex.

KEY WORDS: oral cavity, removable dentures, base resin, microbial cultures, adhesive capacity

Wiad Lek. 2025;78(6):1111-1118. doi: 10.36740/WLek/204798 DOI

INTRODUCTION

Microbial adhesion on the denture surface is a serious issue in the clinical findings of prosthetic dentistry. Physical and chemical features of the oral fluid and physiological conditions in the oral cavity as a whole provide an ideal environment for microbial colonization not only of the surface of the mucous membrane and teeth hard tissues, but dental prostheses as well. Despite the relative biological inertness of most modern prosthetic materials, the surfaces of prostheses can easily retain bacteria, fungi and other microorganisms. Adhesion of the oral microflora representatives is the initial stage of the multispecies biofilm formation. This process is facilitated by such factors as the surface roughness, chemical nature and free surface energy of the material of the dental prosthesis [1]. Colonization of the prostheses surfaces by microorganisms followed by the formation of a biofilm makes them a potential permanent source of oral pathogens [2]. This results in prerequisites for the development (or further progression) of tooth decay, periodontitis, and gingivitis. Epidemiological studies show that the use of removable dentures leads to prosthetic stomatitis in 70% of the examined individuals [3]. Dissemination of infectious microorganisms localized on the denture surface leads to the damage of the gastrointestinal tract, cardiovascular and pleuropulmonary systems [4-6].

The ability of microorganisms to adhere to the polished surface of the base of a removable denture plays a key role in the pathogenesis of prosthetic stomatitis. Such adhesion provides an opportunity to withstand mechanical clearance, which is provided by swallowing movements and the constant washing effect of saliva, and to act as a focus for further colonization [7].

Due to the seriousness of the problem of candidal prosthetic stomatitis The study of the adhesion of *Candida albicans* yeast-like fungi to polymer materials attracts considerable attention of researchers [8-10].

AIM

Therefore, the objective of the research was to compare the adhesive ability of resident and transient representatives of the oral cavity microflora to various base materials used for the manufacture of removable dentures.

MATERIALS AND METHODS

The presented report is an experimental study *in vitro*. 3 types of base materials samples, namely Vertex (Vertex-Dental B.V., Netherlands), Breflex (Bredent, Germany) and Villacryl (Zhermapol, Poland) commonly used in the prosthetic dentistry for the manufacture of bases for complete and partial removable dentures, were used in order to evaluate the adhesive ability of laboratory microbial strains of clinical origin.

The protocols of experiments performed in the laboratory of microbiological research of the Department of Microbiology, Virology and Immunology of the Ivano-Frankivsk National Medical University were developed.

Ready resin samples for the experiment had the form of plates with a thickness of 2 mm and an area of 1 cm^2. Glass plates of similar size were used as controls. The study and control samples were placed in a sealed cellophane package and sterilized by X-ray irradiation at a dose of 0.44 mGy for 1.540 s.

Strains of opportunistic pathogens representing the facultative anaerobic transient microflora of the oral cavity were used for the research: *Streptococcus pyogenes* (Group A β-hemolytic streptococcus), *Streptococcus dysgalactiae ssp. equisimilis* (Group G β-hemolytic streptococcus), methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA) with associated resistance to fluoroquinolones, macrolides, tetracyclines and aminoglycosides, methicillin-susceptible *Staphylococcus epidermidis*; yeast-like fungi *Candida albicans* and *Candida tropicalis* as well as the mitis group α-hemolytic streptococci (*Streptococcus oralis*, *Streptococcus sanguinis*, *Streptococcus gordonii*) as the main representatives of the resident microflora of this biotope. Microbial cultures were isolated from the oral mucosa (prosthetic bed, gingival pockets) of the patients with removable dentures with manifestations of prosthetic stomatitis and identified on the basis of morphological, cultural properties and biochemical microtests "STAPHYtest 16", "STREPTOtest 16" (Lachema, Czech Republic) and VITEK 2 GP and VITEK 2 YST test systems (biomerieux, France) using the VITEK 2 Compact analyzer.

The adhesive ability of microorganisms was evaluated according to the method, where suspensions in an isotonic NaCl solution with a concentration of 1 10^5 CFU/ml were made from daily bacterial cultures grown in blood agar and from 48-hour cultures of *C. albicans* grown in Sabouraud agar according to the optic standard. The studied material sample was cultivated in bacteriological test tubes in a microbial suspension for 1 hour at a temperature of 37°C with constant stirring by means of MR-1 shaker (SIA BIOSAN, Latvia) with a stirring frequency of 20 times/min. Then, the sample was transferred to a new sterile test tube and washed three times in a sterile isotonic solution in order to remove non-adherent microbial cells. The washed samples were placed in a sterile ultrasonic tub-washer for dentures TSM 226 289 (50W, 42KHz) with the ultraviolet irradiator turned off for 5 minutes in order to separate the adhered bacteria from the resin surface. Adhered microorganisms were washed off in 1.0 ml of sterile nutrient broth. Then, the number of viable microbial cells was determined in it by the method of tenfold serial dilutions. The cultivation of staphylococci and streptococci was conducted in blood agar, Escherichia coli cultivation was performed in Endo agar, *Candida* fungi were cultivated in Sabouraud agar.

After the cultures cultivation, the number of isolated colonies grown from the microbial cells that adhered to the material sample was counted. Then, recalculation was performed per 1 $см^2$ of the sample and the value of the decimal logarithm of the number of viable microbial cells was determined. The percentage of adhered microorganisms was determined for each of the test cultures and the adhesion index was calculated according to the formula (1):

$$IA = lgA/lgN, \quad (1)$$

where IA is the index of adhesion;
A is the number of adhered microbes;
N is the number of microbes in the initial suspension.

The experiments to check the adhesion of each test culture to each material sample were repeated three times. The percentages of adhered microbial cells and adhesion indices were calculated for each experiment separately based on the counting of microbial colonies. The quantitative data obtained in the experiments by the type of dispersion corresponded to the normal Gaussian law (based on the Shapiro-Wilk's W test). To describe the central tendency of the quantitative data, the interval (M±m) was used: arithmetic mean (Mean) ± standard error (Standard error), and to assess the reliability of the differences in the results obtained in comparison with the control, a parametric t-test (Student's test) for independent samples.

Table 1. The percentage of microorganisms adhered to different types of base resin materials

Microorganisms	Vertex	Breflex	Villacryl	Glass
S. aureus ATCC 25923	0.16±0.008*	0.38±0.02*	1.13±0.06*	2.13±0.11
S. aureus MRSA	0.01±0.0004*	0 *	0.06±0.003*	0.17±0.09
S. epidermidis	0.03±0.002*	0.14±0.007*	0.07±0.004*	0,80±0,04
β- hemolytic *Str. pyogenes* (group A)	35.29±1.76*	17.65±0.88*	6.18±0.31*	10.88±0.54
β- hemolytic Str. dysgalactiae *ssp. equisimilis* (group G)	22.50±1.13*	2.00±0.10*	3.25±0.16*	7.00±0.35
α- hemolytic *Str. gordonii*	0.71±0.036*	0.48±0.024*	0.48±0.024*	1.75±0.09
α- hemolytic *Str. sanguinis*	5.00±0.025*	3.75±0.19*	1.67±0.08*	12.50±0.63
α- hemolytic *Str. Oralis*	2.89±0.14*	2.11±0.11	0.45±0.022*	2.11±0.11
C. albicans	0.20±0.01*	0.60±0.03*	0.30±0.015	0.09±0.005
C. tropicalis	0 *	0.08±0.004	0.75±0.038*	0.17±0.008

Note. * – $p<0.05$ when compared to the control (glass)

Table 2. Adhesion index of microorganisms to various types of base resins

Microorganisms	Microbial load of the initial suspension, CFU/ml	Index of adhesion			
		Vertex	Breflex	Villacryl	Glass
S. aureus ATCC 25923	4.60±0.14	0.39**	0.47*	0.58	0.64
S. aureus MRSA	4.78±0.15	0.15**	0**	0.32*	0.42
S. epidermidis	4.70±0.14	0.25**	0.39*	0.33*	0.55
β- hemolytic *Str. pyogenes* (group A)	4.23±0.13	0.89*	0.82	0.71	0.77
β- hemolytic *Str. dysgalactiae ssp. equisimilis* (group G)	4.30±0.12	0.85*	0.60*	0.65*	0.73
α- hemolytic *Str. Gordonii*	4.80±0.15	0.55*	0.52*	0.52*	0.63
α- hemolytic *Str. Sanguinis*	4.08±0.11	0.68*	0.65*	0.56*	0.78
α- hemolytic *Str. oralis*	4.28±0.12	0.64	0.61	0.45*	0.61
C. albicans	4.70±0.14	0.43*	0.53**	0.46*	0.35
C. tropicalis	4.78±0.15	0.06**	0.36	0.56*	0.42

Note. * – $p<0.05$, ** – $p<0.01$ when compared to the control (glass)

RESULTS

The adhesion of microorganisms to the control material (glass) was very weak (Table 1). Only β-hemolytic streptococci strains differed in relatively high adhesiveness both to glass and to the tested materials of base resin. Thus, 10.88±0.54% of the cells from the suspension of β-hemolytic streptococcus of group A *Streptococcus pyogenes* adhered to glass, 35.29±1.76% and 17.65±0.88 adhered to Vertex and Breflex resin, respectively ($p<0.05$). A high percentage of adhered cells of β-hemolytic streptococcus of *Streptococcus dysgalactiae ssp. equisimilis* group G was observed when studying glass (7.00±0.35%) and Vertex resin (22.50±1.13%) ($p<0.05$). Among oral cavity-resident α-hemolytic streptococci, only the *Streptococcus sanguinis* strain showed a high percentage of cells adhered to glass. The studied strains of staphylococci and candida showed extremely low percentages of cells adherent to both glass and all base materials.

Table 2 shows the calculated values of the adhesion index of each of the used test strains of microorganisms to the samples of the base materials. Cultures of pathogenic β-hemolytic streptococci of *Streptococcus pyogenes* group A and *Streptococcus dysgalactiae ssp. equisimilis* group G demonstrated the highest adhesion indices to basic materials and glass (the values were within 0.73-0.89). The highest adhesive ability of β-hemolytic streptococci was manifested to Vertex resin. The α-hemolytic streptococcus *Streptococcus sanguinis* as a representative of the resident microflora of the oral cavity showed a high adhesive ability to the control material, namely glass (adhesion index constituted 0.78). However, it adhered to all tested samples of base resin significantly weaker ($p<0.05$), especially to Villacryl resin (adhesion index was 0.56). Weak adhesion to this resin was also demonstrated by α-hemolytic *Streptococcus oralis* (adhesion index was 0.45). α-hemolytic *Streptococcus gordonii* as another representative of the normal oral cavity microflora showed significantly less adhesion to all three samples of the tested base resins compared to glass as the control material (adhesion

Table 3. Comparative analysis of the adhesive ability of base resins (according to the average adhesion index) in relation to different groups of tested microorganisms

Microorganisms	Vertex	Breflex	Villacryl	Glass
Oral α-hemolytic streptococci	0.62±0.07	0.59±0.07	0.51±0.06	0.67±0.09
Oral β-hemolytic streptococci	0.87±0.03*	0.71±0.15	0.68±0.04	0.75±0.03
Oral staphylococci	0.26±0.12*	0.29±0.25	0.41±0.14	0.54±0.11
Candida yeast-like fungi	0.24±0.26	0.44±0.12	0.51±0.07*	0.39±0.05
For all tested microorganisms	0.49±0.17	0.49±0.15	0.51±0.11	0.59±0.12

Note: * – $p<0.05$ when compared to the control (glass)

indices constituted 0.52-0.55 vs. 0.63, $p<0.05$) (Table 2).

The lowest adhesion indices to the control material (glass) were demonstrated by the strains of *C. albicans* and *C. tropicalis* yeast-like fungi constituting 0.35 and 0.42, respectively. *C. tropicalis* strain practically did not adhere to Vertex resin (adhesion index constituted 0.06, $p<0.01$). However, its adhesion to Villacryl resin was even significantly higher than to glass (adhesion index was 0.56, $p<0.05$). The strain of *C. albicans* also showed weak adhesive ability to all tested materials (adhesion index values amounted 0.43-0.53). However, the intensity of adhesion in all cases was higher compared to the control material (glass) ($p<0.05$).

We used glass as a control material. The adhesive properties of the tested base materials (in percent) relative to glass were presented in Fig. 1 for illustration purposes (Fig. 1: 1.1.-1.4.). As it was already mentioned, a very small percentage of *Candida* yeast-like fungi adhered to all tested materials (no more than 0.60-0.75% of those present in the suspension). Moreover, a regularity could be noticed that the adhesive capacity of *C. albicans* (as the most common causative agent of candidal prosthetic stomatitis) was higher than that of *C. tropicalis*. The adhesion index of *C. albicans* to all three samples of base resins was significantly higher than to glass: Vertex – by 20.3%, Breflex – by 49.8% and Villacryl – by 31.6% ($p<0.05$). The test strain of *C. tropicalis* adhered to Breflex resin and, especially, to Vertex resin weaker than to glass (by 15.1% and 84.9%, respectively, $p<0.05$). The adhesion index of *C. tropicalis* to Villacryl resin was 32.7% higher compared to glass ($p<0.05$) (Fig.1).

Considering the fact that the test strains used in the study represented a rather wide range of microorganisms, the adhesive ability to base materials was summarized in Table 3 taking into account their taxonomic and ecological affiliation. According to the average values of adhesion indices of all tested microorganisms, the tested samples of base materials were inferior to the control material (glass) indicating their significant biological inertness. In general, oral streptococci (both α- and-hemolytic) adhered less strongly to Villacryl resin. Staphylococci and *Candida* yeast-like fungi adhered weakly to Vertex resin (Table 3).

DISCUSSION

Implant-supported prostheses improve patients` satisfaction with treatment and quality of life. Improvements in the implant`s surface and in attachment elements have made this type of treatment method very successful. However, some biological and mechanical complications remain [11, 12].

Conventional removable partial dentures are still common option for patient with distal-extension tooth loss [13]. Replacement of missing natural teeth is important to improve function, aesthetics and quality of life for patients, who is treated with partial dentures [14].

In the literature there are many studies devoted to the study effects of partial dentures on the oral health of soft tissues and remaining teeth, comparing commonly used materials with emergency materials for the fabrication of partial dentures [15-17].

In our study, we used 3 types of base material samples to evaluate the adhesive ability of microorganisms: Vertex (Vertex-Dental B.V., the Netherlands), Breflex (Bredent, Germany) and Villacryl (Zhermapol, Poland). The selection of these materials was based on prevalence of their use in the prosthetic dentistry clinic for the manufacture of bases for complete and partial removable dentures.

Analyzing previous studies, scientists studied the level of adhesion of microorganisms of the oral cavity to the soft linings of the bases of removable prostheses. As result, temporary soft lining materials are not resistant to adhesion and possible surface damage caused by oral bacteria, and therefore their use should be limited to short-term periods [18].

In our study, we performed microbiological analysis on equally well-polished prostheses. In this way, we rejected the factor of different roughness of the surfaces of the bases of dentures.

According to the results of the conducted experiment, all studied material samples were microbiologically quite inert. They sorbed and retained a small percent-

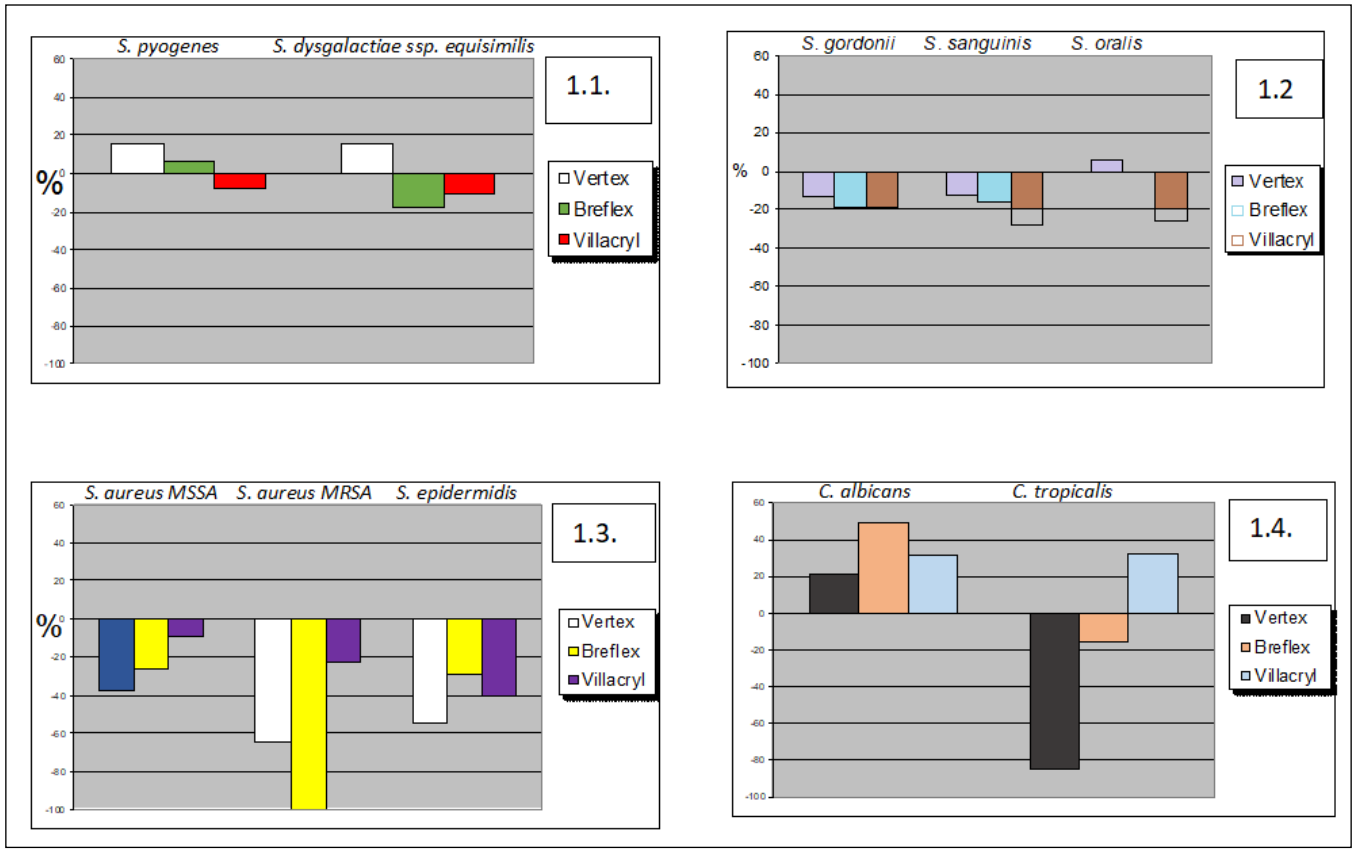

Fig. 1. Adhesive properties of the base materials in relation to the control material (glass). The adhesion index is presented as a percentage: 1). The adhesion index of *S. pyogenes* and *S. dysgalactiae ssp. Equisimilis*; 2) The adhesion index of *S. gordonii*, *S. sanguinis* and *S. oralis*; 3). The adhesion index of *S. aureus* MSSA, S. aureus MRSA and *S. epidermidis*. 4) The adhesion index of *C. albicans* and *C. tropicalis*

age of microbial cells from the suspension under the conditions of the performed experiment.

Staphylococci, especially *S. epidermidis* and methicillin-resistant *S. aureus* (MRSA), adhered to all tested samples of base materials very weakly. Adhesion of methicillin-sensitive *S. aureus* (MSSA) to Villacryl resin was at the level of the control material, i.e. glass (adhesion indices constituted 0.58 and 0.64, respectively, $p<0.05$). It was significantly weaker in relation to Breflex resin (adhesion index was 0.47, $p<0.05$) and, especially, to Vertex resin (adhesion index was 0.39, $p<0.01$).

The results indicate that all materials exhibited significant biological inertness, with microbial adhesion indices generally lower than those of the control material (glass). Among the microorganisms tested, *Streptococcus pyogenes, Streptococcus dysgalactiae*, and *Candida albicans* demonstrated varying degrees of adhesion to the base materials, with *Candida albicans* showing the weakest adhesion to the resins, especially Vertex.

Several previous studies have investigated microbial adhesion to denture materials, and many of their findings complement the results of this study. For example, Dantas et al. (2016) studied the effect of surface finishing and polishing on the adhesion of *Streptococcus sanguinis* to polymethyl methacrylate (PMMA). Their findings indicated that smoother surfaces reduced bacterial adhesion, confirming the importance of surface characteristics in microbial colonization [19].

Similar to the findings of this study, Dantas et al. noted that PMMA-based materials had lower microbial adhesion when compared to rougher surfacesr study by Nikhath Sultana et al. (2023) also found a direct correlation between surface roughness and microbial adhesion. Increased roughness led to higher adhesion rates of bacteria such as *Streptococcus mutans*, a key pathogen in dental caries. While this study controlled for surface roughness by using equally polished materials, it still aligns with the finding that surface properties—such as chemical composition and free surface energy—play a critical role in microbial adhesion [20].

The adhesion of *Candida albicans* to denture materials has been extensively studied, particularly because of its association with prosthetic stomatitis, a common condition affecting denture wearers. In studies like those by Klotz et al. (2005), *Candida albicans* was shown to exhibit higher adhesion to acrylic resins than other Candida species [21]. Our study similarly demonstrated that *Candida albicans* adhered more strongly to the resin materials than *Candida tropicalis*.

However, the adhesion of both yeast species was weak compared to bacterial pathogens, suggesting that these resins may help prevent fungal colonization. This observation is consistent with Klotz et al.'s finding that acrylic resins, particularly those with low surface energy, tend to limit the adhesion of *Candida* species. It was found that adhesion of *Candida albicans* to polymethylmethacrylate depend on morphilogical forms of fungi: yeast cells adhere less comparing with hyphe tubes. Moreover the virulent clinical strains (with capacity to survive in blood and resistance to complement opsonization) adhered to acrylate surfaces more active than collection strain [22].

In contrast, the this study regarding the adhesion of *Staphylococcus aureus* and *Staphylococcus epidermidis* are in line with the findings of a study by Espinel-Ingroff et al. (2007), which suggested that *Staphylococcus species* generally exhibit low adhesion to prosthetic materials, especially when compared to oral streptococci. This study demonstrated that methicillin-resistant *S. aureus* (MRSA) had minimal adhesion to the resins tested, particularly Vertex [23]. In a similar study by Weng et al. (2015), it was found that the adhesion of *S. aureus* to dental materials like acrylic resin was significantly lower compared to *Streptococcus* species [24].

The adhesive ability of orocci, particularly *Streptococcus pyogenes* and *Streptococcus dysgalactiae*, observed in this study contrasts with the general trend reported in other studies. A study by Morin et al. (2014) showed that *Streptococcus mutans*, a prominent oral pathogen, adhered more readily to dental materials compared to other microorganisms like *Streptococcus sanguinis*. The high adhesion observed for β-hemolytic streptococci (*S. pyogenes* and *S. dysgalactiae*) to Vertex resin, in particular, suggests that certain resins might be more prone to bacterial adhesion due to their surface chemistry, although the overall levels of adhesion were still relatively low [25].

The weak most microorganisms to the base materials in this study suggests that these materials could help minimize the risk of biofilm formation and associated infections, such as prosthetic stomatitis, a significant concern in removable denture wearers. Given that *S. aureus*, *Candida albicans*, and Streptococcus species are often implicated in oral infections, the results of this study are promising in terms of reducing the microbial load on denture surfaces, particularly for individuals with compromised immune systems or those prone to infection.

However, while the resins tested showed low microbial adhesion, further research into other factors, such as saliva composition, oral hygiene practices, and patient diet, is essential. Studies by Motallebzadeh et al. (2016) [26] and Gorseta et al. (2019) [27] emphasized that clinical factors like saliva pH, bacterial load, and the oral hygiene routine of denture users significantly influence the microbial colonization of denture surfaces . Therefore, while laboratory results are valuabre essential to confirm these findings in real-world settings.

The obtained results will be the basis for further experimental studies of the base materials influence on the oral microflora.

CONCLUSIONS

1. All tested samples of base materials showed significant biological inertness: the adhesion indices of the vast majority of the tested microorganisms were lower than those of the control material (glass).
2. Oral streptococci (both α- and β-hemolytic) showed the weakest adhesive ability to Villacryl resin (average values of adhesion indices 0.51 and 0.68 appropriately).
3. Staphylococci and *Candida* yeast-like fungi showed a weak adhesive ability to the samples of base materials, especially to Vertex resin (average values of adhesion indices 0.26 and 0.24 appropriately).

REFERENCES

1. Sakr HM, AbdulSalam MR, Fayad MI et al. Microbial Adhesion to Different Thermoplastic Denture Base Materials in Kennedy Class I Partially Edentulous Patients. Cureus. 2024;16(5):e60421. doi: 10.7759/cureus.60421. DOI
2. Al-Akhali MA, El-Kerdawy MW, Ibraheim ZA, Abbas NA. Comparative study on the microbial adhesion to acetal resin and metallic removable partial denture. Indian Journal of Dentistry. 2012, 3:1-4. doi: 10.1016/S0975-962X(12)60002-1. DOI
3. Verhaeghe TV, Wyatt CC, Mostafa NZ. The effect of overnight storage conditions on complete denture colonization by Candida albicans and dimensional stability: A systematic review. J Prosthet Dent. 2020;124(2):176-182. doi: 10.1016/j.prosdent.2019.07.014. DOI
4. Taylor GW, Loesche WJ, Terpenning MS. Impact of oral diseases on systemic health in the elderly: diabetes mellitus and aspiration pneumonia. J Public Health Dent. 2000;60:313–320. doi: 10.1111/j.1752-7325.2000.tb03341.x. DOI
5. Parahitiyawa NB, Jin LJ, Leung WK et al. Microbiology of odontogenic bacteremia: beyond endocarditis. Clin Microbiol Rev 2009;22:46–64. doi: 10.1128/CMR.00028-08. DOI
6. Coulthwaite, L. Verran, J. Potential pathogenic aspects of denture plaque. Br J Biomed Sci. 2007;64:180–189. doi: 10.1080/09674845.2007.11732784. DOI

7. Arzmi MH, Dashper S, McCullough M. Polymicrobial interactions of Candida albicans and its role in oral carcinogenesis. J Oral Pathol Med. 2019;48(7):546-551. doi: 10.1111/jop.12905. DOI
8. Susewind S, Lang R, Hahnel S. Biofilm formation and Candida albicans morphology on the surface of denture base materials. Mycoses. 2015;58(12):719-27. doi: 10.1111/myc.12420. DOI
9. Koch C, Bürgers R, Hahnel S. Candida albicans adherence and proliferation on the surface of denture base materials. Gerodontology. 2013;30(4):309-13. doi: 10.1111/ger.12056. DOI
10. Rapala-Kozik M, Surowiec M, Juszczak M et al. Living together: The role of Candida albicans in the formation of polymicrobial biofilms in the oral cavity. Yeast. 2023;40(8):303-317. doi: 10.1002/yea.3855. DOI
11. Vahidi F, Pinto-Sinai G. Complications associated with implant-retained removable prostheses. Dent Clin North Am. 2015;59(1):215-26. doi: 10.1016/j.cden.2014.08.001. DOI
12. Pelekhan B, Dutkiewicz M, Shatskyi I et al. Analytical Modeling of the Interaction of a Four Implant-Supported Overdenture with Bone Tissue. Materials (Basel). 2022;15(7):2398. doi: 10.3390/ma15072398. DOI
13. Nakai N, Kurogi T, Murata H. Oral health-related quality of life of conventional removable partial dentures, unilateral nonmetal clasp dentures, and shortened dental arch with 2- or 3-tooth unilateral distal extension tooth loss in the mandible: A randomized, crossover, clinical trial. J Prosthet Dent. 2024;131(2):220-226. doi: 10.1016/j.prosdent.2021.07.014. DOI
14. Friel T, Waia S. Removable Partial Dentures for Older Adults. Prim Dent J. 2020;9(3):34-39. doi: 10.1177/2050168420943435. DOI
15. Jayaraman S, Singh BP, Ramanathan B et al. Final-impression techniques and materials for making complete and removable partial dentures. Cochrane Database Syst Rev. 2018 Apr 4;4(4):CD012256. doi: 10.1002/14651858.CD012256.pub2. DOI
16. Al-Qarni FD, Goodacre CJ, Kattadiyil MT et al. Stainability of acrylic resin materials used in CAD-CAM and conventional complete dentures. J Prosthet Dent. 2020;123(6):880-887. doi: 10.1016/j.prosdent.2019.07.004. DOI
17. Więckiewicz W, Kasperski J, Więckiewicz M et al. The adhesion of modern soft relining materials to acrylic dentures. Adv Clin Exp Med. 2014;23(4):621-5. doi: 10.17219/acem/37242. DOI
18. Bal BT, Yavuzyilmaz H, Yücel M. A pilot study to evaluate the adhesion of oral microorganisms to temporary soft lining materials. J Oral Sci. 2008;50(1):1-8. doi: 10.2334/josnusd.50.1. DOI
19. Dantas LC, da Silva-Neto JP, Dantas TS et al. Bacterial Adhesion and Surface Roughness for Different Clinical Techniques for Acrylic Polymethyl Methacrylate. Int J Dent. 2016;2016:8685796. doi: 10.1155/2016/8685796. DOI
20. Sultana N, Ahmed S, Nandini VV et al. An In Vitro Comparison of Microbial Adhesion on Three Different Denture Base Materials and Its Relation to Surface Roughness. Cureus. 2023;15(4):e37085. doi: 10.7759/cureus.37085. DOI
21. Klotz S, Loos U, Bothe B et al. Adhesion of Candida albicans to denture base materials: A critical review. J Prosthet Dent. 2005;93(6):498-502. doi:10.1016/j.prosdent.2005.03.007. DOI
22. Aguayo S, Marshall H, Pratten J et al. Early Adhesion of Candida albicans onto Dental Acrylic Surfaces. J DentRes. 2017;96(8):917-23. doi: 10.1177/0022034517706354. DOI
23. Espinel-Ingroff A, Chaturvedi V, McGinnis MR et al. Low adhesion of Staphylococcus aureus to denture base materials compared to other bacteria. J Med Microbiol. 2007;56(6):821-827. doi:10.1099/jmm.0.47279-0. DOI
24. Weng X, Zhang X, Wang Y et al. Bacterial adhesion on acrylic resins and its association with surface roughness. J Prosthodont. 2015;24(6):450-455. doi:10.1111/jopr.12202. DOI
25. Morin MP, He X, Khalil M et al. The adhesion of Streptococcus mutans to dental materials: A comparative study of various types of resins. J Oral Microbiol. 2014;6:25113. doi:10.3402/jom.v6.25113. DOI
26. Motallebzadeh R, Shahramian K, Rezaei A et al. Influence of saliva on microbial adhesion to denture base materials: A systematic review. J Dent. 2016;44(1):1-7. doi:10.1016/j.jdent.2015.11.006. DOI
27. Gorseta K, Pavičić Z, Gašparović M et al. Influence of patient diet and oral hygiene on microbial adhesion to denture surfaces. J Prosthet Dent. 2019;121(4):604-610. doi:10.1016/j.prosdent.2018.02.003. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Bohdan Pelekhan
Ivano-Frankivsk National Medical University
2 Halytska St., 76000 Ivano-Frankivsk, Ukraine
e-mail: bpelechan@gmail.com

ORCID AND CONTRIBUTIONSHIP
Yurij Kushnir: 0009-0005-4986-3856A D
Mykola Rozhko: 0000-0002-6876-2533 E F
Roman Kutsyk: 0000-0001-9408-9074B C
Roksolana Verbovska: 0000-0003-1781-7909 A B
Bohdan Pelekhan: 0000-0002-1201-0383 D E
Svyatoslav Rozhko: 0009-0006-6338-8227 B E
Lesya Kurovets: 0000-0002-4972-3862 C D

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 16.09.2024
ACCEPTED: 07.05.2025

ORIGINAL ARTICLE

CONTENTS

Diagnostic value of lipoprotein-associated phospholipase A2 in patients in the early recovery period of atherothrombotic stroke

Olga J. Mykhaloiko, Viktoriya A. Gryb, Ivanna-Romana M. Fabryka, Oleksandra I. Hotsaniuk, Uliana P. Shalamai, Tetiana I. Salyzhyn, Igor J. Mykhaloiko
IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

Aim: The purpose of the study is to study changes in Lp-PLA2 in the blood of patients in the early recovery period of atherothrombotic stroke depending on the degree of stenosis and type of atherosclerotic plaque.

Materials and Methods: A clinical and laboratory analysis of 130 patients in the early recovery period of atherothrombotic stroke was conducted. Among those examined were 69 men and 61 women aged (60.42±7.4) years. The control group consisted of 30 practically healthy persons (16 men and 14 women) without a history of severe somatic pathology, aged (58.7±6.3) years. Ultrasound scanning of the vessels of the neck was performed on a Siemens Acuson X 300 device. The amount of lipoprotein-associated phospholipase A2 (Lp-PLA2) was determined by the immunoenzymatic method. STATISTICA 8 software was used for statistical processing.

Results: In all examined patients, an increase in the content of Lp-PLA2 in the blood up to 260 (220.4; 295.7) ng/ml was found compared to individuals of the control group ($p<0.05$). Increased levels of Lp-PLA2 in stroke patients were associated with an increased degree of atherosclerotic stenosis and depended on the type of atherosclerotic plaque, reflecting its instability.

Conclusions: Increased concentrations of Lp-PLA2 in patients with cerebral atherosclerosis can be considered as circulating biomarkers of atherosclerotic plaque vulnerability. Patients in the early recovery period of an ischemic stroke with a soft atherosclerotic plaque according to ultrasound data in combination with an increase in Lp-PLA2 indicators in the blood belong to the group of high risk of developing a repeated stroke.

KEY WORDS: lipoprotein-associated phospholipase A2, atherothrombotic stroke, atherosclerotic plaque, early recovery period of ischemic stroke

Wiad Lek. 2025;78(6):1119-1124. doi: 10.36740/WLek/204797 DOI

INTRODUCTION

Despite significant advances in modern medicine, cardiovascular diseases and their complications, including strokes, remain the main cause of mortality worldwide. 30-40% of all ischemic strokes are the atherothrombotic subtype of stroke, the pathogenetic mechanism of which is arterio-arterial embolism from thrombotic deposits on the surface of atherosclerotic plaque, which lead to occlusion of intracranial arteries. According to modern ideas, the basis of the development and progression of atherosclerosis is endothelial dysfunction, which occurs against the background of chronic inflammation [1-2]. The initial phase of the inflammatory process in the area of atherosclerotic artery damage is asymptomatic. Clinical manifestations are present only in the case of hemodynamically significant atherosclerotic stenosis of the artery, which is manifested by a lack of blood supply to the affected area, or due to the development of thrombogenic complications arising from the destabilization and disintegration of the atherosclerotic plaque [3-4].

The traditional definition of atherosclerotic lesions of cerebral vessels is an ultrasound examination (US) with measurement of the lumen of the stenosis and the characteristics of the atherosclerotic plaque. However, despite the informativeness of ultrasound of atherosclerotic vascular damage, predicting the vulnerability of plaques remains difficult. In search of new opportunities to detect the stage of inflammation in atherosclerotic plaque, vascular markers of inflammation and their relationship with the risk of developing complications have been widely studied in recent years [2, 5]. Determination of potentially new biomarkers of the progression of atherothrosclerosis in comparison with clinical and ultrasound parameters would allow to characterize the activity of the atherosclerotic process, predict the risk of its progression and determine the probability of embolic complications.

One of the most studied markers of inflammation in recent years is lipoprotein-associated phospholipase A2 (Lp-PLA2). The role of lipoprotein A as a risk factor for cardiovascular diseases has been studied for many years [5-6]. Features of Lp-PLA2 that attract the attention of researchers are the specificity for vascular inflammation.

European recommendations for the treatment of dyslipidemias, issued by the European Society of Cardiology together with the European Society of Atherosclerosis, recommend measuring Lp-PLA2 in people with early development of cardiovascular diseases, in people with familial hypercholesterolemia, in people with a family history of early cardiovascular diseases (CVD) and in individuals with recurrent CVD episodes despite optimal lipid-lowering therapy, who have a 10-year SCORE risk ≥5% [6-7]. On the other hand, the American Lipid Association does not include Lp-PLA2 screening as one of the indicators of the standard lipid panel, which is partly due to the difficulty of standardizing methods for its determination [2, 8].

Lp-PLA2 belongs to the phospholipase A2 family and is produced by monocytes, mast cells, Kupffer cells, and T lymphocytes.

In plasma, 80% of Lp-PLA2 is bound to LDL-C, the remaining 20% is bound to HDL-C and VLDL. The main properties of Lp-PLA2 include reflecting the degree of intravascular inflammation and instability of atherosclerotic plaque. That is, Lp-PLA2 has specificity in relation to vascular inflammation, while other biomarkers, such as CRP, reflect the presence of systemic inflammation. Lp-PLA2 takes a direct part in atherogenesis, causing modification of lipids by hydrolysis of phosphatidylcholine with the formation of lyso-phosphatidylcholine and oxidation of free fatty acids, which stimulate the development of atherosclerosis. An increase in Lp-PLA2 in the blood directly reflects an increase in the risk of cardiovascular events [3, 8-9].

According to the results of one of the European studies, when observing patients with stable coronary heart disease, the level of Lp-PLA2 from 30 to 50 mg/dL was associated with a threefold increase in the risk of amputation of the lower limbs, while in patients with Lp-PLA2 >50 mg/dL - with twentyfold [4, 10-11].

The MONICA (The Monitoring Trends and Determinants in Cardiovascular Diseases) study examined the relationship between Lp-PLA2 levels and the risk of coronary events in 934 healthy men aged 45–64 years. Observations were carried out for 14 years. During the follow-up period, 97 men experienced acute coronary events and had significantly higher baseline Lp-PLA2 levels compared to controls.

In the Atherosclerosis Risk in Communities (ARIC) study of 12819 middle-aged men and women followed for 6 years, the combination of high Lp-PLA2 and high CRP was superior to either marker taken alone. by the ability to predict the risk of developing coronary events [2, 10].

The categories of patients who need to determine the concentration of Lp-PLA2, as well as the cut-off level, are actively discussed by experts. A value of ≥200 ng/ml was taken as the clinical threshold of the Lp-PLA2 level, which gives the right to make a decision on reclassification of risks. The researchers approved this threshold, which is based on the results of a study that showed a significant increase in the risk of cardiovascular events in patients who exceeded this threshold. Interpretation of Lp-PLA2 levels in blood serum is carried out as follows: low degree of cardiovascular risk - (< 200 ng/ml); average degree of risk - (200 - 235 ng/ml); high degree of risk - (> 250 ng/ml). The level of Lp-PLA2 more than 250 ng/ml has a high correlation with endothelial dysfunction, which in turn is closely related to the process of progression of atherosclerosis [2, 6, 12].

The understanding that Lp-PLA2 is actively synthesized in the places of atherosclerotic lesions and causes multiple proatherogenic and prothrombotic effects determines the relevance of determining this marker for diagnosis and assessment of the severity of the atherosclerotic process.

AIM

The aim of the study is to study changes in Lp-PLA2 in the blood of patients in the early recovery period of atherothrombotic stroke depending on the degree of stenosis and type of atherosclerotic plaque.

MATERIALS AND METHODS

A clinical and laboratory analysis of 130 patients in the early recovery period of atherothrombotic stroke (ERPAS) was performed. Among the examined were 69 men and 61 women aged (60.42±7.4) years.

The control group consisted of 30 practically healthy persons (16 men and 14 women) without a history of severe somatic pathology and disorders of cerebral blood circulation, aged (58.7±6.3) years.

Ultrasound duplex scanning of the vessels of the neck with the determination of the degree of atherosclerotic stenosis and the nature of the atherosclerotic plaque was performed on a Siemens Acuson X 300 device with a linear multifrequency sensor from 4–10 mHz) according to standard methods.

The classification of stenotic-occlusive lesions of cerebral arteries was carried out according to the classification of B. V. Gaidar et al.. According to these

Table 1. The level of lipoprotein-associated phospholipase A2 in the blood of patients in the early recovery period of atherothrombotic stroke depending on the degree of atherosclerotic stenosis

Lp-PLA2; ng/ml Me (q_1 ; q_3)	control group (n=30)	The degree of atherosclerotic damage			
		group A: <40% (n=26)	group B: 40– 60% (n=48)	group C: 60-75 (n=42)	group D: 75-95% (n=14)
	200.75 (185.1; 202,2)	255.9 (234.5;263.3) p<0,05	272.9 (268.5;280.3) p<0,05 p_1<0,05	280.9 (275.5;285.3) p<0,001 p_1<0,05 p_2>0,05	290.9 (284.5;294.3) p < 0,001, p_1 < 0.05, p_2<0,05, p_3>0,05.

Notes:
p – the reliability of the differences in indicators compared to the control group;
p1 – the reliability of the differences in indicators of groups B, C, D in comparison with group A;
p2 – the reliability of the differences in indicators of groups C, D in comparison with group B;
p3 – the reliability of the differences in the indicators of groups D in comparison with group C.

criteria, stenosis of the main artery of the 1st degree was diagnosed when the vessel narrowed to 40% of the diameter, 2nd degree – 40–59%, 3rd degree – 60–74%, 4th degree – 75–90%, 5th degree – more than 90%, hemodynamically significant considered stenosis IV–V degree.

The nature of atherosclerotic plaques was divided into five types according to the Nicolaidese and Geroulaka classification: I type: only echonegative ("soft" homogeneous plaque); II type: mostly echonegative with more than 50% hypoechoic areas (heterogeneous hypoechoic plaque); Type III: mostly echo-positive with more than 50% hyperechoic areas (heterogeneous hyperechoic plaque); IV type: only echo-positive ("dense" homogeneous plaque); V type: pronounced calcinosis, which gives an acoustic shadow.

The amount of Lp-PLA2 was determined using an enzyme-linked immunosorbent assay (ELISA) kit (Diazyme Laboratories Inc., Poway, California, USA). Plasma was added to the microplate wells with anti-Lp-PLA2 monoclonal antibodies (2C10) and incubated for 10 min at room temperature. Then the second monoclonal antibodies (4B4), labeled with horseradish peroxidase enzyme, were added and incubated for 180 min. Wells were washed and tetramethylbenzidine substrate was added. After 20 min of incubation, absorbance at 450 nm was measured, which is directly proportional to the concentration of Lp-PLA2 in the plasma. The concentration of Lp-PLA2 is expressed in units of ng/ml.

The study was approved by the Bioethics Commission of Ivano-Frankivsk National Medical University (protocol No 21 dated 09.27.2022). Patients gave written informed consent for the above diagnostic procedures and participation in this research project.

STATISTICA 8 software was used for statistical processing. The frequency of qualitative indicators was presented in absolute (n) and relative (%) frequencies. When analyzing quantitative data, the nature of the distribution of indicator values was determined using the Shapiro-Wilk's test method. For quantitative data with a normal distribution, the results were presented in the form of «M (σ)» (where M is the average value, and σ is the mean square deviation), and for quantitative data with a non-normal distribution - in the form of «Me (Q1; Q3)» (where Me is the median, and Q1, Q3 are quartiles). Quantitative indicators with non-normal distribution of values in 2 independent groups were compared by the Mann–Whitney method. Comparison of 2 independent groups according to the qualitative indicator was carried out according to Fisher's exact test.

RESULTS

According to a duplex scan of the vessels of the head and neck, all patients in the early recovery period of atherothrombotic stroke had atherosclerotic stenoses of varying degrees. The localization of the atherosclerotic plaque corresponded to the side of the affected cerebral hemisphere. The largest number of patients had atherosclerotic layers, causing stenosis by 40-75%. There were 14 patients with hemodynamically significant stenoses, 4 of whom had more than 90% stenosis, all of whom were recommended carotid endarterectomy.

An increase in the content of Lp-PLA2 in blood up to 260 (220.4; 295.7) ng/ml (p<0.05) was found in all examined patients with ERPAS compared to 200.75 (185.1; 202.2) in healthy individuals. Depending on the severity of the degree of atherosclerotic stenosis, an increase in the level of Lp-PLA2 was noted. The highest values of Lp-PLA2 were recorded in the group of patients with hemodynamically significant atherosclerotic stenoses (Table 1).

Table 2. The level of lipoprotein-associated phospholipase A2 in the blood of patients in the early recovery period of atherothrombotic stroke depending on the type of atherosclerotic plaques

	Types of atherosclerotic plaques					control group, (n=30)
	I (n=18)	II (n=44)	III (n=34)	IV (n=48)	V (n=16)	
Lp-PLA2; ng/ml Me (q_1; q_3)	292.2 (280.7;293.3) p<0,001	283.9 (274.5;285.5) p<0,05 p_1>0,05	275.9 (268.5;281..5) 280.3) p<0,05 p_1<0,05 p_2>0,05	267.9 (268.5;272.3) p<0,05 p_1<0,05 p_2<0,05 p_3>0,05	258.9 (244.5;262.3) p<0,05 p_1<0,05 p_2<0,05 p_3<0,05 p_4<0,05	200.75 (185.1; 202,2)

Notes:
p– the reliability of the differences in indicators compared to the control group;
p_1 – reliability of differences in indicators from II, III, IV, V in comparison with group I;
p_2 – the reliability of the differences in indicators of groups III, IV, V in comparison with group II;
p_3 – the reliability of the differences in indicators of groups IV, V in comparison with group III;
p_4 – the reliability of the differences in indicators of groups V in comparison with group IV.

All patients were taking antiplatelet agents, statins, and hypoglycemic drugs (in the presence of diabetes) for the purpose of secondary prevention of stroke. It should be noted that statin therapy causes biochemical remodeling of the atherosclerotic plaque with a predominant effect on the lipid components than on the total plaque size. Despite this fact, atherosclerotic plaques of type I (echo-negative homogeneous plaques) and type II (echo-negative with hypoechoic inclusions more than 50%) were noted in 18 patients, which have a high degree of embologenicity and, accordingly, can be the cause of repeated atherothrombotic stroke.

Unstable atherosclerotic plaques, for the most part, had a heterogeneous structure with hypoechoic inclusions, an uneven surface, and existing layers. Stable plaques were homogeneous, hyperechoic. Concentration changes of Lp-PLA2 also depended on the structure of the atherosclerotic plaque. The highest levels of Lp-PLA2 were recorded in patients with I, II and III types of atherosclerotic plaques. Accordingly, in the group with stable, calcified atherosclerotic plaques, the level of Lp-PLA2 was the lowest among the subjects, however, it was higher than in the control group (Table 2).

When analyzing the obtained data, it was established that in patients with the same parameters of the level of stenosis, but different morphological density of atherosclerotic layers, significantly higher values of Lp-PLA2 were recorded in patients with soft, unstable atherosclerotic plaques (285.9 (265.5; 295.3)) compared to stable (250.2 (245.9; 267.3)). That is, the increase in the concentration of Lp-PLA2 depended more on the structure of the atherosclerotic plaque than on its size. Based on the results obtained by us, patients with a soft atherosclerotic plaque according to ultrasound data in combination with an increase in Lp-PLA2 indicators in the blood belong to the group of high risk of recurrent stroke.

DISCUSSION

Atherosclerosis is a chronic inflammatory disease that causes dysfunction of endothelial cells, influx of inflammatory leukocytes into the subendothelial space and oxidation of LDL. As plaque inflammation develops, it destabilizes and becomes prone to rupture. Plaque rupture is responsible for acute manifestations of atherosclerosis, including myocardial infarction, unstable angina, stroke, and death. Identification of markers of plaque destabilization at the preclinical stage is a justified direction in the search for predictors of cardiovascular catastrophes. Among all known systemic markers of inflammation and endothelial dysfunction, Lp-PLA2 has specificity for vascular inflammation, which is why it is of interest. [1, 4, 7].

The results of our study, which indicate the diagnostic significance of determining Lp-PLA2 in patients at high risk of recurrent stroke, echoed the results of other studies. The JUPITER study showed that patients with high Lp-PLA2 activity (fourth quartile) had a more than two-fold increased relative risk (HR 2.15, 95% CI: 1.13-4.08) of cardiovascular events compared to patients with low activity (first quartile). The Bruneck study showed that the population in the third tertile of Lp-PLA2 activity had a higher relative risk of cardiovascular events (HR 2.2, 95% CI: 1.1-4.8) compared with those in the first tertile [2, 11]. Similar results were obtained in the LIPID trial that entailed subjects with history of acute coronary syndrome in whom Lp-PLA2 activity was

associated to a higher risk of cardiovascular mortality (HR 1.32, 95%CI: 1.00-1.75) [12].

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a promising marker of atherosclerotic plaque destabilization, which plays a key role in the metabolism of pro-inflammatory phospholipids and in the generation of proatherogenic metabolites. Since there is much evidence for the key role of inflammation in atherothrombosis, and the main product Lp-PLA2 is a potent pro-inflammatory molecule, it may be not only a predictor of cardiovascular disease risk, but also a target for therapeutic intervention.

CONCLUSIONS

The level of Lp-PLA2 in patients in the ERPAS was significantly higher compared to the control group.

Increased levels of Lp-PLA2 in stroke patients were associated with an increased degree of atherosclerotic stenosis and depended on the type of atherosclerotic plaque, reflecting its instability.

Patients in the early recovery period of an ischemic stroke with a soft atherosclerotic plaque according to ultrasound data in combination with an increase in Lp-PLA2 indicators in the blood belong to the group of high risk of developing a repeated stroke.

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW et al. Heart Disease and Stroke Statistics 2018 update: a report from the American Heart Association. Circulation. 2018;137(12):67-492. doi: 10.1161/CIR.0000000000000558. DOI
2. Garg PK, McClelland RL, Jenny NS et al. Lipoprotein-associated phospholipase A2 and risk of incident cardiovascular disease in a multi-ethnic cohort: The multi ethnic study of atherosclerosis. Atherosclerosis, 2015;241(1):176-182. doi: 10.1016/j.atherosclerosis.2015.05.006. DOI
3. Banerjee C, Chimowitz M. Stroke caused by atherosclerosis of the major intracranial arteries. Circulation Research. 2017;120(3):502–513. doi: 10.1161/CIRCRESAHA.116.308441. DOI
4. Ezhov M, Safarova M, Afanasieva O. Lipoprotein(a) level and apolipoprotein(a) phenotype as predictors of long-term cardiovascular outcomes after coronary artery bypass grafting. Atherosclerosis. 2014;235:477-82. doi: 10.1016/j.atherosclerosis.2014.05.944. DOI
5. Han L, Zhong C, Bu X. Prognostic value of lipoproteinassociated phospholipase A2 mass for all-cause mortality and vascular events within one year after acute ischemic stroke. Atherosclerosis. 2017;266:1–7. doi: 10.1016/j.atherosclerosis.2017.09.013. DOI
6. Marcovina S, Albers J. Lipoprotein(a) measurements for clinical application. J Lipid Res. 2016;(57):526-37. doi: 10.1194/jlr.R061648. DOI
7. Mykhalojko OY, Mykhalojko IY. Potential circulating biomarkers of atherosclerotic plaque vulnerability in patients in the early recovery period of atherothrombotic stroke. Ukrainian Biochemical Journal. 2023;(95)1:58-63. doi: 10.15407/ubj95.01.058. DOI
8. Liu H, Yao Y, Wang Y et al. Association between high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2 and carotid atherosclerosis: A cross-sectional study. J Cell Mol Med. 2018;22(10):5145-5150. doi: 10.1111/jcmm.13803. DOI
9. Huang F, Wang K, Shen J. Lipoprotein-associated phospholipase A2: the story continues. Medicinal Research Reviews. 2020;40(1):79–134. doi: 10.1002/med.21597. DOI
10. Wong N, Zhao Y, Sung J, Browne A. Relation of first and total recurrent atherosclerotic cardiovascular disease events to increased lipoprotein(a) levels among statin treated adults with cardiovascular disease. Am J Cardiol. 2021;(145):12-17. doi: 10.1016/j.amjcard.2020.12.075. DOI
11. Maiolino G, Bisogni V, Rossitto G, Rossi GP. Lipoprotein-associated phospholipase A2 prognostic role in atherosclerotic complications. World J Cardiol. 2015;7(10): 609-620. doi: 10.4330/wjc.v7.i10.609. DOI
12. Karakas M, Koenig W. Lp-PLA2 Inhibition – The Atherosclerosis Panacea? Pharmaceuticals. 2010;3(5):1360-1373. doi: 10.3390/ph3051360. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Olga J. Mykhaloiko
Ivano-Frankivsk National Medical University
2 Halytska St., 760008 Ivano-Frankivsk, Ukraine
e-mail: myhalojko@i.ua

ORCID AND CONTRIBUTIONSHIP
Olga J. Mykhaloiko: 0000-0003-0618-4501 A B C D E F
Viktoriya A. Gryb: 0000-0001-6111-7921 F
Ivanna-Romana M. Fabryka: 0000-0002-1154-3241 A B
Oleksandra I. Hotsaniuk: 0000-0001-9691-7419 B
Uliana P. Shalamai: 0000-0001-7044-3585 B C
Tetiana I. Salyzhyn: 0000-0003-4206-622X B
Igor J. Mykhaloiko: 0000-0002-6288-1806 A B C E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 07.11.2024
ACCEPTED: 07.05.2025

ORIGINAL ARTICLE

CONTENTS

Morphometric analysis of the morphological state of skin vascular plexuses under opioid in an experiment

Ivan S. Diskovskyi, Lesya R. Mateshuk-Vatseba, Orysya O. Syzon, Marianna O. Dasko, Nataliya V. Ivanyushko-Nazarko, Hennadiy Ye Astsaturov, Aksiniia V Netliukh
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Aim: The patterns of qualitative and quantitative changes in the microvascular network in the skin of adult male white rats under of nalbuphine administration.
Materials and Methods: The research employed methods such as vascular bed injection, skin section clearing, and microscopic imaging using an MBI-1 microscope. Morphometric analysis of the microcirculation vessels was conducted, and statistical processing of the results was performed using specialized software.
Results: The nalbuphine significantly impacted the morphological state of the white rat's skin after two weeks of administration, with the initial changes occurring in the blood vessel plexuses. In the injected skin samples, both arterioles and capillaries were dilated, with the diameter of the subpapillary arteriolar network significantly increasing to 28.62±1.07 μm (control – 22.24±0.73 μm), and the diameter of intrapapillary capillary loops expanding to 6.20±0.11 μm (control – 5.91±0.26 μm). Arterioles exhibited tortuosity. After four weeks, the loops of the vascular plexus lost their delicate, lace-like structure, with microaneurysms in arterioles and sacculations in venules becoming evident. After six weeks of opioid exposure, significant structural alterations were observed in the blood vessels of the skin. Capillaries became obliterated, with some destroyed, and this process was accompanied by hemorrhages. The density of intrapapillary capillary loops decreased significantly to 59.0±2.0 (control – 79.60±2.078), while the trophic activity index increased to 39.490±1.307 μm (control – 27.172±1.143 μm),
Conclusions: Morphometric analysis of the morphological state of the vascular plexuses in the skin clearly illustrates the relationship between quantitative and qualitative changes in the structural organization of the microcirculation network under opioid exposure.

KEY WORDS: skin, vessels, morphometry, opioid

Wiad Lek. 2025;78(6):1125-1132. doi: 10.36740/WLek/204796 DOI

INTRODUCTION

Nowadays, medicine, unfortunately, cannot function without the use of opiates and opioids for therapeutic purposes [1-5]. Research on the effects of opioids on organ structure is scarce and contradictory [6=11]. Individuals who are forced to use opioids for extended periods have an increased mortality rate from cardiovascular diseases and a higher likelihood of fatal outcomes due to liver and kidney failure. Besides, regular use of narcotic substances severely damages the immune system [12]. In recent years, the number of inflammatory conditions among injection drug users has increased worldwide [13]. The continuous rise in the number of drug addicts in Ukraine has led to a series of new social, economic and medical problems [14-16].

The skin is the organ that responds first to exogenous and endogenous influences [17, 18]. In the event of any skin damage, the vascular plexuses of the skin are the first to react. Despite the relevance and importance of studying morphological changes in microcirculation network under pathological conditions, the professional literature lacks sufficient information on the vascular network of the skin, and information on its morphometric analysis under both normal physiological conditions and different pathological processes is nearly nonexistent.

The utilization of experimental animals, specifically white rats, for modeling opioid effects on the skin enables the investigation of dynamic structural alterations in the cutaneous microvasculature under prolonged exposure to the narcotic agent. The rationale for using this laboratory animal is the similarity between the skin structure of rats and humans.

AIM

To establish the patterns of qualitative and quantitative changes in the components of the cutaneous microcirculation bed in sexually mature male white rats under different durations of nalbuphine administration.

MATERIALS AND METHODS

The study was conducted on 40 sexually mature male white rats with an initial body weight ranging from 160 to 180 g and an age of 3.0 months

The study was conducted on 40 sexually mature male white rats with an initial body weight ranging from 160 to 180 g and an age of 3.0 months.

The animals selected for the study underwent thorough screening, including clinical examination, weighing, and marking. All animals were housed under standard vivarium conditions at Danylo Halytsky Lviv National Medical University. The experiments were conducted in compliance with ethical guidelines for the humane treatment of laboratory animals, as stipulated by the Law of Ukraine "On the Protection of Animals from Cruelty" (No. 3447-IV, 21.02.2006) and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 18.03.1986).

The study material consisted of skin specimens from white rats with an injected vascular network.

The research utilized the following methodologies: injection of the skin vascular network in white rats, tissue section clearing and subsequent microscopic imaging using an MBI-1 microscope. Morphometric analysis of the microcirculation components of the skin was conducted. Statistical analysis of the research data was performed using specialized software. Furthermore, a model for prolonged opioid exposure in white rats was established and implemented.

The animals were euthanized by intraperitoneal administration of sodium thiopental at a dosage of 2.5 mg/100 g (25 mg/kg) of body weight.

After opening the ventral wall of the abdominal and thoracic cavities, clamps were applied to the intercostal arteries. A glass cannula with a rubber tip was inserted into the thoracic aorta, connected to a syringe, and secured with a silk ligature. The injection mass was then introduced into the vascular system via the syringe. The blood vessels of the rat's skin were filled with an ink-gelatin injection mass. The injection mass was prepared as follows: 100 g of gelatin was poured into 1 L of cold water and left for 24 hours. After the gelatin swelled, the mixture was heated in a water bath and filtered through several layers of gauze. The warm gelatin was then mixed with equal volumes of sodium citrate solution and ink before being injected into the arterial system of a freshly euthanized white rat. The volume of the mixture used for filling the arterial system ranged from 10 to 15 mL. After the injection, a ligature was applied to the abdominal aorta, and the skin from the gluteal region was collected for further study. This injection technique is technically simple and does not require scarce reagents. Moreover, it allows for the injection of both large vessels and microcirculation components, enabling differentiation of arterial, capillary, and venous segments.

The day after the injection with the ink-gelatin mass, the skin was immersed for two days in a 1:1 mixture of glycerin and ethanol. It was then cleared and stored in chemically pure glycerin.

After clearing the specimens, the segments of the skin vascular network were photographed in transmitted light using an MBI-1 microscope at magnifications of ×80 (objective ×10, eyepiece ×8) and ×160 (objective ×20, eyepiece ×8) with an Olympus FE 210 digital camera.

The study of the microcirculatory vessels in injected and cleared specimens allows for a reliable assessment of key quantitative parameters, including the diameter of microvessels, the density of the capillary network (DCN), and the area of trophic tissue activity (ATTA).

For the morphometric analysis of the angioarchitecture of white rat's skin, measurements of the diameters of arterioles, capillaries, and venules were performed. The vessel diameters were measured using an ocular micrometer. These measurements were conducted on cleared skin specimens with an injected vascular network. The actual vessel diameter (D) was determined using an eyepiece micrometer at microscope magnifications of ×20 objective with ×8 eyepiece and ×10 objective with ×8 eyepiece, taking into account the scale division value (C) using the formula: $D=d \cdot C$, where: D is the actual vessel diameter, d is the measured vessel diameter, C is the calibration coefficient of the ocular micrometer scale. The calibration value (C) of the eyepiece micrometer was determined using a standard microscope grid. According to the specifications, the side length of a small square in the grid is 50 μm. When using a ×10 objective and ×8 eyepiece, the calibration value (C) is 100 μm (0.1 mm), while with a ×20 objective and ×8 eyepiece, it is 50 μm (0.05 mm).

The capillary density was quantified by calculating the number of vessels per unit area, with the unit area corresponding to the field of view of the microscope. The tissue trophic activity index (μm), also referred to as the diffusion radius, was determined by measuring the intervascular distance between two adjacent vessels and dividing the obtained value by two.

Statistical analysis of the obtained data was conducted using the InStat software package, which is specifically designed for the statistical processing of biomedical and epidemiological research data.

The long-term effects of opioid exposure in white rats were modeled through daily administration

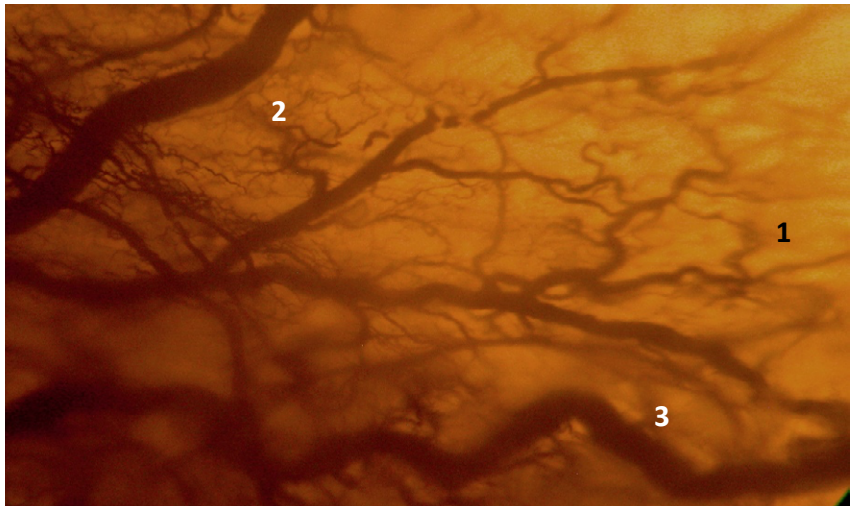

Fig. 1. Subpapillary arterial network and venous plexus of the skin of the white rat's gluteal region after 2 weeks of nalbuphine administration. Microphotograph. Vascular injection. Magnification: objective ×20, eyepiece ×8. 1 – Intrapapillary capillary loop; 2 – Arteriole; 3 – Venule

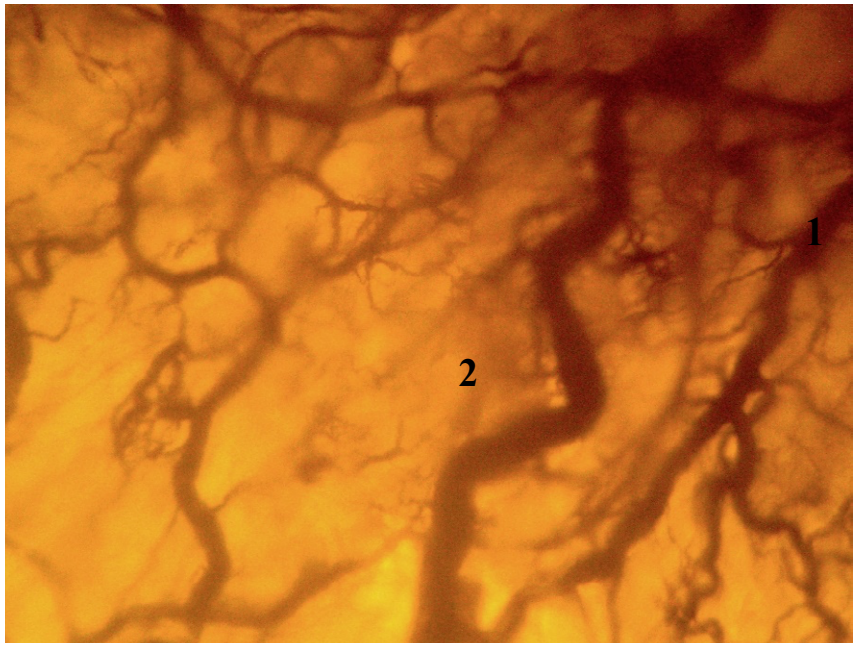

Fig. 2. Dermal arterial network and venous plexus of the skin in the gluteal region of a white rat after two weeks of nalbuphine administration. Micrograph. Vascular injection. Magnification: obj. ×20, ocular ×8. 1 – arteriole; 2 – venule

(once per day at the same time) of the opioid analgesic nalbuphine. Nalbuphine was administered intramuscularly according to the following dosage regimen: week 1 – 8 mg/kg, week 2 – 15 mg/kg, week 3 – 20 mg/kg, week 4 – 25 mg/kg, week 5 – 30 mg/kg, week 6 – 35 mg/kg. The experimental exposure periods lasted two, four, and six weeks from the start of the experiment. This model, which involves a gradual increase in the dose of an accessible opioid analgesic, enables the investigation of its effects on the experimental animals and allows for the assessment of the progressive development of morphological changes in tissues. The proposed method, characterized by weekly dose increments, facilitates the gradual adaptation of opioid receptors in the experimental animals. Age-matched intact animals were used as the control group and received intramuscular injections of a 0.9% sodium chloride solution.

RESULTS

In the skin samples obtained from the gluteal region of the white rat with the injected vascular network, after two weeks of experimental exposure, the following structures were observed, similar to those in the control group: the subpapillary and dermal arterial networks, the subpapillary and dermal venous plexuses, and the subcutaneous venous plexus. The subpapillary arterial network and subpapillary venous plexus are located between the papillary and reticular layers of the skin (Fig. 1).

This is a fine-looped plexus. The capillaries form intrapapillary capillary loops, which have the shape of glomeruli or lace-like networks.

At the boundary between the reticular layer of the skin and the hypodermis lies the dermal vascular plexus. This plexus contains arterioles that form the dermal arterial network and venules that lie deeper, creating the deep dermal venous plexus (Fig. 2). Another vascular plexus is

Fig. 3. Subpapillary arterial network and venous plexus of the gluteal skin in a white rat after four weeks of nalbuphine administration. Micrograph. Vascular injection. Magnification: obj. ×20, ocular ×8. 1 – intrapapillary capillary loop

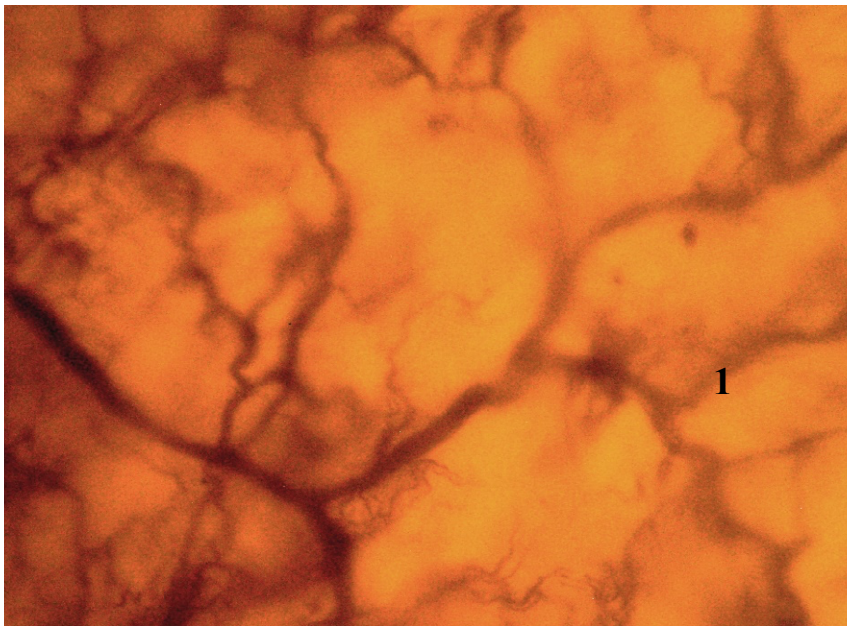

Fig.4. Subcutaneous venous plexus of the gluteal skin in a white rat after six weeks of nalbuphine administration. Micrograph. Vascular injection. Magnification: obj. ×20, ocular ×8. 1 – venule

located in the hypodermis — the subcutaneous plexus. This plexus has a wide-looped structure.

After just two weeks of the experiment, the arteriolar diameter significantly increases. Specifically, the diameter of the arterioles in the subpapillary arterial network reaches 28.62±1.07 μm (control – 22.24±0.73 μm), while in the dermal arterial network, it reaches 49.94±1.74 μm (control – 36.86±1.90 μm). The arterioles appear tortuous. The intrapapillary capillary loops of the skin exhibit slight dilation, with their diameter increasing to 6.20±0.11 μm (control – 5.91±0.26 μm). However, at this stage of the experiment, no significant change in the venular diameter is observed. The diameter of venules in the subpapillary venous plexus is 54.32±0.30 μm (control – 53.97±0.92 μm), while in the subcutaneous venous plexus, it measures 114.93±2.78 μm (control – 112.01±2.25 μm). These changes lead to alterations in other morphometric parameters of the vascular architecture of the white rat's skin under conditions of two-week nalbuphine administration. Notably, the trophic activity index of the skin tissue significantly decreases to 20.36±3.07 μm (control – 33.82±1.38 μm). However, the density of intrapapillary capillary loops in the white rat's skin remains unchanged at this experimental stage.

After four weeks of nalbuphine administration in white rats, the arteriolar lumen exhibits irregularities, characterized by alternating regions of constriction and dilation. Venules undergo expansion, structural deformation, and acquire an irregular morphology,

Table 1. Density of the intrapapillary capillary loop network in the gluteal skin of the white rat

Observation periods	Values	
	M±m (μm)	p
Control	71.000±4.728	p > 0.05
In two weeks after nalbuphine injection	68.000±3.926	p > 0.05
In four weeks after nalbuphine injection	69.200±4.761	p < 0.01
In six weeks after nalbuphine injection	59.000±1.963	p < 0.01

Table 2. Trophic activity index of the gluteal skin tissue in the white rat

Observation periods	Values	
	M±m (μm)	p
1	2	3
Control	33.822±1.376	p > 0.05
In two weeks after nalbuphine injection	20.364±3.066	p < 0.01
In four weeks after nalbuphine injectionIn two weeks after nalbuphine injection	22.472±2.438	p < 0.01
In six weeks after nalbuphine injection	40.410±4.508	p < 0.01

Table 3. Diameter of arterioles in the subpapillary arterial network of the gluteal skin in the white rat

Observation periods	Values	
	M±m (μm)	p
1	2	3
Control	22.240±0.730	p > 0.05
In two weeks after nalbuphine injection	28.616±1.069	p < 0.01
In four weeks after nalbuphine injection	29.540±0.894	p < 0.01
In six weeks after nalbuphine injection	30.120±0.039	p < 0.01

Table 4. Diameter of venules in the subpapillary venous plexus of the gluteal skin in the white rat

Observation periods	Values	
	M±m (μm)	p
1	2	3
Control	53.968±0.919	p > 0.05
In two weeks after nalbuphine injection	54.324±0.298	p < 0.01
In four weeks after nalbuphine injection	59.648±0.832	p < 0.01
In six weeks after nalbuphine injection	62.644±2.080	p < 0.01

with occasional aneurysmal protrusions. Additionally, isolated saccular aneurysms are observed in the microvasculature. These vascular alterations lead to modifications in the spatial organization of the subpapillary and dermal arterial networks, as well as the subpapillary, dermal, and subcutaneous venous plexuses in the gluteal skin of white rats following four weeks of nalbuphine exposure (Fig. 3).

At this stage of the experiment, the subpapillary vascular plexus of the white rat's skin is characterized by the following morphometric parameters: the diameter of the intrapapillary capillary loop is 6.26±0.12 μm, the trophic activity index of the skin tissue is 22.47±2.44 μm, and the diameter of venules in the subpapillary vascular plexus is 59.65±0.83 μm. The diameter of arterioles in the dermal arterial network increases to 55.18±4.18 μm, while the diameter of venules in the dermal venous plexus expands to 142.31±2.46 μm, and in the subcutaneous venous plexus, it reaches 158.57±1.98 μm.

The density of the intrapapillary capillary loop network in the gluteal skin of the white rat is presented in Table 1. A reduction in capillary loop network density to 69.200±4.761 (control – 71.000±4.728) after four weeks of nalbuphine administration indicates a minor disruption in the vascular architecture of the skin at this stage of the experiment.

After six weeks of the experiment, destructive changes in the angiographic pattern of the gluteal skin are observed. The subpapillary arterial network loses its delicate, lace-like appearance. Capillary loops become

dilated and coarse, with some areas showing a loss of capillary connections.

At this stage of the experiment, the diameter of the remaining intrapapillary capillary loops in the gluteal skin of the white rat significantly increases to 6.46±0.19 μm. Additionally, the density of intrapapillary capillary loops decreases markedly, reaching 59.0±2.0.

Changes in the trophic activity index of the skin tissue, as well as the diameters of the arterioles and venules in the subpapillary vascular plexus, are presented in Tables 2–4.

The arterioles of the dermal arterial network appear dilated, tortuous, and irregular in contour. Their diameter increases to 62.46±2.12 μm, while the diameter of venules expands to 158.60±1.99 μm.

Additionally, new arteriovenular anastomoses open, allowing blood to bypass the damaged capillaries and flow directly from the arterioles into the venules. The venules of the subcutaneous venous plexus are dilated and deformed (Fig. 4).

The diameter of venules in the subcutaneous venous plexus of the gluteal skin reaches 162.86±1.94 μm.

Therefore, the statistically significant decrease in the density of the intrapapillary capillary loop network within the subpapillary vascular plexus of the gluteal skin in white rats after four and six weeks of nalbuphine administration, coupled with a significant increase in the trophic activity index of skin tissue, provides compelling evidence of pronounced degenerative alterations in the vascular architecture of the skin resulting from prolonged opioid exposure.

DISCUSSION

Histological analysis of gluteal skin preparations from white rats with injected vascular networks following two weeks of experimentation revealed a clear differentiation of the subpapillary, dermal, and subcutaneous venous plexuses, comparable to that observed in the control group. The scientific literature provides limited data on the structural organization and vascularization of the skin in experimental animals. Existing studies primarily distinguish three vascular plexuses: hypodermal, subdermal, and subpapillary. The present study establishes that two weeks of nalbuphine administration induces a statistically significant increase ($p < 0.05$) in the diameter of arterioles within the subpapillary and dermal arterial networks, accompanied by increased arteriolar tortuosity. These vascular alterations correlate with a significant reduction in the trophic activity index of skin tissue, suggesting an early opioid-induced disruption of cutaneous microcirculation. The vasodilatory effect, specifically the increase in arteriolar diameter observed with nalbuphine administration over varying durations, has been consistently documented by researchers investigating the impact of nalbuphine on the vascular systems of various organs [19]. However, the morphometric parameters presented herein, which are critical for an objective evaluation of skin angioarchitectonics, offer novel contributions to the existing body of knowledge.

The scientific literature suggests that alterations in the skin, associated with various pathological conditions, are primarily accompanied by changes in its microcirculation network [20]. Our findings support these observations. Specifically, after four weeks of nalbuphine administration to white rats, histological examination of skin preparations with injected vascular networks revealed indistinct arteriolar contours and the presence of isolated aneurysmal sacculations within the microvessels. The aforementioned changes result in alterations to the spatial configuration of the subpapillary and dermal vascular networks, as well as the subcutaneous venous plexus in the gluteal skin of white rats following four weeks of nalbuphine administration. After six weeks of nalbuphine exposure, destructive changes are observed in the angiographic pattern of the gluteal skin. Specifically, the subpapillary vascular plexus loses its delicate, lace-like architecture, with capillary loops becoming dilated and coarse, and in certain areas, capillary connections are disrupted. Morphometric analysis of the vascular architecture of the skin under prolonged opioid exposure indicates structural degradation of the vascular network.

CONCLUSIONS

1. The morphological effects of nalbuphine on the white rats' skin become apparent after two weeks of administration, with the first observable changes occurring in the vascular structures of the blood plexuses. Histological analysis of skin specimens with injected vascular networks reveals dilatation of arterioles and capillaries. Specifically, the diameter of arterioles within the subpapillary arterial network significantly increases to 28.62±1.07 μm (control: 22.24±0.73 μm), while the diameter of the subpapillary capillary loops increases to 6.20±0.11 μm (control: 5.91±0.26 μm). The arterioles exhibit tortuosity.
2. After four weeks of experimental exposure, the loops of the vascular plexuses exhibit loss of their previously fine and regular pattern, with the appearance of microaneurysms in arterioles and saccular dilatations in venules. Following six weeks of opioid exposure, significant structural alterations are observed in the

vascular network of the skin. Capillaries are obliterated, and several capillaries are destroyed, a process accompanied by hemorrhages. There is a statistically significant reduction in the density of subpapillary capillary loops, which decreases to 59.0±2.0 (control: 79.60±2.078), while the trophic activity of the tissue increases to 39.490±1.307 μm (control: 27.172±1.143 μm), providing further evidence of the profound destructive changes in the vascular plexuses of the skin.

3. The morphometric analysis of the vascular plexuses in the skin provides clear evidence of the relationship between quantitative and qualitative alterations in the structural organization of the vessels within the microcirculation network in experimental animals subjected to opioid exposure. This analysis enables an objective evaluation of the extent of these changes in correlation with the duration of the experiment.

REFERENCES

1. Slat S, Yaganti A, Thomas J, Helminski D. Opioid Policy and Chronic Pain Treatment Access Experiences: A Multi-Stakeholder Qualitative Analysis and Conceptual Model. Journal of Pain Research. 2021;14:1161–1169. doi: 10.2147/JPR.S282228. DOI
2. Liu X, Hu J, Hu X, Li R. Preemptive Intravenous Nalbuphine for the Treatment of Post-Operative Visceral Pain: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Clinical Trial. Pain therapy. 2021;10:1155-1169. doi: 10.1007/s40122-021-00275-8. DOI
3. Larsen D, Maani ChV. Nalbuphine. In: StatPearls. Treasure Island (FL) : StatPearls Publishing. 2021.
4. Béliveau A, Castilloux A-M, Tannenbaum C, Vincent Ph. Predictors of long-term use of prescription opioids in the community-dwelling population of adults without a cancer diagnosis: a retrospective cohort study. CMAJ OPEN. 2021;9(1):E96–E106. doi: 10.9778/cmajo.20200076. DOI
5. Beck TC, Hapstack MA, Dix TA. Therapeutic Potential of Kappa Opioid Agonists. Pharmaceuticals (Basel). 2019;12(2):95. doi: 10.3390/ph12020095.237. DOI
6. Davis MP, Fernandez C, Regel S et al. Does nalbuphine have a niche in managing pain? J. Opioid Manag. 2018;14(2):143–151. doi: 10.5055/jom.2018.0441. DOI
7. Seth P, Rudd RA, Noonan RK, Haegerich TM. Quantifying the Epidemic of Prescription Opioid Overdose Deaths. Am J Public Health. 2018;108(4):500–2. doi: 10.2105/AJPH.2017.304265. DOI
8. Taqi MM, Faisal M, Zaman H. OPRM1 A118G Polymorphisms and Its Role in Opioid Addiction: Implication on Severity and Treatment Approaches. Pharmacogenomics and Personalized Medicine. 2019;12:361–368. doi: 10.2147/PGPM.S198654. DOI
9. Shekarchizadeh H, Khami MR, Mohebbi SZ et al. Oral health status and its determinants among opiate dependents: a cross-sectional study. BMC Oral Health. 2019;19(1):5. doi: 10.1186/s12903-018-0691-3. DOI
10. Ciurylo W, Noh E. Opioid-associated amnestic syndrome. Cureus J. Med. Sci. 2021;13:16714. doi: 10.7759/cureus.16714. DOI
11. Vandenbosch M, Pajk S, Van den Bogaert W et al. Post-mortem analysis of opioids and metabolites in skeletal tissue. J. Anal. Toxicol. 2022;46:783–790. doi: 10.1093/jat/bkab095. DOI
12. Plein LM, Rittner HL. Opioids and the immune system – friend or foe. British Journal of Pharmacology. 2018;175(14):2717–2725. doi: 10.1111/bph.13750. DOI
13. Alasmari F, Alasmari MS, Assiri MA et al. Liver metabolomics and inflammatory profiles in mouse model of fentanyl overdose treated with Beta-lactams. Metabolites. 2023;13:965. doi: 10.3390/metabo13080965. DOI
14. Kreek MJ, Reed B, Butelman ER. Current status of opioid addiction treatment and related preclinical research. Science Advances. 2019;5(10):9140. doi: 10.1126/sciadv.aax9140. DOI
15. Hurtado I, Garcia-Sempere A, Peiro S, Sanfelix-Gimeno G. Increasing Trends in Opioid Use From 2010 to 2018 in the Region of Valencia, Spain: A Real-World, Population-Based Study. Front Pharmacol. 2020;11:61255. doi: 10.3389/fphar.2020.612556. DOI
16. Bedene A, van Dorp ELA, Faquih T, Cannegieter SC. Causes and consequences of the opioid epidemic in the Netherlands: a population-based cohort study. Scien Rep. 2020;10(1):15309. doi: 10.1038/s41598-020-72084-6. DOI
17. Li J, Zeng X, Yang X, Ding H. Lycopene ameliorates skin aging by regulating the insulin resistance pathway and activating SIRT1. Food Funct. 2022;13(21):11307–11320. doi: 10.1039/d2fo01111e. DOI
18. Korolev AI, Fedorovich AA, Gorshkov AY et al. Structural and functional state of various parts of skin microcirculation at an early stage of hypertension in working-age men. Microvasc. Res. 2023;145:104440. doi: 10.1016/j.mvr.2022.104440. DOI
19. Feng T, Zeng S, Ding J et al. Comparative analysis of the effects of opioids in angiogenesis. BMC Anaesthesiol. 2021;21:257. doi: 10.1186/s12871-021-01475-7. DOI
20. Vereshchaka V. The influence of hypertension on the development of morphological changes in skin: histochemical investigation. Biology. 2014;2(67):9–13.

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Ivan S. Diskovskyi
Danylo Halytsky Lviv National Medical University
22 Pekarska st, 79000 Lviv, Ukraine
e-mail: diskovskuy@gmail.com

ORCID AND CONTRIBUTIONSHIP
Ivan S. Diskovskyi: 0000-0003-2344-2461 B D F
Lesya R. Mateshuk-Vatseba: 0000-0002-3466-5276 D F
Orysya O. Syzon: 0000-0002-7011-2521 E
Marianna O. Dasko: 0000-0001-6441-5326 A
Nataliya V. Ivanyushko-Nazarko: 0000-0001-7524-9247 A
Hennadiy Ye. Astsaturov: 0000-0002-9883-6038 B
Aksiniia V. Netliukh: 0000-0001-8557-8466 A

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 14.03.2025
ACCEPTED: 07.05.2025

ORIGINAL ARTICLE

CONTENTS

Evaluation of serum and urine levels of matrix metalloproteinase (MMP-2) in children with nephrotic syndrome

Tulba Abdul Saahib Hameed[1], Hassan H. Al-Saeed[1], Shatha Hussain Ali[2]

[1]DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY, COLLEGE OF MEDICINE, AL- NAHRAIN UNIVERSITY, BAGHDAD, IRAQ

[2]DEPARTMENTS OF INTERNAL MEDICINE, COLLEGE OF MEDICINE, AL- NAHRAIN UNIVERSITY, IRAQ

ABSTRACT

Aim: To evaluate the serum and urine levels of MMP-2 in children with nephrotic syndrome.

Materials and Methods: This study was conducted at Pediatric Nephrology consultation Clinic in Al Imamain Kadhimain Medical City, Ibn Balady Children and Maternity Hospital, Child Central Teaching Hospital, Baghdad, Iraq and Children Welfare Teaching Hospital/Medical City Complex from 1st of November 2021 to 31th of March 2022 and included 60 Patients who are children with NS , and 60 healthy children age and sex matched as a control group Patients with NS were admitted to pediatric ward or attending the pediatric Nephrology clinic.

Results: found there was no significant difference in age and gender between the three groups, healthy controls, SSNS and SRNS However, SRNS had significantly higher mean SBP and DBP (123.0±15.79 mmHg and 79.97±12.44mmHg, respectively) than either SSNS patients (109.58±13.08 mmHg and 73.5±11.31mmHg, respectively) or controls (99.75±9.23 mmHg and 65.58±5.83 mmHg, respectively).

Conclusions: there was no significant difference in age and gender between the three groups, healthy controls, SSNS and SRNS However, SRNS had significantly higher mean SBP and DBP, However , ACE, cyclosporine and MMF were more common among patients with SRNS For MMP-2 the results found serum MMP-2 and urine MMP-2 was significantly higher in SSNS patients SRNS patients.

KEY WORDS: serum MMP-2 and urine MMP-2, SRNS, SSNS

Wiad Lek. 2025;78(6):1133-1141. doi: 10.36740/WLek/204348 DOI

INTRODUCTION

Collagenases and stromelysins, which make up the majority of the huge family of zinc-containing matrix-degrading MMPs, According to Kontogiorgis et al. [1], the matrix metalloproteinases (MMPs) , a family of calcium- and/or zinc-dependent endopeptidases that are normally involved in the breakdown of extracellular matrix and tissue remodeling. However, under normal circumstances, their activity is extremely low and is tightly controlled by natural tissue inhibitors (TIMPs). Four structurally similar proteins known as the TIMPS (TIMP-1, 2, 3, and 4) exercise dual control over the MMPs by blocking both their activation and their active forms [2]. TGF-b1, among other inflammatory cytokines, stimulates MMP production. Matrix metalloproteinases (MMPs) are a class of zinc-dependent proteinases that are among the MMPs produced in the kidney and whose activities are focused on the breakdown and renewal of extracellular matrix (ECM) proteins. To far, around 30 metalloproteinases have been identified. They are separated into many classes according to their structure andfunction. [3] However A prevalent kind of kidney illness in children is nephrotic syndrome [4] According to estimates, corticosteroid therapy will help roughly 80% of kids with idiopathic nephrotic syndrome completely resolve their proteinuria and edema. This group of people who respond to steroids has a varied clinical outcome, with up to 60% experiencing repeated relapses or becoming reliant on steroid medication to keep their condition in remission. [5] Increased MMPs glomerular expression is strongly correlated with the degree of glomerular damage and the course of kidney disease, according to experimental data and clinical research [6] Higher blood levels and/or urine excretions of MMPs and TIMPs may serve as biomarkers for an early stage of nephrotic syndrome, according to recent research in patients with diabetic nephropathy, chronic kidney disease (CKD) following kidney transplantation. [7]

AIM

To evaluate the serum and urine levels of MMP-2 in children with nephrotic syndrome.

MATERIALS AND METHODS

SUBJECT

This study was conducted at Pediatric Nephrology consultation Clinic in Al Imamain Kadhimain Medical City, Ibn Balady Children andMaternity Hospital, Child Central Teaching Hospital, Baghdad, Iraq andChildren Welfare Teaching Hospital/ Medical City Complex from 1st ofNovember 2021 to 31th of March 2022. The practical part was conducted atdepartment of chemistry and biochemistry, College of Medicine, Al-Nahrain University and the biochemical laboratory at Ibn Balady Children and Maternity Hospital included 60 Patients who are children with NS, and 60 healthy children age and sex matched as a control group Patients with NS were admitted to pediatric ward or attending the pediatric Nephrology clinic. Diagnosis of NS was made depending on to criteria such as : heavy proteinuria >40 mg/h/m2 or >50 mg/kg/day Albustix ≥+++,hypo-albuminemia <2.5 g/dL, edema and hyperlipidemia[8].

STUDY DESIGN

This study included three groups as following

Group 1: consist of 30 children with SSNS ,blood samples and urine were collected from them during relapse, **Group 2** : consist of 30 children with SRNS, blood samples and urine werecollected from them during relapse, **Group 3 (Control)** : consist of 60 healthy children , who are matched withages and sex , recruited from outpatient clinic with normal kidney function.

INCLUSION CRITERIA

Children with nephrotic syndrome aged(1-15)years matched with healthy control.

EXCLUSION CRITERIA

1. Secondary nephrotic syndrome.
2. Congenital Nephrotic Syndrome.
3. Children with thyroid disease.
4. Liver disease.
5. Children with cancer.
6. Children with birth diabetic.
7. Presence of any other medical or surgical illness.

SAMPLE COLLECTION

BLOOD SAMPLES

Five (5) ml of venous blood will be drawn from both patients and controls to collect samples, which will then be placed in a plane tube (without anticoagulant). Blood is allowed to stand for 30 minutes before being centrifuged for 15 minutes at 2000 RPM. Transfer serum to a fresh tube and store at -20 C.

URINE SAMPLES

Patients and healthy kids provided ten milliliter urine samples in the morning, which were later collected in the aircraft. For the following measurement of urinary MMP2, which was determined using an ELISA approach and urinary, the urine sample was centrifuged to remove any foreign objects before being separated into simple tubes and kept at -40Co.

DETERMINATION OF SERUM AND URINE MMP-2

Determination serum and urine MMP-2 was achieved by sandwich ELISA assay according to Kit instructor (Mybiosource/USA) and the concentration was obtained depending on the standard curve in fig. 1.

STATISTICAL ANALYSIS

The data that obtain could be analyzed using SPSS Numeric data were expressed as mean ± SD. ANOVA and Student's t test will be used to calculate individual p-value between normal and patient. Correlation between nephrotic syndrome and other variable will be considered using Pearson correlation test. P value < 0.05 was considered significant.

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

The study included 60 children diagnosed with nephrotic syndrome (30 SSNS, 30 SRNS) and 60 age- and sex-matched healthy controls. There were no significant differences in age and gender among the three groups ($p > 0.05$). However, SRNS patients had significantly higher mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to SSNS and control groups ($p < 0.001$) (Table 1).

Regarding clinical characteristics, steroid therapy was the first-line treatment for all patients, but 90% of SRNS patients required additional immunosuppressive therapy, including angiotensin-converting enzyme (ACE) inhibitors, cyclosporine, and mycophenolate mofetil (MMF).

Analysis of dietary patterns revealed that 20% of SRNS patients had a high-sodium diet, compared to 10% in SSNS and 5% in controls. Hydration status was adequate in all groups, as assessed by urine specific gravity and serum osmolality.

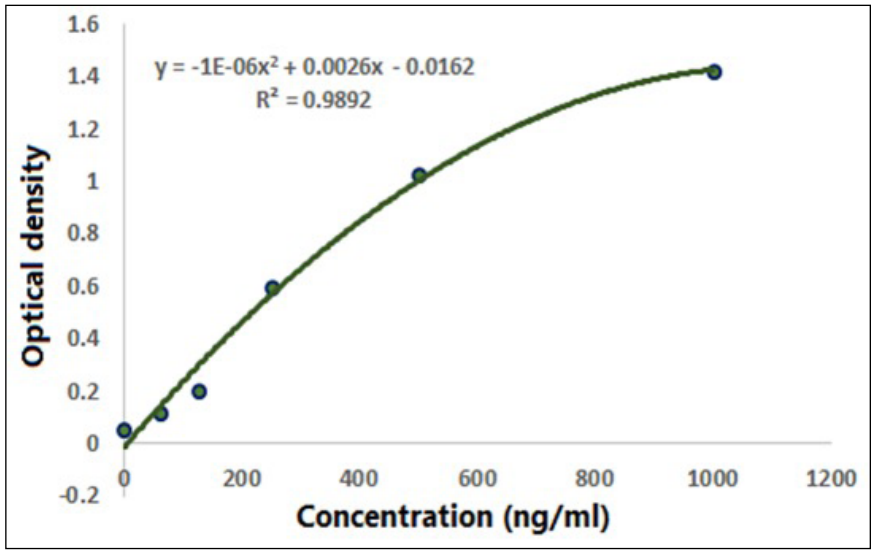

Fig. 1. Calibration curve of MMP-2

There were no significant difference in age between the three groups, healthy controls, SSNS and SRNS as showed in table (3-1) these findings agreed with studies as [9] and agreed[10] , in Iraq also these findings agreed with [11 ; 12] However These earlier investigations discovered substantial differences between the SS and SR groups in terms of age and gender. Additionally, the current study revealed a predominance of male over female patients, and the outcome was consistent with other studies [13] To avoid issues with age differences, the groups in the research were chosen for ages that were near together.

In contrast, our study found that SRNS had significantly higher mean SBP and DBP than either SSNS patients or controls, which was consistent with Roy's study from 2011 [14] and his colleague's study from Bangladesh that found more hypertension events in the SRNS group than SSNS ($p > 0.05$). However, our data disagreed with a study from Indonesia from 2016 that found that blood pressure in the SSNS group was higher than the SRNS group [15], A recent research discovered There were cyclical variations in the systolic blood pressure readings between the two groups, with the SSNS group having a higher systolic median than the SRNS group. In the diastolic blood pressure data, there was no statistically significant difference between the two groups [16].

About 20% of children who develop hypertension have renal problems [17]. Due to steroid toxicity, hypertension can occur in both illness-related conditions and during NS disease progression [18]. By decreasing the retention of salt and water in the kidneys, corticosteroids can lead to hypertension by expanding plasma volume, which in turn raises blood pressure [16] . According to the theory, the major cause of sodium retention in NS is a decreased circulation volume brought on by fluid shifting from intravascular to interstitial compartments as a result of hypoalbuminemia's decreased plasma oncotic pressure. The kidneys' ability to retain water and salt is activated by this shift. While the overfill theory contends that salt retention demonstrates the lack of inherent kidney handling abnormalities, which results in volume growth, [18] , as well as this may associated the long term medication that increase the hypertension[19].

CLINICAL CHARACTERISTICS OF THE PATIENTS

The median duration of illness did not differ significantly between patients with SSNS and SRNS (52.0 months versus 58.0 months). All patients in both groups were on steroid therapy. Beside steroid, 8 patients (26.67%) in SSNS use additional medications compared with 90% in SRNS who used these additional medications with a highly significant difference. In particular, ACE, cyclosporine and MMF were more common among patients with SRNS (43.33%, 46.67% and 26.67%, respectively) than SSNS (16.67%, 6.67% and 3.33%, respectively with significant differences Table 2.

The obtained findings in table (3-2) was agreed with who found the duration of disease 24 (16–38) months and While [21] found. The median duration of NS was 12 months this difference between the studies could be due to a referral bias of difficult cases.

From the other side, the combined high-dose of angiotensin II receptor blocker and high-dose angiotensin-converting enzyme inhibitor treatment is safe and efficient in lowering proteinuria in childhood SRNS, especially ACE, cyclosporine, and MMF were more prevalent among patients with SRNS than SSNS [22] For individuals with primary (idiopathic) nephrotic syndrome, ACE inhibitors are frequently used to control high blood pressure brought on by faulty kidneys that result in fluid retention or overload [23].

Table 1. Demographic characteristics of the study population

Variable	Controls (n=60)	SSNS (n= 30)	SRNS (n=30)	p-value
Age, years				
Mean±SD	8.86±4.09	8.67±4.27	9.62±3.92	0.620
Range	1.4-15.0	1.3-15.0	1.7-15.0	
Gender				
Males	45(75%)	24(80%)	21(70%)	0.670
Females	15(25%)	6(20%)	9(30%)	
SBP, mmHg				
Mean±SD	99.75±9.23	109.58±13.08	123.0±15.79	<0.001
Range	90-120	80-140.5	90-150	
DBP, mmHg				
Mean±SD	65.58±5.83	73.5±11.31	79.97±12.44	<0.001
Range	60-80	40-90	60-100	

SSNS = steroid-sensitive nephrotic syndrome; SRNS = steroid-resistant nephrotic syndrome

Table 2. Clinical characteristics of patients with nephrotic syndrome

Variable	SSNS (n=30)	SRNS (n=30)	p-value
Disease duration, month			
Mean±SD	61.43±43.9	59.37±41.5	0.852
Median	52.0	58.0	
Range	6-140	8-132	
Medication beside steroid			
No medication	22(73.33%)	3(10%)	<0.001
ACE	5(16.67%)	13(43.33%)	0.024
Cyclosporine	2(6.67%)	14(46.67%)	<0.001
MMF	1(3.33%)	8(26.67%)	0.013
Tacrom	1(3.33%)	3(10%)	0.605

SSNS = steroid-sensitive nephrotic syndrome; SRNS = steroid-resistant nephrotic syndrome; ACE = angiotensin converting enzyme

Table 3. Median serum and urine level of MMP-2 and serum levels of TIMP-1 in SSNS, SRNS patients and controls

Variable	Controls(n=60)	SSNS(n= 30)	SRNS(n=30)	p-value
SMMP-2, ng/ml				
Mean±SD	186.14±24.35	322.55±97.28	246.91±89.68	<0.001
Median	193.3	288.05	223.52	
Range	121.6-221	152.6-578.5	148.1-496.1	
UMMP-2, ng/ml				
Mean±SD	177.73±20.69	276.34±62.24	200.12±19.21	<0.001
Median	183.0	272.5	198.7	
Range	124.28-203.1	182.86-427.3	168.7-261.23	

Moreover the results were consistent with [24] who studied 35 patients with SRNS and gave cyclosporine to every patient. using cyclosporine Cyclosporine was originally proposed as a potential therapy for steroid-resistant nephrotic syndrome in 1984. Cyclosporin is a calcineurin inhibitor that reduces the transcription of many cytokine genes to decrease immune response. There have been several studies undertaken up to this point to identify doses, lengths of therapy, and adverse effects [25], which noted the Following the administration of immunosuppressive regimens containing cyclosporin, blood pressure rises quickly. Renal and systemic vasoconstriction are caused by characteristic vascular alterations [19].

However, a prior study discovered that steroid-resistant nephrotic syndrome affected 2 of 18 patients who underwent MMF treatment. The remaining patients (10 patients) all met the requirements for SD [26] The first management of SSNSin children has not yet been studied with MMF. However, it makes sense to take use of MMF's decreased toxicity when compared to glucocorticoids and exploit its efficacy for maintaining remission in the first therapy of SSNS [27].

Last but not least, it was proposed by [28] that TAC is a useful treatment approach for SRNS, including the

Table 4. Diagnostic value of SMMP-2, UMMP-2 in the context of discrimination between SSNS and controls

Markers	AUC	Sensitivity	Specificity	Cut off value
SMMP-2	0.97	97%	100%	221.82 ng/ml
UMMP-2	0.959	93%	78%	195.3 ng/ml

Table 5. Diagnostic value of SMMP-2, UMMP-2 in the context of discrimination between SRNS and controls

Markers	AUC	Sensitivity	Specificity	Cut off value
SMMP-2	0.663	73%	32%	181.19 ng/ml
UMMP-2	0.785	73%	65%	190.41 ng/ml

Table 6. Diagnostic value of SMMP-2, UMMP-2 in the context of discrimination between SSNS and SRNS

Markers	AUC	Sensitivity	Specificity	Cut off value
SMMP-2	0.732	93%	60%	244.05 ng/ml
UMMP-2	0.887	83%	73%	213.55 ng/ml

subset of kids who are unresponsive to the existing therapeutic approaches like cyclophosphamide and cyclosporine. When high-dose steroids are used as the initial line of therapy for adults with minimal change nephrotic syndrome, adverse effects, steroid resistance, and recurrence are frequent problems. Tacrolimus is a steroid-free immunosuppressant that is used to lessen the side effects of prolonged or repeated steroid therapy [29].

MATRIX METALLOPROTEINASE-2

Serum MMP-2 was significantly higher in SSNS patients (median= 288.05 ng/ml, range= 152.6-578.5 ng/ml) than either SRNS patients (median= 223.52 ng/ml, range= 148.1-496.1 ng/ml) or controls (median= 193.3 ng/ml, range= 121.6-221 ng/ml) as shown in table 3 and fig. 2.

Serum MMP-2 levels were significantly higher in SSNS patients (median = 288.05 ng/ml) compared to SRNS patients (median = 223.52 ng/ml) and controls (median = 193.3 ng/ml) ($p < 0.001$).

Similarly, urine MMP-2 levels were significantly elevated in SSNS patients (median = 272.5 ng/ml) compared to SRNS patients (median = 198.7 ng/ml) and controls (median = 183 ng/ml) ($p < 0.001$).

Similarly, urine level of MMP-2 was significantly higher in SSNS patients (median= 272.5 ng/ml, range= 182.8-427.3 ng/ml) than either SRNS patients (median= 198.7 ng/ml, range= 168.7-261.23 ng/ml) or controls (median= 183 ng/ml, range= 124.28-203.1 ng/ml) as shown in fig. 3.

The findings supported [30] whoever discovered MMP-2. It appears to be a possible marker to distinguish steroid sensitivity from resistance since the relative active form of MMP-2 was dramatically raised in SSNS post-treatment. Matrix metalloproteinases have been linked to the development of neuropathy in a few studies. According to Wasilewska and Zoch-Zwierz [31], MMP-2 has both an active and a proenzyme form. Our investigations suggested that, rather than absolute levels, relative ratios of both forms may be more useful in identifying SSNS from SRNS((Tsai et al., 2016). Increases in this ratio may be advantageous for the clinical response to steroids, according to molecular weight forms associated with larger active/proenzyme ratios in SSNS compared to SRNS post-treatment [32].

Wasilewska & Zoch-zwierz, [31] recorded the MMP2/TIMP2 ratio in urine sample in NS children treated with CyA was significantly lower in comparison with healthy controls this due to the cyclosporine, tacrolimusdecrease expression of MMP2 [33] as mentioned in previous most of SRNS patients was in mediction CyA and tacrolimus less than SSNS Patients ,Cyclosporine inhibits the expression of TIMP-1 in and it may further reduce the activation of MMP-2 [34]. In contrast, control group showed higher level of TIMP-1 (median= 2.36 ng/ml, range= 1.62-2.78 ng/ml) than SSNS patients (median= 1.29 ng/ml, range=0.43-1.71 ng/ml) with a significant difference, and SRNS (median= 1.8 ng/ml, range= 1.4-4.5 ng/ml) with no significant difference. Of note, the SRNS differs significantly from SSNS in this regard

The results were comparable to those reported in [35] There were no discernible variations in the median levels of serum TIMPs , MMPs and MMPs/TIMPs ratios between nephrotic patients and controls, while TIMP levels were rising in the control group. The findings were consistent with [35] which found a link between the urine MMP-2/TIMP-1 ratio value in SRSS and the median urinary MMP-2/Cr ratio (P =.01) and urinary TIMP-1/Cr ratio (P =.02) values in children with SRNS.

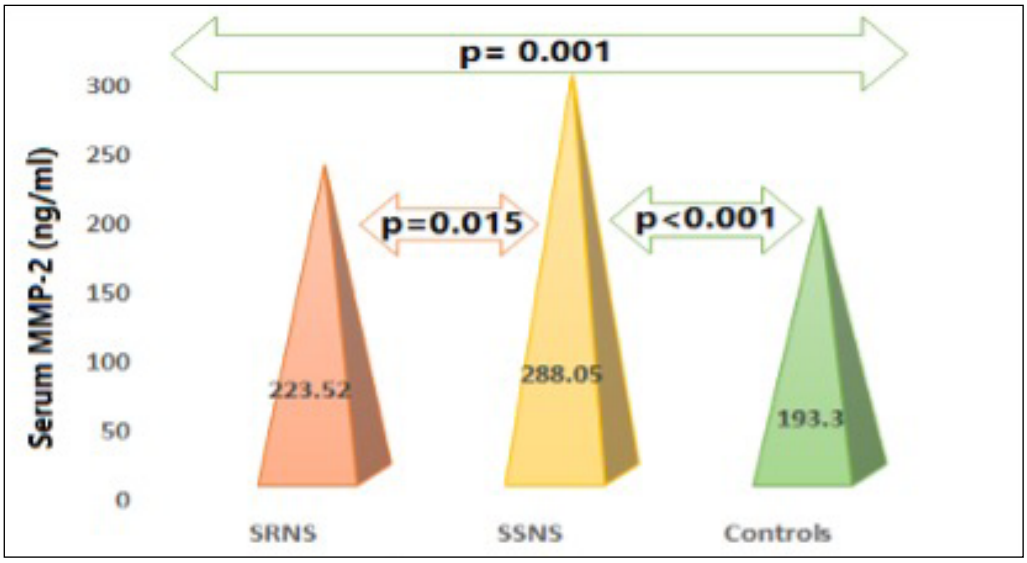

Fig. 2. Median serum level of MMP-2 in SSNS, SRNS patients and controls

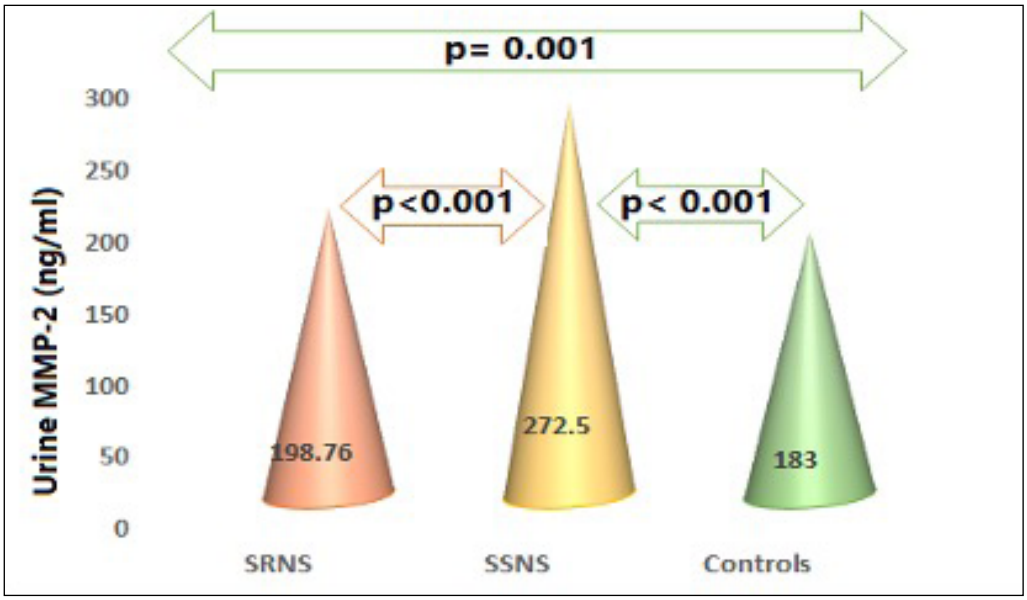

Fig. 3. Median urine level of MMP-2 in SSNS, SRNS patients and controls

DIAGNOSTIC VALUE OF MMP-2 AND ITS INHIBITOR

To assess the diagnostic value of MMP-2 and its inhibitor, the receiver operating characteristic (ROC) curve was used. In the context of discrimination between SSNS and controls, the area under the curve (AUC) for serum MMP-2 level was 0.97, 95% CI= 0.912-1.0, p <0.001. The test's sensitivity and specificity were 97% and 100%, respectively, at a cut-off value of serum MM-2 level = 221.82ng/mL. The AUC for urine MMP-2 level was 0.959, 95% CI= 0.913-1.0, p <0.001. The test's sensitivity and specificity were 93% and 78%, respectively, at a cut-off value of urine MMP-2 level = 195.31ng/ml.

Receiver Operating Characteristic (ROC) curve analysis revealed that serum MMP-2 had an area under the curve (AUC) of 0.97, with 97% sensitivity and 100% specificity for distinguishing SSNS from controls. Urine MMP-2 had an AUC of 0.96, with 93% sensitivity and 78% specificity.

For differentiating SSNS from SRNS, urine MMP-2 performed better (AUC = 0.89) than serum MMP-2 (AUC = 0.73). These findings suggest that urinary MMP-2 may serve as a useful biomarker for predicting steroid responsiveness in nephrotic syndrome (Table 4).

The AUC for serum MMP-2 was 0.663, 95% CI= 0.522-0.804, p = 0.012 in the context of discriminating between SRNS and controls. With a cut-off value of 181.19ng/mL for serum MMP-2, the test's sensitivity and specificity were 73% and 32%, respectively. The AUC for the urine MMP-2 level was 0.785, 95% CI = 0.685-0.885, and p 0.001. At a cut-off value of urine MMP-2 level = 190.41 ng/ml, as shown in table 5, the test's sensitivity and specificity were 73% and 65%, respectively.

The AUC for blood MMP-2 level in the context of differentiating between SSNS and SRNS was 0.732, 95% CI= 0.601-0.863, p = 0.002. At a cut-off value of serum MM-2 level = 244.05ng/mL, the test's sensitivity and specificity were 93% and 60%, respectively. The urine

MMP-2 level's AUC was 0.887, 95% confidence interval (CI): 0.798-0.975, and p 0.001. At a cut-off value of urine MMP-2 level = 213.55 ng/ml, the test's sensitivity and specificity were 83% and 73%, respectively (Table 6).

This Roc analysis result largely concurred with other research on renal diseases, such as those by Altetam et al. [36] who disclosed their findings when analyzing the urine matrix in their study. The optimum cutoff for MMP2 in the diagnosis of Chroinc kidney disease has an area under curve of 0.766, sensitivity of 77.8%, and specificity of 63.9%. Metalloproteinase activity in diabetic kidney disease. The area under the ROC curve for urine MMP activity was 77%. ROC analysis shows that estimating MMP activity is more accurate than predicting people with progressing renal disease.

DISCUSSION

Our findings confirm that SRNS patients exhibit significantly higher blood pressure levels than SSNS patients, consistent with prior studies that reported a higher prevalence of hypertension in SRNS due to increased sodium retention and chronic steroid exposure.

The significantly elevated MMP-2 levels in SSNS compared to SRNS suggest a possible role for MMP-2 in predicting steroid responsiveness. Previous studies have linked MMP-2 to extracellular matrix remodeling in glomerular diseases, but our study specifically highlights its potential in distinguishing SSNS from SRNS [9].

Several studies have shown that cyclosporine and tacrolimus suppress MMP-2 expression, which may explain why SRNS patients had lower MMP-2 levels despite having a more severe disease course [10,11]. This suggests that urinary MMP-2 levels could serve as a dynamic biomarker for treatment monitoring.

Clinical Implications of MMP-2 Assays [12-15].

Given the high sensitivity and specificity of urinary MMP-2, it could serve as an early predictor of steroid responsiveness [16,17], potentially reducing the time required to determine whether a patient should receive second-line immunosuppressants [18,19,20].

Additionally, monitoring MMP-2 levels could help assess disease progression and treatment response in nephrotic syndrome [21,22,23]. Patients who fail to show a decline in MMP-2 levels after initial steroid therapy may require earlier initiation of alternative immunosuppressive agents [24,25].

Future studies should explore whether serial MMP-2 measurements could guide treatment adjustments and improve patient outcomes [26].

CONCLUSIONS

Our study demonstrates that serum and urine mmp-2 levels are significantly elevated in ssns compared to srns and healthy controls. These findings highlight the potential clinical utility of mmp-2 assays in predicting steroid responsiveness in pediatric nephrotic syndrome.

Given the high sensitivity and specificity of urine mmp-2 in differentiating ssns from srns, it may serve as a non-invasive biomarker for early identification of steroid-resistant patients, thereby guiding treatment decisions and minimizing unnecessary steroid exposure.

Future research should explore longitudinal monitoring of mmp-2 levels to assess treatment response and predict relapses.

REFERENCES

1. Kontogiorgis CA, Papaioannou P, Hadjipavlou-Litina DJ. Matrix metalloproteinase inhibitors: a review on pharmacophore mapping and (Q)SARs results. Current Medicinal Chemistry. 2005;12(3):339-55. doi: 10.2174/0929867053363243. DOI
2. Mohammed FF, Smookler DS, Khokha R. Metalloproteinases, inflammation, and rheumatoid arthritis. Annals of the Rheumatic Diseases. 2003;62(2):ii43-7. doi: 10.1136/ard.62.suppl_2.ii43. DOI
3. Varner JD, Matory A, Gbadegesin RA. Genetic basis of health disparity in childhood nephrotic syndrome. American Journal of Kidney Diseases. 2018;72(5):S22-5. doi: 10.1053/j.ajkd.2018.06.022. DOI
4. Hampson KJ, Gay ML, Band ME. Pediatric nephrotic syndrome: pharmacologic and nutrition management. Nutrition in Clinical Practice. 2021;36(2):331-43. doi: 10.1002/ncp.10622. DOI
5. Musiał K, Bargenda A, Zwolińska D. Urine survivin, E-cadherin and matrix metalloproteinases as novel biomarkers in children with chronic kidney disease. Biomarkers. 2015;20(3):177-82. doi: 10.3109/1354750X.2015.1061598. DOI
6. Bieniaś B, Sikora P. Urinary metalloproteinases and tissue inhibitors of metalloproteinases as potential early biomarkers for renal fibrosis in children with nephrotic syndrome. Medicine. 2018;97(8):e9964. doi: 10.1097/MD.0000000000009964. DOI
7. Srivastava RN, Bagga A. Pediatric Nephrology. JP Medical Ltd; 2016.
8. Guimarães FT, Ferreira RN, Brito-Melo GE et al. Pediatric patients with steroid-sensitive nephrotic syndrome have higher expression of T regulatory lymphocytes in comparison to steroid-resistant disease. Frontiers in Pediatrics. 2019;7:114. doi: 10.3389/fped.2019.00114. DOI
9. Pokrajac D, Kamber AH, Karasalihovic Z. Children with steroid-resistant nephrotic syndrome: a single-center experience. Materia Socio-Medica. 2018;30(2):84-88. doi: 10.5455/msm.2018.30.84-88. DOI

10. Jwda NA, Taha HH, Ali SH. Evaluation of Serum and Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) in Children with Nephrotic Syndrome. Medico-Legal Update. 2020;20(2):467.
11. Malik NA, Abbas AA, Ali SH. Association of interleukin 4-C590T gene polymorphism with nephrotic syndrome in children. Annals of Tropical Medicine and Public Health. 2020;23:438-43. doi: 10.36295/ASRO.2020.23725. DOI
12. Ali SH, Ali AM, Najim AH. The predictive factors for relapses in children with steroid-sensitive nephrotic syndrome. Saudi Journal of Kidney Diseases and Transplantation. 2016;27(1):67. doi: 10.4103/1319-2442.174075. DOI
13. Roy RR, Islam MR, Matin A et al. Relationship of childhood idiopathic nephrotic syndrome with asthma, hypertension, complement C3, urinalysis. Bangladesh Journal of Child Health. 2011;35(1):11-5. doi: 10.3329/bjch.v35i1.10367. DOI
14. Mamesah RS, Umboh A, Gunawan S. Hubungan aspek klinis dan laboratorium dengan tipe sindrom nefrotik pada anak. e-CliniC. 2016;4(1).
15. Akbar M, Ramayani OR, Yanni GN. Blood Pressure Differences in Nephrotic Syndrome Patients with Steroid Resistant Nephrotic Syndrome Patients and Steroid Sensitive Nephrotic Syndrome. Open Access Macedonian Journal of Medical Sciences. 2021;9(T3):349-52. doi: 10.3889/oamjms.2021.6315. DOI
16. Edison M, Meunier M, Miller N. The Evaluation of a 19-Year-Old With Hypertension and Proteinuria: A Case Report. Journal of Primary Care & Community Health. 2019;10:2150132719843437. doi: 10.1177/2150132719843437. DOI
17. Dewi DA, Suarta K, Nilawati GA. Risk factors of steroid resistant nephrotic syndrome in children. MEDICINA. 2019;50(1):67-71.
18. Ray EC, Rondon-Berrios H, Boyd CR, Kleyman TR. Sodium retention and volume expansion in nephrotic syndrome: implications for hypertension. Advances in Chronic Kidney Disease. 2015;22(3):179-84. doi: 10.1053/j.ackd.2014.11.006. DOI
19. Taler SJ, Textor SC, Canzanello VJ, Schwartz L. Cyclosporin-induced hypertension: incidence, pathogenesis and management. Drug Safety. 1999;20(5):437-49. doi: 10.2165/00002018-199920050-00004. DOI
20. Mishra K, Kanwal SK, Sajjan SV et al. Predictors of poor outcome in children with steroid sensitive nephrotic syndrome. Nefrología (English Edition). 2018;38(4):414-8. doi: 10.1016/j.nefro.2017.11.022. DOI
21. Fomina S, Pavlenko T, Englund E, Bagdasarova I. Clinical course of steroid sensitive nephrotic syndrome in children: outcome and outlook. The Open Pediatric Medicine Journal. 2011;5(1). doi: 10.2174/1874309901105010018. DOI
22. Supavekin S, Surapaitoolkorn W, Tancharoen W et al. Combined renin angiotensin blockade in childhood steroid-resistant nephrotic syndrome. Pediatrics International. 2012;54(6):793-7. doi: 10.1111/j.1442-200X.2012.03668.x. DOI
23. Herman LL, Padala SA, Ahmed I, Bashir K. Angiotensin converting enzyme inhibitors (ACEI). StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
24. Hamasaki Y, Yoshikawa N, Hattori S et al. Cyclosporine and steroid therapy in children with steroid-resistant nephrotic syndrome. Pediatric Nephrology. 2009;24(11):2177-85. doi: 10.1007/s00467-009-1264-0. DOI
25. Shah SR, Altaf A, Arshad MH et al. Use of cyclosporine therapy in steroid resistant nephrotic syndrome (SRNS): a review. Global Journal of Health Science. 2016;8(4):136. doi: 10.5539/gjhs.v8n4p136. DOI
26. Novak I, Frank R, Vento S et al. Efficacy of mycophenolate mofetil in pediatric patients with steroid-dependent nephrotic syndrome. Pediatric Nephrology. 2005;20(9):1265-8. doi: 10.1007/s00467-005-1957-y. DOI
27. Ehren R, Benz MR, Doetsch J et al. Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil versus prednisone: protocol for a randomised, controlled, multicentre trial (INTENT study). BMJ Open. 2018;8(10):e024882. doi: 10.1136/bmjopen-2018-024882. DOI
28. Gulati S, Prasad N, Sharma RK et al. Tacrolimus: a new therapy for steroid-resistant nephrotic syndrome in children. Nephrology Dialysis Transplantation. 2008;23(3):910-3. doi: 10.1093/ndt/gfm688. DOI
29. Chin HJ, Chae DW, Kim YC et al. Comparison of the efficacy and safety of tacrolimus and low-dose corticosteroid with high-dose corticosteroid for minimal change nephrotic syndrome in adults. Journal of the American Society of Nephrology. 2021;32(1):199-210. doi: 10.1681/ASN.2019050546. DOI
30. Gooding JR, Agrawal S, McRitchie S et al. Predicting and defining steroid resistance in pediatric nephrotic syndrome using plasma metabolomics. Kidney Int Rep. 2020;5(1):81-93. doi: 10.1016/j.ekir.2019.09.010. DOI
31. Wasilewska AM, Zoch-Zwierz WM. Urinary levels of matrix metalloproteinases and their tissue inhibitors in nephrotic children. Pediatr Nephrol. 2008 Oct;23(10):1795-802. doi: 10.1007/s00467-008-0881-3. DOI
32. Tsai SH, Huang PH, Hsu YJ, Peng YJ, Lee CH, Wang JC, Chen JW, Lin SJ. Inhibition of hypoxia inducible factor-1α attenuates abdominal aortic aneurysm progression through the down-regulation of matrix metalloproteinases. Sci Rep. 2016 Jul 1;6(1):1-1. doi: 10.1038/srep28612. DOI
33. Agrawal S, Merchant ML, Kino J, Li M et al. Predicting and defining steroid resistance in pediatric nephrotic syndrome using plasma proteomics. Kidney Int Rep. 2020 Jan 1;5(1):66-80. doi: 10.1016/j.ekir.2019.09.009. DOI
34. Waller JR, Brook NR, Bicknell GR, Nicholson ML. Differential effects of modern immunosuppressive agents on the development of intimal hyperplasia. Transplant Int. 2004 Jan;17(1):9-14. doi: 10.1007/s00147-003-0653-8. DOI
35. Chiu HC, Lu YT, Chin YT, Tu HP, Chiang CY, Gau CH, Nieh S, Fu E. Cyclosporine A inhibits the expression of membrane type-I matrix metalloproteinase in gingiva. J Periodontal Res. 2009 Jun;44(3):338-47. doi: 10.1111/j.1600-0765.2008.01126.x. DOI

36. Altemtam N, El Nahas M, Johnson T. Urinary matrix metalloproteinase activity in diabetic kidney disease: a potential marker of disease progression. Nephron Extra. 2012;2(1):219-32. doi: 10.1159/000339645. DOI

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Tulba Abdul Saahib Hameed
AL- Nahrain University
60 Kazimiyah District, 70044 Baghdad, Iraq
e-mail: tulba.a.hameed.s@ced.nahrainuniv.edu.iq

ORCID AND CONTRIBUTIONSHIP
Tulba Abdul Saahib Hameed: 0000-0001-6155-7302 A B C D E F
Hassan H. Al-Saeed: 0000-0000-0000-0001 C F
Shatha Hussain Ali: 0000-0002-0778-1159 C F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.11.2024
ACCEPTED: 01.06.2025

ORIGINAL ARTICLE

CONTENTS

Modern paradigms of treatment of coronary heart disease: consistency of opinions of participants in the treatment process

Maryna M. Dolzhenko[1], **Natalia A. Bilousova**[1], **Vasyl M. Mykhalchuk**[1], **Natalia O. Tkachenko**[2], **Liudmyla I. Yakovenko**[1]

[1]SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

[2]ZAPORIZHZHIA STATE MEDICAL AND PHARMACEUTICAL UNIVERSITY, ZAPORIZHZHIA, UKRAINE

ABSTRACT

Aim: To study the consistency of opinions of participants in the treatment process of coronary heart disease with comorbid conditions with further analysis of the quality of pharmaceutical care and development of a strategy for improving interprofessional interaction of pharmacists in integrated care teams.

Materials and Methods: The materials of the study were the results of a survey, conducted among the pharmacists of pharmaceutical stores, patients with coronary heart disease with comorbid conditions and doctors, according to the specified criteria for providing pharmaceutical care. The following research methods were used: analysis, deduction, induction, comparison, systematization, generalization, forecasting, statistical and bibliographic.

Results: An intermediately satisfactory level of pharmaceutical care was determined. It was found that the implementation of pharmaceutical care requires the development of clinical competencies and communication skills of pharmacists with patients and the improvement of regulatory and legal support. Kendall's consistency coefficient W = 0.85.

Conclusions: A sufficiently high level of agreement of opinions (W = 0.85) of doctors, pharmacists and patients regarding the criteria for providing pharmaceutical care has been reliably confirmed. Directions for the development and improvement of mechanisms for providing pharmaceutical care have been identified. It is proposed to develop standards for providing pharmaceutical care to patients with coronary heart disease with comorbid conditions in accordance with the ESC/AHA recommendations and taking into account the compatibility of medicines of different pharmacological groups used to cure the cardiovascular diseases.

KEY WORDS: pharmaceutical care, coronary heart disease, pharmaceutical care criteria, integrated care team, interprofessional interaction, rational pharmacotherapy

Wiad Lek. 2025;78(6):1142-1149. doi: 10.36740/WLek/207372 DOI

INTRODUCTION

It is known that the main cause of mortality in the world among non-communicable diseases is coronary heart disease (CHD) [1].. The highest incidence and mortality from CHD among European countries is observed in Ukraine [2]. It is obvious that during the war in Ukraine, the incidence of CHD increases under the influence of stress factors of war and socioeconomic factors [3]. To address the issues of reducing the incidence of cardiovascular pathologies in the world and improving the quality of medical care for patients with CHD with comorbid conditions, the World Health Organization has proposed patient-oriented interdisciplinary approaches with the participation of pharmacists as part of integrated care teams [4]. The clinical guidelines of the American Heart Association (AHA) and the European Society of Cardiology (ESC) also emphasize the interprofessional interaction of pharmacists as part of integrated care teams including doctors of different specialties, nurses, dietitians, medical psychologists and social workers [5;6] in order to provide high-quality patient-centered care to patients with cardiovascular diseases. The International Pharmaceutical Federation (FIP) has proposed actions to implement pharmaceutical care at a qualitatively new level with value-oriented approaches [7]. The Roles and Functions of Pharmacists in Good Pharmacy Practice (GPP) have been expanded [8, 9] by transforming pharmaceutical provision, ensuring the sustainability of pharmacy institutions [10] with the further integration of pharmacists into primary health care. The document on regulatory pharmaceutical policy and practice in Eastern Europe emphasizes the need to review the critical attitude of healthcare professionals towards the integration of pharmacists into primary health care [7]. It is expected that these actions will improve access to primary health care in the future.

Under martial law in Ukraine, the population's access to primary health care is decreasing due to bombings and missile attacks on health care facilities, medical workers (their shortage and professional burnout), mobilization and other reasons [11]. Conceptually new approaches to integrating pharmacists into primary health care and reviewing marketing approaches by pharmacy business owners with a patient-centered approach to pharmaceutical care in the health care structure could improve the population's access to medicines. The proposed measures for primary and secondary prevention, monitoring of pharmacotherapy and checking the compatibility of prescribed pharmacotherapy with medicines would likely contribute to early diagnostics, disease prevention and adherence to treatment in patients with coronary heart disease with comorbid conditions, as emphasized in the EUROASPIRE IV,V observational studies [12, 13] and ESC/AHA clinical guidelines [14, 15].

At the state level, it is also planned to implement the outlined measures with conceptually new approaches [8, 9] to the provision of pharmaceutical care to patients with CHD for the purpose of early diagnostics and prevention of the disease. However, at the sectoral level, pharmaceutical care for such patients is regulated by pharmacists' protocols when dispensing medicines that are subject to reimbursement [16], a significant part of which is not included in the clinical protocol "Stable ischemic heart disease" [17] and requires significant revision [18, 19].

Thus, it is especially relevant in the conditions of martial law to determine the consistency of opinions of doctors, patients and pharmacists regarding the quality of pharmaceutical care for patients with CHD with comorbid conditions with the subsequent development of a strategy for implementing interprofessional interaction of pharmacists as part of integrated care teams.

AIM

The purpose of the article is to study the consistency of opinions of participants in the treatment process of coronary heart disease with comorbid conditions and further analysis of the quality of pharmaceutical care and development of a strategy for improving interprofessional interaction of pharmacists in integrated care teams.

MATERIALS AND METHODS

The study was conducted at the Department of Cardiology of the Shupyk National Healthcare University of Ukraine using an online survey of doctors, patients and pharmacists using Google Forms from April to December 2024. The questionnaires were distributed via the social network Facebook, the Viber messenger, communities of general practitioners of family medicine, the pharmaceutical community, pharmacy chains "Low Price Pharmacy" ("Apteka Nyzkykh Tsin"), "We wish you good health" ("Bazhayemo Zdorovya"), "CE Pharmacy", "Vitamin". The questionnaires for all respondents contained 19 questions each. In this study, we used 8 questions: 2 of which determined the age and regional distribution of respondents, 6 questions determined the criteria for providing pharmaceutical care and made it possible to find out the consistency of respondents' opinions regarding the state of pharmaceutical care for patients with CHD with comorbid conditions. The answers were ranked from the best to the worst results. The remaining answers were processed in another study. The questionnaires were anonymous, previously the survey participants provided verbal consent, confirmed by one of the questions in the online survey. A total of 527 questionnaires (331 doctors, 86 patients, 110 pharmacists) from 23 regions of Ukraine were processed. The study was attended by general practitioners of family medicine (88%) and doctors of therapeutic specialties (6%) - cardiologists and neurologists; patients with CHD with comorbid conditions who participated in the EUROASPIRE IV, V studies; pharmacists with specializations in "general pharmacy" (86.4%), "clinical pharmacy" (13.6%). Incomplete questionnaires were the exclusion criteria. The difference in indicators was considered significant at the level of the CI 95%, $p<0.0001$. The Kendall agreement coefficient was calculated using the formula:

$$W=\frac{12\sum_{i=1}^{k}(R-R1)^2}{n(n^2-1)}$$

where W is the Kendall consistency coefficient, R is the sum of the rank scores for each pharmaceutical care criterion, R1 is the average value of the sum of the rank scores, n is the number of pharmaceutical care criteria.

The methods of analysis, deduction, induction, comparison, systematization, generalization, forecasting, statistical and bibliographic were used.

The accumulation, correction, systematization of information, visualization of results and calculations were carried out in Microsoft Office Excel spreadsheets. Statistical processing was carried out using the STATISTICA.13 program.

RESULTS

The average age of respondents was determined as the following: doctors - 54.5 ± 4.0 years; patients - 52.7 ± 4.0 years; pharmacists - 43.8 ± 4.0 years.

The overall satisfaction of respondents with pharmaceutical care provided in pharmacies in the country was

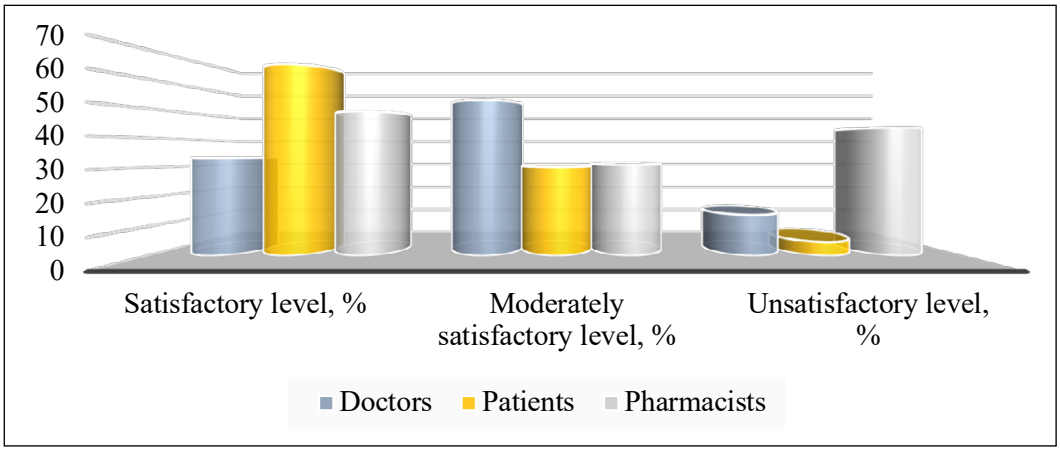

Fig. 1. Overall satisfaction of respondents with pharmaceutical care provided to patients with CHD with comorbid conditions

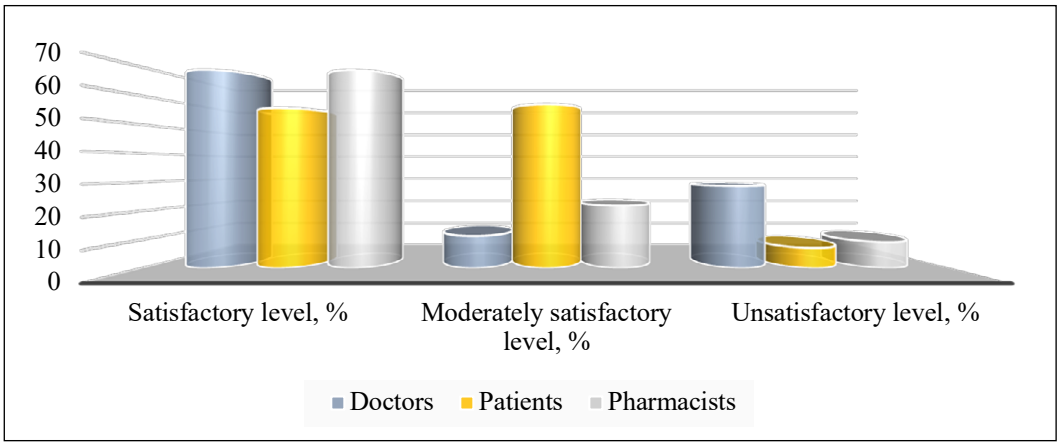

Fig. 2. Determination of the level of information support for patients CHD with comorbid conditions regarding the rational use of medicines

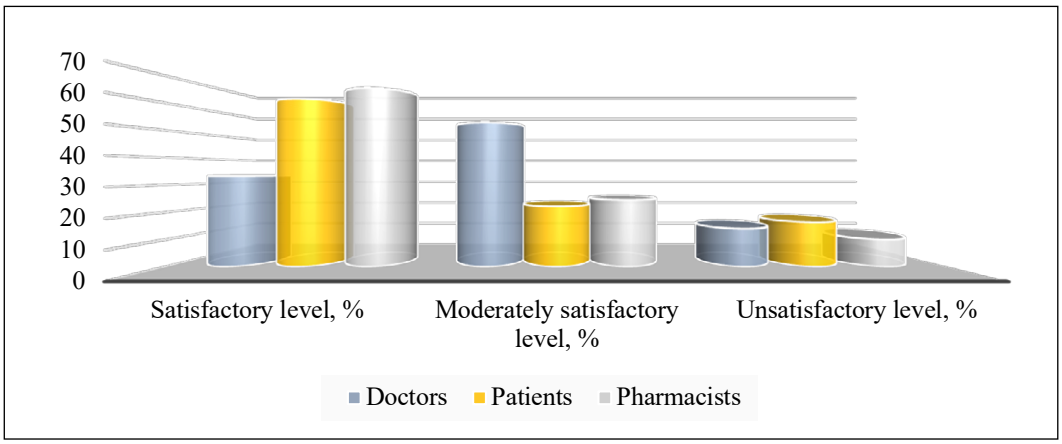

Fig. 3. Level of effectiveness of pharmacists' response to patients' questions

investigated and includes pharmaceutical provision; explanations for patients regarding the safe use of medicines; promotional offers in pharmacies; attentiveness and friendliness of pharmacists, etc. (Fig. 1). It should be noted that patients with ischemic heart disease with comorbid conditions, in most cases (65.6% [CI 95% 65.6 ± 0.05, p<0.0001]), are satisfied with the provision of pharmaceutical care. The majority of doctors noted that the provision of pharmaceutical care to such patients is at an intermediate satisfactory level (52.9% [CI 95% 52.9 ± 0.03, p<0.0001]). However, pharmacists themselves are critical of the quality of pharmaceutical care and 43.6% [CI 95% 43.6 ± 0.05, p<0.0001] noted an unsatisfactory level.

The level of information support for patients with CHD and comorbid conditions regarding the rational use of medicines was determined (Fig. 2). In general, doctors (69.2% [CI 95% 69.2 ± 0.03, p<0.0001]) and pharmacists (69.1% [CI 95% 69.1 ± 0.04, p<0.0001]) determined a satisfactory level of information support for patients, however, according to the patients themselves, information support is at a satisfactory (55.8% [CI 95% 55.8 ± 0.05, p<0.0001]) and moderately satisfactory levels (57.1% [CI 95% 57.1 ± 0.05, p<0.0001]).

The effectiveness of pharmacists' responses to patients' questions was determined (Fig. 3). Overall, pharmacists (65.5% [CI 95% 65.5 ± 0.05, p<0.0001]), patients

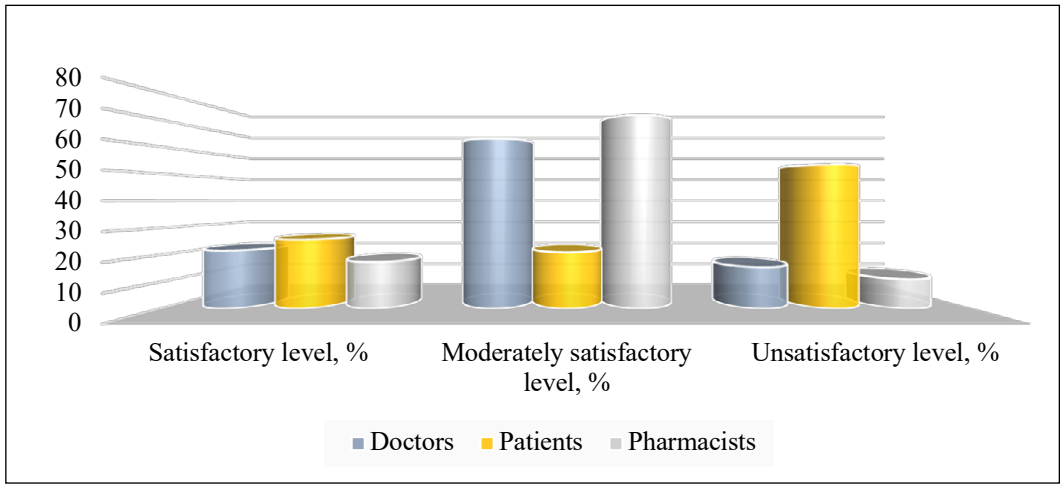

Fig. 4. Assessment of the effectiveness of pharmacists' communication with patients regarding the education of patients with CHD with co-morbid conditions regarding the safe use of medicines

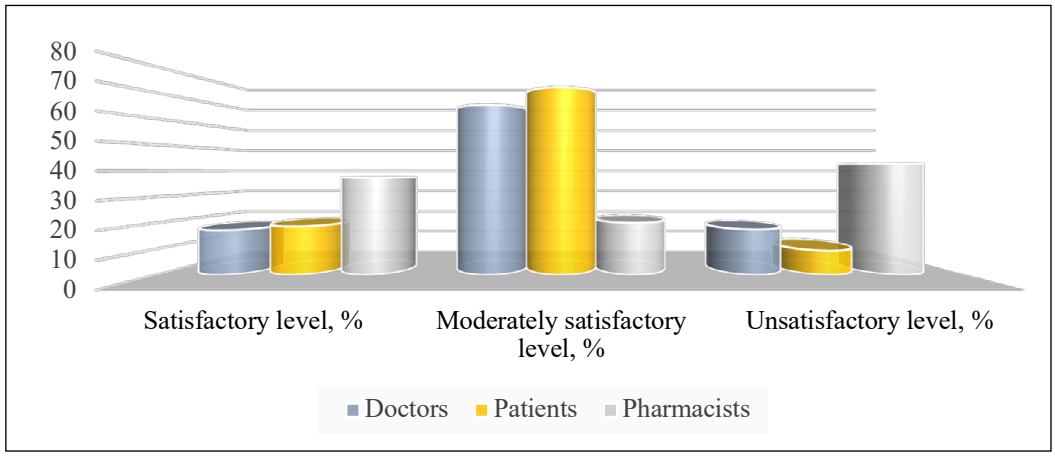

Fig. 5. Assessment (self-assessment) of clinical competencies of pharmacists when providing consultations to patients with CHD with co-morbid conditions

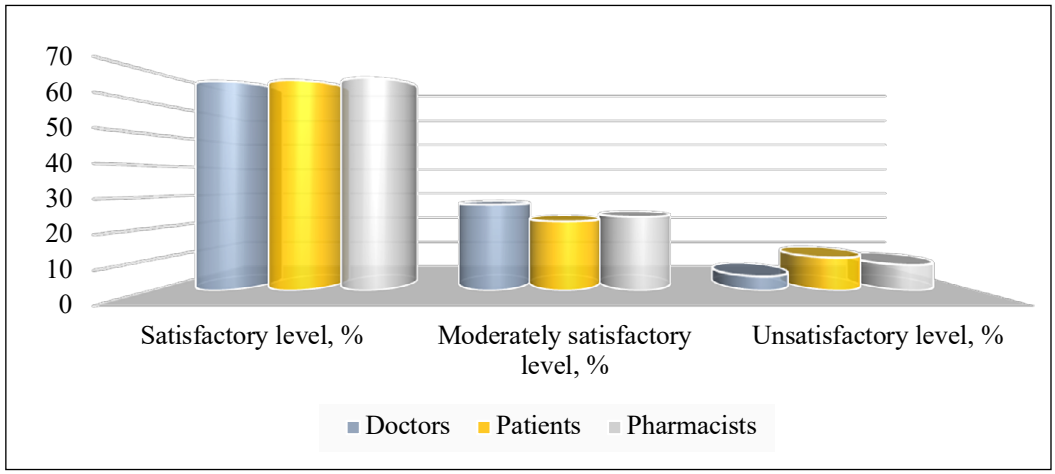

Fig. 6. Level of pharmacists' provision of confidentiality of patients' medical data

(61.6% [CI 95% 61.6 ± 0.05, p<0.0001]) and physicians (33.2% [CI 95% 33.2 ± 0.03, p<0.0001]) were satisfied with pharmacists' responses to patients' questions, but physicians (52.9% [CI 95% 52.9 ± 0.03, p<0.0001]) would like to see better responses from pharmacists and more responsiveness to patients.

The assessment of the effectiveness of pharmacists' communications with patients regarding the awareness of patients with CHD with comorbid conditions regarding the safe use and compatibility check of medicines was documented. Pharmacists (71.8% [CI 95% 71.8 ± 0.04, p<0.0001]) and doctors (63.1% [CI 95% 63.1 ± 0.03, p<0.0001]) noted a moderately satisfactory level of effectiveness of such communications. However, patients themselves (53.5% [CI 95% 53.5 ± 0.05, p<0.0001]) noted that in half of the cases such support does not occur in pharmacies and after purchasing medicines, pharmacists are generally reluctant to provide explanations regarding the safe intake and use of medicines (Fig. 4).

Respondents were also asked to assess (self-assess) the clinical competencies of pharmacists when providing consultations to patients with CHD and comorbid

Table 1. Ranking of aspects of pharmaceutical care provision by different groups of respondents according to levels of pharmaceutical care quality

Pharmaceutical care criteria	Levels of pharmaceutical care provision					
	Doctors	Rank	Patients	Rank	Pharmacists	Rank
Overall satisfaction with pharmaceutical care	Moderately satisfactory	2	Satisfactory	1	Satisfactory	1
Informational support of patients regarding the use of medicines	Satisfactory	1	Moderately satisfactory	2	Satisfactory	1
Effectiveness of pharmacists' response to patients' questions	Moderately satisfactory	2	Satisfactory	1	Satisfactory	1
Effectiveness of communications with patients and education on the use of medicines	Moderately satisfactory	2	Unsatisfactory	3	Moderately satisfactory	2
Examination of clinical competencies of pharmacists when providing consultations to patients	Moderately satisfactory	2	Moderately satisfactory	2	Unsatisfactory	3
Ensuring confidentiality of patient medical data	Satisfactory	1	Satisfactory	1	Satisfactory	1

conditions (Fig. 5). After assessing the clinical competencies of pharmacists, it was determined that doctors (65.3% [CI 95% 65.3 ± 0.03, p<0.0001]) and patients (72.1% [CI 95% 72.1 ± 0.05, p<0.0001]) noted a mediocre level of clinical competencies. However, pharmacists' opinions on this matter were divided. The majority of pharmacists were very critical of such self-assessment and believed that the level of clinical knowledge, skills and abilities was unsatisfactory (42.7% [CI 95% 42.7 ± 0.05, p<0.0001]). The rest of the pharmacists noted a satisfactory level (37.3% [CI 95% 37.3 ± 0.05, p<0.0001]) of their own clinical competencies.

The level of pharmacists' ensuring of confidentiality of patients' medical data was investigated (Fig. 6). All three groups of respondents: doctors (67.1% [CI 95% 67.1 ± 0.03, p<0.0001]), patients (67.4% [CI 95% 67.4 ± 0.05, p<0.0001]) and pharmacists (68.2% [CI 95% 68.2 ± 0.04, p<0.0001]) assessed the pharmacists' ensuring of confidentiality of patients' medical data satisfactorily. However, all groups of respondents noted that the confidentiality of medical data could be improved.

Furthermore, the obtained data was ranked according to the criteria for providing pharmaceutical care to patients with CHD with comorbid conditions, different groups of respondents and levels of quality of pharmaceutical care (Table 1).

The calculated Kendall coefficient W = 0.85 indicates a high result of the consistency of opinions between doctors, patients and pharmacists for the studied criteria for the provision of pharmaceutical care. The statistical significance of the Kendall coefficient W = 0.85 was confirmed: $\chi 2 = 12.71$ at a given confidence level $\alpha = 0.05$, which indicates the consistency of opinions of doctors, patients and pharmacists for most criteria for the provision of pharmaceutical care. The results obtained regarding the quality of pharmaceutical care for patients suffering from CHD with comorbid conditions indicate the possibilities of developing communications between pharmacists and patients, the need to develop clinical competencies of pharmacists and improve information support for patients in terms of the safe use of medicines by pharmacists.

DISCUSSION

The results of the analysis of scientific data show that the study of interprofessional interaction in integrated care teams attracts the attention of researchers from different countries of the world [20-23]. The study of the general opinion regarding the criteria for providing pharmaceutical care of doctors, pharmacists and patients allows us to identify the main problems that arise between participants in the treatment process of CHD with comorbid conditions in modern conditions of martial law when providing pharmaceutical care. These criteria are considered as generalized criteria for providing pharmaceutical care in a systematic review of 19 randomized clinical trials [24] and a meta-analysis on primary and secondary prevention of strokes in patients with CHD with atrial fibrillation [22], which are confirmed by the pharmacoeconomic effectiveness of pharmacists' interventions in the process of interprofessional interaction.

The results of the study obtained by us allow us to determine the general opinion of all respondents for further development of a strategy for the development of interprofessional interaction and integration of pharmacists into primary health care. This survey showed the main obstacles that arise in the provision of pharmaceutical care: insufficient level of commu-

nication between pharmacists and patients, clinical competencies of pharmacists and information support for patients with ischemic heart disease, which includes the safety of using medicines. The results of our study are confirmed by the data of a systematic review [25]. The patients themselves who participated in the study noted that the information provided by pharmaceutical store pharmacists regarding the proper use of medicines is not always clear and understandable. Accordingly, pharmaceutical store pharmacists are assigned tasks to develop mechanisms for information support for patients, which may include paper notes for patients, development of mobile applications for monitoring health status and compliance with the medication regimen of patients with CHD with comorbid conditions.

In accordance with the standards of higher education in the specialty 226 Pharmacy, Industrial Pharmacy [26], good pharmacy practice (GPP) [8], pharmacists' protocols [16], pharmacists of pharmaceutical stores should pay attention to pharmaceutical care, which includes primary prevention of CHD with comorbid conditions, such as diabetes mellitus, arterial hypertension and chronic kidney disease. In addition, pharmacists, in accordance with modern legislation [8;9;16] and standards of higher education [26], should check the compatibility of medicines used by patients with ischemic heart disease, promote their rational use; monitor adverse reactions; provide information support on the correct use and storage of medicines in addition to pharmaceutical provision in order to improve the population's access to medicines.

However, in our study, doctors and patients indicate an intermediately satisfactory level of the listed criteria. Pharmacists realize that in many cases they do not always provide such support to patients due to workload at the workplace, orientation towards pharmaceutical provision of medicines, marketing agreements of pharmacy chains with pharmaceutical companies, promotion of private labels of dietary supplements in pharmacy chains and insufficient development of communication skills. The current Ukrainian legislation has contradictions and needs to be normalized in accordance with the requirements of the European Union countries [27]. The quality standards of pharmacy services [8] are of a recommended nature, the new version of the law "On Medicines" [9] comes into force a year after the end of martial law in Ukraine, and pharmacists' protocols [16] do not contain all pharmacological groups of medicines used by patients with CHD with comorbid conditions. In addition, electronic health systems do not allow tracking the entire list of medicines taken by a patient, so monitoring pharmacotherapy and checking the compatibility of medicines takes a lot of time, which makes it impossible to implement these measures if there are queues in pharmacies. Such contradictions affect the quality of pharmaceutical care and remove responsibility for patient safety from pharmacists and pharmacy business owners regarding the rational use of medicines. The lack of mandatory requirements for continuous professional development of pharmaceutical store pharmacists makes it impossible to develop clinical competencies and requires a review of approaches to modern regulatory and legal regulation of pharmacists' activities in Ukraine.

In the world pharmaceutical practice, there is a rapid transformation and reorientation of pharmaceutical services, therefore the problems and factors influencing the quality of pharmaceutical care outlined by us are also characteristic of other countries of the world [23, 28-30].

The consistency of opinions (W = 0.85) regarding the criteria for providing pharmaceutical care in the structure of medical care for patients with CHD with comorbid conditions, reliably confirmed by our research, indicates the same understanding between all participants during the treatment process within the interprofessional interaction. The shortcomings we have identified allow us to identify the main tasks for improving the quality of pharmaceutical care: development of communication skills and clinical competencies of pharmacists, development of information booklets for patients, development of mobile applications for monitoring the health status and compliance with the medication regimen of patients with ischemic heart disease with comorbid conditions, improvement of the regulatory field of pharmaceutical care in accordance with the Law of Ukraine "On Medicines" [9].

CONCLUSIONS

1. A sufficiently high level of agreement of opinions (W = 0.85) regarding the criteria for providing pharmaceutical care in the structure of medical care for patients with CHD with comorbid conditions has been reliably confirmed.
2. The directions for the development of pharmaceutical care have been identified: the development of pharmacists' communication skills, clinical competencies and information support on the rational use of medicines for patients with CHD with comorbid conditions, which is confirmed by the results of systematic reviews and meta-analyses of international studies.
3. The need to improve the regulatory field of pharmaceutical care in accordance with the Law of Ukraine "On Medicines" has been identified.

REFERENCES

1. The Heart of the World. Global Heart. Global Heart. doi:10.5334/gh.1288. DOI
2. Health Profile Ukraine. World Life Expectancy. 2024. https://www.worldlifeexpectancy.com/country-health-profile/ukraine [Accessed 14 December 2024]
3. Bilousova NA, Mykhalchuk VM. Analytical review of the inf l uence of socio-economic factors on the state of pharmaceutical care for patients with cardiovascular diseases. Pol Merkur Lek. 2024;52(3):347-355. doi:10.36740/merkur202403112. DOI
4. Framework for action on the health and care workforce in the WHO European Region 2023-2030: Draft resolution cosponsored by Andorra, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands (Kingdom of the), Poland, Portugal, Republic of Moldova, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Tajikistan, Türkiye and Ukraine of 26.10.2023 no. EUR/RC73/CONF./4 Provisional agenda item. 2023. https://www.juniordoctors.eu/sites/default/files/2023-12/73wd08e-HealthCareWorkforce-230575.pdf. [Accessed 14 December 2024]
5. Marx N, Federici M, Schütt K та ін. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J. 2023. doi:10.1093/eurheartj/ehad192. DOI
6. Virani SS, Newby LK, Arnold SV et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023. doi:10.1161/cir.0000000000001168. DOI
7. Community pharmacy regulatory and practice models in eastern Europe and central Asia. Copenhagen: WHO Regional Office for Europe; 2024. Licence: CC BY-NC-SA 3.0 IGO. https://iris.who.int/bitstream/handle/10665/376552/9789289060776-eng.pdf?sequence=1&isAllowed=y [Accessed 14 December 2024]
8. Nalezhna aptechna praktyka: Standarty yakosti aptechnykh posluh (Spilna nastanova MFF/VOOZ z NAP), Standart Vsesvitnoi orhanizatsii okhorony zdorovia, 1 sichnia 2011 [Good Pharmacy Practice: Quality Standards for Pharmacy Services (Joint IFF/WHO Guidelines on NAP), World Health Organization Standard, 1 January 2011.]. https://zakon.rada.gov.ua/laws/show/897_009#Text [Accessed 14 December 2024] (Ukrainian)
9. Pro likarski zasoby: Zakon Ukrainy [On medicinal products] vid 28.07.2022 r. No 2469. Vidomosti Verkhovnoi Rady Ukrainy (VVR). Kyiv: Verkhovna Rada Ukrainy; 1996,No22,86. https://zakon.rada.gov.ua/laws/show/2469-20#Text [Accessed 14 December 2024] (Ukrainian)
10. International Pharmaceutical Federation (FIP). Economic sustainability and pharmacy: A commentary article. The Hague: International Pharmaceutical Federation. 2023, p. 21. https://www.fip.org/file/5870 [Accessed 14 December 2024]
11. Khanyk N, Hromovyk B, Levytska O et al. The impact of the war on maintenance of long-term therapies in Ukraine. Front Pharmacol. 2022. doi:10.3389/fphar.2022.1024046. DOI
12. Kotseva K, De Backer G, De Bacquer D et al. Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries. Eur J Prev Cardiol. 2020:204748732090869. doi:10.1177/2047487320908698. DOI
13. OUP accepted manuscript. Eur J Prev Cardiol. 2021. doi:10.1093/eurjpc/zwab115. DOI
14. McEvoy JW, McCarthy CP, Bruno RM et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024. doi:10.1093/eurheartj/ehae178. DOI
15. Vrints C, Andreotti F, Koskinas KC et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024. doi:10.1093/eurheartj/ehae177. DOI
16. Pro zatverdzhennia protokoliv farmatsevta [On approval of pharmacist protocols]: Nakaz Ministerstva okhorony zdorovia Ukrainy vid 05.01.2022 r. № 7. Kyiv: MOZ Ukrainy; 2022. https://zakon.rada.gov.ua/rada/show/v0007282-22#Text [Accessed 14 December 2024] (Ukrainian)
17. Unifikovanyy klinichnyy protokol pervynnoyi, vtorynnoyi (spetsializovanoyi) ta tretynnoyi (vysokospetsializovanoyi) medychnoyi dopomohy «Stabil'na ishemichna khvoroba sertsya». [Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care "Stable coronary heart disease"]. Kyiv: MOZ Ukrainy. 2021. https://www.dec.gov.ua/wp-content/uploads/2021/12/2021_2857_ykpmd_stabihs.pdf. [Accessed 14 December 2024] (Ukrainian)
18. Bilousova NA. Primary prevention of a coronary heart disease within the structure of pharmaceutical care provision: functional role fulfillment of the pharmacist. Pharmaceutical Review Farmacevtičnij časopis. 2024;(3):42-52. doi:10.11603/2312-0967.2024.3.14862. DOI
19. Bilousova N. Justification for expanding the pharmacist's role in the prevention of coronary heart disease at secondary and tertiary levels of medical care. Mod Med Pharm Psychol Health. 2024;(3):41-50. doi:10.32689/2663-0672-2024-3-7. DOI
20. Chaudhri K, Caleres G, Saunders S et al. Does Collaboration between General Practitioners and Pharmacists Improve Risk Factors for Cardiovascular Disease and Diabetes? A Systematic Review and Meta-Analysis. Glob Heart. 2023;18(1):7. doi:10.5334/gh.1184. DOI
21. Improving Collaboration between Primary Care Providers and Community Pharmacists: A CrossSectional Survey. Fam Med Prim Care. 2024;8(1). doi:10.29011/2688-7460.100250. DOI

22. Al-Qahtani S, Jalal Z, Paudyal V et al. The Role of Pharmacists in Providing Pharmaceutical Care in Primary and Secondary Prevention of Stroke: A Systematic Review and Meta-Analysis. Healthcare. 2022;10(11):2315. doi:10.3390/healthcare10112315. DOI
23. Zielińska-Tomczak Ł, Cerbin-Koczorowska M, Przymuszała P et al. Pharmacists' Perspectives on Interprofessional Collaboration with Physicians in Poland: A Quantitative Study. Int J Environ Res Public Health. 2021;18(18):9686. doi:10.3390/ijerph18189686. DOI
24. Angibaud M, Jourdain M, Girard S et al. Involving community pharmacists in interprofessional collaboration in primary care: a systematic review. BMC Prim Care. 2024;25(1). doi:10.1186/s12875-024-02326-3. DOI
25. Hatton K, Bhattacharya D, Scott S, Wright D. Barriers and facilitators to pharmacists integrating into the ward-based multidisciplinary team: A systematic review and meta-synthesis. Res Soc Adm Pharm. 2021. doi:10.1016/j.sapharm.2021.02.006. DOI
26. Pro zatverdzhennia Standartu vyshchoi osvity zi spetsialnosti 226 Farmatsiia, promyslova farmatsiia dlia druhoho (mahisterskoho) rivnia [On approval of the Standard of Higher Education in specialty 226 Pharmacy, industrial pharmacy for the second (master's) level] : Nakaz Ministerstva osvity i nauky Ukrainy vid 04.11.2024 № 981. Kyiv: MON Ukrainy; 2024. https://mon.gov.ua/npa/pro-zatverdzhennya-standartu-vishoyi-osviti-zi-specialnosti-226-farmaciya-promislova-farmaciya-dlya-drugogo-magisterskogo-rivnya-vishoyi-osviti. [Accessed 14 December 2024] (Ukrainian)
27. Henman MC, Ravera S, Lery FX. Council of Europe Resolution on the Implementation of Pharmaceutical Care—A Step Forward in Enhancing the Appropriate Use of Medicines and Patient-Centred Care. Healthcare. 2024;12(2):232. doi:10.3390/healthcare12020232. DOI
28. Wang C, Li M, Huang Y, Xi X. Factors influencing clinical pharmacists' integration into the clinical multidisciplinary care team. Front Pharmacol. 2023;14. doi:10.3389/fphar.2023.1202433. DOI
29. Zajac S, Woods A, Tannenbaum S et al. Overcoming Challenges to Teamwork in Healthcare: A Team Effectiveness Framework and Evidence-Based Guidance. Front Commun. 2021;6. doi:10.3389/fcomm.2021.606445. DOI
30. Zaij S, Pereira Maia K et al. Intervention of pharmacist included in multidisciplinary team to reduce adverse drug event: a qualitative systematic review. BMC Health Serv Res. 2023;23(1). doi:10.1186/s12913-023-09512-6. DOI

We see the development of standards for providing pharmaceutical care to patients with coronary heart disease with comorbid conditions in accordance with ESC/AHA recommendations and taking into account the compatibility of medicines of different pharmacological groups used in cardiovascular diseases as prospects for further research.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Natalia Bilousova
Shupyk National Healthcare University of Ukraine
9 Dorohozhytska St, 04112 Kyiv, Ukraine
e-mail: arinatala@gmail.com

ORCID AND CONTRIBUTIONSHIP

Maryna M. Dolzhenko: 0000-0002-8559-9598 A E F
Natalia A. Bilousova: 0000-0001-6732-426X A B C D E F
Vasyl M. Mykhalchuk: 0000-0002-5398-4758 A F
Natalia O. Tkachenko: 0000-0002-8566-5938 E F
Liudmyla Yakovenko: 0009-0003-8811-8782 B

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 12.01.2025
ACCEPTED: 27.05.2025

REVIEW ARTICLE

CONTENTS

The application of holter monitoring in the diagnosis of atrial fibrillation and its significance in the context of ischemic strokes

Wojciech Jędrzej Bieńkowski[1], Michał Bieńkowski[2], Bartłomiej Kusy[3], Monika Nowakowska[3], Anna Żerańska[4], Patrycja Retman[3], Piotr Kucharczyk[3], Julia Charkot[1]

[1]INTERNAL MEDICINE DEPARTMENT, GROCHOWSKI HOSPITAL NAMED AFTER DR. RAFAŁ MASZTAK, WARSAW, POLAND
[2]JAGIELLONIAN UNIVERSITY IN CRACOW, CRACOW, POLAND
[3]MEDICAL UNIVERSITY OF WARSAW, WARSAW, POLAND
[4]INDEPENDENT PUBLIC CLINICAL HOSPITAL NAMED AFTER PROF. WITOLD ORŁOWSKI, WARSAW, POLAND

ABSTRACT

Aim: This study aims to evaluate the effectiveness of prolonged Holter monitoring in detecting atrial fibrillation (AF) and other arrhythmias in patients following ischemic stroke. We seek to establish the optimal duration of monitoring that maximizes detection rates while considering clinical feasibility and cost-effectiveness.

Materials and Methods: We conducted a systematic review of recent literature, analyzing data from randomized clinical trials and observational studies that assessed the yield of AF detection through various durations of Holter monitoring. Key metrics included detection rates of AF and other relevant arrhythmias, along with patient outcomes related to therapeutic interventions initiated based on monitoring results.

Conclusions: This review highlights the crucial role of prolonged Holter monitoring, particularly 7-day monitoring, in detecting paroxysmal atrial fibrillation (AF) among ischemic stroke survivors, especially those with cryptogenic strokes. Extended monitoring significantly improves AF detection, enabling timely anticoagulation therapy and better stroke prevention. While challenges like patient compliance and cost-effectiveness remain, integrating prolonged Holter monitoring into standard care could enhance diagnostic accuracy and reduce recurrent stroke risk.

KEY WORDS: Holter monitoring, ischemic stroke, atrial fibrillation, stroke prevention, cardiac arrhythmias, cryptogenic stroke

Wiad Lek. 2025;78(6):1150-1159. doi: 10.36740/WLek/205119 DOI

INTRODUCTION

Atrial fibrillation (AF) is recognized as the most prevalent cardiac arrhythmia, significantly contributing to the burden of cardiovascular morbidity and mortality worldwide [1]. The relationship between AF and ischemic stroke is well-established, as AF is a major risk factor for thromboembolic events that can lead to debilitating strokes [2, 3]. Despite advancements in diagnostic techniques, the timely detection of AF, particularly in patients presenting with cryptogenic stroke, remains a formidable challenge in clinical practice.

Ischemic strokes, which account for a substantial proportion of all strokes, are characterized by a sudden disruption of blood flow to the brain, leading to neurological deficits [4]. Among the various subtypes of ischemic stroke, cardioembolic strokes are particularly concerning due to their association with AF [5]. Current estimates suggest that a significant percentage of ischemic strokes are of undetermined origin, often classified as cryptogenic strokes [6]. In this context, the role of continuous cardiac monitoring, particularly through Holter monitoring, has garnered increased attention as a viable strategy for identifying episodes of AF that may have contributed to the stroke event [3]. Holter monitoring, a non-invasive technique that allows for continuous recording of electrocardiographic (ECG) data, has emerged as a critical tool in the assessment of patients with suspected arrhythmias. The ability of Holter monitors to capture transient AF episodes is paramount in guiding therapeutic decisions and initiating appropriate anticoagulation strategies to mitigate the risk of recurrent strokes [3]. However, the efficacy of Holter monitoring in detecting AF varies significantly with the duration of monitoring, highlighting the need for prolonged observation periods to enhance diagnostic yield [7].

In this chapter, we will explore the advancements in Holter monitoring technology, its clinical applications in the context of ischemic stroke, and the implications of AF detection for patient management. Through an examination of current

evidence and guidelines, we aim to elucidate the critical role of extended cardiac monitoring in improving outcomes for patients with stroke and potential underlying AF, ultimately contributing to enhanced stroke prevention strategies.

AIM

The primary aim of this study is to evaluate the effectiveness of Holter monitoring in detecting atrial fibrillation (AF) and other arrhythmias in patients who have experienced ischemic strokes, with a particular focus on cryptogenic strokes. By examining the diagnostic yield of various durations of Holter monitoring, this research seeks to determine the optimal monitoring period that maximizes the detection of clinically significant arrhythmias while remaining feasible and cost-effective.

MATERIALS AND METHODS

A comprehensive literature review was conducted using PubMed and Google Scholar databases to investigate the use of Holter monitoring in detecting atrial fibrillation (AF) in ischemic stroke patients. The search focused on studies published from 2018 onward, while also considering older key publications. Keywords such as *Holter monitoring, atrial fibrillation, ischemic stroke, AF detection,* and *cardiac monitoring* were employed to ensure the identification of relevant articles.

Studies included in the review were selected based on their relevance to AF detection via Holter monitoring in ischemic stroke patients, covering a range of study designs such as clinical trials, observational studies, and systematic reviews. Recent clinical guidelines from organizations like the European Society of Cardiology (ESC) were also consulted to align the review with current best practices.

Studies were excluded if they were not focused on human subjects, did not use Holter monitoring for AF detection, or were unrelated to ischemic stroke. Animal studies, non-peer-reviewed articles, case reports, and conference abstracts were also excluded. Additionally, studies in languages other than English were not considered due to language limitations in data analysis.

This approach ensured a comprehensive and up-to-date synthesis of the role of Holter monitoring in ischemic stroke patients.

REVIEW AND DISCUSSION

HOLTER MONITORING: TECHNOLOGY AND APPLICATIONS

Holter monitoring is a crucial technology in modern medicine and is indispensable for the diagnosis of numerous arrhythmias. In recent years, significant advancements have been made in its development. The advancement of technology has enabled the creation of compact, lightweight (approximately 50 g) portable tape recorders capable of continuously recording over 24 hours of electrocardiographic (ECG) data, capturing more than 100,000 heartbeats. In comparison, conventional ECG recordings over an equivalent timeframe would require nearly a mile of ECG paper [8].

The Holter monitor has a wide range of applications, primarily used for detecting arrhythmias that occur intermittently and are often not visible on standard ECG recordings due to their brief duration. However, it is not suitable for long-term (over 7 days) cardiac rhythm monitoring, which is better achieved using external and internal loop recorders and wearable devices [2].

The diagnostic capabilities of Holter monitoring can be tailored to specific clinical needs by adjusting the number of leads utilized. The number of leads in Holter monitoring plays a significant role in its diagnostic accuracy and scope [9]. 2 to 3 leads are sufficient to monitor heart rate and rhythm [10]. In contrast, if the purpose is to establish the origin of premature beats/dysrhythmias or tachycardia, then a 12-lead Holter electrocardiography is verry accurate and it can instantly diagnose supraventricular tachycardia (SVT), ventricular tachycardia (VT), atrial flutter, atrial fibrillation, monomorphic or Polymorphic VTs, long QT syndrome, supraventricular premature complexes, ventricular premature complexes, dominant atrioventricular accessory pathways, atrioventricular block, right and left bundle branch block, and left anterior and posterior fascicular block [9-11].

PATHOPHYSIOLOGY OF ISCHEMIC STROKE AND CARDIAC IMPLICATIONS

Ischemic strokes represent one of the most critical global health challenges, being a leading cause of disability without curative therapies currently available [4]. According to estimates from 2016, stroke was associated with approximately 5.5 million deaths worldwide, with one-fifth of these deaths attributable to cardiovascular causes [12]. In Poland, ischemic strokes account for 88% of all strokes, emphasizing their prominence in clinical practice [5]. These strokes are broadly classified into lacunar strokes, caused by small vessel disease, and non-lacunar strokes, which make up the majority. Of the non-lacunar strokes, approximately 35% are cardioembolic in origin, while 45% are cryptogenic, underscoring the substantial diagnostic and therapeutic challenges posed by these subtypes [5].

Cryptogenic strokes, defined as strokes of undetermined origin, account for an estimated 20–40% of all ischemic strokes [6]. Paroxysmal atrial fibrillation (AF), considered the most common underlying cause of cryptogenic strokes, is associated with a significant risk of thrombus formation in the left atrium or left atrial appendage. These thrombi, once dislodged, can travel to the brain, causing cardioembolic strokes that are typically more severe and linked to higher morbidity and mortality compared to other stroke subtypes [3, 13, 14]"URL":"https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(17. However, paroxysmal AF, often referred to as silent AF in the literature, is particularly difficult to diagnose in ischemic stroke patients due to its asymptomatic nature. As a result, detecting this arrhythmia requires advanced and often prolonged monitoring strategies, as many patients do not exhibit noticeable symptoms until a major event, such as a stroke, occurs [15]by using a 7-day Holter ECG which has proved to be superior to the standard 24-h recording, and to evaluate the possible association between brain lesions and arrhythmias. One hundred and twenty patients with cryptogenic ischemic stroke underwent clinical and neuroimaging assessment and were monitored with a 7-day Holter ECG. Analysis of the rhythm recorded over 7 days was compared to analysis limited at the first 24 h of monitoring. 7-day Holter ECG detected AF in 4% of patients, supraventricular extrasystole (SVEB.

Evidence from the reviewed studies indicates that device-detected atrial fibrillation (AF) correlates with stroke risk across a broad range of episode durations in older adults [16]. Several studies documented that very short episodes - as brief as 30 seconds or 5 minutes - are associated with significantly elevated risk, with hazard ratios ranging from 1.76 to 4.41 and a relative risk near 2.49 [16]. Intermediate durations - typically 1 hour up to 5.5 hours—are linked with hazard and odds ratios between 2.11 and 4.2 [16]. Extended episodes, particularly those exceeding 23 hours, show the highest risk estimates (*odds ratio* around 5.00), especially when considered alongside factors such as the CHA2DS2-VASc score. [17]

While cardioembolism is a well-established and extensively documented cause of ischemic stroke, the intricate relationship between stroke and subsequent cardiovascular events is an area of ongoing investigation. Emerging data suggest that ischemic stroke may disrupt the autonomic nervous system, leading to dysregulation of heart rate and blood pressure. This autonomic imbalance, characterized by alterations in sympathetic and parasympathetic activity, is supported by evidence of impaired heart rate variability and increased catecholamine release, which can affect myocardial receptors [15]by using a 7-day Holter ECG which has proved to be superior to the standard 24-h recording, and to evaluate the possible association between brain lesions and arrhythmias. One hundred and twenty patients with cryptogenic ischemic stroke underwent clinical and neuroimaging assessment and were monitored with a 7-day Holter ECG. Analysis of the rhythm recorded over 7 days was compared to analysis limited at the first 24 h of monitoring. 7-day Holter ECG detected AF in 4% of patients, supraventricular extrasystole (SVEB. Notably, certain brain regions, including the insula and temporal and parietal lobes, have been implicated in the development of new arrhythmias following stroke [18, 19]. These findings suggest that brain-heart interactions may play a significant role in post-stroke cardiovascular complications.

Further complicating the clinical picture is the lack of a consistent temporal relationship between thromboembolic events and arrhythmias, as highlighted by findings from the TRENDS study [20]. This disconnect creates diagnostic challenges in identifying the true cause of ischemic strokes and raises questions about the mechanistic pathways linking arrhythmias to embolic events. As a result, the precise causality in many cases of ischemic stroke remains elusive, emphasizing the need for additional research to improve diagnostic accuracy and guide therapeutic decision-making.

In conclusion, ischemic stroke remains a multifaceted clinical entity, with cardioembolic and cryptogenic subtypes posing significant diagnostic challenges. The interplay between arrhythmias, embolic mechanisms, and post-stroke cardiovascular changes underscores the complexity of stroke pathophysiology. Future studies are essential to unravel these connections, refine diagnostic strategies, and optimize patient outcomes.

EVIDENCE SUPPORTING ECG MONITORING AFTER ISCHEMIC STROKE

After an ischemic stroke, one of the primary objectives in patient management is to prevent recurrent stroke. Achieving this goal necessitates identifying the underlying cause of the stroke. In cases of cryptogenic stroke, stroke specialists often suspect that a significant proportion of these events are caused by subclinical atrial fibrillation (AF) [1]. Detecting AF is crucial, as it allows the timely initiation of oral anticoagulation therapy, which has demonstrated a highly favorable therapeutic effect in significantly reducing the risk of recurrent stroke. The detection of AF relies on cardiac rhythm monitoring through devices capable of recording elec-

Table 1. Comparison of AF detection rates across different monitoring durations [22-25]

Monitoring Duration	AF Detection Rate
24-Hour Holter	1-6%
48-Hour Holter	5-10%
7-Day Holter	10-15%
30-Day Event Monitoring	25-50%

trocardiographic (ECG) data. Early identification of AF is therefore pivotal for improving patient outcomes [3].

Several methods are available for detecting atrial fibrillation, including standard ECG at hospital admission, serial in-hospital ECG recordings, telemetry, inpatient or outpatient Holter monitoring, and external ambulatory ECG recorders, such as wearable devices or implantable loop recorders (ILRs) [21]. Each of these techniques offers unique advantages and limitations, presenting a significant challenge in clinical practice regarding the selection of the most appropriate method for individual patients [8].

Alternative strategies to improve AF detection include prolonged Holter monitoring, telemetry-based ECG, and patient-activated external recorders. While these methods offer non-invasive or minimally invasive solutions, their accessibility and availability remain inadequate in many healthcare settings [8]. Expanding access to advanced monitoring technologies could greatly enhance the ability to identify AF and improve the care provided to patients following ischemic stroke [21].

Implantable monitoring devices, while highly effective for long-term monitoring and the detection of AF, are associated with invasive procedures and higher costs. These factors often limit their use to select patient populations [21]. In contrast, Holter monitoring is a non-invasive, widely accessible, and cost-effective method. However, its optimal application for stroke patients remains a topic of ongoing debate [6]. Efforts to enhance its utility focus on determining the most effective duration and protocol to maximize AF detection while maintaining feasibility and cost-efficiency [8].

Despite guideline recommendations advocating for prolonged ECG monitoring, typically 48–72 hours, many clinical practices still rely on 24-hour Holter monitoring. This standard approach significantly limits the detection of paroxysmal AF in stroke patients, potentially missing cases that could benefit from therapeutic intervention. [3] Implantable loop recorders are considered the most effective option for detecting subclinical AF due to their ability to monitor cardiac rhythm over extended periods. However, their widespread implementation is constrained by their invasive nature and high cost [21].

In conclusion, the choice of an optimal monitoring method for AF detection in stroke patients must balance efficacy, accessibility, and patient safety (Table1). Non-invasive methods, such as extended Holter monitoring, hold promise as cost-effective and practical solutions. However, improving the availability of advanced techniques, such as wearable ECG recorders or implantable devices, may further enhance diagnostic accuracy and enable timely therapeutic interventions, ultimately reducing the risk of recurrent stroke.

EXTENDED MONITORING WITH HOLTER EXAMINATION

The detection of atrial fibrillation (AF) in stroke survivors remains a critical challenge, particularly due to the limited effectiveness of short-term cardiac monitoring. Evidence suggests that standard 24-hour Holter monitoring demonstrates a relatively low detection rate for AF, identifying arrhythmias in only 1–2% of patients. For instance, Jabaudon et al. reported a detection rate of 5% with 24-hour Holter monitoring, while extending the monitoring duration to seven days identified an additional 5.7% of cases [6, 26]. This highlights the limitations of short-term monitoring and underscores the value of extended observation periods.

Numerous studies have consistently demonstrated that the yield of AF detection increases with prolonged cardiac rhythm monitoring. However, despite this clear trend, the optimal maximum duration of monitoring remains uncertain [21]. Prolonged monitoring carries potential resource and cost-effectiveness implications, particularly given diminishing returns with excessively extended durations. Current guidelines recommend a minimum of 24 hours of cardiac monitoring following a stroke, but extended monitoring for durations exceeding 48 hours is strongly suggested, particularly in patients with ischemic stroke or transient ischemic attack (TIA) of undetermined origin [27].

Randomized clinical trials further emphasize the benefits of extended cardiac monitoring. Longer durations significantly increase AF detection rates compared to standard practices. For example, one randomized study found that in patients aged 55 years or older with cryptogenic ischemic stroke or TIA within the previous six months, AF lasting at least 30 seconds was detected in 16.1% of those monitored with a 30-day event recorder versus 3.2% in the standard monitoring group. This finding, supported by a 95% confidence interval (CI) of 8.0–17.6% and a p-value of <0.001, underscores the value of prolonged monitoring in identifying clinically significant arrhythmias [5].

Ambulatory 7-day Holter monitoring has emerged as a particularly effective approach for detecting previous-

ly unidentified AF. Among patients with embolic stroke of undetermined source (ESUS), this method detected AF in 6.8% of cases (95% CI: 4.1–11.1%), compared to standard 24-hour Holter monitoring. Notably, the median time to the first documented episode of AF during 7-day monitoring was approximately 50 hours, emphasizing the importance of extending monitoring beyond the standard 24-hour period [28].

Prolonged monitoring also outperforms guideline-recommended 72-hour recording durations. For instance, three 10-day Holter recordings yielded higher detection rates for AF compared to standard procedures. Furthermore, intermittent 21-day ECG screening demonstrated superiority over 48-hour Holter monitoring, with detection rates of 11.4% *vs.* 2.8% (p=0.001) [21, 29]. Transtelephonic ECG monitoring represents another effective alternative, identifying paroxysmal AF in 9.2% of patients following a recent stroke or TIA who had negative 24-hour Holter results.

Repeated Holter monitoring also offers substantial benefits. In patients aged 60 years or older with recent strokes, repeated monitoring identified AF in 14% of cases compared to 5% with a single round of monitoring (p=0.002) [21, 30]. Similarly, 14-day ECG patches demonstrated superior detection rates for cardiac arrhythmias compared to 24-hour Holter monitoring, with detection rates of 69.9% *vs*. 21.7%, respectively. Another study found that 66% of patients with paroxysmal AF were diagnosed using a 14-day ECG patch, compared to only 9% with 24-hour Holter monitoring [7, 31].

The current guidelines do not specify which subgroups of stroke patients should undergo extended cardiac monitoring, highlighting the need to identify high-risk populations [27]. Such targeted strategies could optimize resource utilization and improve patient outcomes. Notably, age serves as a significant demographic factor, as older patients are more likely to experience cardiac arrhythmias, such as atrial fibrillation (AF), which are more easily detected through prolonged monitoring. Studies have indicated that older adults present with more comorbidities, including hypertension and heart failure, thus enhancing the diagnostic yield of Holter monitoring [32]. Moreover, clinical characteristics significantly impact the effectiveness of Holter monitoring. Patients with symptomatic arrhythmias, especially those presenting with palpitations or unexplained syncope, show higher rates of relevant arrhythmia detection [33]. Extended monitoring has proven especially useful in post-procedural settings, where arrhythmic events are common due to underlying cardiomyopathies or recent surgeries, leading to improved diagnostic outcomes [34]. Furthermore, the evaluation of patients with cryptogenic stroke has highlighted a higher detection rate of AF in those who received prolonged monitoring, emphasizing the importance of targeted monitoring in high-risk populations [23].

Although initial evidence suggests the potential utility of biomarkers, including brain natriuretic peptide (BNP), left atrial diameter (LAD), and the frequency of atrial premature contractions (APCs), their routine use in clinical practice is not yet fully justified. These biomarkers may, however, provide critical insights to guide decisions regarding extended cardiac monitoring. Further research is needed to validate their clinical applicability and establish standardized protocols. In patients with transient ischemic attack (TIA) or cryptogenic stroke, prolonged ECG monitoring lasting beyond 48 hours is strongly recommended, ideally initiated during hospitalization [21]. Supplementing inpatient monitoring with outpatient follow-up can significantly improve AF detection rates, facilitating timely therapeutic interventions. Notably, the identification of arrhythmias lasting at least 30 seconds should prompt the initiation of anticoagulant therapy [21].

LONG-TERM MONITORING WITH A HOLTER RECORDER

The detection of atrial fibrillation (AF) long after an ischemic stroke does not necessarily indicate that the prior stroke was caused by subclinical AF, as the likelihood of developing arrhythmias increases with age [21]. Nevertheless, long-term cardiac rhythm monitoring appears critical in this patient population to identify potential episodes of paroxysmal AF that might have clinical relevance. While standard 24-hour Holter monitoring remains a valuable tool, its effectiveness in detecting paroxysmal AF is limited [29]. Emerging technologies, such as ambulatory devices and implantable rhythm recorders, offer greater detection efficacy due to their capacity for prolonged monitoring, significantly enhancing the identification of arrhythmias [7].

Extended monitoring approaches, including telemetry and implantable loop recorders (ILRs), have demonstrated particular efficacy in detecting AF in patients with cryptogenic stroke [29, 35, 36]. These methods are especially beneficial for high-risk patients, such as those with elevated CHA_2DS_2-VASc scores, as they enhance the likelihood of capturing clinically significant arrhythmias [7, 37].

Despite the effectiveness of extended monitoring, alternative methods, such as implantable loop recorders, offer even higher sensitivity. However, these techniques are less accessible and may not be cost-effective for routine use [21]. The 7-day Holter ECG remains a non-in-

vasive, cost-efficient, and practical approach, providing substantial benefits in AF detection rates. This method allows for timely therapeutic interventions, particularly anticoagulation, which is critical for reducing the risk of recurrent strokes [38].

COST-EFFECTIVENESS AND ECONOMY OF HOLTER MONITORING

Extended Holter monitoring in low-resource healthcare settings faces numerous operational and technical limitations that hinder its effective implementation. A major challenge is resource scarcity—many facilities lack adequate funding, trained personnel, and infrastructure to support the use of such devices [39, 40]. Access to advanced devices, such as 14-day adhesive patch monitors, is often limited, and standard Holter monitors may not support extended durations, reducing diagnostic yield [27].

Patient compliance is another issue, as wearing devices for prolonged periods can interfere with daily life, particularly in environments where comfort and privacy are limited [41, 42]. Cost also presents a barrier - while some newer systems aim to be cost-effective, setup, maintenance, and follow-up expenses remain prohibitive for many facilities [43-45].

On the technical side, data quality and reliability can suffer due to motion artifacts or equipment malfunction, especially in settings where device maintenance is deprioritized (Tsukada et al., 2019; Dagan & Mechanic, 2020) [46, 47]. Even with extended monitoring durations, diagnostic sensitivity is limited; short-term Holter devices often miss infrequent or asymptomatic arrhythmias, and even extended systems may not reliably detect paroxysmal AF [48-50].

Additionally, interpreting complex monitoring data requires specialized expertise, which is often lacking in low-resource environments, leading to underutilization of the technology [32, 44]. The lack of real-time feedback further complicates care, as most devices are designed for retrospective analysis, delaying interventions for acute events. [46] Finally, infrastructure challenges, including unreliable electricity and frequent power outages, pose logistical difficulties for maintaining device functionality [43, 51].

The cost-effectiveness of 7-day ECG Holter monitoring compared to implantable loop recorders (ILRs) for atrial fibrillation (AF) detection depends on diagnostic yield, patient characteristics, and long-term outcomes [52, 53]. While 7-day Holter improve detection rates over standard 24-hour monitoring, with yields reported between 10% and 15% [52], ILRs—capable of continuously monitoring cardiac rhythms for up to three years - offer significantly higher yields, particularly in patients with intermittent or asymptomatic AF [23, 54]. Studies indicate that ILRs can consistently identify AF in various clinical contexts, including in post-stroke patients, with detection rates ranging from 25% to as high as 50%, depending on the population studied [53, 55].

Although Holter monitors are more accessible and less costly upfront, they may miss critical AF episodes, potentially leading to expensive downstream complications like stroke [52]. In contrast, ILRs have higher initial costs due to implantation, but their continuous monitoring facilitates early detection and timely initiation of anticoagulation, lowering the risk of recurrent strokes [56]. Studies report favorable cost-effectiveness ratios for ILRs - between $15,000 and $25,000 per quality-adjusted life year (QALY) - which fall well within accepted thresholds for healthcare interventions [52].

ILRs also offer clinical advantages beyond detection. Research shows that patients monitored with ILRs are more likely to initiate anticoagulation therapy in a timely manner, significantly reducing stroke risk [23]. Additionally, continuous monitoring enables real-time treatment adjustments, unlike Holter monitors which only provide brief snapshots of cardiac activity [55, 57]. ILRs may also reduce the need for frequent follow-up visits, as the actionable data they generate supports more proactive clinical decisions, potentially lowering hospitalization rates and associated healthcare costs [58].

RECOMMENDATIONS AND FUTURE DIRECTIONS

Transitioning from 24-hour to 7-day Holter monitoring demonstrates both clinical and cost-effectiveness benefits in the diagnostic evaluation of cardiac arrhythmias. Clinically, extended Holter monitoring significantly increases the detection rates of paroxysmal atrial fibrillation (AF) and other arrhythmias, particularly in high-risk populations, such as those experiencing cerebral ischemia. Research indicates that 7-day monitoring can nearly double the proportion of patients diagnosed with AF compared to standard 24-hour monitoring, which allows for timely anticoagulant treatment and potentially averts recurrent strokes [23].

From a cost-effectiveness perspective, the implementation of 7-day Holter monitoring has been shown to be economically beneficial. The extension leads to the identification of additional new cases of AF that require anticoagulant therapy, ultimately resulting in decreased overall healthcare costs due to stroke prevention and related complications [45]. Furthermore, studies suggest that while the additional costs of extended monitoring should be weighed against the clinical

benefits, the long-term savings from prevented strokes and hospitalizations make it a valuable investment in patient management [45, 59].

The transition from standard clinical assessments to the incorporation of novel biomarkers and advanced imaging techniques offers a promising enhancement in accurately identifying patients who could significantly benefit from extended Holter monitoring. Recent studies have evaluated specific biomarkers such as symmetric dimethylarginine (SDMA) in predicting unrecognized atrial fibrillation (AF) among ischemic stroke patients. For instance, Hannemann et al. [60] elucidated that elevated levels of SDMA could be indicative of increased risk for AF, highlighting that targeted monitoring of patients with high SDMA could lead to timely identification of arrhythmias that standard assessments might overlook. This suggests a tailored approach to monitoring, where patients presenting with higher levels of SDMA benefit from extended Holter monitoring over the conventional 24-hour assessment.

Advanced imaging techniques, particularly echocardiography, complement the utility of biomarkers in stratifying risk for AF and improving monitoring protocols. Imaging can reveal structural heart abnormalities that predispose individuals to atrial arrhythmias. Recent meta-analyses indicate that enhanced imaging in conjunction with Holter monitoring increases the detection rates of paroxysmal AF, which is critical given that standard monitoring tools often only capture sustained AF events [23, 28].

For example, Huang et al. [61] highlighted that integrating echocardiographic assessments with long-term electrocardiographic monitoring led to improved identification of AF in stroke patients, emphasizing the complex interrelationship between structural heart disease and arrhythmia risk. This combined approach can lead to a more comprehensive risk stratification model, allowing healthcare providers to implement preventive strategies more effectively.

CONCLUSIONS

This comprehensive review underscores the critical role of prolonged Holter monitoring in the early detection of atrial fibrillation (AF) among ischemic stroke survivors, particularly those with cryptogenic strokes. Our analysis of current literature reveals that standard 24-hour Holter monitoring significantly underperforms when compared to extended monitoring periods, with 7-day monitoring emerging as notably more effective in identifying paroxysmal AF. This enhanced detection capability is pivotal, considering the established link between AF and an increased risk of recurrent ischemic strokes.

Importantly, our findings advocate for a paradigm shift in clinical practice, suggesting that the adoption of prolonged monitoring protocols could substantially improve stroke prevention strategies. Specifically, monitoring durations extending beyond 48 hours - ideally up to 7 days - have been shown to optimize AF detection, thereby enabling timely initiation of anticoagulation therapy to mitigate the risk of secondary stroke events.

However, despite the compelling evidence supporting the utility of extended Holter monitoring, its implementation is not without challenges. Issues such as patient compliance, resource allocation, and cost-effectiveness remain pertinent concerns that necessitate further investigation. Additionally, the exploration of emerging technologies and novel biomarkers presents an exciting frontier that could enhance the precision and efficiency of AF detection in post-stroke patients.

In conclusion, our review strongly supports the integration of prolonged Holter monitoring into the standard of care for ischemic stroke patients, particularly those with an elusive AF diagnosis. Future research should aim to address the operational barriers to widespread adoption and explore innovative solutions that could further refine and personalize monitoring protocols. By doing so, we can improve diagnostic accuracy, optimize patient outcomes, and ultimately reduce the global burden of stroke.

REFERENCES

1. European Stroke Organisation (ESO) guideline on screening for subclinical atrial fibrillation after stroke or transient ischaemic attack of undetermined origin - Marta Rubiera, Ana Aires, Kateryna Antonenko, Sabrina Lémeret, Christian H Nolte, Jukka Putaala, Renate B Schnabel, Anil M Tuladhar, David J Werring, Dena Zeraatkar, Maurizio Paciaroni, 2022 [Internet].: https://journals.sagepub.com/doi/10.1177/23969873221099478 [Access: 2024 Dec 11].
2. Wytyczne ESC 2020 dotyczące diagnostyki i leczenia migotania przedsionków opracowane we współpracy z European Association of Cardio-Thoracic Surgery (EACTS) [Internet]. [cited 2024 Nov 22]. https://ptkardio.pl/wytyczne/40-wytyczne_esc_2020_dotyczace_diagnostyki_i_leczenia_migotania_przedsionkow_opracowane_we_wspolpracy_z_european_association_of_cardiothoracic_surgery_eacts (Polish)
3. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial. Lancet Neurology [Internet]. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(17)30002-9/abstract [Access: 2025 Jan 15].

4. Balch MHH, Nimjee SM, Rink C, Hannawi Y. Beyond the Brain: The Systemic Pathophysiological Response to Acute Ischemic Stroke. J Stroke. 2020 May;22(2):159–72.
5. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke [Internet]. 2021 Jul;52(7). https://www.ahajournals.org/doi/10.1161/STR.0000000000000375 [Access: 2024 Dec 11]
6. Kułach A, Dewerenda M, Majewski M, Lasek-Bal A, Gąsior Z. 72 hour Holter monitoring, 7 day Holter monitoring, and 30 day intermittent patient-activated heart rhythm recording in detecting arrhythmias in cryptogenic stroke patients free from arrhythmia in a screening 24 h Holter. Open Med. 2020 Jul 18;15(1):697–701.
7. Chen WC, Wu YL, Hsu YC, et al. Comparison of continuous 24-hour and 14-day ECG monitoring for the detection of cardiac arrhythmias in patients with ischemic stroke or syncope. Clin Cardiol. 2024;47(3):e24247.
8. Paudel B, Paudel K. The Diagnostic Significance of the Holter Monitoring in the Evaluation of Palpitation. J Clin Diagn Res [Internet]. 2013 https://jcdr.net/article_fulltext.asp?issn=0973-709x&year=2013&volume=7&issue=3&page=480&issn=0973-709x&id=2802 [Access: 2024 Nov 13]
9. Abdullah MY, Zarei TL, Althaidy MM, et al. Indications, Contraindications, and Clinical Significance of Holter Monitoring Device. J Pharm Res Int. 2021 Dec 23;1035–41.
10. Mubarik A, Iqbal AM. Holter Monitor. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. http://www.ncbi.nlm.nih.gov/books/NBK538203/ [Access: 2024 Dec 23]
11. Wang R, Blackburn G, Desai M, Phelan D, Gillinov L, Houghtaling P, et al. Accuracy of Wrist-Worn Heart Rate Monitors. JAMA Cardiol. 2017 Jan 1;2(1):104–6.
12. Sposato LA, Hilz MJ, Aspberg S, et al. Post-Stroke Cardiovascular Complications and Neurogenic Cardiac Injury. J Am Coll Cardiol. 2020 Dec 8;76(23):2768–85.
13. Ok T, Lee SH, Kim JY, Lee KY, Jung YH. Nonsustained atrial tachycardia in 24-hour Holter monitoring: a potential cardiac source of embolism in acute ischemic stroke. Ann Transl Med. 2022 Apr;10(8):433.
14. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. | Oxford Academic [Internet]. https://academic.oup.com/eurheartj/article/42/5/373/5899003 [Access: 2025 Jan 15].
15. Carrarini C, Di Stefano V, Russo M, et al. ECG monitoring of post-stroke occurring arrhythmias: an observational study using 7-day Holter ECG. Sci Rep. 2022 Jan 7;12(1):228.
16. Boriani G, Glotzer TV, Santini M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10 000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). Eur Heart J. 2013 Dec 11;35(8):508–16.
17. Kaplan RM, Koehler J, Ziegler PD, Sarkar S, Zweibel S, Passman RS. Stroke Risk as a Function of Atrial Fibrillation Duration and CHA \ textsubscript2 DS \textsubscript2 -VASc Score. Circulation. 2019 Nov 12;140(20):1639–46.
18. Seifert, F. et al. Neuroanatomical correlates of severe cardiac arrhythmias in acute ischemic stroke. J Neurol. 262, 1182–1190 (2015).
19. Rincon, F. et al. Stroke location and association with fatal cardiac outcomes: Northern manhattan study (NOMAS). Stroke 2008;39:2425–2431.
20. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J, Ziegler PD; TRENDS Investigators. Temporal relationship of atrial tachyarrhytmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. Heart Rhythm 2011; 8:1416-1423.
21. Rubiera M, Aires A, Antonenko K, et al. European Stroke Organisation (ESO) guideline on screening for subclinical atrial fibrillation after stroke or transient ischaemic attack of undetermined origin. Eur Stroke J. 2022 Sep;7(3):107–139.
22. Jickling GC, Xu H, Stamova B, Ander BP, Zhan X, Tian Y, et al. Signatures of Cardioembolic and Large-vessel Ischemic Stroke. Ann Neurol. 2010;68(5):681–92.
23. Gladstone DJ, Spring M, Dorian P, et al. Atrial Fibrillation in Patients With Cryptogenic Stroke. N Engl J Med. 2014;370(26):2467–77.
24. Chien DV, Bình NT, Nguyen K, Son PT. Applicability of a Novel Wearable Wireless Electrocardiogram Monitoring Device (Spyder) for Arrhythmia Detection in Patients With Suspected Cardiac Arrhythmias. Cardiol Res Pract. 2021;2021:1–6.
25. Yu EH, Lungu C, Kanner R, Libman R. The Use of Diagnostic Tests in Patients With Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 2009;18(3):178–84.
26. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7 day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. Stroke. 2004;35:1647–51.
27. Himmelreich JC, Lucassen WA, Coutinho JM, Harskamp RE, de Groot JR, CPM van Weert H. 14-day Holter monitoring for atrial fibrillation after ischemic stroke: The yield of guideline-recommended monitoring duration. Eur Stroke J. 2023 Mar 1;8(1):157–67.
28. Miyazaki Y, Toyoda K, Iguchi Y, et al. Atrial Fibrillation After Ischemic Stroke Detected by Chest Strap-Style 7-Day Holter Monitoring and the Risk Predictors: EDUCATE-ESUS. J Atheroscler Thromb. 2021;28(5):544–54.

29. Onder H, Yilmaz S. The Rationale of Holter Monitoring After Stroke. Angiology. 2017 Nov 1;68(10):926–7.
30. Yushan B, Tan BYQ, Ngiam NJ, et al. Association between bilateral infarcts pattern and detection of occult atrial fibrillation in embolic stroke of undetermined source (ESUS) patients with insertable cardiac monitor (ICM). J Stroke Cerebrovasc Dis. 2019;28:2448–2452.
31. Chua S-K, Chen L-C, Lien L-M, et al. Comparison of arrhythmia detection by 24-Hour and 14-day continuous electrocardiography patch monitoring. Acta Cardiol Sin. 2020;36(3):251–259.
32. Hyun S, Lee S, Hong YS, Lim S, Kim DJ. Evaluation of the Diagnostic Performance and Efficacy of Wearable Electrocardiogram Monitoring for Arrhythmia Detection After Cardiac Surgery. J Chest Surg. 2024;57(2):205–12.
33. Chiang L kin. Holter Monitoring (Ambulatory Electrocardiography) Defined Cardiac Arrhythmia Among Patients Presented With Palpitation in the Primary Care Setting. J Fam Med Health Care. 2017;3(1):12.
34. Kim S, Choi Y, Lee K, Kim S, Kim HJ, Shin S, et al. Comparison of the 11-Day Adhesive ECG Patch Monitor and 24-H Holter Tests to Assess the Response to Antiarrhythmic Drug Therapy in Paroxysmal Atrial Fibrillation. Diagnostics. 2023;13(19):3078.
35. Sanna T, Diener HC, Passman RS, Crystal AFSC. Cryptogenic stroke and atrial fibrillation. N Engl J Med. 2014;371(13):1261.
36. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370(26): 2467-2477.
37. Locati ET, Moya A, Oliveira M, et al. External prolonged electrocardiogram monitoring in unexplained syncope and palpitations: results of the SYNARR-Flash study. Europace. 2016;18(8):1265-1272.
38. Wachter R, Weber-Krüger M, Hamann GF, et al. Long-Term Follow-up of Enhanced Holter-Electrocardiography Monitoring in Acute Ischemic Stroke. J Stroke. 2021 Dec 17;24(1):98–107.
39. Barrett P, Komatireddy R, Haaser S, et al. Comparison of 24-Hour Holter Monitoring With 14-Day Novel Adhesive Patch Electrocardiographic Monitoring. Am J Med. 2014;127(1):95.e11–95.e17.
40. Alriyami WB, Sadiq MA, Al Rawahi M, Ahmed S, Kindi FA, Khatri MA. The Role of 24-Hour Holter Electrocardiogram in the Early Detection of Atrial Fibrillation in Newly Diagnosed Acute Ischemic Stroke Patients. Cureus. 16(6):e62566.
41. Nalesso F, Garzotto F, Cattarin L, et al. A Continuous Renal Replacement Therapy Protocol for Patients With Acute Kidney Injury in Intensive Care Unit With COVID-19. J Clin Med. 2020;9(5):1529.
42. Freund O, Caspi I, Alcalay I, Brezis MR, Frydman S, Bornstein G. An old diagnostic tool for new indications: inpatient Holter ECG for conditions other than syncope or stroke. Sci Rep. 2023 Aug 2;13(1):12510.
43. Alriyami WB, Muhammad AS, Rawahi MA, Ahmed S, Kindi FA, Khatri MA. The Role of 24-Hour Holter Electrocardiogram in the Early Detection of Atrial Fibrillation in Newly Diagnosed Acute Ischemic Stroke Patients. Cureus. 2024;
44. İnci F, Tokel O, Wang S, et al. Nanoplasmonic Quantitative Detection of Intact Viruses From Unprocessed Whole Blood. Acs Nano. 2013;7(6):4733–45.
45. Mayer F, Stahrenberg R, Gröschel K, et al. Cost-Effectiveness of 7-Day-Holter Monitoring Alone or in Combination With Transthoracic Echocardiography in Patients With Cerebral Ischemia. Clin Res Cardiol. 2013;102(12):875–84.
46. Dagan A, Mechanic O. Use of Ultra-Low Cost Fitness Trackers as Clinical Monitors in Low Resource Emergency Departments. Clin Exp Emerg Med. 2020;7(3):144–9.
47. Tsukada Y, Tokita M, Murata H, et al. Validation of Wearable Textile Electrodes for ECG Monitoring. Heart Vessels. 2019;34(7):1203–11.
48. Meyer C, Martinek M, Pürerfellner H. Implantable Cardiac Monitors for the Detection of Atrial Fibrillation – How Far Have We Come? Eur Cardiol Rev. 2011;7(1):34.
49. Go AS, Reynolds K, Yang J, et al. Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation. JAMA Cardiol. 2018 Jul 1;3(7):601.
50. Kwon S, Lee SR, Choi EK, et al. Comparison Between the 24-hour Holter Test and 72-hour Single-Lead Electrocardiogram Monitoring With an Adhesive Patch-Type Device for Atrial Fibrillation Detection: Prospective Cohort Study. J Med Internet Res. 2022 May 9;24(5):e37970.
51. Steinhubl SR, Feye D, Levine AC, Conkright C, Wegerich S, Conkright G. Validation of a Portable, Deployable System for Continuous Vital Sign Monitoring Using a Multiparametric Wearable Sensor and Personalised Analytics in an Ebola Treatment Centre. BMJ Glob Health. 2016;1(1):e000070.
52. Adasuriya G, Barsky A, Kralj-Hans I, et al. Remote Monitoring of Atrial Fibrillation Recurrence Using mHealth Technology (REMOTE-AF). Eur Heart J - Digit Health. 2024;5(3):344–55.
53. Kaura A, Sztriha L, Chan FK, et al. Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial. Eur J Med Res. 2019 Jul 26;24(1):25.
54. Nölker G, Mayer J, Boldt L, et al. Performance of an Implantable Cardiac Monitor to Detect Atrial Fibrillation: Results of the DETECT AF Study. J Cardiovasc Electrophysiol. 2016;27(12):1403–10.
55. Cho HJ, Lee CH, Hwang J, et al. Accuracy of Implantable Loop Recorders for Detecting Atrial Tachyarrhythmias After Atrial Fibrillation Catheter Ablation. Int J Arrhythmia. 2020;21(1). https://arrhythmia.biomedcentral.com/articles/10.1186/s42444-020-00013-9 [Access: 2024 December]
56. Müller-Leisse J, Hillmann HAK, Iserloh L, Fruehauf B, Duncker D. Diagnostic Yield and Clinical Implications of Implantable Loop Recorders in Patients With Syncope in Germany: A National Database Analysis. J Clin Med. 2024;13(6):1564.

57. Adasuriya G, Barsky A, Kralj-Hans I, Mohan S, Gill S, Chen Z, et al. Remote Monitoring of AF Recurrence Using mHealth Technology (REMOTE-AF). Eur Heart J Digit Health. 2024 Feb 12;5(3):344–355
58. Arcinas LA, McIntyre WF, Hayes C, Ibrahim O, Baranchuk A, Seifer C. Atrial Fibrillation in Elderly Patients With Implantable Loop Recorders for Unexplained Syncope. Ann Noninvasive Electrocardiol. 2019 May;24(3):e12630
59. Rizos T, Güntner J, Jenetzky E, Marquardt L, Reichardt C, Becker R, et al. Continuous Stroke Unit Electrocardiographic Monitoring Versus 24-Hour Holter Electrocardiography for Detection of Paroxysmal Atrial Fibrillation After Stroke. Stroke. 2012;43(10):2689–94.
60. Hannemann J, Wasser K, Mileva Y, Kleinsang F, Schubert M, Schwedhelm E, et al. Symmetric Dimethylarginine Predicts Previously Undetected Atrial Fibrillation in Patients With Ischemic Stroke. J Am Heart Assoc. 2024;13(17):e034994.
61. Huang W, Lee M, Sung S, Tang S, Chang K, Huang YS, et al. Atrial Fibrillation Trial to Evaluate Real-World Procedures for Their Utility in Helping to Lower Stroke Events: A Randomized Clinical Trial. Int J Stroke. 2020;16(3):300–10.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Wojciech Jędrzej Bieńkowski
Internal Medicine Department
Grochowski Hospital Named after Dr. Rafał Masztak
Warsaw, Poland
e-mail: wbienkowski3@gmail.com

ORCID AND CONTRIBUTIONSHIP

Wojciech Jędrzej Bieńkowski: 0009-0005-1776-8862 A B D E F
Michał Bieńkowski: 0009-0008-8516-0201 A B
Bartłomiej Kusy: 0009-0000-8355-2262 B E
Monika Nowakowska: 0009-0008-2013-3106 A E F
Anna Żerańska: 0009-0003-1208-2007 A B
Patrycja Retman: 0009-0009-6825-5601 A E F
Piotr Kucharczyk: 0009-0005-7382-9690 D E F
Julia Charkot: 0009-0000-1224-3251 E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 05.02.2025
ACCEPTED: 14.05.2025

REVIEW ARTICLE

CONTENTS

Concept of a multifunctional prosthetic and rehabilitation center with an innovative educational component for patients with limb amputation in the context of war in Ukraine

Oksana K. Biloshytska[1,2], Olena Ya. Bespalova[1], Nataliia V. Seminska[1,3], Oleksandr Yu. Galkin[1,4]

[1]NATIONAL TECHNICAL UNIVERSITY OF UKRAINE "IGOR SIKORSKY KYIV POLYTECHNIC INSTITUTE", KYIV, UKRAINE

[2]STATE INSTITUTION OF SCIENCE «CENTER OF INNOVATIVE HEALTHCARE TECHNOLOGIES» STATE ADMINISTRATIVE DEPARTMENT, KYIV, UKRAINE

[3]LIMITED LIABILITY COMPANY «SCIENCE PARK OF ADDITIVE TECHNOLOGIES SIKORSKI CHALLENGE», KYIV, UKRAINE

[4]BIOMEDICINE AND BIOENGINEERING ASSOCIATION, KHARKIV, UKRAINE

ABSTRACT

Aim: The development of a multifunctional prosthetic and rehabilitation center with an innovative educational component for patients with limb amputations.

Materials and Methods: The authors analyzed contemporary literature sources, including descriptions and discussions of the key aspects of developing a multifunctional prosthetic and rehabilitation center for patients with limb amputations.

Conclusions: A modern multifunctional prosthetic and rehabilitation center with an innovative educational component implements a multimodal approach to habilitation and rehabilitation of patients with amputated limbs. This approach encompasses medical-therapeutic interventions, functional physical rehabilitation, psychosocial support, and a mandatory comprehensive educational preparation program for patients. The development of such multidisciplinary centers significantly expands the spectrum of opportunities for effective rehabilitation and subsequent social reintegration of patients into society. The strategic objectives of these centers correlate with global priorities of the healthcare system and align with the integrated medical care model paradigm, which organically combines primary and specialized levels of medical service provision. The strategic objectives of these centers align with the global healthcare priorities and correspond to the paradigm of an integrated healthcare model, which organically combines primary and specialized levels of medical service provision. Implementing a comprehensive approach that integrates accessible therapeutic and preventive services, high-tech rehabilitation methods, and preventive medical supervision enables the Center to not only improve individual health indicators and quality of life for patients with amputations but also achieve broader public health objectives, including reducing the economic burden on healthcare systems associated with suboptimal medical rehabilitation services for individuals with disabilities due to amputations.

KEY WORDS: amputation, artificial limbs, rehabilitation, rehabilitation centers

Wiad Lek. 2025;78(6):1160-1167. doi: 10.36740/WLek/207373 DOI

INTRODUCTION

Limb loss due to combat-related trauma represents a critical public health and medical challenge in multiple global contexts. According to the Limb Loss and Amputation Center in the USA, between 2001 and 2017, at least 1,718 military personnel experienced one or more limb amputations (excluding digit amputations). Notably, approximately 31% of these service members sustained two or more amputations, with explosive injuries accounting for 73% of such cases [1, 2].

In Ukraine, the significance of this medical issue has dramatically escalated with the onset of hostilities in 2014, precipitated by Russian aggression in Eastern Ukraine. Epidemiological investigations reveal that 62,5% of injuries sustained by Anti-Terrorist Operation (ATO) and Joint Forces Operation (JFO) participants involve limb trauma [2]. High-energy weaponry emerges as the primary causative factor, with mine and explosive-related injuries responsible for 74,8% of amputations. Despite improvements in medical intervention strategies, amputation rates remain relatively elevated at approximately 4% (168 cases) [3].

In Ukraine, traumatic injuries sustained during military operations, as well as during aerial attacks and missile strikes on residential and industrial buildings, have become a major concern in terms of both significance and the number of amputations.

Lower limb amputation is a life-altering event that significantly impacts physical function, health, quality of life, and psychosocial well-being. Lower limb ampu-

tations account for 94,8% of all amputations, whereas upper limb amputations constitute only 5,2% [3]. Traumatic lower limb amputations commonly occur among younger individuals, posing unique professional and psychosocial challenges compared to lower limb amputations in older adults caused by peripheral arterial disease or diabetes mellitus.

The necessity of improving healthcare services at all stages of treatment and rehabilitation, as well as developing clear algorithms based on the experience of leading NATO countries, remains a critical and urgent task. In the United States, for example, a veteran amputation prevention program has been established to prevent or delay limb loss [4].

Prosthetic rehabilitation has demonstrated its effectiveness not only in the physical domain—specifically, improving mobility and functional independence—but also in mental health, as it often reduces social isolation and enhances patients' self-confidence. Recent studies emphasize the importance of accessible and high-quality rehabilitation as a global public health priority aimed at supporting societal independence and productivity [5]. By investing in specialized centers, healthcare systems can enhance the quality of life for individuals with amputations and facilitate their full reintegration into society.

The demand for specialized rehabilitation services for individuals with amputations in Ukraine is a pressing healthcare issue due to the recent surge in war-related amputations. Military injuries generate a high demand for specialized care as they frequently result in complex physical and psychological consequences. Research indicates that timely and specialized rehabilitation significantly improves quality of life and functional independence among war survivors [6].

The socioeconomic impact of limb loss is substantial, as individuals with amputations often face decreased employment opportunities and greater dependence on family or social support services, creating economic strain. Numerous studies have quantified the financial consequences of untreated or inadequately treated amputations, demonstrating that comprehensive rehabilitation can reduce these costs and facilitate the return of individuals to economic productivity [7, 8].

According to recent health statistics [9], individuals with amputations encounter significant barriers to employment [10], social integration [11, 12], and mental health stability [13, 14]. Addressing these challenges through the establishment of a rehabilitation center can mitigate socioeconomic costs and support the reintegration of both veterans and civilians into society.

The United States Department of Veterans Affairs has developed clinical guidelines for post-amputation medical care, which include the involvement of multidisciplinary teams. These teams comprise specialists from various medical and rehabilitation disciplines, such as surgeons, physiotherapists, occupational therapists, prosthetists, social workers, psychologists, and others [15].

The International Society for Prosthetics and Orthotics (ISPO) has attempted to standardize key indicators of successful prosthetic rehabilitation. Studies indicate that while physical functioning is often emphasized, psychological and social aspects of the patient experience tend to be overlooked [4].

The World Health Organization (WHO) initiative "Rehabilitation 2030," announced in 2019, underscores that rehabilitation should be an integral part of universal health coverage, ensuring access to essential services for all individuals, regardless of socioeconomic status [15].

Rehabilitation following war-related traumatic limb loss often requires a multidisciplinary approach, encompassing physical rehabilitation, psychological support, and vocational training [16-19]. These services not only aid individuals in restoring physical independence but also alleviate the overall burden on mental health services.

Developing and implementing the concept of a multifunctional prosthetic and rehabilitation center is a crucial task for Ukraine, particularly in the context of war, which has dramatically increased the number of individuals with amputations. These patients often face multifaceted challenges encompassing physical, psychological, social, and economic dimensions. Limb amputation is not only a medical issue but also a significant social challenge, as it affects patients' ability to secure employment, integrate into society, and meet basic needs. The Center will serve not only as a treatment facility but also as a platform for innovation, education, and social integration, ensuring high-quality service delivery in accordance with international standards.

AIM

The aim of the review was to substantiate the necessity of establishing a multifunctional prosthetic and rehabilitation center and to develop the conceptual framework for its operation.

MATERIALS AND METHODS

The authors conducted an extensive analysis of contemporary scientific literature, international rehabilitation standards, and guidelines provided by organizations such as the World Health Organization (WHO), the Inter-

national Society for Prosthetics and Orthotics (ISPO), and the United Nations Convention on the Rights of Persons with Disabilities. The research methodology included a systematic review of global practices in prosthetic rehabilitation, case studies of multidisciplinary rehabilitation centers, and an assessment of socio-economic impacts related to limb loss and rehabilitation interventions.

A combination of qualitative and quantitative research approaches was employed to evaluate the effectiveness of different rehabilitation models, with a specific focus on integrated care, assistive technologies, and the role of psychological and vocational rehabilitation. Additionally, comparative analysis was used to assess the applicability of international rehabilitation models in the Ukrainian healthcare context.

ETHICS

The preparation of the article adhered to the principles of scientific ethics and academic integrity.

REVIEW AND DISCUSSION

The development and implementation of the concept of a Multifunctional Prosthetic and Rehabilitation Center is an urgent task for Ukraine, especially in the context of war, which has significantly increased the number of individuals with amputations. These patients face multidimensional challenges encompassing physical, psychological, social, and economic aspects.

According to the World Health Organization (WHO) [20], rehabilitation is a key element in health restoration, particularly for patients with traumatic injuries. In conflict-affected countries, the absence of effective rehabilitation services often results in long-term public health and economic consequences. In Ukraine, the need for specialized care for individuals with amputations is particularly acute due to the increasing incidence of such cases among both military personnel and civilians.

Under wartime conditions, rehabilitation must extend beyond physical assistance. It should include psychological support, vocational training, and social reintegration opportunities. The experience of other countries that have endured armed conflicts, such as Israel, underscores the importance of a comprehensive approach to the rehabilitation of individuals with amputations. For example, at the Sheba Rehabilitation Center in Israel [21], innovative prosthetic solutions are actively implemented, significantly improving patients' quality of life.

Ukrainian legislation, particularly the Law on Rehabilitation in Healthcare [22], defines the principles of a multidisciplinary approach, integrating medical, social, and psychological support. However, the healthcare system in Ukraine faces significant limitations, including outdated infrastructure, insufficient funding, and a shortage of qualified personnel.

A Multifunctional Rehabilitation Center could serve as the foundation for the development of modern rehabilitation medicine in Ukraine. It would not only provide treatment for individuals with limb loss but also serve as a scientific hub for introducing innovations in prosthetics. Integrating advanced technologies, such as bionic prosthetics and digital telemedicine platforms, offers new possibilities for enhancing rehabilitation quality. Studies [23] demonstrate that bionic prosthetics with artificial intelligence integration provide greater functionality and adaptation for patients.

Additionally, the center would play an educational role, offering training programs for healthcare professionals and patients, thereby contributing to the long-term sustainability of the rehabilitation system.

Special attention should be given to family members of amputees, who often encounter difficulties in providing care. Educational programs for relatives can help create a supportive environment for patients, a factor confirmed by studies published by the American Psychological Association [24].

A WHO report from 2019 [25] highlights the significant gaps in the accessibility of prosthetic rehabilitation services, particularly in low- and middle-income regions, where limited infrastructure and funding constrain specialized care.

Current health indicators reveal a high incidence of comorbidities among individuals with untreated amputations. Lack of prosthetic rehabilitation exacerbates these issues, leading to secondary health complications, such as cardiovascular diseases, due to reduced physical activity. Recent research [26] highlights that comprehensive rehabilitation significantly reduces these risks. However, without adequate funding and infrastructure, these services remain inaccessible to many.

The Ukrainian healthcare system and rehabilitation infrastructure may not be sufficient to meet the needs of the growing number of amputees [27]. Financial constraints represent a major barrier to prosthetic rehabilitation, as current healthcare budgets often prioritize emergency care over long-term rehabilitation. WHO emphasizes the funding gap between acute care and rehabilitation services [28], underlining the necessity for dedicated financial resources to support comprehensive prosthetic rehabilitation.

Analyses [29] indicate that rehabilitation systems benefit significantly from international partnerships [30], which facilitate the implementation of cutting-edge technologies and training programs.

The regulatory framework for prosthetics varies significantly across regions, impacting the standardization of care. In many countries, the lack of clear clinical guidelines for prosthetic services leads to inequities in quality and accessibility. The development of standardized protocols is essential for ensuring consistent, high-quality care for patients. Ukraine's healthcare system may require updated regulations and additional funding to meet the increasing demand for prosthetic rehabilitation.

The analysis of the current situation reveals both high demand and a shortage of prosthetic rehabilitation services. Addressing these issues requires targeted investment in infrastructure, funding, and regulatory standards to ensure access to rehabilitation for all individuals with limb loss.

The primary goal of establishing the Center in Ukraine is to improve the health and well-being of individuals who have undergone limb amputations, as well as to provide education and training for them and their families. Achieving this goal entails addressing a range of pressing healthcare needs, including improving access to rehabilitation services, reducing the frequency of post-amputation complications, and enhancing overall quality of life. The main task of the center is to improve the health and functional capacity of individuals with amputations, particularly military personnel. Studies show that comprehensive, trauma-focused rehabilitation improves long-term functional outcomes and mental health in patients with combat-related injuries [31, 32]. The Center's activities can be directed toward providing high-quality, personalized care, focused on restoring independence, mobility, and psychological resilience among patients.

A key objective of this concept is to increase the availability of services for individuals with amputated limbs. Research on the WHO Rehabilitation Initiative launched in 2019 [15] highlighted the need for universal access to rehabilitation services to improve healthcare, emphasizing that all people, regardless of origin, should have access to necessary resources for optimal functioning and quality of life.

The Center's tasks include facilitating access to specialized care, ensuring timely treatment to reduce secondary complications, and enhancing the psychological resilience of patients. Research emphasizes that achieving these outcomes requires immediate rehabilitation and psychological support [33].

Multifunctional prosthetic rehabilitation centers with an innovative educational component are becoming an integral part of modern medicine. They offer a comprehensive approach to rehabilitation, which includes medical, physical, and psychological support, and educational training for patients with amputations. The development of such centers creates new opportunities for patient rehabilitation and social integration.

The Center's goals align with global health priorities, providing an integrated, holistic model of care that combines primary and specialized medical services. The combination of accessible services, advanced technologies, and preventive care will enable the Center to contribute not only to individual health improvements but also to broader public health objectives, reducing healthcare costs associated with amputations due to inadequate or insufficient treatment of individuals with disabilities.

The Center will provide comprehensive prosthetics and rehabilitation services, combining advanced technologies, a personalized approach, and multidisciplinary collaboration. The Center will also function as a platform for education, research, and social integration, facilitating the return of patients to an active and independent life.

The main components of the Center include:

1. Medical and Rehabilitation Services. The Center will offer specialized medical services related to the recovery of patients following prosthetic fitting, rehabilitation services, and psychological support, focusing on the individual needs of each patient. Key services will include:
   - Assessment and Diagnosis: A comprehensive evaluation of both the physical and psychological condition of patients is crucial for successful prosthetic rehabilitation.
   - Prosthetics and Customization: Improving flexibility, mobility, and user satisfaction, especially with bionic limbs.
   - Physical Rehabilitation: Task-oriented training that enhances motor learning and the integration of prosthetics into daily life.
   - Occupational Therapy: Early integration of occupational therapy significantly enhances long-term functionality and user satisfaction with prosthetics.
   - Psychological Support: Early psychological intervention improves mental health and accelerates the rehabilitation process for individuals with amputations.
2. Innovation and Scientific Research. The Center will serve as a hub for innovation in prosthetics and rehabilitation, continuously exploring new technologies and methodologies:
   - Scientific Research and Development in Prosthetics: Utilizing modern manufacturing technologies to create lightweight, durable, and affordable prostheses.

- 3D Printing: This will significantly change the methods of prosthesis production, enabling the creation of custom solutions for patients with high precision, speed, and cost-efficiency.
- Robotics: Automation of production processes and the integration of bionic components will expand the functional capabilities of prosthetics.
- Intelligent Prostheses: Bionic prosthetics that use neural sensors and artificial intelligence will provide patients with enhanced control and more natural limb movements.
- Virtual Reality Therapy: Creating safe and controlled environments for training and recovery, aiding in rehabilitation.

3. Education and Workforce Training. The Center will be an educational institution offering training programs for professionals, students, and the public:
   - For Specialists: Certified courses, advanced training, thematic improvement cycles, workshops, and masterclasses for healthcare professionals, prosthetists, and rehabilitation specialists, focusing on the latest advancements in prosthetics and patient care.
   - For Patients: Training programs for patients and their families on the use and maintenance of prostheses are essential for maximizing the functionality of devices and supporting overall health.
   - For Higher Education Students and Researchers: Opportunities for internships, scientific research, employment, and participation in multidisciplinary teams.
   - Inclusion and Social Integration. The Center will promote inclusion and remove barriers for individuals with amputations:
   - Accessibility: Ensuring full participation in rehabilitation services for individuals with amputations is critical for their successful rehabilitation.
   - Support Groups: Social connections positively influence rehabilitation outcomes and overall well-being.
   - Inclusive Sports Events: Organizing adaptive sports programs will contribute to physical health and social interaction, which are vital for the comprehensive rehabilitation of individuals with limb loss.
   - Public Awareness Campaigns: Raising awareness and creating a more accepting environment for individuals with amputations, as well as providing education and advocacy.

Quality standards and digital solutions will also play a crucial role in the implementation strategy of the center. The quality standard ISO 9001:2015 [34], which focuses on improving organizational efficiency and patient safety, can be adopted in the management practices of the center to ensure a high level of service.

Given the psychological impact of traumatic amputations, providing comprehensive psychological support services is essential. Recent studies [35, 36] indicate that integrated psychological support in rehabilitation centers improves treatment outcomes and quality of life for patients affected by war-related injuries.

Healthcare professionals require specialized training in traumatology for treating combat-related injuries. Training programs focused on trauma-informed approaches help reduce professional burnout among specialists and improve patient treatment outcomes [37, 38]. Furthermore, creating a supportive working environment for medical staff is crucial for retaining skilled personnel. Enhancing job satisfaction and opportunities for professional development for healthcare workers helps reduce turnover. Research in healthcare [39, 40] shows that well-equipped and supportive workplaces lead to better patient treatment outcomes and contribute to the sustainable functioning of healthcare systems.

By focusing on key aspects such as preventive measures, advanced technologies, quality standards, and support for professionals, aimed at ensuring the ability to meet current and future healthcare needs, the Center will be able to provide comprehensive, effective, and high-quality care for individuals with amputations.

CONCLUSIONS

The establishment of an advanced prosthetics and rehabilitation center focused on restoring mobility, functionality, and quality of life for individuals with amputations will enable their reintegration into society. Individuals who regain mobility and independence through proper rehabilitation and prosthetics experience significant improvements in mental health, social integration, and overall quality of life. Restoring physical and psychological independence through effective rehabilitation significantly reduces the risk of secondary conditions, such as cardiovascular problems caused by a sedentary lifestyle.

By implementing these innovations, the Center can lower the cost of high-quality prosthetics, making them more accessible to a broader population, especially in resource-limited settings. The integration of advanced technologies will lead to substantial improvements in the design and functionality of prosthetics, enabling patients to participate in a wider range of activities, from basic tasks to complex movements. This will set a global precedent for the accessibility and economic efficiency of prosthetics.

The Center aims to achieve measurable improvements in patient health outcomes, service quality, and healthcare efficiency, contributing to broader health goals, such as ensuring equal access to essential rehabilitation services.

The research and practical applications of the Center can not only enhance rehabilitation outcomes at the local level but also influence the development of international policy, setting a global standard for prosthetic and social rehabilitation with an educational component. By collaborating with international organizations, government agencies, and private partners, the Center can impact healthcare delivery models worldwide, ensuring the best possible treatment for individuals with amputations.

REFERENCES

1. Bespalenko AA, Shcheglyuk OI, Kikh AY et al. Algorytm reabilitatsii viyskovosluzhbovtsiv z amputatsiyeyu kintsivok na osnovi multiprofesiynoho ta indyvidual'noho pidkhodu. [Algorithm for the rehabilitation of servicemen with limb amputation based on a multiprofessional and individualized approach]. Ukr J Mil Med. 2020;1(1): 64-72. doi: 10.46847/ujmm.2020.1(1)-064. (Ukrainian) DOI
2. Tsema YV, Khomenko IP, Bespalenko AA et al. Kliniko-statystychne doslidzhennya rivnya amputatsii kintsivky u poranenykh. [Clinical and statistical study of the level of limb amputation in wounded individuals]. Klinichna khirurhiya. 2017;10:51. doi: 10.26779/2522-1396.2017.10.51. (Ukrainian) DOI
3. Ghai S, Hitzig SL, Eberlin L et al. Reporting of Rehabilitation Outcomes in the Traumatic Lower Limb Amputation Literature: Arch Phys Med Rehabil. 2024;105(6):1158–1170. doi: 10.1016/j.apmr.2023.08.028. DOI
4. Heinemann AW, Feuerstein M, Frontera WR et al. Rehabilitation Is a Global Health Priority. Am J Occup Ther. 2020;74(2):7402170010p1-7402170010p3. doi: 10.5014/ajot.2020.742006. DOI
5. McGill G, Wilson G, Caddick N et al. Rehabilitation and transition in military veterans after limb-loss. Disabil Rehabil. 2020;43(23):3315–3322. doi: 10.1080/09638288.2020.1734875. DOI
6. Rodrigues D, Silva R, Castanheira S et al. Needs of Family Caregivers of People with Lower Limb Amputations: A Scoping Review. Behav Sci. 2024;14(4):326. doi: 10.3390/bs14040326. DOI
7. Jo SH, Kang SH, Seo WS et al. Psychiatric understanding and treatment of patients with amputations. Yeungnam Univ J Med. 2021;38(3):194–201. doi: 10.12701/yujm.2021.00990. DOI
8. Tough H, Siegrist J, Fekete C. Social relationships, mental health and wellbeing in physical disability: a systematic review. BMC Public Health. 2017;17(1). doi: 10.1186/s12889-017-4308-6. DOI
9. Lee SP, Chien LC, Chin T et al. Financial difficulty in community-dwelling persons with lower limb loss is associated with reduced self-perceived health and wellbeing. Prosthet Orthot Int. 2020;44(5):290–297. doi: 10.1177/0309364620921756. DOI
10. Miroshnychenko O, Nazarenko V, Stepanenko O et al. Pratsevlashtuvannya osib z invalidnistyu: praktychnyi posibnyk. Za redaktsiyeyu O. Miroshnychenka. [Employment of Persons with Disabilities]. Kyiv: 2023. https://pwd.employers.org.ua/uploads/Працевлаштування%20осіб%20з%20інвалідністю.pdf [Accessed 13 November 2024] (Ukrainian)
11. Sotsialna reintegratsiya veteraniv v Ukraini. Pidsumkovyi analitychnyi zvit. [Social Reintegration of Veterans in Ukraine: Final Analytical Report]. Kyiv; 2023. https://ukraine.iom.int/sites/g/files/tmzbdl1861/files/documents/2024-01/veterans-social_reintegration_ukr.pdf [Accessed 28 October 2024] (Ukrainian)
12. Maslyanikova I, Osmanova A, Davidenko H et al. Sotsialno-psykholohichna pidtrymka osib z invalidnistyu v umovakh viyny: kol. monogr.; za zah. red. I. Maslyanikovoi. [Socio-psychological support for persons with disabilities in wartime conditions]. Kyiv: University "Ukraine"; 2023. doi: 10.36994/978-966-388-674-9-2023-218. (Ukrainian) DOI
13. Pidtrymka mentalnoho zdorov'ya v chasy viyny. [Support for Mental Health in Times of War]. https://niss.gov.ua/news/komentari-ekspertiv/pidtrymka-mentalnoho-zdorovya-v-chasy-viyny [Accessed 07 December 2024] (Ukrainian)
14. Kulkarni A, Luthringer M, Fried A et al. Building a Multidisciplinary Clinic Dedicated to Upper-Extremity Limb Loss. J Hand Surg Am. 2024;49(3):267–274. doi: 10.1016/j.jhsa.2023.11.022. DOI
15. Rehabilitation 2030 initiative. World Health Organization (WHO). https://www.who.int/initiatives/rehabilitation-2030 [Accessed 21 November 2024]
16. Farmaha M, Vilenskyi A, Aleynik V. Kompleksnyi pidkhid do reabilitatsii patsiyentiv z amputovanymy kintsivkamy ta metabolichnymy rozladamy u multydyscyplinarnii komandi blakhodiynoi orhanizatsii «Blahodiinyi fond «SUPERLYUDY». [Comprehensive Approach to the Rehabilitation of Patients with Amputated Limbs and Metabolic Disorders in a Multidisciplinary Team of the Charitable Organization «Charitable Fund 'SUPERHUMANS'»]. International Journal of Endocrinology. 2024;20(5):389–393. doi: 10.22141/2224-0721.20.5.2024.1425. (Ukrainian) DOI
17. Keszler MS, Crandell DM, Morgenroth DC. Rehabilitation of Individuals with Limb Loss due to Trauma. Curr Trauma Rep. 2020;6(2):96–104. doi: 10.1007/s40719-020-00193-8. DOI

18. The Multidisciplinary Approach in Rehabilitation Centers. https://usa.satisform.com/the-multidisciplinary-approach-in-rehabilitation-centers.html [Accessed 22 December 2024]
19. Voropaiev DS, Brizhata IA, Stepanenko OS, Petrenko NV. Particularities of Multidisciplinary Approach in Physical Therapy. Acta Balneol. 2022;64(1);77–82. doi: 10.36740/abal202201116. DOI
20. Rehabilitation. World Health Organization (WHO). https://www.who.int/health-topics/rehabilitation [Accessed 28 August 2024]
21. The Rehabilitation Hospital In Israel. https://www.shebaonline.org/department/rehabilitation-hospital-in-israel/ [Accessed 23 July 2024]
22. Pro reabilitatsiyu u sferi okhorony zdorov'ya. Zakon Ukrainy vid 03.12.2020 № 1053-IX zi zminamy. [On Rehabilitation in the Healthcare Sector. Law of Ukraine dated 03.12.2020 № 1053-IX with amendments]. https://zakon.rada.gov.ua/laws/show/1053-20#Text [Accessed 11 September 2024] (Ukrainian)
23. Chopra S, Emran T. Advances in AI-based prosthetics development-editorial. Int J Surg. 2024;110(8):4538-4542. doi: 10.1097/js9.0000000000001573. DOI
24. American Psychological Association. https://www.apa.org/ [Accessed 23 September 2024]
25. World health statistics 2019: monitoring health for the SDGs, sustainable development goals. World Health Organization (WHO). https://www.who.int/publications/i/item/9789241565707 [Accessed 28 August 2024]
26. Van Helm S, Krops L, Dekker R, Vrieling A. Effectiveness of (Active) Lifestyle Interventions in People With a Lower Limb Amputation: A Systematic Review. Arch Rehabil Res Clin Transl. 2022;4(4):100207. doi: 10.1016/j.arrct.2022.100207. DOI
27. Klymenko IS. Innovative approaches in the rehabilitation of military prisoners of war and residents of temporarily occupied territories. Psychiatry, Neurology and Medical Psychology. 2024;11(23):50–56. doi: 10.26565/2312-5675-2024-23-06. DOI
28. Rehabilitation in health financing: Opportunities on the way to universal health coverage. World Health Organization (WHO). 2023. https://iris.who.int/bitstream/handle/10665/375712/9789240081826-eng.pdf [Accessed 11 September 2024]
29. World Rehabilitation Alliance. World Health Organization (WHO). 2023. https://www.who.int/initiatives/world-rehabilitation-alliance [Accessed 16 October 2024]
30. Meakes S, Enninghorst N, Weaver N et al. Long-term functional outcomes in polytrauma: a fundamentally new approach is needed in prediction. Eur J Trauma Emerg Surg. 2024;50(4):1439–1452. doi: 10.1007/s00068-023-02430-6. DOI
31. Pezzin LE, Dillingham TR, MacKenzie EJ. Rehabilitation and the long-term outcomes of persons with trauma-related amputations. Arch Phys Med Rehabil. 2000;81(3):292–300. doi: 10.1016/s0003-9993(00)90074-1. DOI
32. Roșca AC, Baciu CC, Burtăverde V, Mateizer A. Psychological Consequences in Patients With Amputation of a Limb. An Interpretative-Phenomenological Analysis. Front Psychol. 2022;12:134-142. doi: 10.3389/fpsyg.2021.537493. DOI
33. Bikk A, Sekhon S, Snider D et al. Postoperative Casting of Below-Knee Amputation Reduces Stump Complications. Ann Vasc Surg. 2024;108:10–16. doi: 10.1016/j.avsg.2024.03.011. DOI
34. DSTU ISO 9001:2015 Systemy upravlinnya yakistyu. Vymohy (ISO 9001:2015, IDT). [DSTU ISO 9001:2015 Quality Management Systems. Requirements (ISO 9001:2015, IDT)]. Kyiv: DP "UkrNDNC"; 2016. https://ontu.edu.ua/download/pubinfo/dcc/standard-ISO-9001-2015-ua.pdf [Accessed 12 October 2024]. (Ukrainian)
35. Geurts RM, Reetz D, Willems LH et al. Reamputation Rate, Mortality, and the Incidence of Risk Factors for Ipsilateral Reamputation Among Patients with Dysvascular Major Lower Limb Amputation. Ann Vasc Surg. 2025;110:340–348. doi: 10.1016/j.avsg.2024.07.116. DOI
36. Vus VI, Shkoliar MV, Proskuriako S, Fradelos E. Maintaining the mental health of Ukrainians in time of war: searching for a mechanism to provide a comprehensive system of psychosocial support and mental health awareness. Pol Merkur Lekarski. 2024;52(3), 373–379. doi: 10.36740/merkur202403116. DOI
37. Elisseou S. Trauma-Informed Care: A Missing Link in Addressing Burnout. J Healthc Leadersh. 2023;15:169–173. doi: 10.2147/jhl.s389271. DOI
38. Goldstein E, Chokshi B, Melendez-Torres G et al. Effectiveness of Trauma-Informed Care Implementation in Health Care Settings: Systematic Review of Reviews and Realist Synthesis. The Permanente Journal. 2024;28(1):135–150. doi: 10.7812/tpp/23.127. DOI
39. Dyachuk D, Lishchishina O, Zyukov O, Gandzyuk V. Indykatory Yakosti v Systemakh Okhorony Zdorovia: V Fokusi Natsionalnykh Resursiv Rezultaty, Protsesy ta Produktyvnist [Quality indicators in health care systems: National Resources Focus on Results, Processes and Productivity]. Klinichna ta profilaktychna medytsyna. 2022:1(19):90-101. doi: 10.31612/2616-4868.1(19).2022.11. (Ukrainian) DOI
40. Murray J, Sorra J, Gale B et al. Ensuring Patient and Workforce Safety Culture in Healthcare. PSNet [internet]. Rockville (MD): Agency for Healthcare Research and Quality, US Department of Health and Human Services. 2024. https://psnet.ahrq.gov/perspective/ensuring-patient-and-workforce-safety-culture-healthcare [Accessed 29 August 2024]

This work was supported by a grant from the National Research Foundation of Ukraine No. 149/0073, "Development of the Concept of a Polyfunctional Prosthetic and Rehabilitation Center with an Innovative Educational Component for Patients with Limb Amputations," as part of the scientific research and development program for 2025, and KOLO Charitable Foundation.

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Oksana K. Biloshytska
National Technical University of Ukraine
"Igor Sikorsky Kyiv Polytechnic Institute"
37 Beresteiskyi Ave, 03056 Kyiv, Ukraine
e-mail: biloshytska.oksana@lll.kpi.ua

ORCID AND CONTRIBUTIONSHIP
Oksana K. Biloshytska: 0000-0002-2901-9667 D F
Olena Ya. Bespalova: 0000-0003-1507-1445 A B
Nataliia V. Seminska: 0000-0001-7950-4655 B D
Oleksandr Yu. Galkin: 0000-0002-5309-6099 A E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 15.01.2025
ACCEPTED: 29.05.2025

REVIEW ARTICLE

CONTENTS

Balancing body and health: The impact of obesity on oral health condition

Karolina Trytek-Miś[1], Patrycja Ochman-Pasierbek[2], Kinga Cogiel[2], Magdalena Jaskółka[3]

[1]DENTIST, EURODENT DENTAL CENTER, TARNOW, POLAND

[2]POSTGRADUATE MEDICAL INTERNSHIP, DR. B. HAGER MULTI-SPECIALIST DISTRICT HOSPITAL IN TARNOWSKIE GORY, TARNOWSKIE GORY, POLAND

[3]POSTGRADUATE MEDICAL INTERNSHIP, INDEPENDENT PUBLIC HEALTH CARE CENTER OF THE MUNICIPAL HOSPITAL COMPLEX, CHORZOW, POLAND

ABSTRACT

Aim: This paper explores the relationship between obesity and oral diseases. Early detection and prevention of risk factors are essential for indispensable for promoting long-term health and elevating the quality of life in affected patients.

Materials and Methods: A search of PubMed and Google Scholar on November 10, 2024, retrieving 48 articles from 2016-2024. After screening criteria, 45 articles were included. All authors verified the final content.

Conclusions: Evidence suggests a notable association between obesity and oral health issues, including periodontitis, peri-implantitis, and other gum diseases. Certain research point to the possibility that patients who undergo bariatric surgery could also experience worsening dental health. Inadequate oral hygiene and excessive sugar consumption, along with obesity, contribute to the worsening of dental problems in both children and adults.

Further studies are required to better elucidate the underlying mechanisms of this association, which remains insufficiently explained in literature.

KEY WORDS: obesity, tooth condition, periodontitis, oral health, bariatric surgery

Wiad Lek. 2025;78(6):1168-1175. doi: 10.36740/WLek/204813 DOI

INTRODUCTION

It is well known that an unhealthy lifestyle is the cause of many civilization diseases. Along with hypertension and diabetes, obesity is one of the primary lifestyle-related conditions. Obesity is becoming more common around the world and is increasingly recognized as one of the primary health dangers. It is an escalating global health issue with significant effects not only on general health but also on oral health. Defined as excessive fat storage in adipose tissue, obesity involves larger and more numerous adipocytes. It's classified by BMI: 30 and more for obesity and 25–29.99 for overweight. Recent studies suggests a correlation between oral health and obesity/overweight. This paper explores the relationship between obesity and oral diseases. Early detection and prevention of risk factors are essential for indispensable for promoting long-term health and elevating the quality of life in affected patients.

AIM

This paper discusses the impact of obesity and its connections with the most prevalent oral conditions.

MATERIAL AND METHODS

The materials used in this work were selected through open-access databases such as PubMed and Google Scholar. The literature search was performed November 10, 2024, using the query string "(obesity) AND (oral health) AND (periodontitis) AND (tooth condition)" to retrieve relevant articles. The search criteria covered the years 2016 to 2024, yielding a total of 48 articles. In order to expand the search, we reviewed the reference lists of retrieved publications to capture additional relevant studies, some pre-2016 studies were included as exceptions. The inclusion criteria were the publication type (original research, review, systematic review, case

report, observational studies) and published in English. Following a detailed evaluation, 45 articles met the inclusion criteria and were ultimately included. The final version of the review was read, verified, and revised by all authors. Any unclear parts were discussed as a group and adjusted to ensure accuracy.

REVIEW AND DISCUSSION

If it comes to obesity, it is defined as accumulation of abnormal or excessive fat in the adipose tissue [1] in which the number and size of adipocytes are enlarged [2]. The indicator describing obesity is BMI (Body Mass Index), which is determined using the formula: body weight (in kilograms) divided by height (in meters)^2 [2,3,4,5]. Obesity is classified as having a body mass index (BMI) of 30 kg/m^2 or more, while overweight is classified as having a BMI between 25 and 29.99 kg/m^2 [2]. Recent studies suggests a correlation between oral health and BMI, as both are impacted by shared risk factors, such as diet, genetics, lifestyle choices and socioeconomic conditions [6]. Obesity is caused by an unhealthy diet high in sugars, which promotes the accumulation of excess plaque, leading to the development of various oral health problems, such as gingivitis, periodontitis, and dental caries [7].

According to the World Health Organization, in 2022, one out of every eight people globally was affected by obesity. Additionally, the WHO states that 43% of adults aged 18 and older (43% of men and 44% of women) were overweight in 2022 marking an increase from 1990, when 25% of adults in this age group were overweight. Each year, around 3.4 million people die due to obesity and overweight [3, 6].

ASSOCIATIONS BETWEEN OBESITY AND PERIODONTAL DISEASES

The association between obesity and periodontitis is a frequently discussed topic in the literature. In research conducted by Leena Alsalihi et al., it was found that periodontitis was highly prevalent (97%) among obese patients [8]. Periodontitis is an inflammatory disorder of the tissues that support the teeth, caused by certain groups of microorganisms. This leads to progressive destruction of the gingival tissue, periodontal ligament, cementum and alveolar bone. [9,10]. The chronic inflammatory condition caused by periodontitis can result in various systemic issues, including, for example, cardiovascular disease, osteoarthritis, and type 2 diabetes [9, 11, 12]. Obesity, as defined in the introduction, is an excess of fat in the adipose tissue. The adipose tissue located around the visceral organs (visceral adiposity) secretes specific proteins known as adipokines. These proteins are classified to two groups: pro-inflammatory mediators: leptin, resistin, visfatin and anti-inflammatory mediators: adiponectin and omentin-1 [9]. Obesity results in higher production of pro-inflammatory adipokines and reduced synthesis of anti-inflammatory adipokines [2, 13], leading to an imbalance between them and, consequently, a state of low-grade inflammation [2, 14, 15].

Checa-Ros et al. described, that there is an inverse relationship between the level of adiponectin and periodontitis [9]. Adiponectin is a strong inhibitor of osteoclasts, so its low levels lead to the exacerbation of periodontitis [16, 17]. What is more, reduced salivary omentin-1 levels were observed in patients with chronic periodontitis, correlating with elevated periodontal parameters, whereas increased salivary omentin-1 levels following non-surgical periodontal therapy were associated with improvements in periodontal health. [9]. As far as pro-inflammatory adipokines are concerned, leptin impairs the regenerative ability of periodontal ligament cells and additionally activates the secretion of proinflammatory cytokines, such as Tumor Necrosis Factor Alpha (TNF-α) and IL-6 which are recognized as mediators of tissue damage [9]. Resistin affects the metabolism of soft and hard tissues in the periodontium by decreasing alkaline phosphatase activity and markers associated with bone tissue and matrix development [9]. Visfatin could enhance periodontal inflammation and bone degradation through the production of matrix metalloproteinase-1 (MMP-1) and chemokine ligand 2 (CCL2). [9, 18]. Obesity is associated with an increase in waist circumference. Recker EN et al. identified a positive correlation between waist circumference and the severity of periodontitis in their study [19]. Ling Liu and Lin Yu Xia et al. also found a similar relationship, stating that with each 1-unit increase in waist circumference, the incidence of periodontitis rises by 1% [20]. On the other hand, Leena Alsalihi et al. noted a positive correlation between waist circumference and periodontitis in men, but no such correlation was found between waist circumference and periodontitis in women [8]. If additional studies confirm the connection between waist circumference and the severity of periodontitis, waist circumference could become an important indicator for monitoring the progression of periodontitis [21].

The study by L. Martens et al. states that, among children and adolescents, there is a positive correlation between obesity/overweight and various periodontal issues, including increased plaque and calculus accumulation, gingivitis, probing pocket depth (>4 mm), and a higher presence of bacterial oral microbiota.

What is more, age (17–21 years) and gender (male) were factors that positively impacted the risk of periodontal disease in obese/overweight children [1].

PREGNANCY, OBESITY AND PERIODONTITIS

The prevalence of obesity and excessive weight gain are frequently observed issues in the context of pregnancy. Elevated hormones can compromise connective tissue remodeling, which may raise inflammation and bacterial growth in periodontal tissues, heightening the risk of periodontal diseases in pregnancy [22-24]. Over the past few years, research has focused on confirming or rejecting a potential association between obesity in pregnancy and periodontitis. In their 2018 publication, Gomes-Filho et al. demonstrated that the association was found to be statistically non-significant. Periodontitis prevalence was observed at 17.24% using the Gomes-Filho, et al. criteria and at 66.92% according to the Center For Disease Prevention and Control and American Academy of Periodontology (CDC/AAP) criteria [25]. However, an extensive systematic review and meta-analysis by Foratori-Junior, et al. did not substantiate these findings in 2022. The study found a positive link between obesity/overweight and periodontitis, showing that, an average 61.04% of overweight or obese women also presenting with periodontitis [23]. Additional studies have also established a relationship between excess weight and periodontitis in pregnancy, showing a more pronounced connection in overweight pregnant women who suffer from both tooth loss and periodontitis [22].

GINGIVAL INFLAMMATION AND OBESITY

Gingivitis refers to an inflammatory condition that develops from the patient's immune response interacting with the biofilm of dental plaque. This inflammatory process can be reversed with a reduction in plaque presence [26, 27]. Both periodontitis and gingivitis arise from the same mechanism of inflammation, however gingivitis does not lead to periodontitis in every case [26, 28]. Evidence supporting the thesis that elevated BMI leads to a greater incidence of gingivitis includes studies indicating increased salivary cytokine concentrations in obese patients compared to those with overweight or normal statuses [29]. Such cytokines contribute to chronic systemic inflammation, which potentially weakens the immune system and predisposes individuals to infections [26,30]. It is noteworthy to mention that the systematic review and meta-analysis by da Silva et al. indicated that obesity is associated with an increased level of gingivitis among patients diagnosed with periodontitis against to those without obesity [26].

ORAL MICROBIOTA IN OBESE PATIENTS

Porphyromonas gingivalis, *Treponema denticola* and *Tannerella forsythia* are a group of microorganisms located in the subgingival biofilm that induce the long-term inflammatory condition known as periodontitis [2]. Al-Rawi and Al-Marzooq observed that obese individuals had notably higher levels of *Tannerella forsythia*, *Fusobacterium spp*., and *Porphyromonas gingivalis* compared to those who were not obese, but further studies are required to clarify whether obesity leads to the overgrowth of these or other pathogenic microorganisms, contributing to periodontal damage [2, 31]. Tam et al. also recorded a variation in the composition of the oral microbiota between obese and nonobese individuals [2, 32].

The study by Fanny Le Sage et al. described how lipopolysaccharide (LPS) from *Porphyromonas gingivalis* influences the release of inflammatory adipokines. Their findings indicate that *P. gingivalis* LPS can modify the inflammatory condition of adipocytes by interfering with their adipokine secretion, leading to a decrease in adiponectin release, which is recognized as an anti-inflammatory factor inversely correlated with body fat mass [33].

OBESITY, SALIVA COMPOSITION AND ORAL HEALTH

It is widely known that saliva could be a potential source of biomarkers that may have associations with oral diseases. The markers analyzed in recent years have been assembled in Table 1. Recker et al. reported a positive association between body fat percentage and levels of Granzyme B and negative association between levels of sCD40L and BMI, but none of those correlations showed statistical significance after multiple comparison correction [19]. Some studies report elevated levels of interleukins in obese patients [29,30]. Al-Ameri et al. performed a study that examined Thy-1 (CD90) levels across four patient groups (obese, obese with periodontitis, healthy, and those with periodontitis). They found that periodontitis leads to higher salivary Thy-1 levels, independent of obesity [34].

BARIATRIC SURGERY

As the most effective approach to treating morbid obesity, bariatric surgery not only benefits individuals with related conditions, including hypertension,

Table 1. Biological salivary markers of periodontitis and/or obesity

Study	Biomarkers	Correlation with obesity
Recker et al. [19]	• sCD40L • Granzyme B • Interleukin-1 receptor antagonist (IL-1ra) • Alpha-fetoprotein (AFP)	• Positive association between body fat percentage and levels of Granzyme B • Negative association between levels of sCD40L and BMI
Doğan et al. [29]	• IL-6 • IL-10	• IL-6 levels in saliva were elevated in obese patients • Positive association between BMI and IL-6 levels • Negative association between IL-10 levels in the gastro-intestinal tract and saliva
Vohra et al. [30]	• IL-6 • IL-1β	• Significant differences in periodontal clinical measures and salivary IL-1β and IL-6 were found between class I of obese and classes II and III (between class II and III values were found to be similar)
Al-Ameri et al. [34]	• Thy-1 (CD90)	• Periodontal inflammation increases salivary Thy-1 levels, independent of obesity status.

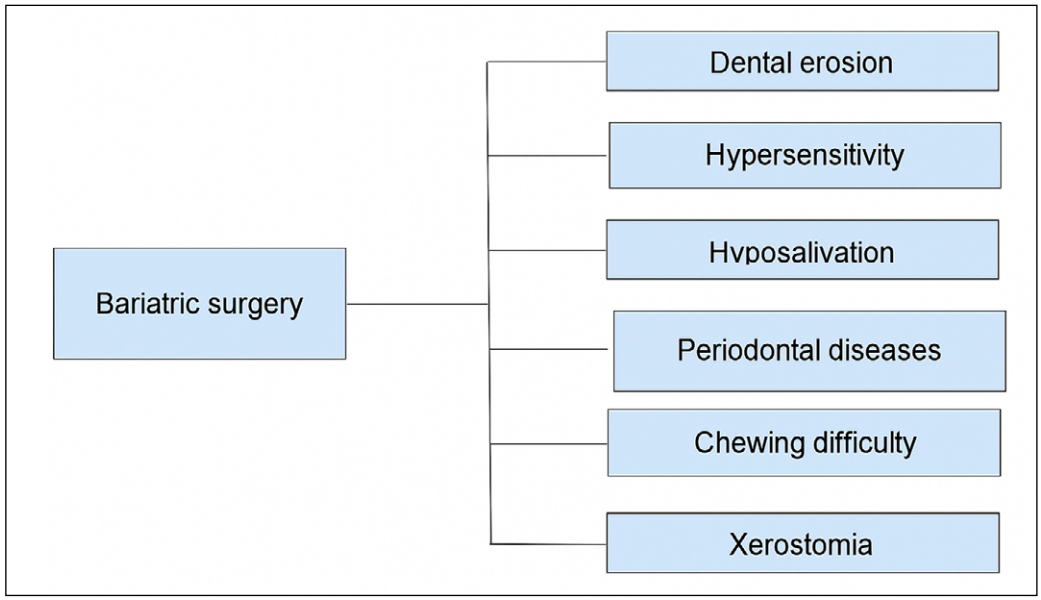

Fig. 1. Oral conditions that can potentially be affected by bariatric surgery [35-37]

diabetes, and sleep apnea but also enhances patients' quality of life [35-37]. According to certain studies, undergoing bariatric surgery could potentially lead to a decline in dental health [37-39]. Figure1 shows oral conditions that can potentially be affected by bariatric surgery. Alterations in the rate of salivary flow may constitute one of the mechanisms influencing oral cavity health. A decline in salivary flow is linked to an increased proliferation of microorganisms. In a cohort study conducted by Hashizume, et al. on 27 morbidly obese patients, documented a rise in mutans streptococci levels in the saliva of these patients six months post-bariatric surgery, as compared to the pre-operative baseline [36]. Moreover, de S Porcelli, et al., observed that bariatric surgery increases the risk of tooth erosion in patients [39]. It is worth noting that not all studies confirm the effect of bariatric surgery on dental health. Ferraz, et al., in an extensive systematic review and meta-analysis, determined that for patients undergoing bariatric surgery, the rates of missing teeth and caries remain unaffected [35]. This shows how important additional studies are for reaching unified conclusions.

PERI-IMPLANTITIS

Lost teeth are increasingly replaced with dental implants. Due to the increase in life expectancy, the percentage of elderly patients who decide to have implants is growing. This implies an increase in the number of side effects of such a procedure [40]. Despite the effectiveness and high safety index, the incidence of complications such as peri-implantitis and crestal bone loss is escalating [12, 40, 41]. According

to medical literature, this complication may affect up to 50% of implanted dental implants [41]. Peri-implantitis is a destructive inflammation around a tooth implant caused by numerous bacteria. It damages both soft and hard tissues surrounding the implants, causing bone loss [40, 41]. Untreated peri-implantitis may cause implant loss and even lead to permanent damage to the jaw bone [40]. Unfortunately, due to the lack of targeted and effective treatment, reducing the risk factors of peri-implantitis in patients is very important during treatment [12, 40, 41]. Many risk factors contribute to the development of the disease [12]. The authors mention, among others: smoking, drugs, old age, depression, and environmental factors [41]. Obesity, metabolic syndrome and diabetes are among the main modifiable factors that increase the risk of developing peri-implantitis. Inflammation and oxidative stress are mediators of metabolic disorders in the body, these mediators increase the incidence of peri-implantitis [40].The relationship between obesity and an increased risk of developing inflammation around the implant is confirmed by Vorha's study. This study shows that people with normal body weight are less susceptible to developing inflammation around the implant than people with obesity. In the future, the number of patients with metabolic disorders will increase, which may elevate the risk of complications related to dental implants [41]. Appropriate treatment of obesity and other metabolic disorders and quitting smoking are the main factors that should be taken into account when planning dental implantation and treatment of peri-implantitis [40].

ASSOCIATIONS AMONG OBESITY AND TOOTH LOSS

Tooth loss may be due to periodontal disease caused by chronic inflammation. Obesity contributes to the development of such chronic inflammation and the increase in markers such as C-reactive protein (CRP) [42, 43]. According to the authors, it has been shown that obesity is a modifiable risk factor for tooth loss and there is a connection between obesity and an increased number of lost teeth [42, 43]. When talking about general obesity, it should be noted that central obesity itself also influences the development of systemic inflammatory diseases. Therefore, it will also predispose to the development of caries, periodontal diseases and ultimately lead to tooth loss. Studies have shown that patients with central obesity also have an increased risk of tooth loss. The impact of both central and general obesity is important and should become a key element in oral health prevention [42].

OBESITY AND ORAL HEALTH IN PAEDIATRIC PATIENTS

Childhood obesity has reached epidemic proportions worldwide, with its prevalence continuing to rise [1]. According to data published by the World Health Organization (WHO) in 2022, 160 million children and adolescents aged 5-19 suffered from obesity [3]. Some cross-sectional studies indicate that overweight and obese children and adolescents experience more dental caries in permanent teeth, greater plaque accumulation, and increased gingival inflammation. Additionally, they have lower saliva flow rates and reduced buffering capacity compared to children of normal weight [44]. Often first observes in adults but typically beginning earlier in life in children. Among children and adolescents, plaque-induced gingivitis is the most commonly encountered periodontal disease. The prevalence of gingivitis in children can be as high as, or even exceed, that of dental caries, yet it has not received the same level of attention regreading its long-term effects on overall health [1].

Meta-analyses, which incorporated both descriptive and quantitative data, have revealed a positive association between obesity and the prevalence of periodontal diseases. Several theories have been proposed to explain the biological interactions between obesity and periodontal diseases. These include alterations in pro-inflammatory and immune responses, insulin resistance, changes in lipid profiles, modifications of the immune system, heightened activation of macrophages, impaired microvascular function, physiological responses to psychosocial stress, and the release of pro-inflammatory molecules from adipose tissue, such as TNF-α, IL-6, and C-reactive protein. Despite these insights, the precise molecular and cellular mechanisms underlying these associations remain unclear, and further research is needed to deepen our understanding of these processes. Such research could provide valuable insights into potential targets for prevention and treatment [1].

Studies have not demonstrated a clinically significant association between oral health factors, overweight/obesity, and stress variables [44, 45]. However, a significant association exists between obesity and periodontal disease in children. Pediatric dentists should be mindful of potential periodontal changes related to obesity, recognizing them as a possible health risk [1].

Given the significance of overweight and obesity as major public health concerns, both medical and dental professionals should assess health-related behaviors and the connections between oral and overall health. Additionally, they should promote interdisciplinary communication to identify and address early signs of dental and periodontal diseases in children and adolescents [4]

CONCLUSIONS

The aim of this review was to collect and evaluate existing data on the relationship between obesity and oral health. As a result, it was found that there is a significant association between obesity and the development of various oral health diseases, such as gum diseases, periodontitis, peri-implantitis. A diet high in sugar, combined with poor oral hygiene and obesity, promotes the occurrence of dental issues both in adults and children. Nevertheless, additional studies are needed to better understand the mechanisms of this relationship. Future studies should also consider the development of more effective preventive strategies that could help prevent oral diseases in obese individuals.

REFERENCES

1. Martens L, De Smet S, Yusof MY, Rajasekharan S. Association between overweight/obesity and periodontal disease in children and adolescents: a systematic review and meta-analysis. Eur Arch Paediatr Dent. 2017 Apr;18(2):69-82. doi: 10.1007/s40368-017-0272-1 DOI
2. Jepsen S, Suvan J, Deschner J. The association of periodontal diseases with metabolic syndrome and obesity. Periodontol 2000. 2020 Jun;83(1):125-153. doi: 10.1111/prd.12326 DOI
3. Obesity and overweight. WHO [online] https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [Access: 10 December 2024].
4. Kesim S, Çiçek B, Aral CA, Öztürk A, Mazıcıoğlu MM, Kurtoğlu S. Oral Health, Obesity Status and Nutritional Habits in Turkish Children and Adolescents: An Epidemiological Study. Balkan Med J. 2016 Mar;33(2):164-72. doi: 10.5152/balkanmedj.2016.16699 DOI
5. Gerber FA, Sahrmann P, Schmidlin OA, Heumann C, Beer JH, Schmidlin PR. Influence of obesity on the outcome of non-surgical periodontal therapy - a systematic review. BMC Oral Health. 2016 Sep 2;16(1):90. doi: 10.1186/s12903-016-0272-2 DOI
6. Issrani R, Reddy J, Bader AK, Albalawi RFH, Alserhani EDM, Alruwaili DSR, Alanazi GRA, Alruwaili NSR, Sghaireen MG, Rao K. Exploring an Association between Body Mass Index and Oral Health-A Scoping Review. Diagnostics (Basel). 2023 Feb 27;13(5):902. doi: 10.3390/diagnostics13050902 DOI
7. Deszczyńska K, Górska R, Haładyj A. Clinical condition of the oral cavity in overweight and obese patients. Dent Med Probl. 2021 Apr-Jun;58(2):147-154. doi: 10.17219/dmp/127873 DOI
8. Alsalihi L, Bain C, Milosevic A, Hassan A, Janahi A, Sivaramakrishnan G. Prevalence of periodontitis in obese patients in Bahrain: a cross-sectional study. BMC Oral Health. 2021 Jul 24;21(1):376. doi: 10.1186/s12903-021-01720-y DOI
9. Checa-Ros A, Hsueh WC, Merck B, González-Torres H, Bermúdez V, D'Marco L. Obesity and Oral Health: The Link Between Adipokines and Periodontitis. touchREV Endocrinol. 2024 Apr;20(1):25-31. doi: 10.17925/EE.2024.20.1.7 DOI
10. Gasner NS, Schure RS. Periodontal Disease. 2023 Apr 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32119477
11. Carvalho R, Botelho J, Machado V, Mascarenhas P, Alcoforado G, Mendes JJ, Chambrone L. Predictors of tooth loss during long-term periodontal maintenance: An updated systematic review. J Clin Periodontol. 2021 Aug;48(8):1019-1036. doi: 10.1111/jcpe.13488 DOI
12. Darby I. Risk factors for periodontitis & peri-implantitis. Periodontol 2000. 2022 Oct;90(1):9-12. doi: 10.1111/prd.12447 DOI
13. Zhu J, Guo B, Gan X, Zhang L, He Y, Liu B, Chen X, Zhang S, Yu H. Association of circulating leptin and adiponectin with periodontitis: a systematic review and meta-analysis. BMC Oral Health. 2017 Jun 29;17(1):104. doi: 10.1186/s12903-017-0395-0 DOI
14. Adamczak M, Wiecek A. The adipose tissue as an endocrine organ. Semin Nephrol. 2013 Jan;33(1):2-13. doi: 10.1016/j.semnephrol.2012.12.008 DOI
15. Krysiak R, Handzlik-Orlik G, Okopien B. The role of adipokines in connective tissue diseases. Eur J Nutr. 2012 Aug;51(5):513-28. doi: 10.1007/s00394-012-0370-0 DOI
16. Kubić-Filiks B, Szymańska J. Problemy stomatologiczne u pacjentów z otyłością [Dental problems in obese patients]. Pediatr Med Rodz. 2018;14:386-391 [Polish]. doi: 10.15557/PiMR.2018.0049 DOI
17. Ryba B, Pytko-Polonczyk J. Molecular aspects of periodontitis in obese patients - Review of literature. Czasopismo Stomatologiczne. 2013;66:246-255. doi: 10.5604/00114553.1035089 DOI
18. Nokhbehsaim M, Eick S, Nogueira AV, Hoffmann P, Herms S, Fröhlich H, Jepsen S, Jäger A, Cirelli JA, Deschner J. Stimulation of MMP-1 and CCL2 by NAMPT in PDL cells. Mediators Inflamm. 2013;2013:437123. doi: 10.1155/2013/437123. DOI
19. Recker EN, Brogden KA, Avila-Ortiz G, Fischer CL, Pagan-Rivera K, Dawson DV, Smith KM, Elangovan S. Novel biomarkers of periodontitis and/or obesity in saliva-An exploratory analysis. Arch Oral Biol. 2015 Oct;60(10):1503-9. doi: 10.1016/j.archoralbio.2015.07.006 DOI
20. Liu L, Xia LY, Gao YJ, Dong XH, Gong RG, Xu J. Association between Obesity and Periodontitis in US Adults: NHANES 2011-2014. Obes Facts. 2024;17(1):47-58. doi: 10.1159/000534751 DOI
21. Xu L, Liu Y, Zhao C, Wang J, Zhou H. Association between weight-adjusted waist index and periodontitis: A population-based study. PLoS One. 2024 Jun 6;19(6):e0305010. doi: 10.1371/journal.pone.0305010 DOI

22. Batista JET, Figueiredo ACMG, Souza ES, et al. Excessive weight in pregnant women increases the chance of diagnosing periodontitis combined with tooth loss. J Periodontol. 2024 Nov;95(11):1097-1108. doi: 10.1002/JPER.23-0745 DOI
23. Foratori-Junior GA, Pereira PR, Gasparoto IA, de Carvalho Sales-Peres SH, Storniolo de Souza JM, Khan S. Is overweight associated with periodontitis in pregnant women? Systematic review and meta-analysis. Jpn Dent Sci Rev. 2022 Nov;58:41-51. doi: 10.1016/j.jdsr.2022.01.001 DOI
24. Silva de Araujo Figueiredo C, Gonçalves Carvalho Rosalem C, Costa Cantanhede AL, Abreu Fonseca Thomaz ÉB, Fontoura Nogueira da Cruz MC. Systemic alterations and their oral manifestations in pregnant women. J Obstet Gynaecol Res. 2017 Jan;43(1):16-22. doi: 10.1111/jog.13150 DOI
25. Gomes-Filho IS, Batista JET, Trindade SC, et al. Obesity and periodontitis are not associated in pregnant women. J Periodontal Res. 2020 Jan;55(1):77-84. doi: 10.1111/jre.12690 DOI
26. da Silva FG, Pola NM, Casarin M, Silva CFE, Muniz FWMG. Association between clinical measures of gingival inflammation and obesity in adults: systematic review and meta-analyses. Clin Oral Investig. 2021 Jul;25(7):4281-4298. doi: 10.1007/s00784-021-03961-1 DOI
27. Chapple ILC, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol. 2018 Jun;45 Suppl 20:S68-S77
28. Chapple IL, Van der Weijden F, Doerfer C, et al. Primary prevention of periodontitis: managing gingivitis. J Clin Periodontol. 2015 Apr;42 Suppl 16:S71-6. doi: 10.1111/jcpe.12366 DOI
29. Doğan GE, Toraman A, Şebin SÖ, Doğan Ç, Güngör A, Aksoy H, Asutay H. Salivary IL-6 and IL-10 levels in subjects with obesity and gingivitis. Am J Dent. 2016 Oct;29(5):261-265
30. Vohra F, Akram Z, Bukhari IA, Sheikh SA, Riny A, Javed F. Comparison of Periodontal Inflammatory Parameters and Whole Salivary Cytokine Profile Among Saudi Patients with Different Obesity Levels. Int J Periodontics Restorative Dent. 2018 Nov/Dec;38(6):e119-e126. doi: 10.11607/prd.3411 DOI
31. Al-Rawi N, Al-Marzooq F. The Relation between Periodontopathogenic Bacterial Levels and Resistin in the Saliva of Obese Type 2 Diabetic Patients. J Diabetes Res. 2017;2017:2643079. doi: 10.1155/2017/2643079 DOI
32. Tam J, Hoffmann T, Fischer S, Bornstein S, Gräßler J, Noack B. Obesity alters composition and diversity of the oral microbiota in patients with type 2 diabetes mellitus independently of glycemic control. PLoS One. 2018 Oct 1;13(10):e0204724. doi: 10.1371/journal.pone.0204724 DOI
33. Le Sage F, Meilhac O, Gonthier MP. Porphyromonas gingivalis lipopolysaccharide induces pro-inflammatory adipokine secretion and oxidative stress by regulating Toll-like receptor-mediated signaling pathways and redox enzymes in adipocytes. Mol Cell Endocrinol. 2017 May 5;446:102-110. doi: 10.1016/j.mce.2017.02.022 DOI
34. Al-Ameri HW, Shetty S, Rahman B, Gopalakrishnan ARK, Ismail AA, Acharya AB. Evaluation of salivary Thy-1 in health, periodontitis, and obesity. Oral Dis. 2024 May;30(4):2670-2677. doi: 10.1111/odi.14652 DOI
35. Ferraz AX, Gonçalves FM, Ferreira-Neto PD, et al. Impact of bariatric surgery on oral health: a systematic review and meta-analysis. Clin Oral Investig. 2023 May;27(5):1869-1884. doi: 10.1007/s00784-023-04959-7 DOI
36. Hashizume LN, Bastos LF, Cardozo DD, et al. Impact of Bariatric Surgery on the Saliva of Patients with Morbid Obesity. Obes Surg. 2015 Aug;25(8):1550-5. doi: 10.1007/s11695-015-1741-4 DOI
37. Quintella MCM, Farias TMCP, SoutoMaior JR, Casado BGDS, Leão RS, Moraes SLD. Relationship between bariatric surgery and dental erosion: a systematic review. Surg Obes Relat Dis. 2020 Sep;16(9):1283-1290. doi: 10.1016/j.soard.2020.04.044 DOI
38. de Moura-Grec PG, Yamashita JM, Marsicano JA, et al. Impact of bariatric surgery on oral health conditions: 6-months cohort study. Int Dent J. 2014 Jun;64(3):144-9. doi: 10.1111/idj.12090 DOI
39. de S Porcelli IC, Roma CC, Nunes MCP, Maciel SM, Pascotto RC Effects of Bariatric Surgery on The oral Health of Patients. Int J Dent Oral Health 2016;2(2). doi http://dx.doi. org/10.16966/2378-7090.181
40. Gasmi Benahmed A, Gasmi A, Tippairote T, Mujawdiya PK, Avdeev O, Shanaida Y, Bjørklund G. Metabolic Conditions and Peri-Implantitis. Antibiotics (Basel). 2022 Dec 29;12(1):65. doi: 10.3390/antibiotics12010065 DOI
41. de Oliveira PGFP, Bonfante EA, Bergamo ETP, et al. Obesity/Metabolic Syndrome and Diabetes Mellitus on Peri-implantitis. Trends Endocrinol Metab. 2020 Aug;31(8):596-610. doi: 10.1016/j.tem.2020.05.005 DOI
42. Kang J, Smith S, Pavitt S, Wu J. Association between central obesity and tooth loss in the non-obese people: Results from the continuous National Health and Nutrition Examination Survey (NHANES) 1999-2012. J Clin Periodontol. 2019 Apr;46(4):430-437. doi: 10.1111/jcpe.13091 DOI
43. Meisel P, Holtfreter B, Völzke H, Kocher T. Sex Differences of Tooth Loss and Obesity on Systemic Markers of Inflammation. J Dent Res. 2014 Aug;93(8):774-9. doi: 10.1177/0022034514535604 DOI
44. Panagiotou E, Agouropoulos A, Vadiakas G, Pervanidou P, Chouliaras G, Kanaka-Gantenbein C. Oral health of overweight and obese children and adolescents: a comparative study with a multivariate analysis of risk indicators. Eur Arch Paediatr Dent. 2021 Oct;22(5):861-868. doi: 10.1007/s40368-021-00643-0 DOI

45. Schmidt J, Strecker P, Kreuz M, et al. Stress-related hormones in association with periodontal condition in adolescents-results of the epidemiologic LIFE Child study. Clin Oral Investig. 2019 Apr;23(4):1793-1802. doi: 10.1007/s00784-018-2599-3 DOI

CONFLICT OF INTEREST
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Patrycja Ochman-Pasierbek
Postgraduate Medical Internship,
Dr. B. Hager Multi-Specialist District Hospital in Tarnowskie Góry,
Tarnowskie Góry, Poland
e-mail: patrycja.ochman09@gmail.com

ORCID AND CONTRIBUTIONSHIP
Karolina Trytek-Miś: 0009-0008-1317-6538 A B D F
Patrycja Ochman-Pasierbek: 0009-0008-0125-2564 A B D F
Kinga Cogiel: 0009-0000-6456-2887 E F
Magdalena Jaskółka: 0009-0004-1522-3976 D F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.02.2025
ACCEPTED: 02.06.2025

REVIEW ARTICLE

CONTENTS

Macrophages and their involvement in mandibular reparative osteogenesis: Current insights

Igor S. Brodetskyi [1], Vladislav A. Malanchuk [1], Nataliia M. Savielieva [2], Mykhailo S. Myroshnychenko [2], Yevheniia A. Hromko [2], Andrii A. Boiko [1], Liudmyla O. Brodetska [1], Yaroslava A. Kulbashna [1], Sergey B. Brodetskyi [3], Halyna V. Zhurakovska [1]

[1]BOHOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2]KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE
[3]TARAS SHEVCHENKO NATIONAL UNIVERSITY OF KYIV, KYIV, UKRAINE

ABSTRACT

Aim: The purpose of this study was to analyze current literature data regarding the involvement of the macrophage population in the processes of reparative osteogenesis in the mandible.

Materials and Methods: The authors conducted a review of scientific sources available in databases such as PubMed, Web of Science, Scopus, Google Scholar, and ResearchGate.

Conclusions: It was shown by the authors that macrophages play a crucial role at all stages of reparative osteogenesis in the mandible. Their high degree of plasticity enables them to adapt to changes in the microenvironment by dynamically shifting their phenotype (from M1 to M2 and vice versa). Alterations in the morphofunctional state of macrophages and an imbalance between M1 and M2 populations under pathological conditions lead to disruptions in the reparative osteogenesis process. Currently, macrophages are recognized as key therapeutic targets for modulating reparative osteogenesis in cases of mandibular bone pathology.

KEY WORDS: macrophages, mandible, reparative osteogenesis, literature data analysis

Wiad Lek. 2025;78(6):1176-1181. doi: 10.36740/WLek/205957 DOI

INTRODUCTION

Reparative osteogenesis in the mandible of humans and experimental animals is a complex process resulting in the restoration of the integrity and function of bone tissue. Bone tissue, as is well known, is one of the few types of tissue capable of healing without the formation of fibrous scar tissue. The process of reparative osteogenesis is characterized by the sequential progression through the inflammatory, proliferative-reparative, and remodeling phases [1]. An important role in both the initial and final stages of reparative osteogenesis is assigned to immunocompetent cells, among which macrophages are considered key players [2]. It has been proven that their effects on reparative osteogenesis are mediated by more than 100 secretory products. Investigating the role of the macrophage population in mandibular reparative osteogenesis remains highly relevant, as it expands the understanding of the underlying mechanisms and provides a foundation for improving existing treatment methods and developing new therapeutic approaches.

AIM

The purpose of this study was to analyze current literature data regarding the involvement of the macrophage population in the processes of reparative osteogenesis in the mandible.

MATERIALS AND METHODS

The authors conducted a review of scientific sources available in databases such as PubMed, Web of Science, Scopus, Google Scholar, and ResearchGate. Article selection was based on their relevance to the purpose of the study.

REVIEW AND DISCISSION

The cellular composition of mandibular bone tissue includes various macrophage populations, among which osteoclasts, osteomacs, resident macrophages of the periosteal and endosteal bone surfaces, and bone marrow macrophages are distinguished [3].

Numerous studies have demonstrated that macrophages are plastic cells capable of altering their phenotype in response to various environmental factors. Currently, macrophages are classified into three main states or phenotypes: M0, M1, and M2. Their biological plasticity underlies their ability to regulate intercellular interactions, coordinate reparative processes, and serve as targets for immune-mediated therapies in pathological conditions affecting bone tissue [4]. Also, M2 macrophages include several phenotypes, such as M2a, M2b, M2c, and M2d. M1 macrophages, induced by classical activation signals such as interferon-γ (IFN-γ), lipopolysaccharide (LPS), and tumor necrosis factor-α (TNF-α), are characterized by pro-inflammatory activity. In contrast, macrophages polarize into the M2 phenotype in response to alternative activation signals, including interleukins (IL) (IL-4, IL-10, IL-13) and exhibit anti-inflammatory properties [5].

Owing to their phenotypic flexibility, macrophages adapt their functions to the microenvironment, playing a key role in regulating tissue homeostasis and osteogenesis, particularly under conditions of injury [5].

It has been demonstrated that under physiological conditions, M2 macrophages predominate to maintain bone tissue homeostasis. In cases of mandibular bone injury, the distribution of macrophage phenotypes varies depending on the stage of reparative osteogenesis. During the first week following trauma, M1 macrophages prevail. They initiate the cascade of the inflammatory response, recruit immune cells, and secrete IL-1α, IL-1β, IL-6, monocyte chemoattractant protein-1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), IL-12, IL-23, tumor necrosis factor-α (TNF-α), and inducible nitric oxide synthase (iNOS). By the end of the inflammatory phase, M2 macrophages become predominant, producing arginase-1, IL-4, IL-10, tumor necrosis factor-β (TNF-β), and promoting angiogenesis, mesenchymal stem cell migration, and osteoblast differentiation [1, 6].

Available experimental and clinical data confirm that impaired functional activity of the macrophage pool or an imbalance between M1 and M2 macrophage populations significantly reduces the effectiveness of reparative osteogenesis [7, 8].

Reparative osteogenesis in the mandible is characterized by the sequential progression through the inflammatory, proliferative-reparative, and remodeling stages, which are regulated by integrated mechanisms of inflammation, regeneration, and tissue remodeling [1].

The inflammatory phase begins immediately after bone tissue injury. During this period, neutrophils migrate to the injury site, followed by monocytes, which subsequently differentiate into macrophages. Among these, M1 macrophages predominate, producing pro-inflammatory cytokines and phagocytosing necrotic and apoptotic cells. It has been shown that M1-derived IL-1, TNF-α, and IL-6 enhance the proliferative potential and resorptive activity of osteoclasts, while simultaneously inhibiting the morphofunctional state of osteoblasts, thereby suppressing bone tissue formation.

Studies have shown that inflammatory macrophages inhibit osteocyte maturation and tissue mineralization via regulating the Notch signaling pathway [9].

IL-1 and TNF-α activate osteoclastogenesis by stimulating the expression of RANKL (Receptor Activator of Nuclear Factor Kappa B Ligand) and suppressing the production of osteoprotegerin by osteoblasts and fibroblasts. The signaling system composed of RANK (Receptor Activator of Nuclear Factor Kappa B), its ligand RANKL, and osteoprotegerin is known to be the primary regulator of the morphofunctional state of osteoclasts. Increased RANKL expression, followed by its interaction with RANK, induces genomic changes in bone marrow-derived osteoclast precursors, leading to their transformation into mature, active osteoclasts. Osteoprotegerin acts as a decoy receptor for RANKL [10].

Interestingly, M1 macrophages interact with mesenchymal stem cells and stimulate their transformation into osteogenic cells. This process is significantly enhanced when there is an increase in M2 macrophages accompanied by a reduction in M1 macrophages [11, 12].

Experimental studies have shown that selective depletion of macrophages at this stage leads to impaired osteogenesis and a reduction in the volume of newly formed bone tissue [8, 13].

The proliferative-reparative stage of osteogenesis follows the elimination of damaged tissues and is characterized by the predominance of M2 macrophages. Alternatively activated macrophages stimulate angiogenesis, produce osteoinductive factors such as transforming growth factor-beta (TGF-β) and bone morphogenetic protein-2 (BMP-2), and promote the proliferation and differentiation of mesenchymal stem cells toward the osteoblastic vector [14].

The remodeling phase is the final stage, lasting several weeks or months, and involves the replacement of primary bone tissue with lamellar bone. During this period, macrophages maintain the balance between bone resorption and formation by interacting with osteoclasts and osteoblasts, and also participate in the regulation of vascular network involution [1, 8].

Blood vessels are known to provide trophic support to bone tissue, which is essential for the

processes of reparative osteogenesis. It has been demonstrated that M2 macrophages are involved in angiogenesis and vascular remodeling. Specifically, M2a macrophages produce platelet-derived growth factor-BB (PDGF-BB), while M2c macrophages secrete matrix metalloproteinase-9 (MMP-9). Some studies have also indicated that M1 macrophages contribute to angiogenesis through the production of vascular endothelial growth factor (VEGF) [15, 16].

Reparative osteogenesis is highly sensitive to changes in the functional activity of macrophages. Various pathological conditions can significantly alter the course of bone regeneration by disrupting macrophage polarization or causing insufficient macrophage responses. It has been established that with aging, macrophages lose their ability to transition in a timely manner from the pro-inflammatory M1 phenotype to the reparative M2 phenotype, leading to delayed resolution of inflammation and impaired osteogenesis. A study using an aging rat model demonstrated reduced levels of M2 macrophages and decreased quality of newly formed bone tissue [17]. Similar results have been confirmed in studies utilizing engineered coatings to induce the transition from the M1 to the M2 macrophage phenotype under aging conditions, where a partial restoration of reparative function was observed [18].

Hormone-dependent regulation of macrophage functions in the process of osteogenesis should also be noted. For example, diabetes mellitus alters the immune microenvironment of regeneration, leading to a sustained dominance of the pro-inflammatory response. This is supported by findings in diabetic rat models, which show increased expression of M1 markers, impaired M2 polarization, and reduced angiogenesis and osteogenesis. However, it has been demonstrated that the use of nanostructured biomaterials, particularly PCLLA-nanoHA, helps restore the balance by activating M2 macrophages and improving tissue regeneration [19].

Under conditions of estrogen deficiency in ovariectomized mice, elevated levels of pro-inflammatory cytokines and disruption of the macrophage profile at the fracture site have been observed, which correlates with reduced quality of the regenerative bone tissue [20].

Due to the recognized role of macrophages in bone tissue regeneration, there is growing interest in methods aimed at therapeutically modulating their phenotype. The primary objective of such approaches is to induce the transition from the M1 to the M2 phenotype and to maintain the M2 profile, particularly during the critical phases of reparative osteogenesis [21]. Among the classical strategies is the use of IL-4, which stimulates M2 polarization. Experimental studies have shown that IL-4, in vitro, activates the production of anti-inflammatory mediators and enhances mineralization in cultures of osteogenic mesenchymal stem cells, particularly in the presence of low-activity macrophages [22].

Some studies have noted that RANKL-activated M1 macrophages exhibit osteogenic properties by modulating osteoblastic transcription factors, indicating the potential for controlled utilization of the M1 phenotype [23]. At the same time, immunoregulatory molecules such as VIP (vasoactive intestinal peptide) and PACAP (pituitary adenylate cyclase-activating polypeptide), despite their potential to stimulate the M2 phenotype, did not produce a significant effect in the context of alveolar bone healing, highlighting the complexity of such regulation [24].

Particular interest is drawn to the sex-specific effectiveness of regulating the transition of macrophages from the M1 to the M2 phenotype. Researchers have shown that the immunomodulatory response differs significantly between males and females, likely due to hormonal influences [25].

Modern tissue engineering strategies are increasingly incorporating the immunomodulatory potential of macrophages into the design of biomaterials aimed at enhancing reparative osteogenesis. In this context, modified biomaterials serve not only as physical scaffolds for cellular repair but also as active regulators of the cellular microenvironment by directing macrophage polarization and maintaining immune homeostasis at the osteogenic site. The concept involves not merely creating an inert matrix for cell adhesion and growth, but developing surfaces and carriers capable of modulating immune cell behavior, particularly by specifically inducing M2 macrophage polarization [26].

One of the promising approaches involves the use of calcium phosphate-based coatings, which stimulate the transition of macrophages from the M1 to the M2 phenotype. Experimental studies have shown that such coatings promote phenotypic transformation in aged macrophages, restoring their reparative activity [18]. Hybrid hydrogels and nanocomposites, which combine a structural carrier with active therapeutic functionality, are also of considerable interest. For instance, the application of a multimodal hydrogel containing exosomes and immunotherapy has been shown to simultaneously activate osteoblasts, osteoclasts, and M2 macrophages, thereby accelerating the reparative process [27]. Silane-based biomaterials, used as endodontic irrigants, have demonstrated the ability to alter the biochemical profile of tissues and promote macrophage polarization [28].

An immunoregulatory effect was observed in an experimental study involving the filling of mandibular bone defects in rats with nanostructured hydroxyapatite combined with local injection of thymalin into the surrounding soft tissues. This comprehensive therapy stimulated reparative osteogenesis by activating both innate and adaptive immunity, which morphologically manifested in the post-traumatic regenerate as an increased presence of T and B lymphocytes and macrophages. Among the latter, a decrease in M1 macrophages and an increase in M2 macrophages were noted [29, 30].

Another important strategy involves the use of PCLLA-nanoHA composites, which promote M2 macrophage polarization and enhance alveolar bone regeneration under diabetic conditions [31].

One of the promising directions is targeted immunomodulation, which involves the localized regulation of the M1/M2 macrophage ratio at specific stages of osteogenesis. This approach utilizes biomaterials with controlled release of signaling molecules or surface modifications that facilitate the recruitment of the desired macrophage phenotype. For example, in a study by Y.H. Kim et al., the concept of «springboard immunomodulation» was proposed, which envisions the active reprogramming of the local immune microenvironment as a launching platform for osteoregeneration [26].

Currently, the field of macrophage or macrophage precursor transplantation is developing as a potential form of cell therapy. Particular attention is being given to methods involving ex vivo induction of the desired phenotype prior to transplantation into the defect site, as this approach allows for predictable therapeutic activity while minimizing undesired immune responses [31].

Another promising direction involves the use of exosomes – nanovesicles produced by cells, including macrophages, which contain active molecules such as mitochondrial RNA, proteins, and lipids. Exosomes derived from M2 macrophages have demonstrated the potential to stimulate osteogenesis and angiogenesis, acting as natural signaling mediators without directly interfering with the cellular structure of the microenvironment [27].

Systematic reviews highlight the emerging concept of «smart» biomaterials, which not only serve as matrices for cell growth but also actively interact with the immune system, functioning as regulatory platforms. These materials may contain embedded immunotherapeutic agents, control cytokine release in response to external stimuli, or alter their behavior depending on the phase of healing [11, 32]. A key aspect in this context is the issue of timing: premature or prolonged activation of a particular macrophage phenotype may lead to adverse outcomes. Therefore, the current paradigm of immunoregulation in osteogenesis is based not only on the binary distinction between M1 and M2 phenotypes, but also on the dynamic monitoring and modulation of the plastic transitions between these states in accordance with the specific phase of reparative osteogenesis [33].

CONCLUSIONS

Macrophages play a crucial role at all stages of reparative osteogenesis in the mandible. Their high degree of plasticity enables them to adapt to changes in the microenvironment by dynamically shifting their phenotype (from M1 to M2 and vice versa). Alterations in the morphofunctional state of macrophages and an imbalance between M1 and M2 populations under pathological conditions lead to disruptions in the reparative osteogenesis process. Currently, macrophages are recognized as key therapeutic targets for modulating reparative osteogenesis in cases of mandibular bone pathology.

REFERENCES

1. Sukhonos O, Korenkov O, Sukhodub L. A modern view on reparative osteogenesis: main stages and their patterns. Eastern Ukrainian Medical Journal. 2024;12(3):476-491. doi:10.21272/eumj.2024;12(3):476-491. DOI
2. Nikovics K, Durand M, Castellarin C, Burger J, Sicherre E, Collombet JM, Oger M, Holy X, Favier AL. Macrophages Characterization in an Injured Bone Tissue. Biomedicines. 2022 Jun 11;10(6):1385. doi: 10.3390/biomedicines10061385. DOI
3. Iglesias-Velazquez O, Gf Tresguerres F, F Tresguerres I, Leco-Berrocal I, Lopez-Pintor R, Baca L, Torres J. OsteoMac: A new player on the bone biology scene. Ann Anat. 2024;254:152244. doi: 10.1016/j.aanat.2024.152244. DOI
4. Chen S, Saeed AFUH, Liu Q, Jiang Q, Xu H, Xiao GG, Rao L, Duo Y. Macrophages in immunoregulation and therapeutics. Signal Transduct Target Ther. 2023;8(1):207. doi: 10.1038/s41392-023-01452-1. DOI
5. Hu Y, Huang J, Chen C, Wang Y, Hao Z, Chen T, Wang J, Li J. Strategies of Macrophages to Maintain Bone Homeostasis and Promote Bone Repair: A Narrative Review. J Funct Biomater. 2022;14(1):18. doi: 10.3390/jfb14010018. DOI
6. Hu K, Shang Z, Yang X, Zhang Y, Cao L. Macrophage Polarization and the Regulation of Bone Immunity in Bone Homeostasis. J Inflamm Res. 2023;16:3563-3580. doi: 10.2147/JIR.S423819. DOI

7. Hozain S, Cottrell J. CDIIb+ targeted depletion of macrophages negatively affects bone fracture healing. Bone. 2020;138:115479. doi: 10.1016/j.bone.2020.115479. DOI
8. Frade BB, Dias RB, Gemini Piperni S, Bonfim DC. The role of macrophages in fracture healing: a narrative review of the recent updates and therapeutic perspectives. Stem Cell Investig. 2023;10:4. doi: 10.21037/sci-2022-038. DOI
9. Wang S, Xiao L, Prasadam I, Crawford R, Zhou Y, Xiao Y. Inflammatory macrophages interrupt osteocyte maturation and mineralization via regulating the Notch signaling pathway. Mol Med. 2022;28(1):102. doi: 10.1186/s10020-022-00530-4. DOI
10. Yasuda H. Discovery of the RANKL/RANK/OPG system. J Bone Miner Metab. 2021 Jan;39(1):2-11. doi: 10.1007/s00774-020-01175-1. Epub 2021 Jan 3. Erratum in: J Bone Miner Metab. 2021;39(1):12. doi: 10.1007/s00774-021-01203-8. DOI
11. Shin RL, Lee CW, Shen OY, Xu H, Lee OK. The Crosstalk between Mesenchymal Stem Cells and Macrophages in Bone Regeneration: A Systematic Review. Stem Cells Int. 2021;2021:8835156. doi: 10.1155/2021/8835156. DOI
12. Maruyama M, Rhee C, Utsunomiya T, Zhang N, Ueno M, Yao Z, Goodman SB. Modulation of the Inflammatory Response and Bone Healing. Front Endocrinol (Lausanne). 2020;11:386. doi: 10.3389/fendo.2020.00386. DOI
13. Fan S, Sun X, Su C, Xue Y, Song X, Deng R. Macrophages-bone marrow mesenchymal stem cells crosstalk in bone healing. Front Cell Dev Biol. 2023;11:1193765. doi: 10.3389/fcell.2023.1193765. DOI
14. Schlundt C, Fischer H, Bucher CH, Rendenbach C, Duda GN, Schmidt-Bleek K. The multifaceted roles of macrophages in bone regeneration: A story of polarization, activation and time. Acta Biomater. 2021;133:46-57. doi: 10.1016/j.actbio.2021.04.052. DOI
15. Liu Z, Luo X, Xu R. Interaction between immuno-stem dual lineages in jaw bone formation and injury repair. Front Cell Dev Biol. 2024;12:1359295. doi: 10.3389/fcell.2024.1359295. DOI
16. Gou M, Wang H, Xie H, Song H. Macrophages in guided bone regeneration: potential roles and future directions. Front Immunol. 2024;15:1396759. doi: 10.3389/fimmu.2024.1396759. DOI
17. Löffler J, Sass FA, Filter S, Rose A, Ellinghaus A, Duda GN, Dienelt A. Compromised Bone Healing in Aged Rats Is Associated With Impaired M2 Macrophage Function. Front Immunol. 2019;10:2443. doi: 10.3389/fimmu.2019.02443. DOI
18. Alhamdi JR, Peng T, Al-Naggar IM, Hawley KL, Spiller KL, Kuhn LT. Controlled M1-to-M2 transition of aged macrophages by calcium phosphate coatings. Biomaterials. 2019;196:90-99. doi: 10.1016/j.biomaterials.2018.07.012. DOI
19. Wang D, Wei L, Hao J, Tang W, Zhou Y, Zhang C, Wang J. PCLLA-nanoHA Bone Substitute Promotes M2 Macrophage Polarization and Improves Alveolar Bone Repair in Diabetic Environments. J Funct Biomater. 2023 Oct 30;14(11):536. doi: 10.3390/jfb14110536. DOI
20. Chen L, Cheng S, Sun K, Wang J, Liu X, Zhao Y, Yang J, Zhao D, Xue C, Tao Y, Zhao S, Zhang H, Lu S, Shi Q, Wang Y, Shu B. Changes in macrophage and inflammatory cytokine expressions during fracture healing in an ovariectomized mice model. BMC Musculoskelet Disord. 2021;22(1):494. doi: 10.1186/s12891-021-04360-z. DOI
21. Niu Y, Wang Z, Shi Y, Dong L, Wang C. Modulating macrophage activities to promote endogenous bone regeneration: Biological mechanisms and engineering approaches. Bioact Mater. 2020;6(1):244-261. doi: 10.1016/j.bioactmat.2020.08.012. DOI
22. Yang L, Xiao L, Gao W, Huang X, Wei F, Zhang Q, Xiao Y. Macrophages at Low-Inflammatory Status Improved Osteogenesis via Autophagy Regulation. Tissue Eng Part A. 2024;30(23-24):e766-e779. doi: 10.1089/ten.TEA.2021.0015. DOI
23. Huang R, Wang X, Zhou Y, Xiao Y. RANKL-induced M1 macrophages are involved in bone formation. Bone Res. 2017;5:17019. doi: 10.1038/boneres.2017.19. DOI
24. Azevedo MCS, Fonseca AC, Colavite PM, Melchiades JL, Tabanez AP, Codo AC, de Medeiros AI, Trombone APF, Garlet GP. Macrophage Polarization and Alveolar Bone Healing Outcome: Despite a Significant M2 Polarizing Effect, VIP and PACAP Treatments Present a Minor Impact in Alveolar Bone Healing in Homeostatic Conditions. Front Immunol. 2021;12:782566. doi: 10.3389/fimmu.2021.782566. DOI
25. Nathan K, Lu LY, Lin T, Pajarinen J, Jämsen E, Huang JF, Romero-Lopez M, Maruyama M, Kohno Y, Yao Z, Goodman SB. Precise immunomodulation of the M1 to M2 macrophage transition enhances mesenchymal stem cell osteogenesis and differs by sex. Bone Joint Res. 2019;8(10):481-488. doi: 10.1302/2046-3758.810.BJR-2018-0231.R2. DOI
26. Kim YH, Oreffo ROC, Dawson JI. From hurdle to springboard: The macrophage as target in biomaterial-based bone regeneration strategies. Bone. 2022;159:116389. doi: 10.1016/j.bone.2022.116389. DOI
27. Mi B, Chen L, Xiong Y, Yang Y, Panayi AC, Xue H, Hu Y, Yan C, Hu L, Xie X, Lin Z, Zhou W, Cao F, Xiao X, Feng Q, Liu G. Osteoblast/Osteoclast and Immune Cocktail Therapy of an Exosome/Drug Delivery Multifunctional Hydrogel Accelerates Fracture Repair. ACS Nano. 2022;16(1):771-782. doi: 10.1021/acsnano.1c08284. DOI
28. Daood U, Ilyas MS, Ashraf M, Akbar M, Bapat RA, Khan AS, Pichika MR, Parolia A, Seow LL, Khoo SP, Yiu C. Biochemical changes and macrophage polarization of a silane-based endodontic irrigant in an animal model. Sci Rep. 2022;12(1):6354. doi: 10.1038/s41598-022-10290-0. DOI
29. Boiko AA, Malanchuk VA, Myroshnychenko MS, Markovska OV, Shapkin AS, Marakushyn DI. Expression features of T-lymphocytes, B-lymphocytes and macrophages in the post-traumatic regenerate of the mandible rats under conditions of filling a bone defect with hydroxyapatite-containing osteotropic material and thymalin injecting the surrounding soft tissues. Pol Merkur Lekarski. 2024;52(2):171-177. doi: 10.36740/Merkur202402105. DOI

30. Boiko AA, Malanchuk VA, Myroshnychenko MS. Reparative osteogenesis in mandible in cases of filling a bone defect with hydroxyapatite-containing osteotropic material and injecting the surrounding soft tissues with thymalin: experimental and morphological study. Wiad Lek. 2024;77(1):68-76. doi: 10.36740/WLek202401110. DOI
31. Wan Z, Shin LY, Wang YF, Huang Z, Dong Y, Lee CW, Kumta SM, Lee OK. Role of skeletal macrophages in fracture repair: A systematic review. Biomed Rep. 2020;13(6):53. doi: 10.3892/br.2020.1360. DOI
32. Orvalho JM, Fernandes JCH, Moraes Castilho R, Fernandes GVO. The macrophage's role on bone remodeling and osteogenesis: a systematic review. Clinical Reviews in Bone and Mineral Metabolism. 2023;21(1-4):1-13. doi: 10.1007/s12018-023-09286-9 DOI
33. Bi Z, Cai Y, Shi X, Chen J, Li D, Zhang P, Liu J. Macrophage-mediated immunomodulation in biomaterial-assisted bone repair: Molecular insights and therapeutic prospects. Chemical Engineering Journal. 2024;488:150631

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Mykhailo S. Myroshnychenko

Department of General and Clinical Pathological Physiology
named after D.O. Alpern, Kharkiv National Medical University
4 Nauky Avenue, Kharkiv, 61022, Ukraine
e-mail: msmyroshnychenko@ukr.net

ORCID AND CONTRIBUTIONSHIP

Igor S. Brodetskyi: 0000-0002-9434-4079 B D
Vladislav A. Malanchuk: 0000-0001-8111-0436 B
Nataliia M. Savielieva: 0000-0002-9670-0997 D
Mykhailo S. Myroshnychenko: 0000-0002-6920-8374 E
Yevheniia A. Hromko: 0009-0004-2454-4608 F
Andrii A. Boiko: 0000-0003-0432-5091 B
Liudmyla O. Brodetska: 0000-0002-0570-3085 A
Yaroslava A. Kulbashna: 0000-0002-2571-091X E
Sergey B. Brodetskyi: 0000-0002-6175-2797 B
Halyna V. Zhurakovska: 0000-0003-3191-2590 F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 20.02.2025
ACCEPTED: 25.05.2025

REVIEW ARTICLE

CONTENTS

Comparative analysis of the roles of PBRM1 and SETD2 genes in the pathogenesis and progression of renal cell carcinoma: An analytical review

Ammar Yasir Ahmed, Maysaa Ali Abdul Khaleq, Rusul Qasim Mohammed
COLLEGE OF PHARMACY, UNIVERSITY OF AL MAARIF, AL ANBAR, IRAQ

ABSTRACT

Clear cell renal cell carcinoma (ccRCC) is characterized by frequent mutations in chromatin-modifying genes, notably PBRM1 and SETD2, which play critical roles in tumorigenesis and disease progression. These mutations affect chromatin remodeling and histone methylation, influencing cellular functions such as tumor suppression, genomic integrity, and cell cycleregulation. Despite their prevalence, the distinct biological impacts and clinical implications of PBRM1 and SETD2 mutations remain incompletely understood. This review aims to elucidate the functional similarities and differences between PBRM1 and SETD2 mutations in ccRCC, investigate their roles in tumor progression and metastasis, and assess the potential clinical and therapeutic implications of these genetic alterations in the context of precision oncology. A comprehensive literature review was conducted, analyzing genomic, transcriptomic, and clinical data from ccRCC cohorts. Functional studies of PBRM1 and SETD2 mutations were examined alongside gene set enrichment analyses (GSEA), histopathologic observations, and molecular profiling of primary and metastatic tumor sites. Recent advances in therapeutic strategies targeting these mutations were also reviewed. PBRM1 mutations occur early in ccRCC development, altering chromatin accessibility and acting as tumor co-initiators, while SETD2 mutations arise later, exacerbating genomic instability and promoting metastasis. Both genes share tumor suppressor functions but differ in their genetic interactions and pathways. Co-mutation of PBRM1 and SETD2 correlates with increased tumor aggressiveness, poor prognosis, and higher metastatic potential. Emerging therapeutic approaches, including targeted molecular therapies and immunotherapies, show promise in addressing these mutation-driven pathways. PBRM1 and SETD2 mutations critically influence the molecular pathogenesis and clinical outcomes of ccRCC. Understanding their distinct and cooperative roles can enhance molecular profiling and guide personalized treatment strategies. Further research is warranted to develop targeted therapies that exploit the vulnerabilities associated with these chromatin-modifying gene mutations, ultimately improving prognosis and therapeutic response in ccRCC patients.

KEY WORDS: renal cell carcinoma, kidney cancer, surgical intervention, genetic syndrome

Wiad Lek. 2025;78(6):1182-1192. doi: 10.36740/WLek/205136 DOI

INTRODUCTION

Renal Cell Carcinoma (RCC) is the most common type of kidney cancer. Each year, approximately 270,000 individuals are diagnosed worldwide with RCC, while over 116,000 deaths are attributed annually to this disease, making it the 14th leading cause of cancer-related deaths [1]. RCC is a cancer of kidney tubular cells and frequently progresses asymptomatically. The symptoms that are suggestive of RCC always appear at a time when the disease is already advanced and has a poor prognosis [2]. Despite surgical intervention, 20-30% of patients will have a relapse or develop metastases within five years, while treatment of metastatic RCC is mainly palliative and ineffective. Due to the unique heterogeneity of RCC, discovering effective therapy is particularly challenging. Advanced RCC represents the genetic syndrome associated with a number of gene mutations whose products are involved in general cellular processes [3]. Although CCRC and paRCC are closely related by genetic and histological features, the gene mutations responsible for the tumor genesis of these tumours have completely distinct sets. The loss of different chromatin regulators is the main carcinogenic event leading to different RCC histotypes [4]. Clear cell RCC (ccRCC) is caused by the inactivation of the VHL gene and at least one out of three genes coding for chromatin regulators: BAP1, PBRM1, and SETD2. A significant reduction of the disease-free interval between the primary tumour resection and the onset of tumour metastatization was observed in patients with a mutation in one of the VHL, BAP1, PBRM1, or SETD2 genes [5]. CCRC is usually diagnosed too late to be salvaged. Consequently, it is necessary to deepen the molecular background of ccRCC to reduce the number of deaths caused by kidney cancer [6]. BAP1, PBRM1, and SETD2 are important chromatin regulators whose products

are often damaged in ccRCC [7]. Nearly 350 mutations are known in the BAP1 gene, while more than 700 and 500 variations are known in the PBRM1 and SETD2 genes respectively [5]. A thorough experimental examination of the effect of these changes is particularly burdensome. Bioinformatics tools were used to predict the effects of all known mutations within BAP1, PBRM1, and SETD2 genes [8].

AIM

This review aims to elucidate the functional similarities and differences between PBRM1 and SETD2 mutations in ccRCC, investigate their roles in tumor progression and metastasis, and assess the potential clinical and therapeutic implications of these genetic alterations in the context of precision oncology.

MATERIALS AND METHODS

A comprehensive literature review was conducted, analyzing genomic, transcriptomic, and clinical data from ccRCC cohorts. Functional studies of PBRM1 and SETD2 mutations were examined alongside gene set enrichment analyses (GSEA), histopathologic observations, and molecular profiling of primary and metastatic tumor sites. Recent advances in therapeutic strategies targeting these mutations were also reviewed.

REVIEW AND DISUSSION

DEFINITION AND CLASSIFICATION OF RENAL CELL CARCINOMA

Renal Cell Carcinoma (RCC) is not a single disease, but several histologically defined cancers with different genetic drivers, clinical courses, and therapeutic responses [1]. The prevalence of RCC is rising worldwide. To grasp advances in the pathogenesis and clinical progression of RCC, it is crucial to understand its taxonomy. According to the histopathological and molecular levels, RCC can be classified into many subtypes, of which clear cell RCC accounts for the majority of cases, followed by papillary RCC and chromophobe RCC. Each RCC subtype has unique histological features, although some subtypes share an overlapping microscopic morphology. To improve the diagnostic consistency and assist the selection of modern targeted therapy, numerous criteria have been established to define RCC at the histopathological level. Epidemiological studies suggest that different RCC subtypes exhibit distinct genetic alterations, aggressiveness, and prognosis [9]. Therefore, it is necessary to develop a subtype-specific biomarker and identify therapeutic vulnerabilities based on the genetic hallmarks of each RCC subtype. For example, PBRM1 mutations are predominant in patients with ccRCC and are considered as an independent worse prognostic hallmark [10].

EPIDEMIOLOGY AND RISK FACTORS

Renal Cell Carcinoma (RCC) accounts for about 80-90% of kidney cancers and is the sixth most common cancer in men and the tenth in women. In the United States, it was estimated that 73,820 new cases of RCC would be diagnosed in 2019, and there were 14,770 estimated deaths [11]. The incidence rate of RCC varies globally and is rapidly rising in more developed regions. The overall 5-year survival for kidney and renal cancers is 73%. In more developed regions, the 5-year survival is 65%. RCC is about twice as common in males as in females after adjusting for age. The highest incidence rate of RCC is in North America (12 per 100,000) and the lowest is in South Central Asia (4 per 100,000). Some side-by-country comparisons include the following: Age-standardized mortality rates in Japan have been decreasing 4.9% per year, whereas rates in Spain have been increasing 1.8% per year. The mean age-adjusted incidence rate over the past years has increased fairly steadily worldwide, but at different rates in more versus less developed regions [12]. RCC is cystic, which enables it to often grow to a relatively large size before causing symptoms. Indeed, while localized disease is usually asymptomatic, metastatic disease presents more often with the classic symptoms. RCC has subtypes based on cell histology. Different histologic types of RCCs have distinct cytogenetic abnormalities and demonstrate various susceptibilities to environmental carcinogens. Clear cell RCC (ccRCC) is the most common histologic subtype of RCC and is significantly associated with striking chromosomal loss on the short arm of chromosome 3. Analysis of the central TCGA cohort revealed frequent, previously unreported, hemizygous loss of 9p in von Hippel-Lindau (VHL) wild-type papillary RCC [13]. Likewise, the frequency of 9p loss was significantly elevated in wild-type TCGA ccRCCs. The 15 suppressor gene commonly mutated in this setting, demonstrating 9p hemizygous loss, for which silencing significantly increased proliferation, was PBRM1 [14].

GENETIC ALTERATIONS IN RENAL CELL CARCINOMA

1 in 63 individuals will develop Renal Cell Carcinoma (RCC). It is clear that both tumors and normal tissues accumulate multiple mutations and genomic alterations.

Fortunately, the latest technologies have addressed whole-exome and next generation sequencing [15]. As for the other tissues, more than 1.5 × 1010 of the bases exposed to UV or of the bases wandering in electrons, are changed every day. The early-stage detection, classification of the cancer and prediction of drug responses are typically based on the examination of a layout of a tissue obtained from a patient by biopsy. Uncovering of key genetic alterations could pave a way to identify potential biomarkers, useful for early detection and prediction of the cancer. Nevertheless, what is more crucial is the revelation of mechanism of the cancer development, so that tailored therapy may be proposed. The advancement in next-generation sequencing methods offers the detailed exploration of cancer's genetic complexities for the different tissues [2]. A shift to the molecular view of the disease had encouraged whole-genome, whole-exome and targeted next-generation sequencing to analyze the genetic changes in Renal Cell Carcinoma. Vaccine therapy was found to decelerate Renal Cell Carcinoma progress. Vaccination against mutant PBRM1 can prevent Renal Cell Carcinoma growth, including the out-of-frame switch peptide. RCC is a highly drug-resistant and recalcitrant disease of the kidney. The prevalence among men reaches 2% and among woman 1%; more than 100,000 individuals die of it [16].

OVERVIEW OF KEY GENES INVOLVED IN RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) is the leading cause of mortality among all urological cancers. Overall survival at 5 years for patients with advanced RCC is less than 10% [17]. Recent genomic analysis has revealed the landscape of genetic alterations in RCC that appear to involve genes mutated at low frequency. The three genes most commonly mutated in clear cell RCC (ccRCC, accounting for over 75% of cases) are VHL, PBRM1, and SETD2 [16]. The Products of these genes are part of the nuclear protein ubiquitin-ligase module or epigenetic complex involved in chromatin remodeling, transcriptional regulation of targeted genes, and cell cycle control. The frequent, and often mutual, mutation of these genes in ccRCC suggests the existence of a complex network portraying the oncogenic nature of this cancer type, and provides the opportunity for a comprehensive study to clarify better ways of intervention for ccRCC patients. The involvement of interactions of these tumor-associated genes is supported by recent papers suggesting a novel aspect of PBRM1 biology implicating the PBRM1 interaction with H3K27me3 marking in the control of transcript level [18]. The relevance of those interactions in RCC carcinogenesis is broadened here, providing evidence of the involvement of PBRM1 and SETD2 in ccRCC-stromal cell communication, and their reciprocal participation in crosstalk between ccRCC cells and fibroblasts. Independent results obtained on PBRM1 silencing in ccRCC cell lines, and co-culturing IHH and HEK 293T cells confirm that CD70, TNFSF13 and IL1RL1 genes are up-regulated or down-regulated, respectively, in response to PBRM1 loss. Furthermore, evidence of mutually exclusive mutation of PBRM1 and SETD2 in RCC patients provides more information to that reported in the existing literature, and is suggestive of its involvement in common RCC carcinogenic pathways [18, 19].

PBRM1 GENE

Via its Gln-rich domain, the PBRM1 gene encodes tumor suppressive proteins with significant roles in chromatin regulation and gene expression [20]. This gene was the most under-reconstructed in PCC, indicating that it is a rare gene that is frequently mutated or epigenetically altered in most types of cancer. In ccRCC, it is the second-most changed gene among 124 cases [21]. Moreover, the transformation of PBRM1 is the dominant genetic and epigenetic change in mutations, deep deletion, DNA methylation and the processes of histone modification in all types of changes in ccRCC [22]. To explore the mechanism of PBRM1 transformation in ccRCC, we note that PBRM1 prefers to interact with DNA-binding or chromatin-remodeling proteins and those with PAAR; the PAAR domain is closer to the transformation profile of PBRM1; discuss and argue the mechanism of PBRM1 transformation in ccRCC. This research suggests that mutations in PBRM1 are correlated with genomic stability, which has been considered a cause of cancer in previous observations. But at the individual gene level, mutations of PBRM1 alone did not result in the occurrence of ccRCC or other cancers. Analyzing data from a variety of tumor forms and observing that the proliferation of tumors in which PBRM1 is transformed is slower than in tumors without transformation. Comparing the effects of altered PBRM1 on OS and DFS in a diversity of cancers, it is found that PBRM1 has a significantly greater effect on both OS and DFS specifically in ccRCC [8].

STRUCTURE AND FUNCTION OF PBRM1

The polybromo-1 protein, encoded by the PBRM1 gene, can structure a Transcriptional inhibits a repressor complex with SWI/SNF subunits and BCL7B inhibits transcription. Polybromo-1 is a nuclear protein pres-

ent in a wide range of human tissues and commonly expressed in neoplastic cells, which has potential value for the differential diagnosis of carcinoma and melanoma. This discovery of PBRM1 has enhanced the understanding of the broad and critical role of SWI/SNF gene misregulation in human cancer pathogenesis by providing the ability to directly study a near universal and extensive set of tumors related to the highly conserved SWI/SNF core ATPase machinery [23]. PBRM1 mutation is particularly common when ARID1A is silenced or mutated and demonstrates that ARID1A, PBRM1 or BRM suppresses or promotes melanocyte neoplasia and invasion in a BRAFV600E context-dependent manner with distinct kinetics. Hence, both BRCA1 and Polybromo-1 are independently necessary for the repair of DNA double-strand breaks [24]. Polybromo-1 is thought to have important functions in cell cycle regulation, gene transcription, and chromatin architecture [20]. Polybromo-1 (PBRM1) is a chromatin remodeling factor that belongs to the protein associated with the Brg/Brm and BRCA1 complex. BRCA1 is a tumor suppressor gene associated with breast and ovarian cancer, and its product has E3 ubiquitin-protein ligase that acts on histone H2A and regulates the repair of DNA double-strand breaks. PBRM1 is a DNA binding protein containing six BRCT domains, similar to BRCA1 with an ordinary 1,863 amino acids. BRCA1 and PBRM1 co-localize in the nucleus and exhibit similar expression patterns in various normal human tissues. It was found for the first time that BRCA1 interacts with PBRM1 through the third BRCT domain of BRCA1 and the sixth BRCT domain of PBRM1. BRCA1 is combined with PBRM1 during DNA replication and/or DNA repair after irradiation. The coexistence of these two proteins is thought to be necessary for the repair of DNA double-strand breaks, and RNA interference-mediated knockdown or gene mutation of BRCA1/PBRM1 will lead to increased sensitivity to ionizing radiation [25].

ROLE OF PBRM1 IN RENAL CELL CARCINOMA

There are many recent studies, much of them website-based, which have estimated the impacts of gene mutations on tumor initiation, progression, or the prognosis of disease. However, few studies have explicitly estimated the genetic roles of PBRM1 in a large tumor base in the pattern of transcriptome expression, immune cell infiltration, and disease prognosis. Epigenetic modifier genes are described as the second maximal transformative genes in many tumors following well-established tumor suppressor, oncogene, and DNA reparation genes. For instance; ATM, BAP1, BRCA2, CUX1, KMT2D, MGMT, and PBRM1 [20]. Therefore, in ccRCC, who has been reporting epidemiological and clinical aspects with estimates of specific metabolic patterns, many crucial the features of genetic and epigenetic alterations to PBRM1 as well as results of experiments related to anti-PD-1 immunotherapy for clear cell renal cell carcinoma [26]. Further attention is given to the genetic or epigenetic mutations that occur in PBRM1, which have formed as one of the two crucial genes correlated with chromatin regulation in the complete reinterpretation of ccRCC [18]. It is noted about the systems through which such changes lead to the appearance, mapping, shape, histone remodeling, and DNA methylation reconfiguration of tumor [27]. Directions also address the genetic condition and molecules separately or jointly transforming when the mutation of PBRM1 arises in different exon domain amino acids or amino-acid residues of introns. Indicates that effects include tumor endophytic reprogramming, skin alteration, tumor metabolic reconfiguration, and inhibition of T cell activity, genetic instability, and upregulation of noncanonical oncogene paths, such as JAK/Stat [28]. It is also noted that the epigenetic mechanics conduce to the reconfiguration of immune cells in the TME away from an anti-tumor phorotype [22]. Such the end Duarte shedding light on the mechanism's result in immunotherapy and may have the potential to help the further innovative treatment of RCC [29].

SETD2 GENE

Recent advances in genomic studies reveal that the genetic landscape of Renal Cell Carcinoma (RCC) includes mutations in tumor-suppressor genes, prominently PBRM1, encoding ARID2[31]. PBRM1 is the second most altered gene in clear cell RCC (ccRCC) [31]. Another important gene, SETD2, which encodes a histone methyltransferase, also contributes to adverse clinical outcomes in ccRCC by repressing pathogenic LINE-1 [30]. In cases where SETD2 is mutated or downregulated, LINE-1 repression is homogeneously reactivated, showing a complementary functional enrichment compared to PBRM1 [31]. Reports detail the contributions of SETD2 mutations to ccRCC progression, indicating these mutations result in poorer outcomes [32]. SETD2, the fourth most frequently altered gene, plays a critical role in DNA damage repair. Its trimethylated H3K36 mark associates with open-chromatin linked to elongating RNA polymerase II. Loss of H3K36 trimethylation due to SETD2 functional loss correlates with inhibited repair of DNA double-stranded breaks and decreased survival [31]. Gene alterations in SETD2 show branched patterns in multi-regional samples of treated ccRCC [30]. Furthermore, several chemotherapy drugs are significant for

treating ccRCC with pathological SETD2 alterations and correlate with H3K36 depletion [31]. Results indicate that SETD2 gene alterations are linked to unfavorable clinical outcomes, underscoring its potential as a drug target and biomarker [31, 32].

STRUCTURE AND FUNCTION OF SETD2

SETD2 (SET domain containing 2) is a ubiquitously expressed SET domain-containing histone 3 lysine 36 trimethylase (H3K36me3) that interacts with elongating RNA pol II via the RNA pol II-associated factor complex (PAF1c), for the recruitment of H3K36me3 to transcribing gene bodies, being the principal mediator of H3K36me3 [32]. The functions for H3K36me3 include the regulation of Pol II and nucleosome density across exons, alternative splicing, and DNA repair. Biallelic inactivation in SETD2 is associated in clear cell renal cell carcinoma (ccRCC) with reduced survival and earlier time to recurrence [18]. SETD2 mutant tumors harbored global and tumor-specific alterations in bulk DNA methylation patterns. There is enrichment of bis-synchronous methylation events in tumors harboring mutations in genes of several pathways. Notably, mutual exclusivity of methylation events was observed in tumors with alternative mechanisms of pathway deregulation, suggesting a branched epigenetic evolution [33]. In SETD2 WT cells, hypomethylation-induced replication stress activates the DNA damage response (DDR). Recent findings have characterized an epigenetic determinism associated with reduced H3K36 tri-methylation, detected in ccRCC molecular subtypes and correlated with unfavorable outcomes, suggesting that SETD2 loss may not be restricted to VHL disease [18]. SETD2, ubiquitously expressed SET-containing methyltransferase, trimethylates lysine 36 of histone H3 (H3K36me3) along transcribed gene bodies encompassing in a wide-open chromatin structure. H3K36me3 enriches across exons and, due to histone-DNA contacts, induces higher nucleosome density. Decreasing nucleosome occupancy at exon boundaries increases nucleosome turnover, facilitating Pol II passage across splice sites to promote exon definition and splicing fidelity. By adopting decompacted nucleosomal arrays, tumor-specific mutations impair H3K36me3-mediated exon definition, decrease fidelity of co-transcriptional splicing, and increase the inclusion of unique exons. Additionally, ectopically methylated loci generated by mutant tumors exhibit genome-wide altered nucleosome positioning [34]. Collectively, these findings mechanistically define how SETD2 mutations dysregulate alternative splicing and actively utilize physiologic chromatin forces to directly impact splicing fidelity [35].

ROLE OF SETD2 IN RENAL CELL CARCINOMA

The findings and functions of PBRM1 and SETD2 genes on renal cell carcinoma, and the interrelation between PBRM1 deletions and SETD2 mutations propose a potential therapeutic approach, have attracted a great deal of attention and have been studied actively by various research groups [31]. The nature of the gene mutations that occur in PBRM1 and SETD2 is different: for PBRM1, the majority of gene alterations are deletions, some of which may be germline variations; and for SETD2, the majority are single nucleotide substitutions or insertions and deletions. Concerning how these gene alterations contribute to renal carcinogenesis, some studies report that mutations in PBRM1 or SETD2 have few, if any, effects on the expression of their target genes. Detailed examination of the TCGA database indeed showed that PBRM1 deletion mutations had no effect on the RNA expression of theoretically related genes [8, 26]. Similar results were found for PBRM1 deletions [36]. Rather than these expressions, alterations in PBRM1 and SETD2 mutations were found to be significantly correlated with the histological grade and stage of RCC [18]. This result was also found in studies using The Cancer Genome Atlas database [37] more than a half patients with high stage and grade in the ccRCC deletion group belong to group 1 or 2, respectively. Similarly, 70% of the carcinoma setting occur in individuals falling into group 1 or 2 [38]. Together, these data suggest that PBRM1 deletion and SETD2 mutations are likely to be tumor-promoting by enhancing tumor malignancy, and that the molecular pathways influenced by these mutations are not involved in cell proliferation [39]. According to them mutational analysis, the novel variant of SETD2 V882I was determined as loss-of-function [38]. In the single cell growth assay, RCC4 Setd2-/- V882I and pFLAG-SETD2 V882I did not exhibit significant effects on colony formation with or without the supplementation of doxycycline. In addition to no significant increase in H3K36me3 at 23% GC loci, fluctuation H3K36me3 expression was not shown by IF. On the other hands, the supplementation of doxycycline in this setting portrayed that H3K36me3 enrichment was significantly elevated to similar baseline wt levels just after 5 days [39]. These results suggest that not only R1621 and V1662, the loss of SETD2 activity by mutating the highly conserved motif in the bifurcated SET domain, also showed a loss of the H3K36me3 increase function during the last month, leading to accumulation of SETD2 substrate and genome instability [40]. Hadlots of H3K36me3 enrichment on GC notably failed to elevate cellular level of CDC9A in RCC4 Setd2-/- V882I, suggesting that optimal cell condition might be crucial for regulating SETD2 bioorthogonal activity.

Together, the above results demonstrate that successful analytical approach using the simple model used enabled the identification of potentially deleterious SETD2 mutations in RCC [18].

COMPARATIVE ANALYSIS OF PBRM1 AND SETD2 IN RENAL CELL CARCINOMA

There are now five major gene families known to be significantly mutated in ccRCC, with an overarching mutational frequency range of 2.3–8.5% and including mutations of tens to hundreds of genes. However, very little is known regarding the relationships between PBRM1 or SETD2 and the genes in the other families and how they synergize to create the ccRCC landscape [41]. Future studies are needed to reveal deep biological relationships between PBRM1 and SETD2 [18]. Upset plots represent the intersections between gene sets, with bar plots showing the individual set sizes. These plots illustrate that different potential biological consequences result from truncating mutations of PBRM1 and VHL, BAP1, and/or SETD2 in ccRCC, indicating distinct or complementary functional relationships among these genes [40]. Annotation, enrichment, and network analysis of the downstream genes of this unique set of ccRCC samples revealed that PBRM1Δ and VHLΔBAP1ΔSETD2Δ could play complementary roles in activating fibroblast growth factor signaling through dysregulation of the KLF5-GNA13-ERBB3-MAPK pathway [41]. Published data from patient ccRCC samples were retrieved [42]. Renal cell carcinoma (RCC) is the most lethal urological tract malignancy in adults, with clear cell RCC (ccRCC) accounting for 75–80% of cases [25]. The majority of sporadic cases are associated with inactivation of the von Hippel-Lindau (VHL) gene [43]. Besides VHL loss, ccRCC exhibits deregulation of multiple signaling pathways that promote angiogenesis and tumor growth [5]. Exome sequencing of ccRCC samples has identified several novel genes, with PBRM1 and SETD2 identified as two of the five most significantly mutated in ccRCC [18]. PBRM1 and SETD2 are both classified as tumor suppressor genes (TSGs) given that the majority of their mutations are inactivating [39] [7]. Tumors with PBRM1 mutations appear to have distinct biology from those with SETD2 mutations [18]. PBRM1-mutated ccRCCs exhibit a two-fold lower mutation burden than wild-type tumors and are the most common type of ccRCC defined by chromosome aberrations [44]. In contrast, either PBRM1 or SETD2 can drive a high number of copy number variations (CNVs), which are in turn associated with a worse outcome [45]. This integrated analysis asserts the unique contributions of PBRM1 and SETD2 in driving ccRCC genomic instability and tumor progression and adds a new layer of understanding to the complex biology of ccRCC [18].

SIMILARITIES AND DIFFERENCES IN FUNCTION

PBRM1 and SETD2 mutations are the 1st and 3rd most frequent gene mutations (~40% and ~20% mutation rate in ccRCC tumors) in ccRCCs, respectively [18][44]. Both genes function in a chromatin remodeling context, but PBRM1 is a SWI/SNF family chromatin remodeler and a regulator of transcription while SETD2 encodes a histone methyltransferase. The results of this review suggest that the two genes share several functional similarities (tumor suppression, alteration of cell cycle regulation and genomic integrity), but the context of PBRM1 and SETD2 mutations will have discordant genetic interactions and associated pathways [46]. Elucidating these distinctions in ccRCC tumorigenesis will be important to understand how PBRM1 and SETD2 mutations influence clinical outcomes and response to therapeutics [47]. Taken together, this comparative dialogue will provide insight into the gene-specific roles of PBRM1 and SETD2 in ccRCC carcinogenesis and will ultimately help to optimize patient therapies. Loss-of-function mutations in the Polybromo-1 (PBRM1) and SET Domain Containing 2 (SETD2) genes in renal cell carcinoma (RCC) patients have been highly associated with tumor aggressiveness and poor patient prognosis [25]. Genomic analysis of primary and metastatic RCC tumors has revealed a connection between the timing of PBRM1 and SETD2 mutations and disease state progression, where PBRM1 mutations are earlier events that alter chromatin accessibility, and later acquisition of SETD2 mutations exacerbates these changes [31].

IMPACT ON DISEASE PROGRESSION

The impact of PBRM1 and SETD2 mutations on determining either association with decreased survival or propensity to metastasize is analyzed and discussed, while summarizing and reviewing recent reports directed at this each aim [18]. The role of the two genes in the development of consecutive primary clear cell renal cell carcinoma (ccRCC) is also assessed, examining the molecular profile of the two genes for possible clonal relations, and investigating whether the development of metastasis is dependent on the multi-regionally heterogeneous aspect of these genes [48]. Comparatively few reports deal with the clinical effect of PBRM1 and SETD2 gene mutations on renal cell carcinoma (RCC), currently the third most deadly genitourinary tract cancer [18]. However, as their biological effects on RCC and

ccRCC are elucidated, analyses encompassing larger cohorts of RCC and ccRCC patients either with or without gene mutations are being reported [49]. Thus, current knowledge comprising this review mostly focuses on alterations to PBRM1 and SETD2 genes found in ccRCC and gnom AD information considering their changes in RCC pan-cancer cohorts [50]. Adverse clinical results are more apparent in ccRCC patients experiencing changes in both genes when analyzed in all commonly altered kidney cancer genes [51]. In addition, based on single-nucleotide variant (SNV) and copy number variant (CNV) data of PBRM1 and SETD2, a gene set enrichment analysis (GSEA) is also reviewed for insight into the biological effect these changes bring to ccRCCs [52]. The correlation between changes to two genes and the formation of metastasis in ccRCC is then looked upon through histopathologic and molecular observations made on primary sites and its metastasized sites in ccRCC patients [53]. Ultimately, it is hoped a push is given to oncologists in paying regards to these genes mutations in molecular profiling of ccRCC patients, which in turn may influence decisions made on how best to manage such individuals [29].

CLINICAL IMPLICATIONS AND THERAPEUTIC STRATEGIES

In this precision medicine era, advances in technologies are providing the opportunities to detect various molecular abnormalities that can be targets for individualized treatment approaches [54]. Starting from inherited genes, the spectrum of these molecular targets has been expanded to somatically acquired changes, and companion diagnostics in therapeutic strategies [55]. However, many clinicians do not yet integrate genetic profiling into routine oncological practice [56]. This text aims to summarize the recently defined implications of PBRM1 and SETD2 genes in renal cell carcinoma (RCC)-genealogies, prognosis, preferred therapeutic strategies, and challenges [55]. A good understanding of genetic contexts underlying PBRM1 and SETD2 abnormalities can offer essential information to the considerations of therapeutic strategy [44][47]. Additionally, it is worthy for researchers to further elucidate the mechanisms of the pronounced mutagenicity of PBRM1 and SETD2 mutations and to develop drugs targeting distinctive pathways and diseases caused by the alterations of these genes [52]. Advanced clear cell Renal Cell Carcinoma (ccRCC) has a poor prognosis and is generally refractory to standard chemotherapy and/or radiation therapy, so novel therapies are urgently needed [57]. RCC provides an attractive case study for this challenge, due to the remarkable progress in understanding molecular pathogenesis [29]. Large efforts have been made in identifying and understanding the alterations that drive RCC and kill off key checkpoints [15]. Therapy approaches in RCC, including the most recent ones [17]. In recent years, a deeper understanding of the molecular basis of RCC was obtained, and several new drugs have been tested in clinical trials, demonstrating additional to significant therapeutic promise [58]. Various promising strategies are currently under investigation, including targeted therapies, immunotherapies, and their combinations [59]. Using genetic information to stratify patients and to select more appropriate treatments is a crucial point in the decision-making process that can significantly improve the ability to benefit from therapy and, therefore, enhance outcomes [60]. Further research and, above all, the integration of genetic research into ongoing clinical trials and routine clinical practice aim to adjust the current strategy and help the development of novel efficient therapeutic approaches [61].

CURRENT THERAPIES TARGETING PBRM1 AND SETD2

Clear cell Renal Cell Carcinoma (ccRCC) is one of the tumors with a complicated genetic background, in which PBRM1 gene is one of the most frequently altered genes [22]. SMARCB1/2 mostly contain genes that encode the SWI/SNF complex, which can help generate an open chromatin state by moving or ejecting nucleosomes [62]. BRG1 and BRM encode a DNA-dependent ATPase of the SWI/SNF complex [63]. It is known that mutations in PBRM1 often occur in the domain encoding the protein-protein interaction (PPI) site of the SWI/SNF complex [62]. PBRM1 has three KID domains, two BAH domains and one HMG box domain. Acetylation and methylation marks are involved in chromatin remodeling, which can be recognized by chromatin remodeling complexes and modified the nucleosome structure, impacting the accessibility of other proteins to DNA [64]. CC2D1A, BCL11A, BRD7, and UAP1 are mutated in less than 10% of ccRCC samples, and KDM5C, SETD2, BAP1, and TCEB1 are more susceptible to biallelic inactivation [63]. SET domain containing 2 (SETD2) gene RING-type E3 ligase comprises an array of RING finger proteins and really interesting new gene finger domain proteins are components of distinct E3 ubiquitin ligases, which mediate ubiquitination of target proteins [65]. RING finger proteins often act in complexes with specific E2 ubiquitin-conjugating enzymes [64], ccRCC is one of the most common malignant tumor types in the world, accounting for approximately 65,000 to 100,000 deaths worldwide [66]. The development of surgery, includ-

ing targeted molecular therapy, has led to increased disease-free survival rates. However, patients with advanced and metastatic RCC have limited treatment options, including surgical tumor resection, radiotherapy, new drug therapy, and immunotherapy [67].

CONCLUSIONS

Synthesizing the invaluable insights and extensive knowledge gained throughout the rigorous and comprehensive review serves as a crucial reminder that renal cell carcinoma (RCC) is an intricate, polygenetic, and invasive type of solid tumor that is driven by a diverse and multifaceted array of genetic alterations. Within this complex landscape, the PBRM1 and SETD2 genes frequently play critical and pivotal roles during the evolutionary stages of clear cell renal cell carcinoma (ccRCC) and exhibit a wide range of variable subclonal genetic alterations that significantly expand their already expansive clonal evolutionary history over time. However, a thorough and comprehensive understanding of the driver genetic alterations that influence RCC is not only absolutely necessary but could also provide fundamental and essential genetic insights that are invaluable for advancing clinical practices in oncology. The analyses reviewed in this context not only substantiate but also reinforce the vital relationship between mutations in PBRM1 and SETD2 and the complex genetic evolution of ccRCC. Given the notable and high prevalence of genetic alterations involving PBRM1 and SETD2 in ccRCC cases, these significant findings might possess substantial practical and implicational values that could influence the field of oncology. Specifically, (i) PBRM1 mutation could serve as a tumor co-initiator that actively cooperates with other driver gene mutations in the formation of the preneoplastic cell population, thus highlighting its essential role in the process of tumorigenesis. (ii) Furthermore, the formation of a subclonal copy number loss could act as a new and distinctive branch, promoting the advancement of the PBRM1 mutated clone to a more dominant and predominant status within the tumor hierarchy itself. (iii) Moreover, the cooperation of SETD2 mutation with PBRM1 mutation is absolutely crucial in establishing the potential for distant metastatic spread of the disease, enhancing the complexity of the tumor environment. The above predictions and hypotheses may pave the way for the development of collaborative and innovative therapeutic avenues and fundamentally reinforce the pressing necessity for the ongoing exploration and investigation of PBRM1 and SETD2 genes in this crucial context. Furthermore, the pharmacologic studies undertaken thus far suggest the considerable potential for identifying promising and innovative treatment strategies that could prove to be effective against RCC. By actively integrating those crucial discoveries into larger and more diverse RCC research communities and institutions, there exists significant potential for transformational novel therapies to emerge in the future landscape of cancer treatment that could positively impact patient outcomes. These informative and promising prospects illustrate the hopeful benefits and positive impacts of the emerging genetic findings combined with advanced technologies in the understanding, prevention, and comprehensive management of renal cell carcinoma in both clinical and research settings.

REFERENCES

1. Ricketts CJ, De Cubas AA, Fan H, et al. The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma. Cell Rep. 2018 Apr 3;23(1):313-326.e5. doi: 10.1016/j.celrep.2018.03.075 DOI
2. Piva F, Giulietti M, Occhipinti G, et al. Computational analysis of the mutations in BAP1, PBRM1 and SETD2 genes reveals the impaired molecular processes in renal cell carcinoma. Oncotarget. 2015 Oct 13;6(31):32161-8. doi: 10.18632/oncotarget.5147.2015 DOI
3. Riggio AI, Varley KE, Welm AL. The lingering mysteries of metastatic recurrence in breast cancer. British journal of cancer. 2021;Jan;124(1):13-26. doi: 10.1038/s41416-020-01161-4 DOI
4. Sehgal P, Chaturvedi P. Chromatin and cancer: implications of disrupted chromatin organization in tumorigenesis and its diversification. Cancers. 2023; Jan 11; 15(2): 466. doi: 10.3390/cancers15020466 DOI
5. Mazumder S, Higgins PJ, Samarakoon R. Downstream targets of VHL/HIF-α signaling in renal clear cell carcinoma progression: mechanisms and therapeutic relevance. Cancers. 2023;Feb 19;15(4):1316. doi: 10.3390/cancers15041316 DOI
6. Fernández NB, Sosa SM, Roberts JT, Recouvreux MS, Viegas LR, Christenson JL, et al. RUNX1 Is Regulated by Androgen Receptor to Promote Cancer Stem Markers and Chemotherapy Resistance in Triple Negative Breast Cancer. Cells. 2023 Jan 29;12(3):444. doi: 10.3390/cells12030444 DOI
7. Walton J. Targeting epigenetic regulation in clear cell renal cell carcinoma reveals PRMT1 as a novel target. 2020;80(16 Suppl):1766-1766: doi: 10.1158/1538-7445.AM2020-1766 DOI
8. Aili A, Wen J, Xue L, Wang J. Mutational analysis of PBRM1 and significance of PBRM1 mutation in anti-PD-1 immunotherapy of clear cell renal cell carcinoma. Sec Molec Cell Oncol. 2021;11: doi: 10.3389/fonc.2021.712765 DOI

9. Mohd AB, Ghannam RA, Mohd OB, et al. Etiologies, gross appearance, histopathological patterns, prognosis, and best treatments for subtypes of renal carcinoma: an educational review. Cureus. 2022 Dec 9;14(12):e32338. doi: 10.7759/cureus.32338 DOI
10. Dias Carneiro APC, Marques Monteiro FS, Soares A. PBRM1 mutations as a predictive biomarker for immunotherapy in metastatic renal cell carcinoma: a systematic review. Kidney Cancer 2021;5:79-92: doi 10.3233/KCA-210111 DOI
11. Olav DD, Morten S, Wilhelm LC. Renal cell carcinoma and kidney transplantation: a narrative review. Transplantation. 2022; 106(1): e52-e63. doi: 10.1097/TP.0000000000003762 DOI
12. Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, et al. Epidemiology of Renal Cell Carcinoma. World J Oncol. 2020; 11(3): 79–87. doi: 10.14740/wjon1279. DOI
13. Zarrabi K, Walzer E, Zibelman M. Immune checkpoint inhibition in advanced non-clear cell renal cell carcinoma: leveraging success from clear cell histology into new opportunities. Cancers. 2021; 13(15): 3652. doi: 10.3390/cancers13153652 DOI
14. Kabaria R, Klaassen Z, Terris MK. Renal cell carcinoma: links and risks. Int J Nephrol Renovasc Dis. 2016;9:45-52. doi: 10.2147/IJNRD.S75916 DOI
15. Jonasch E, Lyn Walker C, and Rathmell WK. Clear cell renal cell carcinoma ontogeny and mechanisms of lethality. Nature Rev Nephrol. 2021;17(4):245-261. doi:10.1038/s41581-020-00359-2 DOI
16. Mehdi A, Riazalhosseini Y. Epigenome Aberrations: Emerging Driving Factors of the Clear Cell Renal Cell Carcinoma. Int J Mol Sci. 2017; 18(8): 1774. doi: 10.3390/ijms18081774 DOI
17. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M, and Mafakhe L. Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment. G Ital Nefrol. 2022; ISSN: 1724-5990.
18. Walton J, Lawson K, Prinos P, Ailles L, Arrowsmith C, Ailles L. PBRM1, SETD2 and BAP1 - the trinity of 3p in clear cell renal cell carcinoma. Nat Rev Urol. 2023;20(2):96-115. doi: 10.1038/s41585-022-00659-1 DOI
19. Liu Y, Li Y, Xu H, Zhou L, Yang X , Wang C. Exploration of Morphological Features of Clear Cell Renal Cell Carcinoma with PBRM1, SETD2, BAP1, or KDM5C Mutations. Int J Surg Pathol. 2023; 31(8): 1485-1494. doi: 10.1177/10668969231157317 DOI
20. Liu J, Xie X, Xue M, et al. A Pan-Cancer Analysis of the Role of PBRM1 in Human Tumors. Stem Cells Int. 2022;2022:7676541. doi: 10.1155/2022/7676541 DOI
21. Hwang J, Bang S, Choi MH, Yang JH, Park US, Lee HE. Discovery and Validation of Survival-Specific Genes in Papillary Renal Cell Carcinoma Using a Customized Next-Generation Sequencing Gene Panel. Cancers. 2024;16:2006. doi: 10.3390/cancers16112006 DOI
22. Aili A, Wen J, Xue L, Wang J. Mutational Analysis of PBRM1 and Significance of PBRM1 Mutation in Anti-PD-1 Immunotherapy of Clear Cell Renal Cell Carcinoma. Front Oncol. 2021; 11:712765. doi: 10.3389/fonc.2021.712765 DOI
23. Yoshida T, Sakai K, Kaibori M, et al. Downregulated expression of PBRM1 in sarcomatoid hepatocellular carcinoma. Oncology letters. 2024;27:124: doi: 10.3892/ol.2024.14257 DOI
24. Mullen J, Kato S, Sicklick JK, Kurzrock R. Targeting ARID1A mutations in cancer. Cancer Treat Rev. 2021;100:102287. doi:10.1016/j.ctrv.2021.102287 DOI
25. Chowdhury B, Porter EG, et al. PBRM1 regulates the expression of genes involved in metabolism and cell adhesion in renal clear cell carcinoma. PLoS One. 2016 Apr 21;11(4):e0153718. doi:10.1371/journal.pone.0153718 DOI
26. Dai J, Cui Y, Liang X, Xu J, et al. PBRM1 mutation as a predictive biomarker for immunotherapy in multiple cancers. Front Genet. 2023 Jan;13:1066347. doi:10.3389/fgene.2022.1066347 DOI
27. Esteller M, Dawson MA, Kadoch C, et al. The epigenetic hallmarks of cancer. Cancer Discov. 2024 Oct;14(10):1783-1809. doi:10.1158/2159-8290.CD-24-0296 DOI
28. Lane KA, Harrod A, Wu L, et al. PBRM1 directs PBAF to pericentromeres and protects centromere integrity. Nat Commun. 2025;16:1980. doi:10.1038/s41467-025-57277-9 DOI
29. Sharma R, Kannourakis G, Prithviraj P. Precision medicine: an optimal approach to patient care in renal cell carcinoma. Front Med (Lausanne). 2022;9:766869. doi:10.3389/fmed.2022.766869 DOI
30. Moreta Moraleda C. Biomarkers and Combinatorial Drug Targets for a Personalized Therapy in Colorectal Cancer. 2022. https://diposit.ub.edu/dspace/handle/2445/186631 [Access: January 2025].
31. Kanu N, Grönroos E, Martinez P, et al. SETD2 loss-of-function promotes renal cancer branched evolution through replication stress and impaired DNA repair. Oncogene. 2015 Nov 12; 34(46): 5699–708. doi: 10.1038/onc.2015.24 DOI
32. Tiedemann RL, Hlady RA, Hanavan PD, Lake DF, Tibes R, Lee JH, Choi JH, Ho TH, Robertson KD. Dynamic reprogramming of DNA methylation in SETD2-deregulated renal cell carcinoma. Oncotarget. 2016 Jan 12;7(2):1927-46. doi: 10.18632/oncotarget.6481 DOI
33. Liang WW, Lu RJH, Jayasinghe RG, Foltz SM, et al. Integrative multi-omic cancer profiling reveals DNA methylation patterns associated with therapeutic vulnerability and cell-of-origin. Cancer Cell. 2023 Aug;41(9):1-19. doi: 10.1016/j.ccell.2023.07.013 DOI
34. Čizmazia V. Roles of histone H3 lysine methylation in the gene expression regulation. 2023. http://hdl.handle.net/20.500.11956/181353 [Access: January 2025].
35. Rivera OD. Alternative mRNA splicing redefines the landscape of commonly dysregulated genes across the acute myeloid leukemia patient population. [Doctoral dissertation]. University of Pennsylvania; 2021.

36. Antonios JP, Yalcin K, Darbinyan A, Koo A. Biallelic inactivation of PBRM1 as a molecular driver in a rare pineoblastoma case: illustrative case. J Neurosurg Case Lessons. 2022Apr 4;3(14):CASE2213 doi: 10.3171/CASE2213 DOI
37. Di Daniele N, Juhl H, Mauriello A, et al. Global mapping of cancers: The Cancer Genome Atlas and beyond. Mol Oncol. 2021; 15(11): 2823–2840. doi:10.1002/1878-0261.13056 DOI
38. Rysz J, Franczyk B, Ławiński J, Gluba-Brzózka A. Characteristics of clear cell papillary renal cell carcinoma (ccpRCC). Int J Mol Sci. 2022; 23(1):151. doi:10.3390/ijms23010151 DOI
39. Langbein LE. Regulation of the Type I Interferon Pathway by Cancer Genes in Clear Cell Renal Cell Carcinoma. Thomas Jefferson University; 2022. https://jdc.jefferson.edu/dissertations/AAI30242033/ [Access: January 2025]
40. Molenaar TM, van Leeuwen F. SETD2: from chromatin modifier to multipronged regulator of the genome and beyond. Cell Mol Life Sci. 2022;79:346. doi:10.1007/s00018-022-04352-9 DOI
41. Wang Y, Guo X, Bray MJ, et al. An integrative genomics approach for identifying novel functional consequences of PBRM1 truncated mutations in clear cell renal cell carcinoma (ccRCC). BMC Genomics. 2016;17(Suppl 7):515. doi:10.1186/s12864-016-2906-9 DOI
42. Papanastasiou AD, Peroukidis S, Sirinian C, Arkoumani E, Chaniotis D, Zizi-Sermpetzoglou A. CD44 expression in clear cell renal cell carcinoma (ccRCC) correlates with tumor grade and patient survival and is affected by gene methylation. Genes (Basel). 2024;15(5):537. doi:10.3390/genes15050537 DOI
43. Hudler P, Urbancic M. The role of VHL in the development of von Hippel-Lindau disease and erythrocytosis. Genes (Basel). 2022; 13(2):362. doi:10.3390/genes13020362 DOI
44. Glennon KI. Investigating the Genomic Underpinnings of Renal Cell Carcinoma, Genetic Predisposition, and Their Clinical Implications. McGill University, Canada;2023.
45. Bai J, Shi J, Li C. Whole genome sequencing of skull-base chordoma reveals genomic alterations associated with recurrence and chordoma-specific survival. Nat Commun. 2021;12:757. doi:10.1038/s41467-021-21026-5 DOI
46. Krishnamurthy N, Kato S, Lippman S, Kurzrock R. Chromatin remodeling (SWI/SNF) complexes, cancer, and response to immunotherapy. J Immunother Cancer. 2022 Sep 2;10(9):e004669. doi:10.1136/jitc-2022-004669 DOI
47. Ahmed AY. Determination and comparison of the relationship between COVID-19 and breast cancer, triple negative breast cancer and clear cell renal cell carcinoma by in silico approaches. M.Sc. thesis. Kirsehir Ahi Evran University, Turkey;2023.
48. Dudani S, de Velasco G, Wells JC, et al. Evaluation of clear cell, papillary, and chromophobe renal cell carcinoma metastasis sites and association with survival. JAMA Netw Open. 2021; 4(1): e2021869. doi:10.1001/jamanetworkopen.2020.21869 DOI
49. Sokouti B. A systematic investigation of clear cell renal cell carcinoma using meta-analysis and systems biology approaches. Mol Genet Genomics. 2024;299:87. doi:10.1007/s00438-024-02180-z DOI
50. Liu W, Fu Q, An H, Chang Y, Zhang W, Zhu Y, Xu L, Xu J. Decreased expression of SETD2 predicts unfavorable prognosis in patients with nonmetastatic clear-cell renal cell carcinoma. Medicine (Baltimore). 2015 Nov; 94(45):e2004. doi:10.1097/MD.0000000000002004 DOI
51. Nezami BG, MacLennan GT. Clear cell renal cell carcinoma: a comprehensive review of its histopathology, genetics, and differential diagnosis. Int J Surg Pathol. 2025; 33(2):265-280. doi: 10.1177/10668969241256111 DOI
52. Kumar SS, Khandekar N, Dani K, Bhatt SR. A scoping review of population diversity in the common genomic aberrations of clear cell renal cell carcinoma. Oncology. 2025; 103(4): 341-350. doi:10.1159/000541370 DOI
53. Bartha Á, Győrffy B. TNMplot.com: a web tool for the comparison of gene expression in normal, tumor and metastatic tissues. Int J Mol Sci. 2021;22(5):2622. doi:10.3390/ijms22052622 DOI
54. Wang RC, Wang Z. Precision medicine: disease subtyping and tailored treatment. Cancers (Basel). 2023;15(15):3837. doi:10.3390/cancers15153837 DOI
55. Claringbould A, Zaugg JB. Enhancers in disease: molecular basis and emerging treatment strategies. Trends Mol Med. 2021 Nov; 27(11): 1060-1073. doi:10.1016/j.molmed.2021.07.012 DOI
56. Cobain EF, Wu Y, Vats P, et al. Assessment of clinical benefit of integrative genomic profiling in advanced solid tumors. JAMA Oncol. 2021;7(4):525-533. doi:10.1001/jamaoncol.2020.7987 DOI
57. Schiavoni V, Campagna R, Pozzi V, et al. Recent advances in the management of clear cell renal cell carcinoma: novel biomarkers and targeted therapies. Cancers (Basel). 2023;15(12):3207. doi:10.3390/cancers15123207 DOI
58. Pontes O, Oliveira-Pinto S, Baltazar F, Costa M. Renal cell carcinoma therapy: Current and new drug candidates. Drug Discov Today. 2022; 27(1):304-314. doi:10.1016/j.drudis.2021.07.009. DOI
59. Butterfield LH, Najjar YG. Immunotherapy combination approaches: mechanisms, biomarkers and clinical observations. Nat Rev Immunol. 2024; 24: 399–416. doi:10.1038/s41577-023-00973-8. DOI
60. Navani V, Heng DYC. Treatment Selection in First-line Metastatic Renal Cell Carcinoma—The Contemporary Treatment Paradigm in the Age of Combination Therapy: A Review. JAMA Oncol. 2022; 8(2): 292-299. doi:10.1001/jamaoncol.2021.4337 DOI
61. Holmes MV, Richardson TG, Ference BA, et al. integrating genomics with biomarkers and therapeutic targets to invigorate cardiovascular drug development. Nat Rev Cardiol. 2021; 18(7): 435–453. doi:10.1038/s41569-020-00493-1 DOI

62. Ntiamoah EB, Li D, Appiah-Otoo I, Twumasi MA, Yeboah EN. Towards a sustainable food production: Modelling the impacts of climate change on maize and soybean production in Ghana. Environ. Sci. Pollut. Res. 2022;29:72777-72796. doi: 10.1007/s11356-022-20962-z DOI
63. Singh A, Modak SB, Chaturvedi MM, et al. SWI/SNF Chromatin Remodelers: Structural, Functional and Mechanistic Implications. Cell Biochem Biophys. 2023; 81(2):167-187. doi:10.1007/s12013-023-01140-5 DOI
64. Tollefsbol TO. Chromatin Readers in Health and Disease. Academic Press;2023.
65. Qi Y, Rezaeian AH, Wang J, Huang D, Chen H, et al. Molecular insights and clinical implications for the tumor suppressor role of SCFFBXW7 E3 ubiquitin ligase. Biophysica Acta (BBA). 2024;1879(5):189140. doi:10.1016/j.bbcan.2024.189140 DOI
66. Khaleq MAA, Ahmed AY, Awad AK, Fahed AA, Fahed FA, Ali GS, Huwadi TM. Point prevalence study of antibiotics use in Ramadi hospitals. Wiad Lek. 2025; 78(2):396-401. doi: 10.36740/WLek/199783. DOI
67. Terzo EA, Lim AR, Chytil A, et al. SETD2 loss sensitizes cells to PI3Kβ and AKT inhibition. Oncotarget. 2019 Jan 18; 10(6): 647-659. doi: 10.18632/oncotarget.26567. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Maysaa Ali Abdul Khaleq
College of Pharmacy, University of Al Maarif
Al Anbar, Iraq
e-mail: dr.maysaa.ali@uoa.edu.iq

ORCID AND CONTRIBUTIONSHIP

Ammar Yasir Ahmed: 0009-0005-1921-8557 B C D
Maysaa Ali Abdul Khaleq: 0000-0003-3548-7835 A F
Rusul Qasim Mohammed: 0009-0007-9843-3523 E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 20.02.2025
ACCEPTED: 15.05.2025