

Wiadomości Lekarskie

Medical Advances

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



Volume LXXVIII, Issue 9, SEPTEMBER 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



Volume LXXVIII, Issue 9, SEPTEMBER 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

Copyright: © ALUNA Publishing

Articles published on-line and available in open access are published under Creative Commons Attribution-Non Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

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

Editor in-Chief:

Prof. Paweł Kalinski – Buffalo, USA

Honorary Editor in-Chief:

Prof. Władysław Pierzchała – Katowice, Poland

Deputy Editor in-Chief:

Prof. Waldemar Kostewicz – Warsaw, Poland
President Polish Medical Association

Statistical Editor:

Dr Lesia Rudenko – Konstancin-Jeziorna, Poland

Managing Editor:

Agnieszka Rosa – amarosa@wp.pl

International Editorial Office:

Nina Radchenko (editor) – n.radchenko@wydawnictwo-aluna.pl

International Editorial Board – in-Chief:

Marek Rudnicki

Chicago, USA

International Editorial Board – deputy in-Chief:

Aleksander Sieroń

Katowice, Poland

International Editorial Board – Members:

Stalbek M. Akhunbaev	Bishkek, Kyrgyzstan	George Krol	New York, USA
Kris Bankiewicz	San Francisco, USA	Jerzy Robert Ładny	Białystok, Poland
Christopher Bara	Hannover, Germany	Stella Nowicki	Memphis, USA
Krzysztof Bielecki	Warsaw, Poland	Alfred Patyk	Gottingen, Germany
Zana Bumbuliene	Vilnius, Lithuania	Waldemar Priebe	Houston, USA
Stanislav Czudek	Ostrava, Czech Republic	Maria Siemionow	Chicago, USA
Mowafaq Muhammad Ghareeb	Baghdad, Iraq	Vladyslav Smiiianov	Sumy, Ukraine
Nataliya Gutorova	Kharkiv, Ukraine	Tomasz Szczepański	Katowice, Poland
Marek Hartleb	Katowice, Poland	Andrzej Witek	Katowice, Poland
Roman Jaeschke	Hamilton, Canada	Jerzy Woy-Wojciechowski	Warsaw, Poland
Andrzej Jakubowiak	Chicago, USA	Zbigniew Wszolek	Jacksonville, USA
Peter Konturek	Saalfeld, Germany	Vyacheslav Zhdan	Poltava, Ukraine

CONTENTS

ORIGINAL ARTICLES

Renata V. Symonenko, Alina I. Kapshyk, Yevhen A. Koval, Zinaida E. Zhehulovich, Olena O. Astapenko, Vitalii D. Chopchyk, Oleg V. Tyrsa

Manifestations of dental diseases following Covid-19: pain and oral health impacts. Using the broad population survey opportunities

1701

Kyryl G. Krymovskyy, Oleksandr A. Kaniura, Zinaida E. Zhehulovych, Kateryna V. Storozhenko, Yurii I. Babaskin, Oleksandr V. Bida, Tetyana M. Brychko

Comparative analysis of cephalometric K-angle index of mixed dentition patients

1710

Yulia M. Volosivska, Anastasiya G. Babintseva, Yuliya D. Hodovanets, Volodymyr A. Petrov, Nataliya I. Kovtyuk, Nataliya O. Popeliuk, Oksana I. Yurkiv

Characteristics of energy metabolism in full-term newborns with neonatal hyperbilirubinemia

1718

Mykhailo Yu. Kochmar, Yuliia V. Lytvak, Oleksandr I. Hetsko, Oleksandr M. Kochmar, Ihor K. Kharkhalis, Olesya O. Valko

Microscopic changes in the pancreas at late stages after experimental exposure to monosodium glutamate

1725

Yaroslav M. Popovych

Indicators of venous blood flow in the long-term period after inferior vena cava thrombosis

1731

Olesya M. Horlenko, Khrystyna A. Hechko, Mykhaylo M. Hechko, Fedir V. Horlenko, Olga A. Pushkarenko

Cytomorphological characteristics of the nasopharyngeal zone mucosa in children with Covid-19

1741

Stepan S. Filip, Rudolf M. Slivka, Yuriy P. Skrypynets, Petro P. Popyurkanych, Andrii M. Bratasiuk

Use of high-intensity laser for prevention and treatment of osteomyelitic complications in patients with traumatic disease

1746

Olexii I. Dronov, Inna O. Kovalska, Andrii I. Horlach, Ivanna A. Shchyhel, Vitaliy R. Balyak, Vadym O. Kostiukevich

Prediction of abdominal compartment syndrome in patients with severe acute pancreatitis

1751

Olha S. Musiienko, Vitalii V. Parii, Oleksii I. Morhun, Ihor G. Diadik

Development of a methodology and study of the stress-strain state of the biomechanical system "jaw-implant"

1758

Anastasiia M. Kaliga, Oksana L. Palladina, Olena A. Dulo, Svitlana A. Burmei, Dmytro V. Shtanagei, Nadiya V. Boyko

Dynamics of gut microbiota in qualified female boxers

1765

Bohdan G. Mykhajlychenko, Vladyslav O. Humeniuk, Iurii O. Mochalov, Ihor V. Tukalo, Tetiana M. Vakhrusheva, Ihor O. Bilichenko, Oleksandr O. Mochalov

The influence of implant channel preparation technique on the mechanical and radiological properties of bone during the dental mini-implants placement (ex-vivo experimental study)

1771

Iryna A. Holovanova, Orest Ya. Vovk, Tetiana P. Mats, Valentina L. Filatova, Olena V. Filatova, Alla M. Podvin, Maksim V. Khorosh

Medical and social substantiation of early detection and prevention of visual forms of cervical cancer

1777 

Dmytro O. Samofalov, Dmytro Androshchuk, Igor Korpusov, Leonid Kopus, Nataliya Izhytska

Management of damage control surgery and resuscitation at different stages of evacuation.

Tough lesson from the frontier of Russian-Ukrainian war

1789 

Grygoriy P. Griban, Natalia A. Lyakhova, Inna O. Asauliuk, Oleksandra Yu. Brezdeniuk, Oksana V. Zeleniuk, Valentin P. Golub, Nataliya A. Prudyvus

Self-assessment of the quality of life by Ukrainians during martial law and ways to improve it

1798 

Yelizaveta Stroj, Andriy Volkohon, Olha Obukhova

Analysis of the association of rs1333049-polymorphic variants of the *ANRIL* gene with the development of clear cell renal cell carcinoma in Ukrainian population

1805 

Grygoriy Griban, Olha S. Zablotska, Inna O. Asauliuk, Dmytro G. Oleniev, Svitlana M. Dmytrenko, Oleh L. Morin, Nataliia O. Terentieva

Peculiarities of rehabilitation of patients with musculoskeletal disorders: what has changed during the war in Ukraine

1813 

Olha L. Korobanova, Neonila I. Korylchuk, Oleh Burliev, Iryna B. Romash, Kateryna V. Dzivak, Mariya V. Blyzniuk, Ihor S. Tymkiv

Training methods for correction of behavioral rigidity in medical students during lifestyle changes

1821 

Svitlana Doroshenko, Oleksandr Opekha, Vladimir Shkarupa, Liliya Gumenyuk

SNP rs2981579 in the *FGFR2* gene as a risk factor for class II malocclusion in the Ukrainian population

1831 

Natalia A. Lyakhova, Iryna A. Holovanova, Ivan Yu. Popovich, Inna V. Bielikova, Alevtyna M. Bilous, Oksana I. Krasnova, Valerii V. Loburets

Prevalence of risk factors for the occurrence of orthodontic pathology among children in the city of Poltava: regional features

1837 

Liudmyla P. Zabrodina, Volodymyr O. Korshnyak, Yuliia V. Bovt, Nataliya M. Pryvalova, Viktor V. Sukhorukov

Coherent connections of brain biopotentials in military personnel during recovery from mine-blast closed craniocerebral injuries

1843 

Tetiana Timokhina, Marina V. Kryvtsova, Mykola Y. Spivak, Nina S. Proshchenko, Alla V. Kharina, Oleksandra Bondarenko

Potential use of bacteriophages for the oral microbiota modulation in periodontal diseases within the context of maxillofacial pathology

1849 

REVIEW ARTICLES

Svitlana V. Kucher, Ulyana O. Mudra, Vitalii V. Tkachuk, Mariia M. Ruda, Tetiana Yu. Chernets, Iryna M. Nikitina, Volodymyr H. Dzhyvak

Impact of lifestyle modification interventions on metabolic syndrome and obesity in adults

1857 

Volodymyr O. Melnyk, Borys I. Palamar

Pseudoexfoliation syndrome: modern concepts of morphological and clinical manifestations, classification and treatment

1866 

Maciej Słomian, Katarzyna Grudnik, Małgorzata Grudnik, Julia Smyczek, Mateusz Jagielski, Karol Płaszewski, Karolina Lau, Janusz Kasperczyk

The path to the first heart transplant and current transplantology in Poland

1874 

Borys P. Savchuk, Olga Y. Snitovska, Halyna M. Tsaryk, Oleg Ya. Dovgij, Ivanna R. Humenna, Larysa Ya. Fedoniuk, Halyna V. Bilavych	
Research of Ukrainian scientists on the development of national medical education systems: A meta-analysis	1886
Kinga Kosiń, Wojciech Liszka, Alicja Polak, Maria Malina, Jakub Kiwior	
Modern biomaterials for direct pulp capping: A literature review	1893
Vladyslav Smiiianov, Olexsander Korniiichuk, Iryna Khomenko, Anatolii Tsarenko, Oleksandra Ivakhno, Viktoriia Yasenok, Olha Smiiianova	
Economic determinants in healthcare quality optimization in Ukrainian metropolises	1899
Alicja Polak, Kinga Kosiń, Wojciech Liszka, Maria Malina, Jakub Kiwior	
Key drivers of antibiotic resistance in <i>Escherichia coli</i> in a One Health context: A literature review	1909

Manifestations of dental diseases following Covid-19: pain and oral health impacts. Using the broad population survey opportunities

Renata V. Symonenko, Alina I. Kapshyk, Yevhen A. Koval, Zinaida E. Zhehulovich, Olena O. Astapenko, Vitalii D. Chopchuk, Oleg V. Tyrsa

BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: This research aimed to examine the post-COVID-19 effects on dental health among JICS survey participants, exploring oral health changes during and following the pandemic.

Materials and Methods: This study utilized random sampling through the JICS survey, involving 201 participants (aged 17–89). The control group (n=65, 32.7%) consisted of individuals without COVID-19 from 2019–2021, while the study group (n=134, 67.3%) included those who contracted the virus during this period. Symptom manifestation, intensity, and localization were assessed up to 9–12 months post-infection (2021–2022) across groups and genders, employing artificial intelligence (AI) and machine learning (ML) techniques, including descriptive analytics for pattern identification and predictive analytics for trend forecasting.

Results: Analysis of dental symptoms potentially linked to COVID-19 identified 16 conditions, including hyperesthesia, grinding teeth, gum bleeding, gum pain, and pain in upper/lower teeth. Among 201 participants (aged 18–89, mean 28.6 years), symptoms lasted an average of 9.6 – max 18 months. Of those surveyed, 134 had contracted COVID-19 at various times prior to the survey. Among them, 90 individuals (67.3% of the total number of infected respondents) reported oral pain, a 44.3% increase over the standard hyperesthesia prevalence. This group consisted of 36 men and 54 women. These 7 people (those with intense pain) constituted 7.8%. Within this subgroup, 2 men and 5 women complained of intense pain, representing 2.2% and 5.6% of those with oral pain, respectively. Older age groups showed more severe symptoms, like gum pain (mean 86 years), while women reported greater severity than men.

Conclusions: The study shows dental symptoms potentially linked to COVID-19 vary by severity and age, with older individuals experiencing severe issues like gum pain. The oral health monitoring could identify symptoms and enhance treatments, especially for older adults. Further research is needed to confirm long-term impacts and refine treatments.

KEY WORDS: dental diseases, oral health, COVID-19, hyperesthesia, periodontitis, Machine Learning, Artificial intelligence (AI)

Wiad Lek. 2025;78(9):1701-1709. doi: 10.36740/WLek/212356 DOI

INTRODUCTION

During a medical appointment at the Dental Medical Center of Bogomolets National Medical University in Kyiv amid the COVID-19 quarantine in 2019–2020 years [1–3], clinicians observed a clear connection between oral health issues and discomfort in patients. This observation prompted the creation of questionnaires for participants in a JICS survey. The findings revealed a link between discomfort reported by survey respondents, including those who hadn't sought medical advice. These detailed surveys were designed to uncover patterns and associations between clinical settings, diseases during epidemics, and their effects on oral health [4,5].

The study of post-COVID conditions has become a focal point in modern medicine, with dentistry emerging as an area of growing interest yet limited exploration.

Current research highlights that COVID-19 extends beyond its respiratory origins, impacting various systems, including oral health. Sporadic reports have identified dental symptoms, such as tooth sensitivity, gum inflammation, and pain post-infection, but these findings lack systematic depth and validation. [3,6–9] Compared to other medical fields, where post-viral effects are more thoroughly documented, dentistry lags, with few peer-reviewed studies addressing chronic or delayed oral manifestations. This gap is striking, given the oral cavity's role as an indicator of systemic health, particularly in the context of a pandemic that has re-defined health challenges [10–12].

Presently, dental research has largely concentrated on managing acute infections, leaving the long-term oral consequences of COVID-19 underexamined. Emerging evidence hints at conditions like hyperesthesia possi-

bly linked to inflammation or neurological changes, yet these remain preliminary without comprehensive analysis [7,13-16]. This study, utilizing the JICS survey and expertise from Ukrainian dentistry professionals, seeks to address this underexplored terrain. Engaging 201 participants, including those affected by COVID-19 and a comparison group, our research examines the current state of dental health post-pandemic. It is guided by questions about symptom prevalence, gender and employment differences, and the timing of oral issues, aiming to shed light on the virus's dental impact [1,9,15]. By doing so, we contribute to a clearer understanding of this evolving field, paving the way for improved clinical responses.

AIM

The aim of this study was to investigate the impact of COVID-19 on dental health, specifically to examine the prevalence, nature, and timing of oral symptoms, such as hyperesthesia, in individuals post-infection compared to a non-infected control group, using survey data and machine learning analysis to identify patterns and inform future dental care strategies. [11,15,16]

MATERIALS AND METHODS

This study was designed to evaluate the dental health effects of COVID-19, focusing on post-viral oral conditions, through a structured survey and computational analysis. The research integrated participant-reported data with advanced analytical methods to investigate these impacts systematically. This study utilized random sampling through the JICS survey, involving 201 participants (aged 18–89), 113 women, 87 men and 1 gender-neutral. The control group ($n=65$, 32.7%) consisted of individuals without COVID-19 from 2019–2021, while the study group ($n=134$, 67.3%) included those who contracted the virus during this period. Symptom manifestation, intensity, and localization were assessed up to 9–12 months post-infection (2021–2022) across groups and genders, employing artificial intelligence (AI) and machine learning (ML) techniques, including descriptive analytics for pattern identification and predictive analytics for trend forecasting.

PARTICIPANT RECRUITMENT

A total of 201 individuals were recruited using a random sampling approach to ensure diversity across age, gender, and occupational backgrounds, following established research guidelines. Participants were divided into two groups: those who had experienced COVID-19

and a control group unaffected by the virus during the study period. Eligibility required participants to be over 18 and capable of providing consent, with exclusions for those with unrelated pre-existing dental conditions or incomplete responses Fig. 1, Fig. 2.

SURVEY IMPLEMENTATION

Data were gathered via the JICS survey, a custom questionnaire designed to collect details on dental symptoms associated with COVID-19, including their timing and characteristics, along with basic demographic information. The survey was distributed electronically through social media platforms from late 2021 to early 2022 to maximize accessibility. Each participant provided explicit consent through the JICS platform prior to completing the survey, agreeing to participate and allow data processing for the study.

DATA PROCESSING AND ANALYSIS

Initial analysis involved compiling descriptive summaries of participant responses to outline key characteristics. Subsequent in-depth analysis utilized machine learning techniques within the Python programming environment to uncover patterns and trends within the dataset. This process included comparisons with existing literature for context and statistical testing of hypotheses at a significance level of $p < 0.05$. No sensitive personal data (names, precise birth dates) was collected to ensure participant privacy.

ETHICAL FRAMEWORK

This survey raised no ethical or legal issues, as all participants voluntarily agreed to participate and permitted the use of their data for this study. Consent was obtained digitally through the JICS survey, and participants were informed of their right to withdraw at any time without consequence. All responses were anonymized and processed in compliance with the General Data Protection Regulation (GDPR), ensuring confidentiality and adherence to data protection standards. The study's reliance on self-reported data without invasive procedures further reinforced its ethical foundation.

RESOURCES

The JICS survey served as the primary data collection instrument, supported by the Python computational software for analysis. No clinical interventions or biological samples were involved, keeping the study observational in nature.

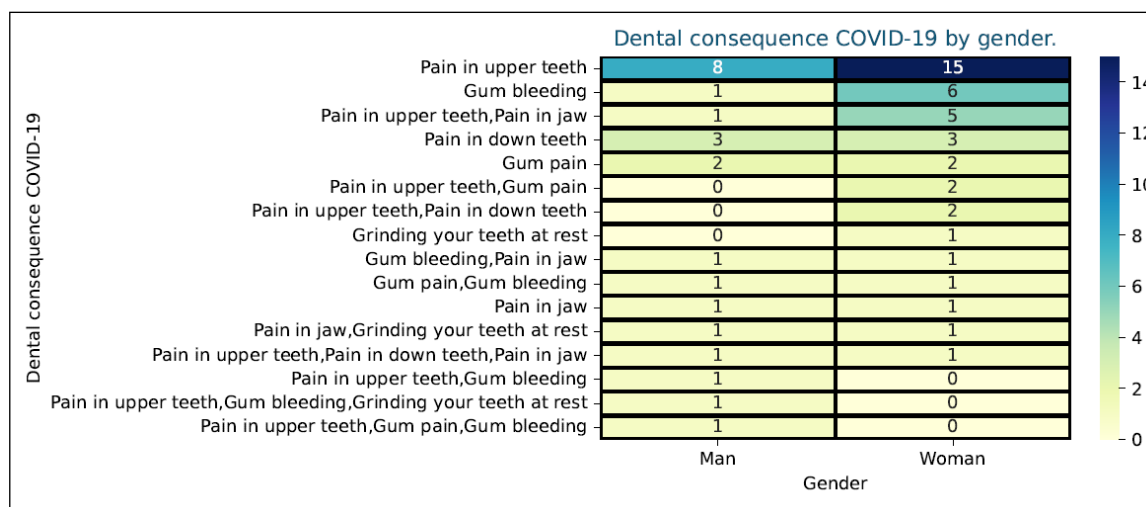


Fig. 1. Age Dental consequence COVID-19 by Gender

Picture taken by the authors

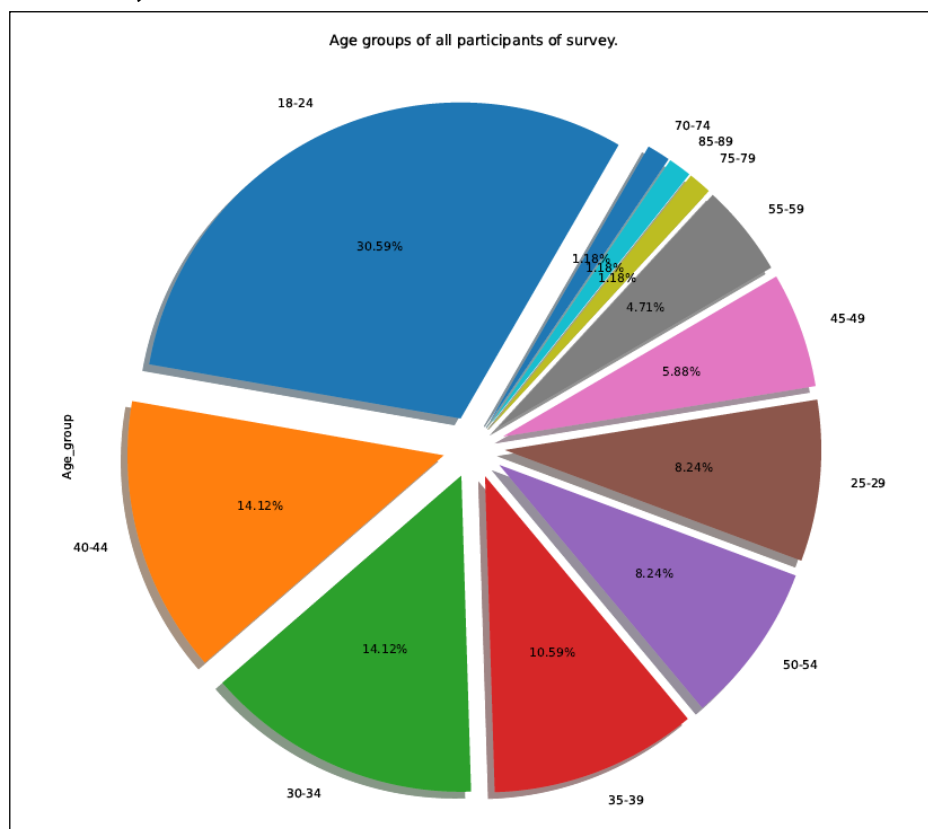


Fig. 2. The age groups of all participants in the survey

Picture taken by the authors

RESULTS

HYPOTESIS TESTING

Our study rejected the null hypothesis (H_0) that the number of dental manifestations did not increase during and after the COVID-19 pandemic based on a comparison with open-source data and prior research. Due to limited historical data, we benchmarked our survey results against reference values for dental sensitivity (hyperesthesia). These comparisons, combined with exploratory and explanatory analyses of our dataset ($n=201$), yielded the following key findings.

PREVALENCE AND SEVERITY OF DENTAL MANIFESTATIONS

Analysis of dental symptoms potentially linked to COVID-19 identified 16 conditions, including hyperesthesia, grinding teeth, gum bleeding, gum pain, and pain in upper/lower teeth. Among 201 participants (aged 18–89, mean 28.6 years), symptoms lasted an average of 9.6 – max 18 months. Of those surveyed, 134 had contracted COVID-19 at various times prior to the survey. Among them, 90 individuals (67,3% of the total number of infected respondents) reported oral pain. This group consisted of 36 men and 54 women. Among the surveyed population,



67.3% of participants who contracted COVID-19 between 2019 and 2022 reported dental manifestations, a 44.3% increase over the standard hyperesthesia prevalence of 23% reported by Dowell and Addy [7]. Symptom severity varied: 32.5% experienced medium symptoms, 30% reported light symptoms, and 5% had severe symptoms from total number who contracted COVID-19. The most common manifestation across all participants was light pain in the upper teeth Fig.3.

The findings from this analysis, presented in Table 1, pertain to participants who had contracted COVID-19 and focus on symptom intensity. Among all surveyed participants who had COVID-19, 45.6% of those who reported experiencing pain described its intensity as moderate (n=90). Furthermore, a decrease in sensitivity was noted by 6 participants.

TEMPORAL DYNAMICS

The results of the analysis on the manifestations of post-COVID hyperesthesia and the number of teeth affected following the illness, which are correlated with the time period, are presented in Table 2. Based on the data in Table 2, the most frequently reported post-COVID oral manifestations include gum bleeding, gum pain, and pain in the upper teeth, often occurring in combination. Symptoms typically emerged within 1 to 18 months after infection, with a mean onset time ranging from 1.5 to 12 months. Patients experiencing multiple symptoms simultaneously as gum bleeding paired with jaw or tooth pain tended to report higher numbers of affected teeth (up to 20 teeth

in severe cases). Overall, these findings suggest that oral post-COVID symptoms vary widely in presentation and severity, with gum-related issues and tooth pain being the most common complaints.

The onset of dental manifestations post-COVID-19 varied significantly. Patients with medium symptoms predominantly reported issues 9 or 12 months after infection, while those with light symptoms experienced them earlier, at 1, 3, or 9 months post-infection. Severe symptoms showed no consistent temporal pattern. The number of symptoms also increased with time elapsed since infection, suggesting a prolonged impact Fig.4, Fig.5.

DEMOGRAPHIC VARIATIONS

Young patients (under 30) primarily exhibited light symptoms, middle-aged patients (30–50) reported moderate symptoms, and both middle-aged and elderly respondents (over 50) experienced unbearable symptoms. Women reported more pronounced symptoms appearing earlier post-infection compared to men, indicating a potential gender disparity. Employed individuals showed a higher incidence of dental manifestations (39.2%) compared to the control group of non-infected individuals (23%), highlighting a possible psychosomatic influence Fig.6.

LOCALIZATION AND CORRELATION

Localized symptoms, primarily affecting a single nerve, predominated over generalized manifestations in

Table 1. Distribution of the studied patients by pain intensity and gender (n/%) (n=90)

Severity of symptoms	MEN		WOMEN		Total	
	n	%	n	%	n	%
Light symptoms	14	15,6%	22	24,4%	36	40%
Medium symptoms	17	18,9%	24	26,7%	41	45,6%
Severe symptoms	2	2,3%	5	5,5%	7	7,8%
Decrease of sensitivity	3	3,3%	3	3,3%	6	6,6%
Total	36	40%	54	60%	90	100%

Source: compiled by the authors of this study

Table 2. Summary Statistics for Post-COVID Oral Symptom Groups

	Age			Time passed months			Teeth affected		
	min	mean	max	min	mean	max	min	mean	max
Consequences COVID 19									
Grinding your teeth at rest	28	28	28	18	18	18	1	1	1
Gum bleeding	21	29.6	37	3	8.4	12	0	6	20
Gum bleeding,Pain in jaw	19	19.5	20	3	3	3	3	3	3
Gum pain	19	48.5	86	1	4.75	6	3	3.75	6
Gum pain,Gum bleeding	19	21	23	3	6	9	3	3	3
Pain in down teeth	19	35	45	1	9.25	18	1	2	3
Pain in jaw	18	18	18	0	1.5	3	0	3	6
Pain in jaw,Grinding your teeth at rest	19	21	23	3	6	9	1	1	1
Pain in upper teeth	18	35.81818	72	0	6.09091	18	0	3.27273	6
Pain in upper teeth,Gum bleeding	21	21	21	6	6	6	3	3	3
Pain in upper teeth,Gum bleeding,Grinding your teeth at rest	22	22	22	12	12	12	1	1	1
Pain in upper teeth,Gum pain	23	33	43	3	6	9	3	4.5	6
Pain in upper teeth,Pain in down teeth	75	75	75	9	9	9	6	6	6
Pain in upper teeth,Pain in down teeth,Pain in jaw	19	19.5	20	1	5	9	3	3	3
Pain in upper teeth,Pain in jaw	19	34.33333	59	1	4.33333	12	1	3.33333	6

Source: compiled by the authors of this study

post-COVID-19 patients. A correlation matrix revealed a significant relationship between the number of affected teeth and symptom severity. The most striking post-pandemic manifestations included pain in the upper teeth, pain in the lower teeth, and gum pain, with post-COVID-specific symptoms such as upper teeth pain and gum bleeding standing out as notable trends.

COMPARISON TO CONTROL GROUP

The level of dental manifestations in pandemic and post-COVID-19 participants significantly exceeded that of the control group (non-infected individuals surveyed concurrently), with a 39.2% prevalence compared to the literature baseline of 23%. This further supports the rejection of H_0 and underscores the pandemic's impact on dental health.

DISCUSSION

This study successfully achieved its scientific objective of evaluating the impact of COVID-19 on dental health, specifically hyperesthesia and related manifestations, using a robust survey methodology and machine learning-assisted analysis. Our findings confirm a significant increase in dental manifestations during and after the pandemic, aligning with the growing recognition of COVID-19's systemic effects. The rejection of H_0 , supported by a 44.3% higher prevalence compared to historical benchmarks, highlights the originality of our work in quantifying post-viral dental outcomes within a Ukrainian context.

The predominance of upper teeth pain and gum bleeding as post-COVID manifestations raises intriguing questions about the virus's vascular effects, such as thrombosis, which may disproportionately affect oral tissues. The temporal

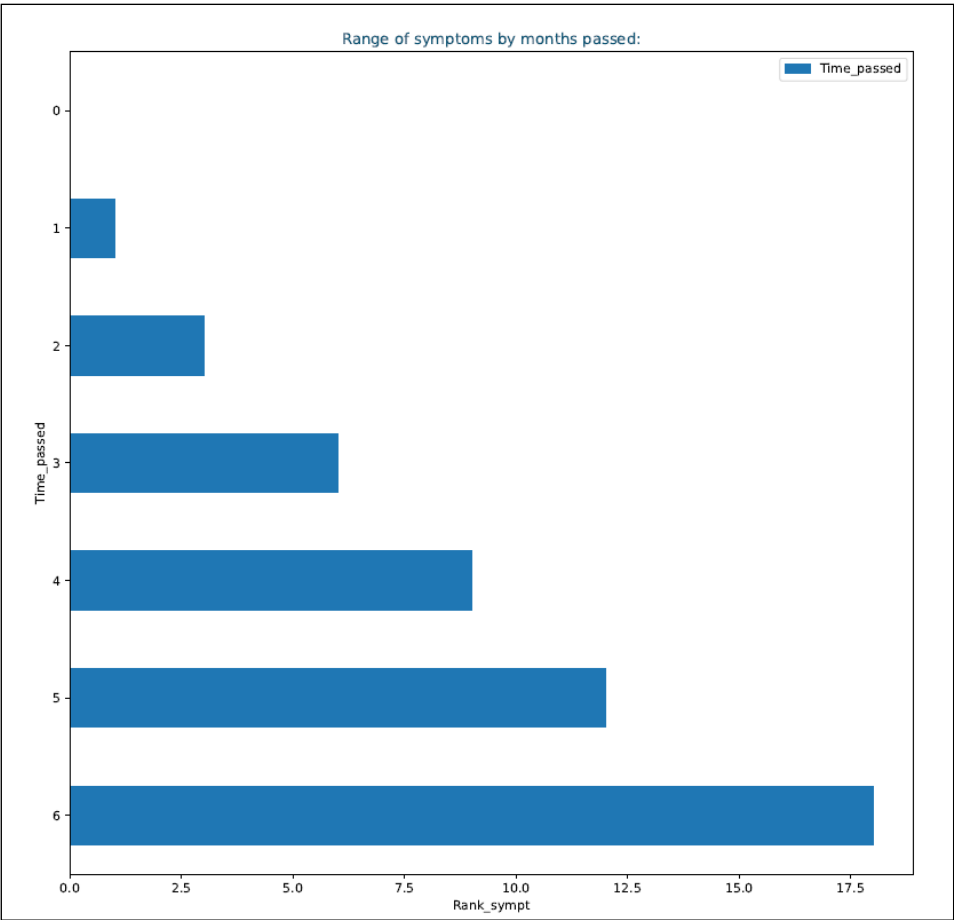


Fig. 4. Range of symptoms by months passed
Picture taken by the authors

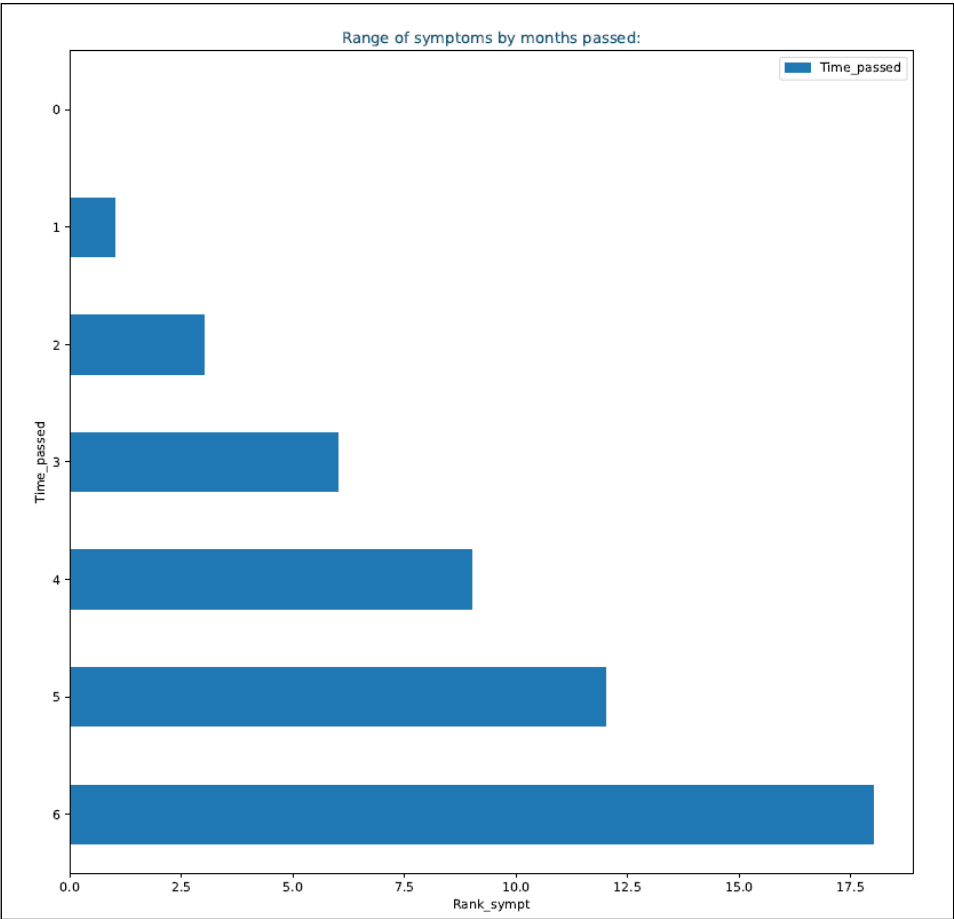


Fig. 5. Range of symptoms by months passed
Picture taken by the authors

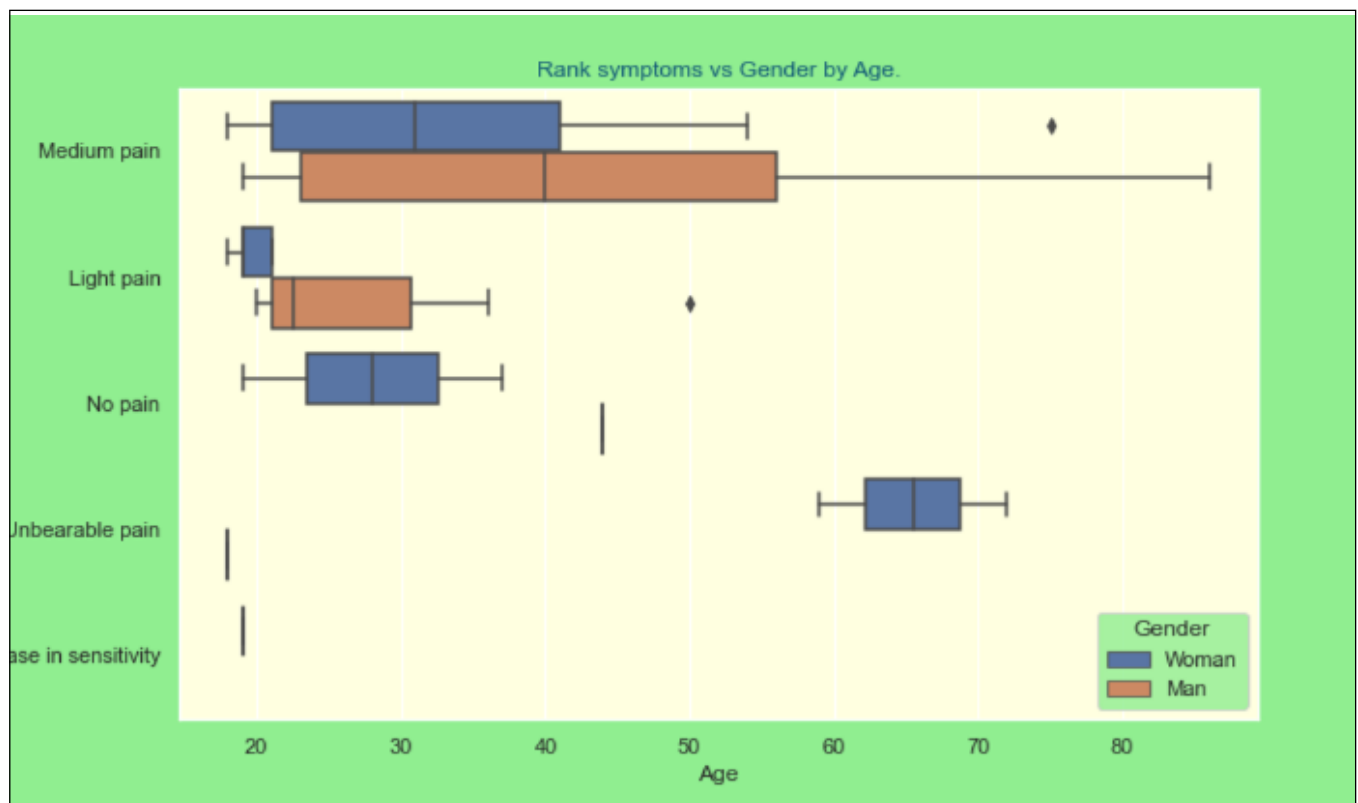


Fig. 6. Range of symptoms by months passed

Picture taken by the authors

variability-medium symptoms peaking at 9-12 months versus light symptoms at 1-3 months suggests a dynamic progression of post-viral sequelae, potentially linked to immune or neurological responses. The gender disparity, with women experiencing earlier and more severe symptoms, could reflect differences in immune response, hormonal factors, or reporting behavior, warranting further investigation. Similarly, the age-related increase in symptom severity and persistence underscores the overlap of COVID-19 effects with age-related physiological decline, a finding consistent with broader post-viral research.

The higher prevalence among employed individuals (39.2%) compared to the control group (23%) points to a psychosomatic component, possibly exacerbated by stress or reduced recovery time, as rest appears critical for mitigating symptoms. This aligns with our hypothesis that lifestyle factors modulate post-COVID dental health. The use of machine learning facilitated the identification of these patterns, demonstrating its value in medical research beyond traditional statistical methods Table 1.

However, our study has methodological limitations. The reliance on self-reported data via the JICS survey and social media distribution may introduce recall bias or selection bias despite our adherence to WHO stratification guidelines. The lack of pre-pandemic baseline data from our population limits direct historical comparisons, forcing reliance on external references

[7,16,15]. Additionally, the sample size ($n=201$), while diverse, may not fully represent the broader population, particularly regarding genomic or regional differences in viral response.

The findings offer practical implications for dental practice, enabling clinicians to prioritize high-risk groups (women and older adults) and tailor diagnostics to post-COVID manifestations like upper teeth pain and gum bleeding. The study lays a foundation for future research, potentially in collaboration with Bogomolets National Medical University and the Ukrainian government. Expanding the scope to include pre-pandemic symptoms, non-random sampling from dental clinics, and genomic analysis could further elucidate the virus's heterogeneous effects.

CONCLUSIONS

The research bridges a critical gap in post-COVID dental health, offering novel evidence of its prevalence, severity, and demographic patterns through a comprehensive survey and analysis. By integrating these findings with ongoing global studies, we aim to enhance patient outcomes and inform dental care in the post-pandemic era, addressing the unique challenges posed by post-viral effects on oral health. A pivotal element of this work is the application of artificial intelligence – Machine

Learning, which has significantly enhanced our ability to uncover complex trends and holds transformative potential for dentistry. Currently, AI, through machine learning, is being utilized to process large medical datasets, enabling the identification of subtle correlations, such as those between symptom severity and affected teeth in our study, while also powering clinical tools like automated imaging diagnostics and predictive risk models. Looking ahead, AI's future in dentistry promises advancements such as personalized treatment plans based on predictive analytics, integration of genomic data to explain variable symptom expression, and scalable research frameworks to tackle evolving viral threats. This synergy will ultimately improve patient well-being in a rapidly changing health landscape.

The relevance of studying the consequences of COVID-19 cannot be overstated. Geopolitical instability,

mass daily migrations, and living in emergency conditions amplify the risks of new epidemics emerging. In this context, researching the impact of COVID-19 and related viruses on pain manifestations in patients remains highly significant and in demand.

Dentistry holds a special place in healthcare system, as dentists are among the most frequently visited specialists and often act as observers of family health, similar to family doctors. Given the significant strain on the oral cavity and its critical role as the initial segment of the gastrointestinal tract, the study of this topic takes on exceptional importance.

The results of our work, leveraging Machine Learning (a core component of Artificial Intelligence – AI), could contribute to improving treatment approaches, adapting medical strategies to new and evolving diseases, and enhancing patients' quality of life.

REFERENCES

1. Afrashtehfar KI, Jurado CA, Abu-Fanas SH, Jaber MA. Health and Well-Being through COVID-19 Vaccination: Physical, Oral, and Psychological Effects. *Int J Environ Res Public Health*. 2023;20(4):3117. doi: 10.3390/ijerph20043117. [DOI](#)
2. Bahşi E, Dalli M, Uzgur R et al. An analysis of the aetiology, prevalence and clinical features of dentine hypersensitivity in a general dental population. *European Review for Medical and Pharmacological Sciences*. 2012;16:1107-1116.
3. Blum IR. Urgent dental care and oral health under the clouds of COVID-19. *Prim Dent J*. 2021 Sep;10(3):2. doi: 10.1177/20501684211033388. Erratum in: *Prim Dent J*. 2021;10(4):100. doi: 10.1177/20501684211067864. [DOI](#)
4. Botros N, Iyer P, Ojcius DM. Is there an association between oral health and severity of COVID-19 complications? *Biomed J*. 2020;43(4):325-327. doi: 10.1016/j.bj.2020.05.016. [DOI](#)
5. Brian Z, Weintraub JA. Oral Health and COVID-19: Increasing the Need for Prevention and Access. *Prev Chronic Dis*. 2020;17:E82. doi: 10.5888/pcd17.200266. [DOI](#)
6. Doceda MV, Gavriloglou M, Petit C, Huck O. Oral Health Implications of SARS-CoV-2/COVID-19: A Systematic Review. *Oral Health Prev Dent*. 2022;20:207-218. doi: 10.3290/j.ohpd.b2960801. [DOI](#)
7. Dowell P, Addy M. Dentine hypersensitivity a review. Etiology. Symptoms and theories of pain production. *J Clin Periodontology*. 1993;10:341 – 350.
8. France K, Glick M. Long COVID and oral health care considerations. *J Am Dent Assoc*. 2022;153(2):167-174. doi: 10.1016/j.adaj.2021.08.007. [DOI](#)
9. Joshi P. Python machine learning cookbook. Birmingham: Packt Publishing. 2016, pp.55-77.
10. Kapila YL. Oral health's inextricable connection to systemic health: Special populations bring to bear multimodal relationships and factors connecting periodontal disease to systemic diseases and conditions. *Periodontol 2000*. 2021;87(1):11-16. doi: 10.1111/prd.12398. [DOI](#)
11. Kiliç G, Akcalı A, Belet N et al. Association among COVID-19, multisystem inflammatory syndrome in children, and oral health status. *Braz Oral Res*. 2023;37:e072. doi: 10.1590/1807-3107bor-2023.vol37.0072. [DOI](#)
12. Ren YF, Rasubala L, Malmstrom H, Eliav E. Dental Care and Oral Health under the Clouds of COVID-19. *JDR Clin Trans Res*. 2020;5(3):202-210. doi: 10.1177/2380084420924385. [DOI](#)
13. Rusu LC, Ardelean LC, Tigmeanu CV et al. COVID-19 and Its Repercussions on Oral Health: A Review. *Medicina (Kaunas)*. 2021;57(11):1189. doi: 10.3390/medicina57111189. [DOI](#)
14. Symonenko RV. The effectiveness of Admira Protect (VOCO) for teeth hyperesthesia elimination as the first step of coordinated manipulation manifestation during the rehabilitation of patients with generalized periodontal disease. *Suchasna Stomatolohiya*. 2020. doi: 10.33295/1992-576X-2020-1-115. (Ukrainian) [DOI](#)
15. Symonenko RV, Vasil'yeva-Katashynskaya NN. Desensitization is an essential part of your patient protocol at the dental appointment. *Suchasna stomatolohyya*. 2020;3:7-13. doi: 10.33295/1992-576X-2020-3-7. [DOI](#)
16. Stennett M, Tsakos G. The impact of the COVID-19 pandemic on oral health inequalities and access to oral healthcare in England. *Br Dent J*. 2022;232(2):109-114. doi: 10.1038/s41415-021-3718-0. [DOI](#)

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Renata V. Symonenko

Bogomolets National Medical University

1 Zoologichna St., 03057 Kyiv, Ukraine

e-mail: renataunting@gmail.com

ORCID AND CONTRIBUTIONSHIP

Renata V. Symonenko: 0000-0003-4618-6229 **A** **B** **C** **D** **E** **F**

Alina I. Kapshyk: 0000-0003-0081-5560 **A** **B** **C** **D** **E** **F**

Yevhen A. Koval: 0000-0002-9005-6686 **B** **E** **F**

Zinaida Y. Zhehulovych: 0000-0002-9996-2060 **B** **E** **F**

Olena O. Astapenko: 0000-0002-2168-9439 **B** **E**

Vitalii D. Chopchuk: 0000-0002-5581-0372 **B** **E**

Oleg V. Tyrsa: 0000-0003-0653-3855 **B** **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: 12.04.2025

ACCEPTED: 29.08.2025



Comparative analysis of cephalometric K-angle index of mixed dentition patients

Kyryl G. Krymovskyy, Oleksandr A. Kaniura, Zinaida E. Zhehulovych, Kateryna V. Storozhenko,
Yurii I. Babaskin, Oleksandr V. Bida, Tetyana M. Brychko
BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: To analyse the effectiveness and reliability of $\angle K$ -angle cephalometric index usage in mixed dentition and to assess the correlation between different types of facial skeleton growth patterns.

Materials and Methods: 52 high-quality cephalograms were randomly selected from the archives of the Bogomolets National Medical University Dental Medical Centre and divided into three groups according to facial skeleton growth patterns and into subgroups according to Engle's malocclusion classes. Multifactorial analysis of variance (ANOVA) was used to identify statistical differences between the mean angular values of studied groups; a p-value ≤ 0.05 was considered statistically significant. Pearson's correlation coefficient was used to assess the correlation between angles.

Results: According to our study results, statistically significant correlation was found among patients in the first group between ANB and K angles and neutral growth type ($p=0.005$); significant correlation was found between the K and APDI angles and horizontal growth pattern ($p=0.002$); statistically significant correlation was found between the APDI parameter and both angles with vertical growth ($p=0.001$). According to the results of multifactorial ANOVA analysis of the mean values of the studied angles, there were no statistically significant differences in the $\angle K$, $\angle ANB$, and APDI parameters between all groups at the level of $p \leq 0.05$.

Conclusions: The K-angle revealed to be the most valid and reliable indicator of sagittal jaw discrepancy assessment among all cephalometric parameters. $\angle K$ index can be a full-fledged alternative to ANB angle during mixed dentition.

KEY WORDS: orthodontics, cone-beam computed tomography, 3D cephalometrics, mixed dentition, cephalometric analysis

Wiad Lek. 2025;78(9):1710-1717. doi: 10.36740/WLek/212379 DOI

INTRODUCTION

Malocclusion occurs as a result of deviations in the normal growth of the craniofacial region in the sagittal, vertical or transversal planes [1]. Sagittal malocclusion is usually the most common orthodontic problem and has significant functional, psychological and aesthetic consequences [2]. The formation of skeletal sagittal malocclusion background of differences in the development of the upper or lower jaw often requires complex and expensive treatment methods in permanent occlusion; therefore, early detection of its signs is an essential step in treatment effectiveness improvement.

Planning of orthodontic treatment depends on precise diagnosis of skeletal discrepancies, the patient's facial skull growth type, and the (dentoalveolar) parameters of the dentition [1-16]. X-rays are the most effective methods to analyse skeletal discrepancies in the sagittal plane, as accurate assessment of the morphology of various skeletal components, as well

as their relationship with surrounding tissues [2, 8]. For the diagnosis of sagittal discrepancies at the level of the skeleton, teeth and soft tissues, the standardised lateral cephalogram has become the gold standard, but 3D cephalometric studies are increasingly being used for this purpose. The results of cephalometric calculations using different approaches are diagnostically significant and reliable for understanding the basic morphological characteristics of patients' skeletal and dental components. They are recommended to be used in combination with each other to obtain a more complete cephalometric diagnostic perspective and to develop an orthodontic treatment plan taking into account the characteristics of each individual. Sam et al.'s systematic review [15] evaluated the high accuracy of various 3D cephalometric landmarks in CBCT imaging. They came to the conclusion that deep learning techniques for automated 3D cephalometric landmarking produced high-accuracy results of modern orthodontic diagnostics [11-17].

Among the common indicators in the diagnosis of sagittal occlusion anomalies in orthodontics, it is customary to consider the ANB angle [4] of Steiner's cephalometric analysis, which shows changes in the position of the jaw bases relative to the skull base, as well as the presence of sagittal discrepancies in their sizes. However, to determine a complete orthodontic diagnosis, it is still necessary to perform a differential diagnosis between dental-alveolar and gnathic forms of occlusion pathology. For this purpose, orthodontists use the APDI parameter according to Kim's cephalometric analysis, which greatly facilitates the diagnostic process [5].

Although the ANB angle is widely used as a reliable indicator of the anteroposterior relationship of the jaws, to date, many famous researchers have conducted studies related to assessing the stability of the ANB angle in connection with changes in growth and instability of the N point position, which affects the size and clarity of the ANB angle during jaw growth [4, 5].

New linear and angular measurements for assessing sagittal discrepancy of both upper and lower jaw bases are proposed in many recent studies: YEN angle, BETA angle, W angle, K angle, etc. [6-9]. Among them, the K-angle illustrates a new strategy in this direction of 3D cephalometry development, which requires more comprehensive research. A K-angle value of 40° to 46° indicates a Class I skeletal occlusion, a value above 46° indicates a Class III skeletal occlusion, and a value below 40° indicates a Class II skeletal occlusion [3].

It has been proven that angle K is a reliable indicator in the permanent occlusion period [3], but the question of the reliability of using this angular indicator in mixed occlusion, depending on the types of facial skull growth, remains poorly understood and requires more detailed and in-depth study.

AIM

This study aimed To analyse the effectiveness and reliability of $\angle$ K-angle cephalometric index usage in mixed dentition and to assess the correlation between different types of facial skeleton growth patterns.

MATERIALS AND METHODS

52 case histories of patients with mixed dentition aged 7 to 11 years (29 females and 23 males; mean age = 8.9 ± 1.2) with high-quality 3D cephalograms, were randomly selected from the archives (of the Dental Medical Centre of the Bogomolets National Medical University for the period from 2021 to 2024. The study was approved by the Bioethics Committee of Bogomolets National Medical University.

The distribution into research groups was based on the available types of facial skull growth (neutral, horizontal, vertical) according to the results of Björk-Jarabak cephalometric analysis. Each of the research groups was divided into two subgroups depending on the class of malocclusion (classes I and II according to Angle).

The criteria for inclusion in the study were: the presence of gnathic or combined Class 1 and 2 malocclusion form according to Angle, and the presence of the first permanent molars before the start of treatment. Exclusion criteria included patients outside the age range, with severe general somatic diseases, psychoemotional disorders, and a group of individuals with Class III sagittal malocclusion according to Angle, due to an insufficient statistically significant sample size for the study.

For accurate determination of anthropometric points and precise measurement of ANB, APDI, and K angles, high-quality 3D cephalograms generated using cone beam computed tomography (CBCT) were selected. The 3D images were obtained using a 64-slice multi-detector tomograph "NewTom Giano HR PROFESSIONAL" manufactured by NewTom (Italy). Technical characteristics of the device (according to the device passport): voltage 60–90 kV, current 1–10 mA (pulse), exposure time 1.6–10 s, voxel size 0.68–300 μ m, radiation exposure during the acquisition of 3D images of the facial skull reaches only 30 microSieverts, which is the lowest among modern tomograph models, since this tomograph has a special SafeBeam mode with radiation dose coNGPol.

Multifactorial analysis of variance (ANOVA) was used to determine statistically significant differences in the angles studied in the three groups. Pearson's correlation coefficient was used to correlate the ANB angle with the K-angle. The results of measuring angular parameters on 3D cephalograms were statistically processed to determine the arithmetic mean (X) and standard deviation (SD) of the angular indicator and its standard error (m). A 95% confidence interval (95% CI) was calculated for the assessment. The collected data were analysed using EZR v. 1.66 (a graphical user interface for R statistical software version 4.3.1 developed by the R Foundation for Statistical Computing in Vienna, Austria) [10].

RESULTS

The first study group included 25 individuals (14 female and 11 male) with a neutral facial skeleton growth pattern (NGP), which was assessed by the total Björk angle and the ratio of posterior facial height to anterior facial

Table 1. Patients’ randomisation with different facial skeleton growth patterns by gender, malocclusion, age and mixed dentition stage (N,%)

Gender	Group 1 (neutral pattern)		Group 2 (horizontal pattern)		Group 3 (vertical pattern)	
	N abs	(%)	N abs	(%)	N abs	(%)
Female	14	53,8	12	70,6	3	70
Male	11	42,3	5	29,4	7	30
Malocclusion Class	N abs	(%)	N abs	(%)	N abs	(%)
Class I	12	23,07	2	3,89	4	7,7
Class II	13	25	15	28,8	6	11,54
Mixed Dentition	N abs	(%)	N abs	(%)	N abs	(%)
Early Stage	20	57,1	10	28,6	5	14,3
Late Stage	5	29,4	7	41,2	5	29,4
Age (years)	X	SD	X	SD	X	SD
	8,46	± 1,58	8,9	± 1,21	9,07	± 1,97

Source: compiled by the authors of this study

Table 2. Results of K-angle multifactorial ANOVA statistical analysis in different facial skeleton growth patterns (N, SD)

Growth pattern	N	Mean value	Standard deviation	Dispersive analysis of variance (ANOVA)	P value
Neutral	15	40,28	± 1,24	1.325	0.184
Horizontal	7	39,5	± 1,19		
Vertical	10	37,7	± 1,33		
Gender	N	Mean value	Standard deviation	Dispersive analysis of variance (ANOVA)	P value
Female	14	40,1	± 1,25	1.336	0.129
Male	11	39,6	± 1,27	1.338	0.129
Malocclusion class	N	Mean value	Standard deviation	Dispersive analysis of variance (ANOVA)	P value
Class 1	12	41,5	± 1,4	1.327	0.147
Class 2	13	38,6	± 1,2	1.329	0.147
Mixed Dent. Stage	N	Mean value	Standard deviation	Dispersive analysis of variance (ANOVA)	P value
Early	20	41,2	± 2,8	1.330	0.165
Late	5	40,9	± 2,3	1.330	0.165

Source: compiled by the authors of this study

height (PFH/AFH) according to Jarabak’s analysis. The second group included 17 children (5 female, 12 male) with a horizontal facial skeleton growth pattern (HGP) ($\angle\text{Sum} \leq 391^\circ$, $\text{PFH/AFH} \geq 0.66$), while the third group included 10 patients with a vertical (VGP) facial skeleton growth pattern ($\angle\text{Sum} \geq 401^\circ$ and $\text{PFH/AFH} \leq 0.61$). For NGP, HGP and VGP, the corresponding mean age and standard deviation were 8.46 ± 1.58 , 8.9 ± 1.21 and 9.07 ± 1.97 , respectively, and did not differ significantly according to ANOVA multivariate analysis of variance ($p > 0.05$). In the initial subgroups of the study groups, patients with class 1 malocclusion according to Angle were identified, while in the subsequent subgroups, patients with class 2 malocclusion were observed.

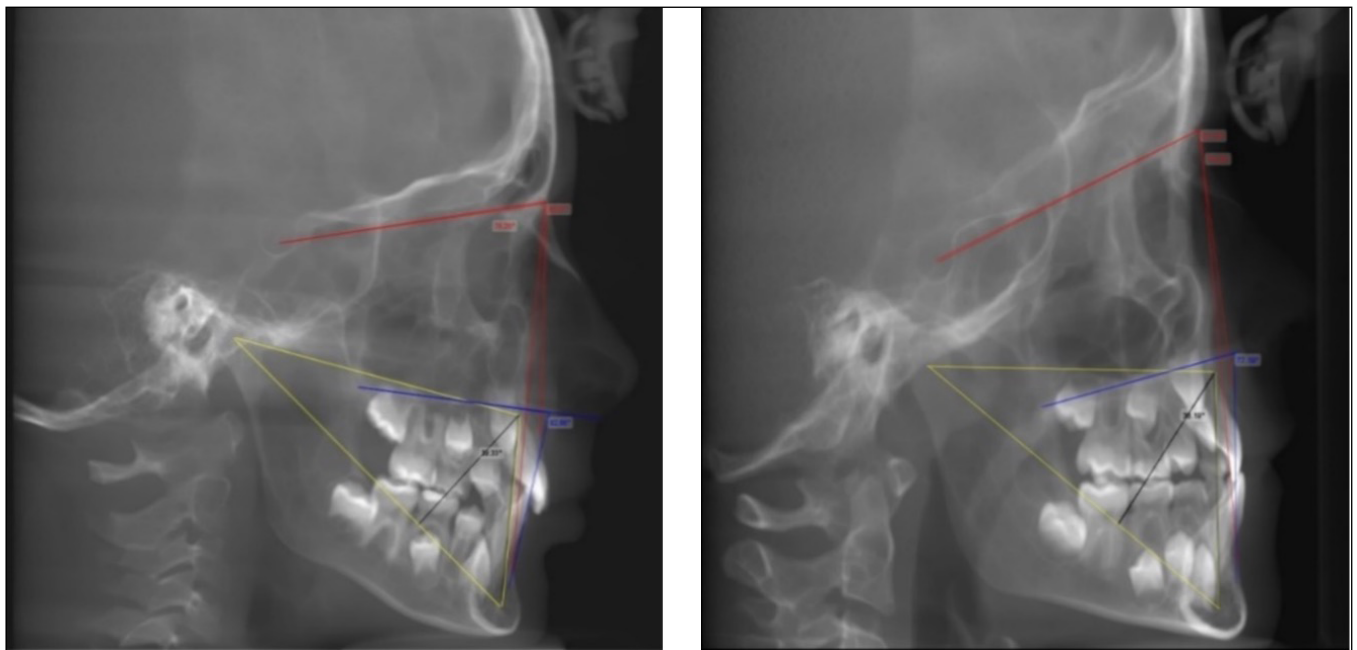
According to the results of the sample composition analysis (Table 1), it should be noted that girls prevailed in the study group 1, 14 persons (53.8%), compared to the number of boys, 11 persons (42.8%), Group 2 was also dominated by girls, 12 persons (70.6%), compared to 5 boys (29.4%). At the same time, in study group 3, on the contrary, the number of boys was 2.3 times greater: 7 (70%) against 3 (30%). It was found that 34 patients had Class II malocclusion according to Angle, which accounted for 65.4% of the total number of subjects, while only 18 children had Class I malocclusion according to Angle (34.6%). In early mixed dentition, NGP was found in 20 individuals (57.1%), HGP in 10 children (28.6%), and VGP was observed in only 5 patients (14.3%).

Table 3. Results of multifactorial ANOVA statistical analysis of patients' studied angles in different facial skeleton growth patterns

Cephalometric index	Growth pattern	Angle value	Normal value	Dispersive analysis of variance (ANOVA)	P value
$\angle K$	NGP	39,3°	43±3°	75.461	0.005
$\angle ANB$	NGP	4,6°	2±2°	74.885	0.005
APDI	NGP	82,1°	81.4± 3,8°	75.261	0.125*
$\angle K$	HGP	40,6°	43±3°	73.565	0.002
$\angle ANB$	HGP	2,5°	2±2°	73.785	0.08*
APDI	HGP	77,2°	81.4± 3,8°	74.273	0.002
$\angle K$	VGP	35,7°	43±3°	74.653	0.001
$\angle ANB$	VGP	2,5°	2±2°	74.658	0.001
APDI	VGP	77,2°	81.4± 3,8°	74.624	0.001

*- non-significant value

Source: compiled by the authors of this study

**Fig. 1.** A-lateral cephalogram of a patient with NGP; B-patient's lateral cephalogram with HGP

Picture taken by the authors

A strong correlation was found between the K angle, ANB angle, and Kim's APDI analysis parameter, although no direct statistical correlation was found between the ANB angle under study and the horizontal type of facial skull growth, which was predominantly due to shortening of the premaxilla, the basis of the upper and/or lower jaw, as well as shortening of the lower jaw branch in patients with different types of facial skull growth.

For groups with neutral growth, horizontal growth and vertical growth, the mean value of angle K and standard deviation were 40.28 ± 1.24 , 39.5 ± 1.19 and 37.7 ± 1.33 , respectively (Table 2). In addition, the K angle values in the groups were not affected by the

age of the children ($p = 0.184$), gender ($p = 0.129$), malocclusion class according to Engle ($p = 0.184$) and periods of mixed dentition ($p = 0.165$).

According to the results (Table 3) of the comparative analysis conducted in patients with NGP (Fig. 1 A) of the facial skull, a direct statistically significant correlation was found between the ANB and K angles and this type of growth ($p=0.005$), but no statistically significant correlation was found between the neutral growth type and the APDI parameter; in patients with HGP (Fig. 1 B), a direct statistically significant correlation was found between the K and APDI angles and this growth type ($p=0.002$), however, no statistically significant correlation ($p=0.08$) was found between the horizontal

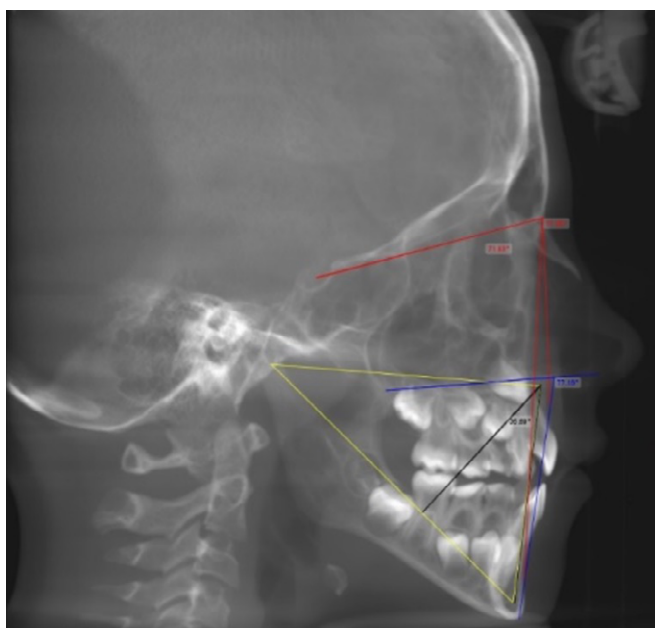


Fig. 2. 3D lateral cephalogram of a patient with VGP

Picture taken by the authors

growth type and the ANB angle, which is associated with the detection of sagittal apical base decrease of the upper jaw; in patients with VGP (Fig. 2), we found a direct statistically significant relationship between the APDI parameter and both angles studied ($p=0.001$), without detected sagittal apical base decrease of the jaws, which confirms previously published studies on the reliability of using the K angle in cephalometric analysis of orthodontic patients in the permanent occlusion period [1, 3, 6–9, 16].

Thus, no statistically significant differences in $\angle K$, $\angle ANB$, and APDI between the three study groups were found at the level of $p \leq 0.05$. We did not find strong correlations between angles K, ANB, APDI and early mixed occlusion ($r=0.231$; $p>0.05$), as well as late mixed occlusion ($r=0.224$; $p>0.05$) according to Pearson's coefficient.

DISCUSSION

In Ukraine, class 2 malocclusions are malocclusions, with a frequency of up to 79.9% during the mixed dentition period [17–19], requiring timely diagnosis and interceptive orthodontic treatment. In the late stage of mixed dentition, HGP was more common (41.2%) than others, since the type of facial skull growth tends to change during the first phase of puberty. Studies by Knigge et al [20] showed that in VGP, the prevalence of class 2 was 51.6% (46 people); in NGP – 35% (210 people); in HGP – 23.7% (68 people).

The difference between gender distribution in study group 3 (VGP) was due to the fact that men had

significantly increased posterior and anterior facial height, lower jaw length, and downward displacement of the posterior upper jaw. This is confirmed by the studies of Taner et al., which determined a statistically significant advantage of the male sex in the sample with vertical growth type in the presence of class 1 malocclusion, and also established that in class 2 malocclusion, the posterior facial height and lower facial height in men were significantly longer compared to girls [18]. Nowadays, no direct or inverse correlation has been established between facial skeleton growth patterns and sagittal occlusal anomalies [21].

Cephalometric assessment of the relationship between the jaws in the sagittal plane is considered extremely important in orthodontics. Since Broadbent introduced lateral cephalometry, many analyses have been conducted to assess the anterior-posterior relationship of the jaws [2, 4]. In many clinical cases with questionable statistical data, it is impossible to make a definitive diagnosis based on the sagittal skeletal pattern, as different skeletal analyses can produce conflicting results. Based on the results of the study of most factors, a 'final diagnosis' of the anterior-posterior skeletal malocclusion class was made. The consistency of diagnostic criteria for various cephalometric parameters was assessed by using kappa statistics, specificity and sensitivity. We compared the diagnostic accuracy of the included skeletal parameters between all study groups: K-angle, ANB-angle, APDI [3, 5].

An important step in orthodontic diagnosis and treatment planning is the assessment of the sagittal relationship between the jaws. Numerous linear and angular measurements have been proposed to assess this relationship, but they can be inaccurate because variations in facial height, jaw inclination, and overall jaw prognathism can alter angular measurements [4, 8]. The ANB angle is still widely used to assess the sagittal relationship of the jaws, but it depends on a number of various factors. Some studies have shown that the length of the anterior cranial base, vertical growth pattern and minor variations in nasion and sella turcica locations can all affect the ANB-angle measurements [6, 8]. In order to evaluate the class and form of malocclusion more accurately than ANB angle analysis, clinicians are still searching for a new reliable cephalometric index [1, 13].

In our research results, the K-angle, ANB angle, APDI parameter, and all study groups showed a low degree of consistency ($k=0.321$, $p<0.01$). In turn, the K-angle, ANB angle, and APDI showed a high degree of consistency in the NGP and VGP of the facial skull ($k=0.845$, $p<0.01$), while in HGP, the kappa coefficient indicated a moderate degree of agreement ($k=0.505$, $p<0.01$) of the studied

angles, which is explained by a change in the ANB angle in these patients due to sagittal dysplasia of the upper jaw. The specificity and sensitivity of each diagnostic parameter were also determined independently for all groups. The ANB angle had the highest specificity (0.930), and the K angle had the highest sensitivity (0.978) in Class I malocclusions. The K angle had the highest sensitivity (0.948) and specificity (0.921) in Class II malocclusions. The ANB angle in group I had the highest sensitivity (0.902), compared to group III (0.813) and group II (0.485). In contrast, the K angle had the best specificity (1.00) throughout all groups under our study, with slightly different sensitivity values of 0.901 (group I), 0.876 (group III) and 0.732 (group II). In research made by Ahmed et al. [8], ANB angle sensitivity was 0.809 in the class 1 group, while in the class 2 group, its value was 0.928, which was slightly different from our findings. They also revealed that the ANB angle is only valid in patients with NGP of the facial skeleton, while in VGP and HGP, more accurate parameters have to be involved in order to precisely assess sagittal jaw discrepancy.

According to Jacobson [4, 6], the patient's age, vertical growth direction, jaw rotation, and length of the anterior skull base affect the change in the value of this angle. In addition, high-quality X-rays are required for accurate identification of point A, which sometimes complicates diagnosis, since it is not always possible to take high-quality images using digital technologies [12, 13].

Angle K has a statistically significant advantage over angle ANB in that it remains stable even when the jaws rotate or increase in the vertical direction [1, 3, 8, 9, 16]. For example, the C-G line rotates in the same direction as point G when it rotates downwards and backwards, carrying with it the perpendicular from point M. Angle K remains relatively constant because the M-G line also rotates in the same direction. Therefore, when the jaws rotate clockwise or counterclockwise, this tends to obscure the sagittal relationship of the jaws in gnathic forms of malocclusion, which angle K can assess. The quality of the cephalogram must be high [14]. However, it is not always easy to find the middle of the premaxilla and determine it correctly [4, 7]. The advantage of determining the centre of the condylar head is that there is no need to accurately trace the

contour of the condylar head; if the centre is within 2 mm of its actual location, the value of angle K will have a minimum error of about 1°, which is not statistically significant ($p=0.01$) [3]. Bajjad et al. [17] compared values of different angles (including K-angle) in class 1 and class 2 malocclusion patients in permanent occlusion with different facial skeleton growth patterns. The author discovered that in both class 1 and class 2 malocclusion patients, despite the growth pattern, with good reliability, $\angle YEN$ displays the greatest alpha value (0.849), followed by $\angle W$ (0.841) and $\angle K$ (0.816). Those results are similar to our findings, which also proved that the K-angle is a reliable cephalometric index which should be taken into consideration, especially when we use 3D cephalometrics for landmark detection. Thus, no statistically significant differences in $\angle K$, $\angle ANB$, and APDI between the three study groups were found at the level of $p \leq 0.05$, which is confirmed by the studies of Mohammadi Shayan et al. [20].

CONCLUSIONS

The K-angle showed a significant correlation with APDI in every facial skeleton growth pattern group and was revealed to be the most valid and reliable indicator of sagittal jaw discrepancy assessment amongst the three studied cephalometric indexes. That's why the K-angle can be used to accurately establish and also precisely differentiate malocclusion's class and its aetiological form during mixed dentition as well.

It is advisable to take this angle into account not only in the permanent occlusion period, but also in the mixed dentition period, regardless of the existing types of facial skeleton growth patterns, as a full-fledged alternative to using the ANB angle to assess the anteroposterior relationships of the upper and lower jaws during the diagnosis and planning of treatment tactics for orthodontic patients with occlusion anomalies, which directly depends on the specific malocclusion and its form.

Further research should focus on a more detailed study of the dependence of the K angle on changes in the position of the jaw bases, as well as sagittal dysplasia of the alveolar ridge of the upper jaw, to fully implement this cephalometric indicator in 3D cephalometric diagnostics in modern orthodontic practice.

REFERENCES

1. Kotuła J, Kuc AE, Lis J et al. New Sagittal and Vertical Cephalometric Analysis Methods: A Systematic Review. *Diagnostics* (Basel). 2022;12(7):1723. doi: 10.3390/diagnostics12071723. [DOI](#)
2. Albarakati SF, Kula KS, Ghoneima AA. The reliability and reproducibility of cephalometric measurements: a comparison of conventional and digital methods. *Dentomaxillofac Radiol*. 2012;41(1):11-7. doi: 10.1259/dmfr/37010910. [DOI](#)

3. Sandeep KM et al. K angle: a new indicator of sagittal jaw relationship. *Int J Cur Res.* 2017;9(2):46243-46247.
4. Brown M. Eight methods of analysing a cephalogram to establish anteroposterior skeletal discrepancy. *Br J Orthod.* 1981;8(3):139-46. doi: 10.1179/bjo.8.3.139. [DOI](#)
5. Oktay H. A comparison of ANB, WITS, AF-BF, and APDI measurements. *Am J Orthod Dentofacial Orthop.* 1991;99(2):122-8. doi: 10.1016/0889-5406(91)70114-C. [DOI](#)
6. Jajoo A, Agarkar SS, Sharma S et al. Comparison of Beta and ANB Angles for Evaluation of Sagittal Skeletal Discrepancy: A Cephalometric Study. *J Contemp Dent Pract.* 2018;19(6):739-742.
7. Baik CY, Verweridou M. A new approach of assessing sagittal discrepancies: the Beta angle. *Am J Orthod Dentofacial Orthop.* 2004;126(1):100-5. doi: 10.1016/j.ajodo.2003.08.026. [DOI](#)
8. Ahmed M, Shaikh A, Fida M. Diagnostic validity of different cephalometric analyses for assessment of the sagittal skeletal pattern. *Dental Press J Orthod.* 2018;23(5):75-81. doi: 10.1590/2177-6709.23.5.075-081.oar. [DOI](#)
9. Bhadr WA, Nayak S, Doshi UH. A new approach of assessing sagittal dysplasia: the W angle. *Eur J Orthod.* 2013;35(1):66-70. doi: 10.1093/ejo/cjr001. [DOI](#)
10. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant.* 2013 Mar;48(3):452-8. doi: 10.1038/bmt.2012.244. [DOI](#)
11. Krymovskyy KG, Zhehulovych ZE, Storozhenko KV, Babaskin YI. Nowadays and the future of the 3d digital technologies in modern orthodontics. *Wiad Lek.* 2024;77(10):2047-2056. doi: 10.36740/WLek/195140. [DOI](#)
12. Durão AR, Pittayapat P, Rockenbach MI et al. Validity of 2D lateral cephalometry in orthodontics: a systematic review. *Progress in Orthodontics.* 2013;14(1):31. doi:10.1186/2196-1042-14-31. [DOI](#)
13. Segner D, Hasund A. Indywidualna cefalometria. [Individual cephalometry]. *Med. Tour Press Int. Otwock.* 2015, p.144. (Polish)
14. Serafin M, Baldini B, Cabitza F et al. Accuracy of automated 3D cephalometric landmarks by deep learning algorithms: systematic review and meta-analysis. *Radiol Med.* 2023;128(5):544-555. doi: 10.1007/s11547-023-01629-2. [DOI](#)
15. Sam A, Currie K, Oh H et al. Reliability of different three-dimensional cephalometric landmarks in cone-beam computed tomography: A systematic review. *Angle Orthod.* 2019;89(2):317-332. doi: 10.2319/042018-302.1. [DOI](#)
16. Kotuła J, Kotuła K, Kotarska M et al. Selected Indicators Used in Cephalometric Analysis and Their Predictive Value in Defining Sagittal Discrepancy Malocclusions: A Comparative Study. *J. Clin. Med.* 2025;14:3429. doi: 10.3390/jcm14103429. [DOI](#)
17. Bajjad A, Chauhan A, Sharma A, Kumar S. Cephalometric analysis for assessing sagittal jaw relationship- A comparative study. *IP Indian Journal of Orthodontics and Dentofacial Research.* 2021;7:150-159. doi: 10.18231/j.ijodr.2021.026. [DOI](#)
18. Taner L, Gürsoy GM, Uzuner FD. Does Gender Have an Effect on Craniofacial Measurements? *Turkish journal of orthodontics.* 2019;32(2):59-64. doi:10.5152/TurkJOrthod.2019.18031. [DOI](#)
19. Smahliuk LV, Dmytrenko MI. Dystalna okliuziia i skupchenist zubiv: stratehiia likuvannia. [Distal occlusion and crowding of teeth: treatment strategies]. *Ukrainskyi stomatolohichnyi almanakh.* 2020;2:103-108. (Ukrainian)
20. Mohammadi Sh, Behroozian A, Sadrhaghghi A et al. Prevalence of dental anomalies in different facial patterns and malocclusions in an Iranian population. *Journal of oral biology and craniofacial research.* 2022;12(5):525-528. doi:10.1016/j.jobcr.2022.07.001. [DOI](#)
21. Knigge RP, Hardin AM, Middleton KM et al. Craniofacial growth and morphology among intersecting clinical categories. *Anatomical record (Hoboken, N.J. : 2007).* 2022;305(9):2175-2206. doi:10.1002/ar.24870. [DOI](#)

The article was written as part of research work entitled "Improvement of digital and analogue protocols for the diagnosis, treatment and prevention of patients of different age groups with dentoalveolar anomalies and deformities" (state registration number 0124U000780).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Kyryl G. Krymovskyy

Bogomolets National Medical University

13 T. Shevchenko Blvd., 01601 Kyiv, Ukraine

e-mail: creyss23@ukr.net

ORCID AND CONTRIBUTIONSHIP

Kyryl G. Krymovskyy: 0000-0003-0484-5329 [A](#) [B](#) [C](#) [D](#)

Oleksandr A. Kaniura: 0000-0002-6926-6283 [A](#) [E](#) [F](#)

Zinaida E. Zhehulovych: 0000-0002-9996-2060 **A** **E** **F**
Kateryna V. Storozhenko: 0000-0003-3509-7124 **A** **B** **E** **F**
Yurii I. Babaskin: 0000-0003-1628-2500 **A** **B** **E**
Oleksandr V. Bida: 0000-0002-6038-6545 **A** **B** **C** **D**
Tetyana M. Brychko: 0009-0004-0453-2001 **A** **B** **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: 10.04.2025

ACCEPTED: 28.08.2025



Characteristics of energy metabolism in full-term newborns with neonatal hyperbilirubinemia

Yulia M. Volosivska, Anastasiya G. Babintseva, Yuliya D. Hodovanets, Volodymyr A. Petrov,
Nataliya I. Kovtyuk, Nataliya O. Popeliuk, Oksana I. Yurkiv
BUKOVINIAN STATE MEDICAL UNIVERSITY, CHERNIVTSI, UKRAINE

ABSTRACT

Aim: To study the peculiarities of energy metabolism in full-term newborns with neonatal hyperbilirubinemia.

Materials and Methods: It was conducted the comprehensive examination of 30 full-term newborns with signs of neonatal jaundice (main group) and 30 healthy infants (control group).

It was determined the level of lactate, pyruvate and lactate/pyruvate ratio in the blood serum; in the bloods lymphocytes – level of Glycerol-3-phosphate Dehydrogenase (GPDH), Succinate Dehydrogenase (SDH), and Nicotinamide Adenine Dinucleotide Dehydrogenase (NADH-D), Aerobic Respiration Rate (AR) and Electronic Transport Chain coefficient (ETC).

Statistical analysis of the results was conducted using STATISTICA (Version 10) software, MedCalc Software (Version 16.1).

Results: Newborns of main group – in comparison to control group was defined: statistically significant lower lactate and pyruvate levels with statistically higher lactate/pyruvate ratio (53.62 ± 6.49 and 29.02 ± 9.87 , $p < 0.0001$ respectively); statistically significant lower GPDH, SDH and NADH-D activities; statistically significant lower ETC coefficient (14.58 ± 3.56 and 21.13 ± 1.51 a.u., $p < 0.0001$ respectively) with statistically significant higher AR coefficient (13.22 ± 9.13 and 8.42 ± 3.29 a.u., $p = 0.0102$ respectively).

Conclusions: Full-term newborns with signs of pathological hyperbilirubinemia have significant disruptions in the relationship between aerobic and anaerobic energy processes in comparison to healthy infants. The higher discriminatory ability level was defined in diagnostic model using ETC coefficient (cut-off level ≤ 19.48 , AUC 0.918; 95 % CI 0.841; 0.966, $p < 0.0001$, sensitivity 92.45 %, specificity 91.67 %).

KEY WORDS: newborn, neonatal hyperbilirubinemia, bilirubin, mitochondrial respiration

Wiad Lek. 2025;78(9):1718-1724. doi: 10.36740/WLek/212384 DOI

INTRODUCTION

Neonatal jaundice and neonatal hyperbilirubinemia (NH) is a clinical condition that is characterized by yellowing of the skin, sclera, and mucous membranes in newborns due to accumulation of bilirubin in tissues [1]. Physiological jaundice has majority (60 – 80 %) of full-term infants and usually it is a transient condition. But excessive accumulation of unconjugated bilirubin (UB), especially with NH (for example as a result of hemolysis, infections, metabolic disorders) may lead to its penetration through blood-brain barrier and to developing of acute bilirubin encephalopathy or its chronic consequences – kernicterus [2, 3]. And at the same time physiological increase in bilirubin may have an impact as a transient antioxidant after birth till maturation of the antioxidant system [4].

Newborns adaption to the life after womb is accompanied by the huge changes in the energy metabolism

aimed on to maintaining of homeostasis, thermoregulation and supplying of the energy for growing and development [5]. The key role in these processes have mitochondria, where the oxidative phosphorylation occurs which is the main way of ATP synthesis [6, 7]. Therefore, the body compensates by switching to a less effective anaerobic way of glucose breakdown which is the key metabolic adaptation to the hypoxia intrauterine. Lactic acid (lactate) is the end product of an anaerobic glycolysis. Its excessive accumulation in blood and tissues leads to the metabolic acidosis (reducing of bloods pH level), known as lactic acidosis. The lactate level is a key marker of severity of hypoxic-ischemic injury in the newborns [8, 9]. Under these conditions, the body's ability to detoxification is significantly reduced, which leads to accumulation of interim products of the exchange, that may have a

negative impact on to bilirubin's metabolism in infants with jaundice accompanied with perinatal pathology.

There are theoretical premises to believe that NH may have an impact on to condition of energy exchange of newborn. Firstly, UB itself in high concentrations is considered as a potential toxin capable to disrupt the cell functions, including mitochondrial respiration [3, 10]. Secondly, one of the mechanisms of bilirubin toxicity is an oxidative stress (OS) induction, which, in turn, is a known factor of mitochondrial injury and energy production disruption [4, 11, 12]. Toxical bilirubin levels, similar to hypoxia, provokes the formation of free radicals and exhausts antioxidant systems – glutathione. On the other hand, bilirubin in physical concentrations can act as endogenous antioxidant [13-15]. Finally, the processes of bilirubin's conjugation and excretion and also cell responsiveness to its potential toxicity may need additional energy consumption. So, perinatal pathology, especially conditions associated with hypoxia significantly affect intracellular energy metabolism in newborns, that leads to a series of metabolic disorders which can be evaluated by certain biochemical indicators. But, in spite of prevalence of the NH and fundamental importance of energy metabolism, the relationship between these conditions in newborns has not been sufficiently studied, especially at the clinical level.

AIM

To study the features of energy metabolism in full-term newborns with neonatal hyperbilirubinemia

MATERIALS AND METHODS

To achieve this goal, a comprehensive clinical and laboratory examination of 30 newborns with gestational age more than 37 weeks (main group) was conducted. Comparison group (control group) consists of 30 conditionally healthy newborns. Inclusion criteria in research: gestational age at birth ≥ 37 weeks, clinical signs of neonatal jaundice. Exclusion criteria: gestational age at birth ≤ 37 weeks, birth defects, neonatal sepsis. Diagnoses were determined according to International classification of diseases X revision. In addition to generally accepted standard methods of clinical and laboratory examination the condition of intracellular energy exchange was determined [12]. List of indicators: blood serum – level of Glycerol-3-phosphate Dehydrogenase (GPDH), Succinate Dehydrogenase (SDH), and Nicotinamide Adenine Dinucleotide Dehydrogenase (NADH-D), Aerobic Respiration Rate (AR) and Electronic Transport Chain coefficient (ETC) were calculated. Lab-

oratory studies were conducted using micromethods using the peripheral and cord blood 1.0 ml in volume.

The scientific researches were conducted in compliance with "Rules of ethical principles of scientific researches conducting involving human subjects" that was adopted by Declaration of Helsinki (1964 – 2013), ICH GCP (1996), Council Directive № 609 (from 24.11.1986), Decree of Ministry of Health of Ukraine № 690 from 23.09.2009. Protocol of the scientific research of the Commission of biomedical ethics of BSMU from 12.09.2015. Before the start of research, informed written consent was obtained from parents with an explanation of the purpose, objectives, and methods of the laboratory study.

Statistical analysis of the results was conducted using STATSTICA (Version 10) software, MedCalc Software (Version 16.1). Comparison of quantitative indicators with normal distribution was carried out using Student's t-test ($p < 0.05$). Analysis of Receiver Operating Characteristic Curve, ROC was conducted using MedCalc Software (Statistical Software Package for Biomedical Research, 2023, Version 16.1).

RESULTS

The results of the study showed that based on sex, gestational age, information about physical development at birth examination groups did not differ statistically significantly. The average indicators of body mass index at birth for infants of main group – 3320.71 ± 440.84 g, infants of comparison group – 3332.67 ± 433.5 g ($p > 0.05$), body height – 53.1 ± 2.38 and 53.11 ± 2.67 cm ($p > 0.05$) recursively. The ratio by sex according to the survey groups was as follows: 18 (60.0 %) and 16 (53.3 %) males ($p > 0.05$); 12 (40.0 %) and 14 (46.7 %) females ($p > 0.05$).

Average Apgar score at birth at the end of 1-st minute of life for infants of main group is 7.4 ± 0.79 points, control group – 7.6 ± 0.74 points ($p > 0.05$), at 5-th minute of life – 8.6 ± 0.97 and 8.2 ± 0.76 points ($p > 0.05$) recursively.

The study of somatic pathology of mothers, features of pregnancy and childbirth showed no statistically significant difference between the study groups. Thus, somatic pathology of mothers is presented in form of anemia (36.7 and 33.3 %, $p > 0.05$), pathology of the thyroid gland (20.0 and 26.7 %, $p > 0.05$), vegeto-vascular dystonia (20.0 and 23.3 %, $p > 0.05$), chronic cholecystitis (16.7 and 13.3 %, $p > 0.05$) and chronic pyelonephritis (13.3 and 20.0 %, $p > 0.05$). The list of gynecological diseases includes previous colpitis (16.7 and 13.3 %, $p > 0.05$) and chronic adnexitis (10.0 and 6.7 %, $p > 0.05$). Medical complications of gestational period are related to placental insufficiency (30.0 and 36.7 %, $p > 0.05$),

Table 1. Level of lactate, pyruvate and lactate/pyruvate ration in blood serum of infants of survey groups on 1 – 3 days of life ($M \pm m$)

Indicator	Main group (n = 30)	Control group (n = 30)	p
Lactate, mmol/l	6.48 ± 1.17	8.78 ± 2.09	< 0.0001
Pyruvate, mmol/l	0.22 ± 0.14	0.42 ± 0.19	< 0.0001
Lactate/Pyruvate	53.2 ± 6.49	29.02 ± 9.87	< 0.0001

Source: compiled by the authors of this study

Table 2. ROC-curve Analysis of lactate, pyruvate levels and lactate/pyruvate ration in blood serum of infants of survey group on 1 – 3 days of life

Indicator	AUC	Standard deviation	P	95% CI	Youden's index	Sensitivity %	Specificity %
Lactate, mmol/l	0.642	0.0693	= 0.0410	0.533 – 0.740	0.5257	88.68	63.89
Pyruvate, mmol/l	0.519	0.0635	= 0.7631	0.411 – 0.626	0.2940	37.74	91.67
Lactate/Pyruvate	0.671	0.0597	= 0.0047	0.563 – 0.767	0.5136	73.58	77.78

Source: compiled by the authors of this study

Table 3. Activity of enzyme's mitochondrial oxidation in blood serum of infants of survey groups on 1 – 3 days of life ($M \pm m$)

Indicator	Main group (n = 30)	Control group (n = 30)	P
GPDH, μm^2	1.75 ± 0.63	3.45 ± 1.22	< 0.0001
SDH, μm^2	6.22 ± 1.64	9.74 ± 0.94	< 0.0001
NADH-D, μm^2	10.39 ± 2.19	14.84 ± 0.96	< 0.0001
AR coeff., a.u.	13.22 ± 9.13	8.42 ± 3.29	= 0.0102
ETC coeff., a.u.	14.58 ± 3.56	21.3 ± 1.51	< 0.0001

Source: compiled by the authors of this study

Table 4. Data of ROC-curve analysis of AR and ETC in blood serum of infants of survey groups in 1 – 3 days of life

Indicator	AUC	Standard deviation	P	95% CI	Youden's index	Sensitivity %
AR coefficient	0.513	0.0641	0.8379	0.405 – 0.621	0.2794	41.51
ETC coefficient	0.918	0.0327	< 0.0001	0.841 – 0.966	0.8412	92.45

Source: compiled by the authors of this study

threat of termination of pregnancy (30.0 and 33.3 %, $p > 0.05$), preeclampsia (16.7 and 13.3 %, $p > 0.05$) and eclampsia (10.0 and 6.7 %, $p > 0.05$). Overall, a difficult obstetric history had a woman of main group in 46.7 %, control group – 53.3 % of cases, $p > 0.05$.

The main group of the survey included 30 newborns with an average gestational age of 38.9 ± 0.66 weeks. 23 infants (76.7 %) were born by vaginal birth, 7 infants (23.3 %) – Caesarean section. Urgent Caesarean section was performed for 3 women (10 %), including 2 (6.7 %) – due to fetal distress. The main pathology observed among the infants of this group is represented by a neonatal encephalopathy in 30.4 % of cases, hemolytic disease of infants – 21.7 % of cases, meconium aspiration syndrome and, as a result, severe respiratory disorders – 2.2 % of cases, moderate respiratory disorders – 2.2 % of cases. One infant (2.2 %) had a birth trauma of cervical spine on C6 – C6 level, low body weight – 2 infants (4.4 %). Majority of infants of main group – 26

(86.7 %) were exclusively on breastfeeding, 4 infants (13.3 %) – mixed feeding.

Control group includes 30 healthy full-term infants with gestational period 38.95 ± 0.87 weeks. Twenty-four infants (80.0 %) were born by natural childbirth, 6 infants (20.0 %) – Caesarean section, out of which 3 cases (10.0 %) – urgent. General condition of newborns of current group was satisfactory during all the stay in maternity hospital, infants stayed in joint stay chambers with mothers and in 96.6 % of cases (29 infants) – exclusively breastfeeding, 1 infant – mixed feeding. It should be noted that 22 of infants (73.3 %) were in risk group about hemolytic disease of newborns, but in no case has the pathological jaundice developed.

All the infants of main group have signs of pathological neonatal jaundice during early neonatal period, which required to conduct advanced diagnostic and medical measures, including control bilirubin level and conducting of phototherapy. Average value of cord

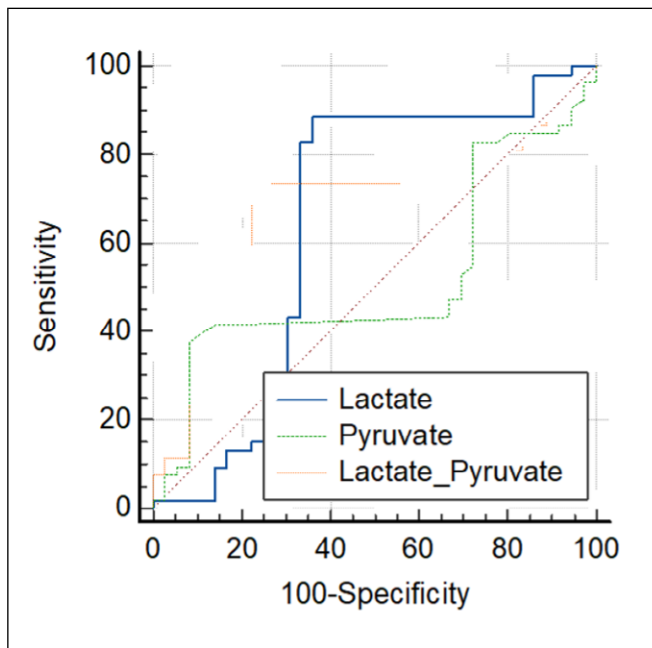


Fig. 1. ROC-curve analysis of lactate, pyruvate levels and lactate/pyruvate ratio in blood serum of infants of survey group on 1 – 3 days of life
Picture taken by the authors

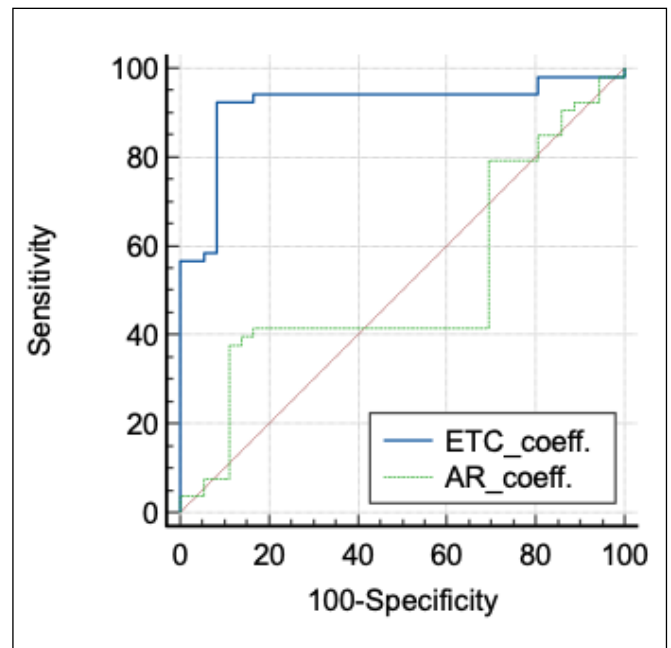


Fig. 2. ROC-curve analysis of AR and ETC in blood serum of infants of survey groups in 1 – 3 days of life
Picture taken by the authors

blood bilirubin level statistically significant did not differ between surveys group and was $38.46 \pm 1.49 \mu\text{mol/l}$ for infants of main group and $32.3 \pm 0.59 \mu\text{mol/l}$ – infants of control group. General bilirubin level of blood serum on 1 – 3 days of life was significant higher in group of infants with signs of pathological neonatal jaundice in comparison to healthy newborns (237.19 ± 18.34 and $164.01 \pm 8,2 \mu\text{mol/l}$, $p < 0.05$ respectively).

The specifics of energy exchange in blood serum of infants of surveys group on 1 – 3 days of life was studied during the research (Table 1).

It is necessary to note the laboratory signs of imbalance between the aerobic and anaerobic processes of energy formation in newborns under the conditions of development of pathological hyperbilirubinaemia. Thus, for infants of main group in comparison to control group it was defined statistically significant lower lactate level (6.48 ± 1.17 and $8.78 \pm 2.09 \text{ mmol/l}$, $p < 0.0001$ respectively) and pyruvate (0.22 ± 0.14 and $0.42 \pm 0.19 \text{ mmol/l}$, $p < 0.0001$ respectively) with simultaneously statistically higher lactate/pyruvate ratio (53.62 ± 6.49 and 29.02 ± 9.87 , $p < 0.0001$ respectively). Ratio lactate/pyruvate himself is marker that objectively characterizes relations between aerobic and anaerobic components of cell metabolism. Its increasing may be a sign aerobic processes activation or pyruvates disposal disruption in mitochondria [9].

We conducted Receiver Operating Characteristic Curve, ROC Analysis for defining of diagnostic and prognostic values of represented laboratory indicators (Table 2 and Fig.1).

Results of statistical analysis showed significant associative lactate level at $\leq 8.51 \text{ mmol/l}$ (AUC 0.642; 95 % CI 0.533; 0,74, $p = 0.041$) and lactate/pyruvate ratio at ≥ 29.02 (AUC 0,671; 95% CI 0.563; 0.767, $p = 0.0047$). These indicators values, based on our data, have average discriminatory ability. The absence of statistically significant AUC level at pyruvate level $> 0.47 \text{ mmol/l}$ (AUC 0.519, 95% CI 0.411; 0.626, $p > 0.05$) confirmed insufficient informative value of this indicator for disruption diagnostics of energy metabolism in newborns with signs of neonatal jaundice.

The Table 3 presents the results of the study of some blood serum enzymes activities in infants of survey groups, that may indirectly indicate about peculiarities of intracellular mitochondrial oxidation and explain its disorders mechanisms.

The generalized results of the study showed the depression of activity of these enzymes in blood serum of infants in main survey group with present signs of pathological jaundice in comparison to healthy full-term infants. GPDH activity in infants of main group is $1.75 \pm 0.63 \mu\text{m}^2$, infants of control group – $3.45 \pm 1.22 \mu\text{m}^2$ ($p < 0.0001$), SDH activity – 6.22 ± 1.64 and $9.74 \pm 0.94 \mu\text{m}^2$ ($p < 0.0001$) respectively, NADH-D – 10.39 ± 2.19 and $14.84 \pm 0.96 \mu\text{m}^2$ ($p < 0.0001$) respectively. This may indirectly indicate on disorders of intracellular mechanisms of energy processes regulation in newborns against the backdrop of high bilirubin level and therapeutic activities conducting.

In comparison to healthy full-term infants, infants with signs of pathological hyperbilirubinaemia has

statistically significant higher aerobic respiration coefficient (AR), which is calculated based on formula $(SDH - GPDH + NADH-D) / GPDH$. This indicator level in infants of main group was 13.22 ± 9.13 a.u., control group – 8.42 ± 3.29 a.u., $p = 0.0102$. Opposite results were noticed on electronic transport chain coefficient (ETC) that is calculated based on formula $SDH - GPDH + NADH-D$. Its level was statistically significant in the main group in comparison to control group (14.58 ± 3.56 to 21.13 ± 1.51 a.u., $p < 0.0001$ respectively). Detected changes on our opinion confirm the thought about mitochondria disruption in newborns together with significant increase of total bilirubin level.

Table 4 and Fig. 2 shows ROC-curve analysis results of AR and ETC coefficients in blood serum of infants of survey groups in 1 – 3 days of life.

AR coefficient > 8.11 shows absence of diagnostic significance of sufficient level to identify the possible difference between groups of full-term newborns with presence of clinical manifestation of pathological jaundice (AUC 0.513; 95 % CI 0.405; 0.621, $p > 0.05$). For ETC coefficient of ≤ 19.48 was spotted the highest level of discriminatory ability among all the laboratory indicators that were studied in this research. This was evidenced by the differ level of AUC (0.918; 95 % CI 0.841; 0.966, $p < 0.0001$) and high indicators of sensitivity (92.45 %) and specificity (91.67 %), and also Yonden's index (0.8412) that confirm the sufficient balance of sensitivity and specificity among the presented indicators.

DISCUSSION

In vitro research on isolated mitochondria or cell cultures (mainly neuronal) showed that high concentration of UB can inhibit activity of main enzyme complex of respiratory chain (especially complex I and IV) and Krebs cycle enzymes [3, 14]. This leads to a decrease in oxygen consumption by mitochondria, reducing the ATP synthesis and potential switching on anaerobic way of metabolism. It was show also that bilirubin may cause mitochondrial swelling and release of cytochrome C, which and apoptosis inductor [14-16]. These effects usually present at toxic bilirubin concentration and may depend on the bilirubin/albumin ratio and on presence of free bilirubin [17].

It should be noted that there are practically no direct studies on determining of the ATP level or mitochondria's enzymes activity in newborns tissues with NH due to ethical considerations, and most scientific data relate to indirect indicators. Thus, increase of lactate level in blood may indicate on tissue hypoxia or mitochondrial dysfunction with activation of anaerobic glycolysis.

Some research discovered increasing of lactate level in newborns together with significant NH, especially for those who needed a blood transfusion, which may indicate on dysfunction of aerobic metabolism [18]. However, other studies have not found a clear correlation between bilirubin level and lactate [19].

The data on interaction of glucose as an energy source and bilirubin is contradictionary. Theoretically, a malfunctioning of oxidative phosphorylation could lead to increased glycolysis level and potential hypoglycemia with existed glycogen reserves. On the other hand, a stress reaction may cause a hypoglycemia. Some studies indicate no significant changes of glycemia when having NH, while others report about hypoglycemia cases in infants with severe jaundice, especially against the backdrop of hemolysis [20].

Numerous studies confirm that significant NH is associated with increased OS markers level (for example, lipid peroxidation products such as malondialdehyde) and decreased activity of antioxidant enzymes (superoxide dismutase, glutathione peroxidase) in newborns [12]. OS can directly damage mitochondrial membranes and components of respiratory chain, leading to a decreasing in the efficiency of ATP synthesis and increasing of the production of active oxygen species, closing the vicious circle [21]. Some authors indicate that OS is the key mechanism of bilirubin-induced neurotoxicity [3, 22, 23].

Scientific interest is the study of the impact of phototherapy, which is the main method of NH treating, on cellular metabolism. Although its effectiveness in lowering of bilirubin levels is proven, its metabolic effects are less well studied. Phototherapy can potentially affect energy balance through increased unconscious water losses and possible effects on thermoregulation [24, 25]. There are also consumptions that phototherapy may increase OS [26], which could theoretically further affect mitochondrial function [27]. However, there is currently no clinical evidence about significant negative impact of standard phototherapy on energy metabolism.

So, NH is a powerful factor that may cause cascade of metabolic disorders related to mitochondrial dysfunctions which is reflected in changes of the relevant laboratory indicators. However, it is always necessary to take into account the presence of comorbidities (hypoxia, acidosis, infections, premature birth) which may increase the negative impact of NH on to these indicators and also individual genetically determined sensitivity of newborns to level and duration of hyperbilirubinemia.

CONCLUSIONS

1. The results of the survey showed that full-term newborns with signs of pathological hyperbiliru-

binaemia in comparison to healthy infants show significant relations disorders of aerobic and anaerobic processes. This is confirmed by the established statistically significantly lower levels of lactate and pyruvate with higher lactate/pyruvate ration and also statistically significantly less activity of GPDH, SDH, NADH-D in blood serum on 1 – 3 days of life.

2. Integral markers of mitochondrial dysfunction confirm significantly higher informativeness than separate substrate or intermediate products of metabolism. The highest level of discriminatory ability has a diagnostic model using ETC coefficient (cut-off level ≤ 19.48 , AUC 0.918; 95 % CI 0.841; 0.966,

$p < 0.0001$, sensitivity 92.45 %, specificity 91.67 %, Yuden's index 0.8412).

PROSPECTS FOR FURTHER RESEARCH

Prospects for further research are aimed at studying of the diagnostic value of modern markers of mitochondrial function (analysis of mitochondrial DNA, specific biomarkers in blood or urine) and conducting of prospective studies for defining of correlation between indicator of energy metabolism and oxidative stress to bilirubin level, clinical severity of NH and its long-term consequences.

REFERENCES

1. Du L, Ma X, Shen X et al. Neonatal hyperbilirubinemia management: Clinical assessment of bilirubin production. *Seminars in Perinatology*. 2021;45(1):151351. doi:10.1016/j.semperi.2020.151351. DOI
2. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. *Lancet Child Adolesc Health*. 2018;2(8):610–620. doi: 10.1016/S2352-4642(18)30139-1. DOI
3. Hegyi T, Kleinfeld A. Neonatal hyperbilirubinemia and the role of unbound bilirubin. *The Journal of Maternal-Fetal. Neonatal Medicine*. 2021;35(25):9201–9207. doi: 10.1080/14767058.2021.2021177. DOI
4. Perrone S, Lembo C, Giordano M et al. Molecular mechanisms of oxidative stress-related neonatal jaundice. *J Biochem Mol Toxicol*. 2023;37:e23349. doi: 10.1002/jbt.23349. DOI
5. Lembo C, Buonocore G, Perrone S. Oxidative Stress in Preterm Newborns. *Antioxidants*. 2021;10(11):1672. doi: 10.3390/antiox10111672. DOI
6. Zhao T, Alder NN, Starkweather AR et al. Associations of Mitochondrial Function, Stress, and Neurodevelopmental Outcomes in Early Life: A Systematic Review. *Dev Neurosci*. 2022;44(6):438–454. doi: 10.1159/000526491. DOI
7. Sun T, Yu H, Li D et al. Emerging role of metabolic reprogramming in hyperoxia-associated neonatal diseases. *Redox Biology*. 2023;66:102865. doi: 10.1007/s11427-019-1735-4. DOI
8. Godovanets OS. Diagnostic value of laboratory markers of enteric dysfunction in preterm infants. *Wiad Lek*. 2024;77(11):2154–2160. doi: 10.36740/WLek/197086. DOI
9. Yilmaz A, Cebi MN, Yilmaz G et al. Long-term neurodevelopmental effects of exclusively high cord lactate levels in term newborn. *J Matern Fetal Neonatal Med*. 2023;36(2):2284115. doi: 10.1080/14767058.2023.2284115. DOI
10. Kumbhar S, Musale M, Jamsa A. Bilirubin metabolism: delving into the cellular and molecular mechanisms to predict complications. *Egypt J Intern Med*. 2024;36:34. doi: 10.1186/s43162-024-00298-5. DOI
11. Basu S, De D, Dev Khanna R et al. Lipid Peroxidation, DNA Damage and Total Antioxidant Status in Neonatal Hyperbilirubinaemia. *J Perinatol*. 2014;34(7):519–23. doi: 10.1038/jp.2014.45. DOI
12. Dani C, Poggi C, Pratesi S. Bilirubin and oxidative stress in term and preterm infants. *Free Radic Res*. 2019;53(1):42–48. doi: 10.1080/10715762.2018.1478089. DOI
13. Soto Conti CP. Bilirubin: The toxic mechanisms of an antioxidant molecule. *Arch Argent Pediatr*. 2021;119(1):e18–e25. doi: 10.5546/aap.2021.eng.e18. DOI
14. Gazzin S, Jayanti S, Tiribelli C. Models of bilirubin neurological damage: lessons learned and new challenges. *Pediatr Res*. 2023;93:1838–1845. doi: 10.1038/s41390-022-02351-x. DOI
15. Zhang Y, Luan H, Song P. Bilirubin metabolism and its application in disease prevention: mechanisms and research advances. *Inflamm Res*. 2025;74:81. doi: 10.1007/s00011-025-02049-w. DOI
16. Yücesoy E, Demir Y, Ateş H et al. Effect of hyperbilirubinemia and phototherapy on apoptotic microparticle levels in neonates. *Blood Coagulation & Fibrinolysis*. 2024;35(5):227–231.
17. Brites D, Silva R. Bilirubin neurotoxicity: a narrative review on long lasting, insidious, and dangerous effects. *Pediatric Medicine*. 2021;4:34. doi: 10.1097/MBC.0000000000001297. DOI
18. Lee IC, Yu CS, Hu YC et al. Unconjugated bilirubin is correlated with the severeness and neurodevelopmental outcomes in neonatal hypoxic-ischemic encephalopathy. *Sci Rep*. 2023;13:23075. doi: 10.1038/s41598-023-50399-4. DOI
19. Sarici SU, Serdar MA, Korkmaz A et al. Incidence, course, and prediction of hyperbilirubinemia in near-term and term newborns. *Pediatrics*. 2004;113(4):775–780. doi: 10.1542/peds.113.4.775. DOI

20. Stanley CA. Perspective on the genetics and diagnosis of congenital hyperinsulinism disorders. *J Clin Endocrinol Metab.* 2016;101(3):815-826. doi: 10.1210/jc.2015-3651. 
21. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. *Cell.* 2012;148(6):1145-1159. doi: 10.1016/j.cell.2012.02.035. 
22. Bulut O, Ereğ A, Duruyen S. Effects of hyperbilirubinemia on markers of genotoxicity and total oxidant and antioxidant status in newborns. *Drug and Chemical Toxicology.* 2020;45(1):451-455. doi: 10.1080/01480545.2019.1710182. 
23. Midan DAR, Bahbah WA, Bayomy NR, Ashour NM. Clinical Assessment of Neuroinflammatory Markers and Antioxidants in Neonates with Hyperbilirubinemia and Their Association with Acute Bilirubin Encephalopathy. *Children.* 2022;9(4):559. doi: 10.3390/children9040559. 
24. Xiong T, Qu Y, Cambier S, Mu D. The side effects of phototherapy for neonatal jaundice: what do we know? What should we do? *Eur J Pediatr.* 2011;170(10):1247-1255. doi: 10.1007/s00431-011-1454-1. 
25. Iskander I, Abdelmonem S, Houchi SE et al. Intensive phototherapy and oxidant-antioxidant status in infants with jaundice. *Early Human Development.* 2021;161:105465 doi: 10.1016/j.earlhumdev.2021.105465. 
26. Aycicek A, Erel O. Total oxidant/antioxidant status in jaundiced newborns before and after phototherapy. *J Pediatr (Rio J).* 2007;83(4):319-322. doi: 10.1590/S0021-75572007000500006. 
27. Wang J, Guo G, Li A et al. Challenges of phototherapy for neonatal hyperbilirubinemia (Review). *Exp Ther Med.* 2021;21:231. doi: 10.3892/etm.2021.9662. 

The study was conducted as part of the research activities of the Department of Pediatrics, Neonatology and Perinatal Medicine of Bukovinian State Medical University (Chernivtsi, Ukraine): "Chronobiological and adaptation aspects and features of vegetative regulation in pathological conditions in children of different age groups" (State registration number 0122U002245, term of execution 01.2020-12.2024).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Anastasiya G. Babintseva

Bukovinian State Medical University

2 Teatralna Sq., 58002, Chernivtsi, Ukraine

e-mail: babintseva@bsmu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Yulia M. Volosivska: 0000-0002-2872-2035    

Anastasiya G. Babintseva: 0000-0002-3859-6431    

Yuliya D. Hodovanets: 0000-0003-0922-8696    

Volodymyr A. Petrov: 0009-0007-5490-0708  

Nataliya I. Kovtyuk: 0000-0001-7917-5003  

Nataliya O. Popeliuk: 0000-0003-2949-2785  

Oksana I. Yurkiv: 0000-0003-2958-3564  

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 23.04.2025

ACCEPTED: 22.08.2025



Microscopic changes in the pancreas at late stages after experimental exposure to monosodium glutamate

Mykhailo Yu. Kochmar, Yuliia V. Lytvak, Oleksandr I. Hetsko, Oleksandr M. Kochmar, Ihor K. Kharkhalis, Olesya O. Valko

UZHGOROD NATIONAL UNIVERSITY, UZHGOROD, UKRAINE

ABSTRACT

Aim: To determine the structural reorganization of the pancreas at late stages after experimental MSG exposure.

Materials and Methods: The study was performed on 20 sexually mature male rats. The experimental group received MSG orally at 70 mg/kg of body weight daily for 8 weeks. The control group was fed a standard diet without MSG. Decapitation was performed at week 18. Pancreatic tissues were collected for histological analysis and processed by standard methods.

Results: Ten weeks after MSG withdrawal, atrophic areas were detected in the exocrine parenchyma. Acini and pancreaticocytes decreased in size. In the ductal epithelium, dystrophic and destructive changes were observed, including cytoplasmic metachromasia, nuclear pyknosis, eccentric localization, and karyorrhexis. Periductal sclerosis and pancreatic lipomatosis were recorded. Vascular walls were thickened and homogeneous due to edema and mucoid swelling. Capillaries were plethoric with stasis and occasional perivascular hemorrhages.

Conclusions: At late stages after MSG exposure, marked alterations in pancreatic structure were revealed. Irreversible atrophic changes of exocrinocytes led to dysfunction of the gland, indicating the toxic effect of monosodium glutamate.

KEY WORDS: monosodium glutamate, pancreas, histological changes

Wiad Lek. 2025;78(9):1725-1730. doi: 10.36740/WLek/212378 DOI

INTRODUCTION

The issue of nutrition and food quality in Ukraine and globally has become particularly relevant, especially nowadays [1-3]. This is associated with the extensive use of a wide range of preservatives, sweeteners, flavor enhancers, and other food additives, the consumption of which can lead to structural changes in various tissues, particularly those of the digestive system [4-6]. The pancreas exhibits high vulnerability to various exogenous and endogenous factors, among which monosodium glutamate occupies a significant place. This food additive affects the physiological function of the pancreas. Receptors for glutamate and transporters have been identified in the islets of Langerhans, ductal cells, and acini [7,8]. Accumulation of monosodium glutamate in pancreatic juice has been proven [7]. Morphological studies in this area allow for the identification of certain links in the structural disturbances of this vital organ under conditions of increased and prolonged exposure to monosodium glutamate [9,10]. The presence of receptors and

transporters in the pancreas indicates that this gland is also a target organ for monosodium glutamate action [11-13].

AIM

To establish the features of structural and morphological reorganization of the pancreas at late stages of monosodium glutamate exposure.

MATERIALS AND METHODS

The studies were conducted on 20 sexually mature male Wistar rats weighing 200–250 g, which were housed in the vivarium of Danylo Halytsky Lviv National Medical University [14]. The object of the study included the exocrine and endocrine parts of the pancreas. Animal care and experimental procedures adhered to international rules and principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and



Fig. 1. Histological changes in the pancreas 10 weeks after monosodium glutamate withdrawal. Staining with hematoxylin and eosin (magnification x200). Disorganization of pancreatic acini, dystrophic and destructive changes in acinar exocrinocytes, karyopyknosis, and vacuolization of nuclei. Slight periductal lymphocytic infiltration
Picture taken by the authors

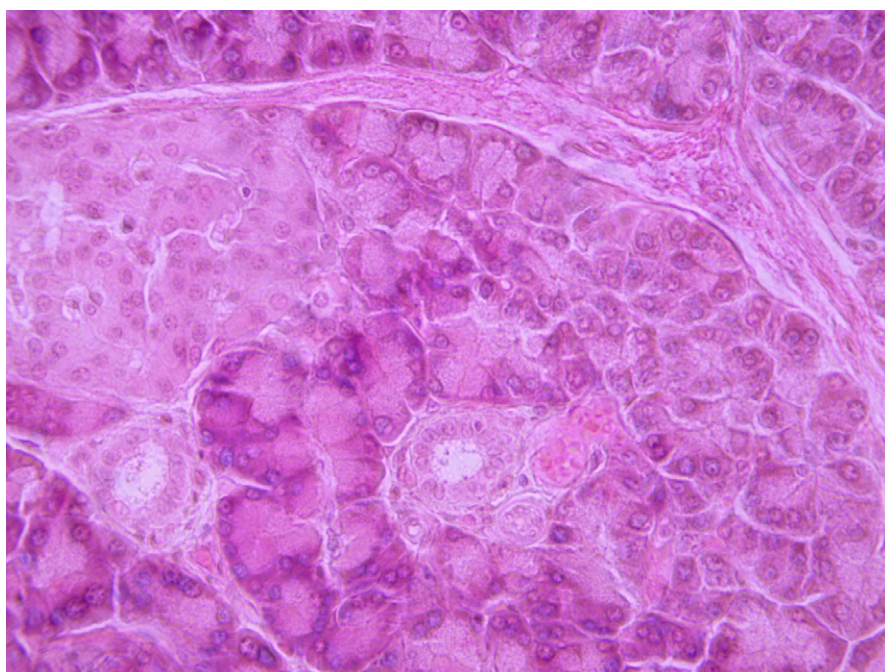


Fig. 2. Histological changes in the pancreas 10 weeks after monosodium glutamate withdrawal. Staining with hematoxylin and eosin (magnification x200). Dystrophic changes in the epithelium of intralobular excretory ducts. Increased volume of collagen fibers and edema of connective tissue in the interlobular spaces of the pancreas
Picture taken by the authors

«On the Protection of Animals from Cruel Treatment, General Principles of Work on Animals (Kyiv, 2001)». This study was approved by the Bioethics Committee of Uzhhorod National University, Bioethics Protocol. Monosodium glutamate was administered orally daily to rats in the experimental group at a dose of 70 mg/kg of body weight for 8 weeks. The control group of animals received a standard diet without the addition of monosodium glutamate. Animals were withdrawn from the experiment at 2, 3, 4, 5, 6, 7, 8 weeks with the addition of the food additive to the diet, and after withdrawal of monosodium glutamate from the diet, animals were withdrawn from the experiment at 10 weeks.

Material collection was performed according to generally accepted methods. For histological examination, collected pancreatic tissue samples were fixed in a neutral 10% formalin solution, followed by dehydration in increasing concentrations of alcohol and embedding in paraffin blocks. Histological sections 4–6 μ m thick, obtained with a sliding microtome Tesla BS-500 (Швеція), were stained with hematoxylin and eosin and Azan [15]. Sections were examined and photographed using a MICROMed SEO SCAN light microscope (objectives x10, x20, x40) and a Vision CCD Camera. The photographs of histological micropreparations were saved in .jpg format.

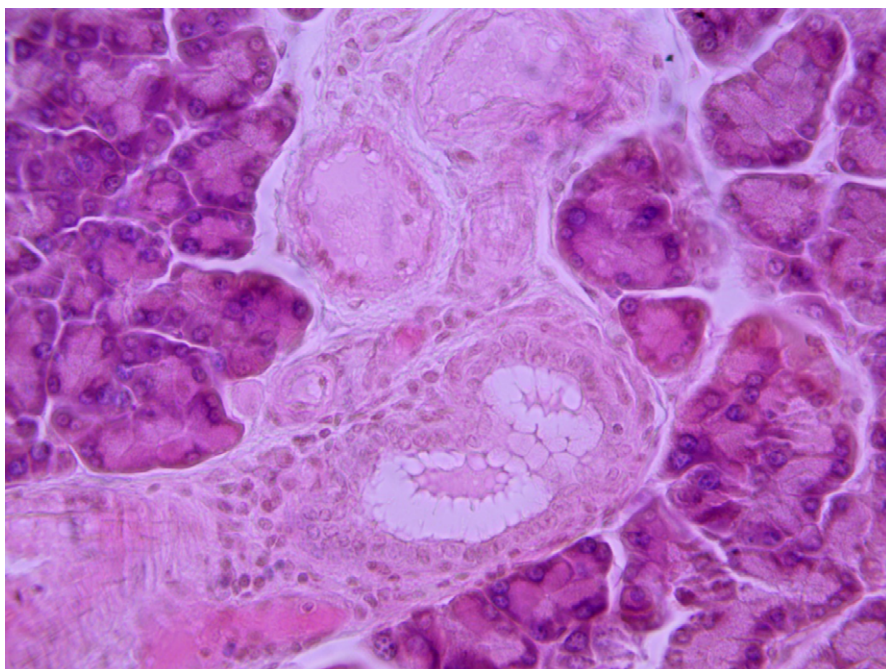


Fig. 3. Histological changes in the epithelium of the interlobular excretory duct wall of the pancreas 10 weeks after monosodium glutamate withdrawal. Staining with hematoxylin and eosin (magnification x200). Deformation and dilation of interlobular pancreatic ducts with secretory stasis in their lumen. Dystrophy and desquamation of the epithelium of interlobular pancreatic ducts
Picture taken by the authors

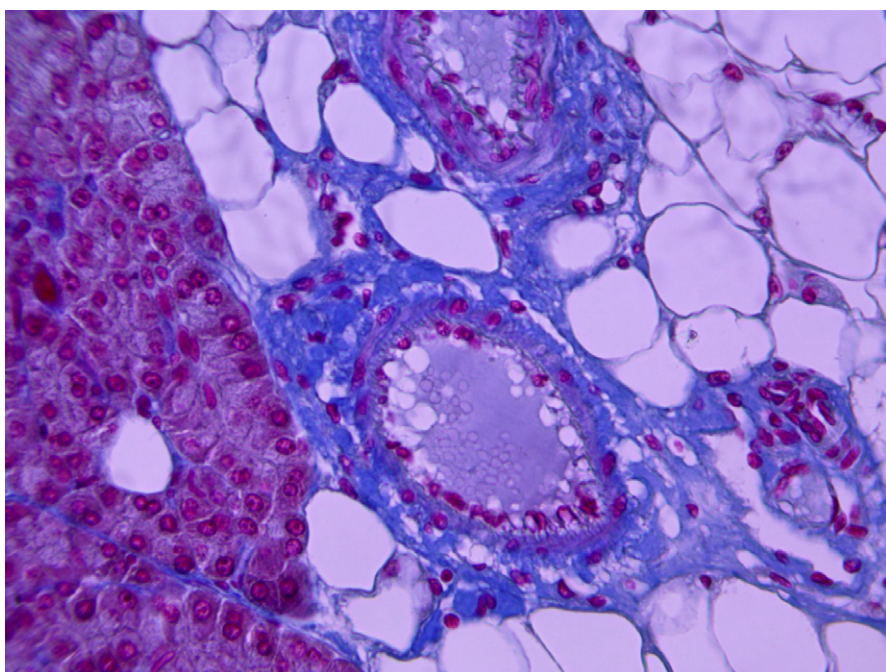


Fig. 4. Late changes in the pancreas 10 weeks after monosodium glutamate withdrawal. Azan staining (magnification x400). Proliferation of adipose tissue in the interlobular connective tissue and around the interlobular excretory ducts of the pancreas
Picture taken by the authors

RESULTS

Histological studies of the exocrine portion of the pancreas at 10 weeks after withdrawal of the MSG food additive revealed edema and an increase in the area of the connective tissue component of the gland. Areas of atrophy of the exocrine part of the organ's parenchyma were evident, along with a chaotic arrangement of exocrinocytes. The area of acini, and consequently pancreatocytes, visually decreased. The most characteristic signs included the loss of apical eosinophilia and basal basophilia of the cytoplasm, pyknosis of the nuclei of pancreatic parenchymal cells, vacuolization of nuclei, and disruption of their intracellular localization (Fig. 1).

The epithelium of the pancreatic ducts also underwent significant dystrophic and necrobiotic changes. Cells of the intercalated ducts were disorganized, largely losing their shape. Some centroacinar ducts had a narrow lumen without secretory content. The epithelium of the intralobular and interlobular ducts was thinned; in places, there was destruction of the epithelial layer, with single desquamated epithelial cells in the lumen. Secretory stasis was observed; the ducts' own connective tissue lamina propria was edematous and thickened. At the 10th week of the experiment, histological changes in the exocrine portion of the pancreas intensified and were characterized by destructive-degenerative and moderate chronic inflam-

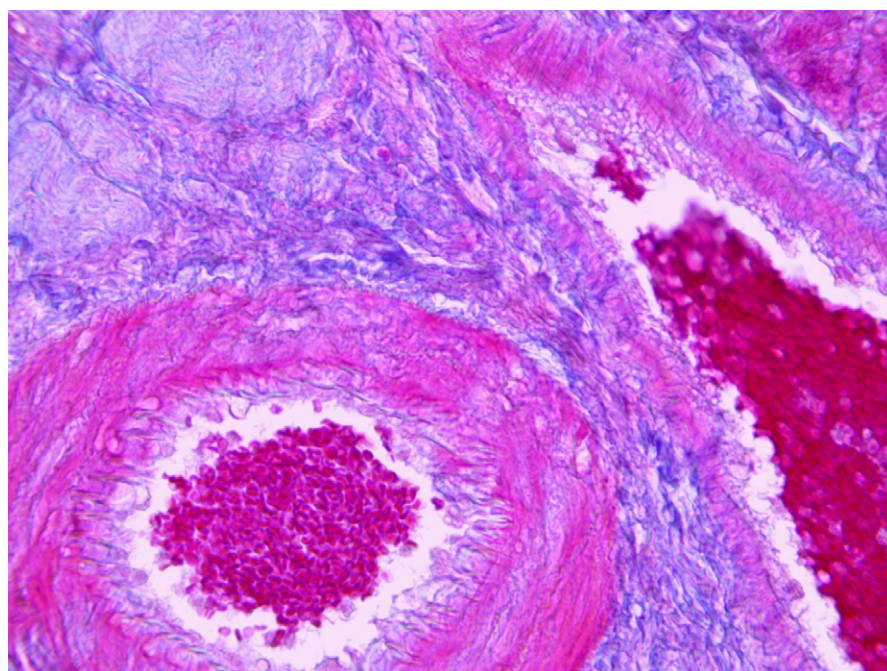


Fig. 5. Microscopic changes in pancreatic vessels 10 weeks after monosodium glutamate withdrawal. Azan staining (magnification x400). Vessel walls are thickened and homogenized due to edema and mucoid degeneration. Vacuolization and desquamation of endothelial cells. Sludge phenomenon of erythrocytes in the vessel lumen
Picture taken by the authors

matory changes in the structural components of the organ. Edema of the connective tissue with numerous collagen fibers was found in the interacinar and, especially, in the interlobular connective tissue; a slight monocytic-lymphocytic infiltration was determined. The diameter of the acini decreased, and polygonal pancreatocytes showed signs of focal dystrophy with intensely basophilic nuclei exhibiting vacuolization and pyknosis (Fig. 2).

Interlobular ducts were deformed, with destruction and fragmentation of the ductal epithelium. Destruction of the ductal epithelium and its detachment from the basement membrane were observed. Numerous desquamated epithelial cells and secretory stasis were present in the ductal lumen (Fig. 3). Accumulation of a large number of adipocytes was noted around the interlobular pancreatic ducts, characteristic of the development of pancreatic lipomatosis (Fig. 4).

The results of microscopic examinations of blood vessels at this observation period revealed dystrophic-destructive and inflammatory perivascular changes, manifested by slight extravasal macrophagic-lymphocytic infiltration. Vessel walls were moderately edematous, homogenized with signs of mucoid degeneration. The inner lining of the vessels also underwent dystrophic and necrobiotic changes, characterized by vacuolization of endothelial cells, karyopyknosis, and destruction of endothelial cell nuclei with desquamation of endothelial cells into the vessel lumen. Microthrombi and erythrocyte aggregation with the development of sludge phenomenon were found in the lumens of small vessels (Fig. 5).

The structure of medium-caliber vessel walls at the 10th week of the experiment was sharply altered, thickened,

with narrowing and deformation of the lumen, which led to a decrease in vascular permeability and, consequently, hypoxic damage to the pancreatic parenchyma, manifested by dystrophic-destructive and atrophic changes in the acini and ducts of the gland. The structure of microvessels also showed characteristic changes: their walls were deformed, thinned, homogenous, with dilated lumens forming thrombi and sludge. Slight monocytic-lymphocytic infiltration of the perivascular connective tissue was observed, with occasional diapedetic hemorrhages. In isolated vessels, lumen obliteration phenomena were observed, leading to a reduction in the pancreatic microvascular bed.

DISCUSSION

Scientific studies by Howell J.A. and Fukushima et al [7]. have demonstrated that the cells of the pancreatic islet apparatus and acini possess trophic receptors for monosodium glutamate (MSG). Consequently, high dietary MSG intake in rats leads to receptor activation, causing damage to the membranes of pancreatic exocrinocytes. This disruption of cellular metabolism results in both superficial and deep dystrophic alterations, including cellular hydropic degeneration, nuclear pyknosis, changes in cytoplasmic staining, and partial necrosis of exocrinocytes. Chronic injury in the pancreatic interstitium provokes a moderate inflammatory response, characterized by lymphocytic-macrophage infiltration.

Structural changes observed in intralobular and interlobular pancreatic ducts are attributable to MSG's ability to enhance pancreatic juice secretion

and its tendency to accumulate therein. This leads to direct epithelial damage via membrane ion-channel dysfunction, manifesting as vacuolar degeneration of cells and nuclei, metachromatic cytoplasmic changes, necrosis, and cell desquamation. Obstruction of duct lumens induces pancreatic juice stasis, resulting in ductal dilation and deformity. Prolonged hypoxia further promotes sclerosis of ductal walls, causing narrowing and partial obliteration, especially of the centroacinar ducts.

Expansion of the interstitial space is associated with toxic injury to capillary endothelium and basement membranes, increasing vascular permeability and leading to interstitial oedema, acinar disorganization, and chaotic arrangement of exocrinocytes. Edema increases the distance between capillaries and exocrinocyte membranes, impairing parenchymal perfusion and inducing hypoxia. This triggers dystrophic and necrobiotic changes in pancreatocytes, eventually culminating in atrophy, fibrosis, reduction of the vascular network, periductal sclerosis, and lipomatosis.

Medium-sized vessels exhibit structural and morphological alterations such as wall thickening and lumen narrowing, driven by mucoid swelling and excessive connective tissue proliferation, both consequences of chronic hypoxia [16].

MSG-induced microcirculatory vascular wall changes include endothelial degeneration (dystrophy, necrosis, desquamation) and basement membrane injury. These

changes result in plasmorrhagia and extravasation of blood cellular components into the pancreatic interstitium, causing increased blood viscosity and slowed capillary flow. This leads to thrombosis, a sludging phenomenon in microvessels, and small perivascular hemorrhages in the interstitium [17].

It should be noted that pancreatic structural remodeling in rats was influenced not only by MSG concentration, exposure duration, and withdrawal period, but also by age-related changes. Biological material was collected from sexually mature male rats at the 18th week of the experiment [18].

CONCLUSIONS

The results of microscopic studies of the exocrine part of the pancreas at late stages after monosodium glutamate withdrawal showed that at 10 weeks, destructive-degenerative changes occur, accompanied by sclerosis, inflammation, and atrophy of the investigated area. Proliferation of fibrous structures, atrophy of exocrinocytes, and the walls of the excretory ducts were found. Destruction and breakdown of the vessel walls were observed, and diapedesis with the formation of inflammatory infiltrates was determined. The study showed that even after the cessation of monosodium glutamate consumption, the gland exhibits a low capacity for regenerative processes.

REFERENCES

1. Bevoz VV. Vyvchennya toksykodynamiky hlutamatu natriyu na orhanizm shchuriv za umov tryvaloho vvedennya. [Study of the toxicodynamics of monosodium glutamate on the organism of rats under conditions of prolonged administration]. *Klinichna ta eksperimentalna patolohiia*. 2016;2(56):13–16. (Ukrainian)
2. Jinap S, Hajeb P. Glutamate. Its applications in food and contribution to health. *Appetite*. 2010;55(1):1–10. doi:10.1016/j.appet.2010.05.002. DOI
3. Vorhees CV. A test of dietary monosodium glutamate developmental neurotoxicity in rats: a reappraisal. *Ann Nutr Metab*. 2018;73(5):36–42. doi:10.1159/000494781. DOI
4. El-Kenawy AEM, Osman HEN, Daghestani MH. The effect of vitamin C administration on monosodium glutamate induced liver injury. An experimental study. *Exp Toxicol Pathol*. 2013;65(5):513–521. doi:10.1016/j.etp.2012.02.007. DOI
5. Gottardo FM, da Silva APA, dos Santos LR et al. Use of monosodium glutamate in foods: the good, the bad, and the controversial. 2022;47:e022305. doi:10.7322/abcshs.2020155.1609. DOI
6. Umukoro S, Oluwole GO, Olamijowon HE et al. Effect of monosodium glutamate on behavioral phenotypes, biomarkers of oxidative stress in brain tissues and liver enzymes in mice. *World J Neurosci*. 2015;5:339–349. doi:10.4236/wjns.2015.55033. DOI
7. Fukushima D, Fukushima DH, Katsura K et al. Glutamate exocrine dynamics augmented by plasma glutamine and the distribution of amino acid transporters of the rat pancreas. *J Physiol Pharmacol*. 2010;61(3):265–271. doi:10.1369/0022155411430095. DOI
8. Howell JA. Molecular identification of high-affinity glutamate transporters in sheep and cattle forestomach, intestine, liver, kidney, and pancreas. *J Anim Sci*. 2001;79(5):1329–1336. doi:10.2527/2001.7951329x. DOI
9. Leshchenko IV, Shevchuk VG, Falalieieva TM, Berehova TV. Vplyv tryvaloho vvedennya hlutamatu natriyu na strukturu pidshlunkovoyi zalozy shchuriv. [Effect of prolonged administration of monosodium glutamate on the structure of the rat pancreas]. *Fiziolohichnyi Zhurnal*. 2012;58(2):59–65. (Ukrainian)
10. Iwanaga T, Goto M, Watanabe M. Cellular distribution of glutamate transporters in the gastrointestinal tract of mice: an immunohistochemical and in situ hybridization approach. *Biol Med*. 2005;26:271–278. doi:10.2220/biomedres.26.271. DOI

11. Brice NL, Varadi A, Ashcroft SJ, Molnar E. Metabotropic glutamate and GABA(B) receptors contribute to the modulation of glucose-stimulated insulin secretion in pancreatic beta cells. *Diabetologia*. 2002;45:242–252.
12. Hinoi E, Takarada T, Ueshima T et al. Glutamate signaling in peripheral tissues. *Eur J Biochem*. 2004;271:12–13. doi:10.1046/j.1432-1033.2003.03907. DOI 
13. Marquard J, Otter S, Welters A et al. Characterization of pancreatic NMDA receptors as possible drug targets for diabetes treatment. *Nat Med*. 2015;21:363–372. doi:10.1038/nm.3822. DOI 
14. Horalskyi LP, Khomyich VT, Kononskyi VT. Osnovy histolohichnoi tekhniki i morfofunktsionalni metody doslidzhen v normi ta pry patologii. [Fundamentals of histological techniques and morphofunctional methods of studies in norm and pathology]. Zhytomyr: Polissia. 2019, p.285. (Ukrainian)
15. Zykova NP, Nebesna ZM, Kramar SB, Lytvyniuk SO. Vplyv ekzo- ta endohennykh chynnykiv na morfolohiiu pidshlunkovoi zalozy (ohliad literatury). [The influence of exogenous and endogenous factors on the morphology of the submucosal glands (literature review)]. *Visnyk medychnykh i biolohichnykh doslidzhen*. 2020;4:143–149. doi:10.11603/bmbr.2706-6290.2020.4.11828. (Ukrainian) DOI 
16. Rutska AV, Hetcko NV, Krynytska IYa. Toksychna diya hlutamatu natriyu na zhyvyy orhanizm (ohlyad literatury). [Toxic effect of monosodium glutamate on the living organism (literature review)]. *Medytsyna ta klinichna khimiia*. 2017;19(1):119–127. doi:10.11603/mcch.2410-681X.2017.v0.i1.7685. (Ukrainian) DOI 
17. Wiese ML, Aghdassi AA, Markus M, Steveling LA. Excess body weight and pancreatic disease. *Visc Med*. 2021;37:281–286. doi:10.1159/000517147. DOI 
18. Walker R, Lupien JR. The safety evaluation of monosodium glutamate. *J Nutr*. 2000;130(4S):1049S–1052S. doi:10.1093/jn/130.4.1049S. DOI 

The study was carried out within the framework of the scientific topic “Morpho-functional features of organs in the pre- and postnatal periods of ontogenesis, under the influence of opioids, food additives, reconstructive surgeries and obesity”, state registration number 0120U002129 of the state university “Uzhhorod National University”.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Yuliia V. Lytvak

Uzhhorod national university

1 Narodna Sqr, 88000 Uzhhorod, Ukraine

e-mail: mykhailo.kochmar@uzhnu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Mykhailo Yu. Kochmar: 0000-0002-0219-0552  

Yuliia V. Lytvak: 0000-0003-4820-9682  

Oleksandr I. Hetsko: 0000-0003-1607-2714  

Oleksandr M. Kochmar: 0000-0003-4040-7561  

Ihor K. Kharkhalis: 0000-0001-9487-4785  

Olesya O. Valko: 0000-0001-8648-6571  

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 10.04.2025

ACCEPTED: 29.08.2025



Indicators of venous blood flow in the long-term period after inferior vena cava thrombosis

Yaroslav M. Popovych^{1,2}

¹UZHGOROD NATIONAL UNIVERSITY, UZHGOROD, UKRAINE

²MUNICIPAL NON-PROFIT ENTERPRISE «UZHGOROD CITY MULTIDISCIPLINARY CLINICAL HOSPITAL» OF UZHGOROD CITY COUNCIL, UZHGOROD, UKRAINE

ABSTRACT

Aim: To evaluate central haemodynamic parameters in the long-term period after inferior vena cava (IVC) thrombosis depending on the treatment method.

Materials and Methods: Blood flow parameters were evaluated in 25 patients after IVC thrombosis. All patients formed the I (main) group. The results of the examination of patients in group I were compared with group II (control) consisting of 10 healthy individuals.

Results: Open thromboectomy from the lumen of the IVC combined with incomplete mechanical cavaplication allows not only to restore the lumen of the venous trunk and prevent the development of pulmonary embolism, but also to quickly normalise the parameters of central and regional venous haemodynamics. Analysis of blood flow parameters in the early and late postoperative periods allows us to conclude that partial mechanical cavaplication does not impair venous return to the heart, and open thromboectomy prevents the development of post-thrombotic changes. Conservative treatment of IVC thrombosis accelerates recanalisation processes compared to the natural course of thrombosis, but during this time, natural venous collaterals develop, which ensure venous outflow from the lower half of the body and remain active even after restoration of the IVC lumen.

Conclusions: Open thrombectomy of the inferior vena cava allows restoration of the lumen, ensuring effective venous blood flow, prevent post-thrombotic syndrome. Cavoplication prevents thromboembolic complications, increases blood flow velocity and leads to spontaneous restoration of the lumen of the inferior vena cava within 14.3 ± 2.2 months ($p \leq 0.01$).

KEY WORDS: inferior vena cava, venous hemodynamics, surgical intervention, conservative treatment, pulmonary embolism.

Wiad Lek. 2025;78(9):1731-1740. doi: 10.36740/WLek/212416 DOI

INTRODUCTION

The annual incidence of deep vein thrombosis (DVT) is 1 case per 10,000 people under the age of 40 and 5–6 cases per 1,000 people over the age of 80. The recurrence rate for DVT reaches 5–10% per year, and the mortality rate reaches 4.6–10.0% within the first month [1]. In 15% of patients with DVT, thrombotic masses are found in the inferior vena cava (IVC) [2].

IVC thrombosis doubles the risk of fatal pulmonary embolism (PE) [3, 4]. Treatment of IVC thrombosis depends on the patient's clinical condition, the cause of thrombosis, the identification of risk factors and the benefits of the proposed treatment method, as well as the treatment methods available at the medical facility [5].

In cases of IVC thrombosis, the authors suggest starting anticoagulant therapy, thromboaspiration and/or thrombolytic therapy [6–8]. The use of cava-filters in IVC thrombosis is quite controversial, as complications after their implantation may exceed the therapeutic effect [9, 10], in particular, recurrent thrombosis is observed

in 1.6–33% of patients [6, 11, 12]. In the presence of implant thrombosis, stenting of the IVC with subsequent radio- or chemotherapy has been proposed, which ensures rapid regression of clinical manifestations [13].

In the absence of adequate treatment of IVC thrombosis, post-thrombotic syndrome occurs in 20–90% of patients, leading to severe venous insufficiency in 5–45% of cases and the development of trophic ulcers in 15–18.8% of patients [1, 6, 14–16], causing significant damage to quality of life with professional and financial consequences [1, 15]. The recurrence rate of PE increases to 30% with a fatal outcome in 5.3% of patients [6, 14, 16].

However, according to Klein-Weigel P.F. et al. (2021), despite a number of studies, many clinically important questions in the management of patients with IVC remain unresolved, including optimised strategies for patient selection for interventions, antithrombotic and antiplatelet treatment regimens to prevent thrombosis recurrence [5]. In addition, the available literature does not assess haemodynamic changes in IVC thrombosis.

AIM

To evaluate central haemodynamic parameters in the long term after inferior vena cava thrombosis, depending on the treatment method.

MATERIALS AND METHODS

An assessment of blood flow parameters in the IVC was performed in 25 patients 3–5 years after IVC thrombosis. All patients with long-term consequences of IVC thrombosis were examined on an outpatient basis and formed the first (main) group. The average age of patients in the first group was 53.4 ± 2.2 years ($p \leq 0.01$). There were 4 women (16.0%) and 21 men (84.0%). The results of the examination of patients in group I were compared with group II (control group) consisting of 10 people who had no signs of pathology in the IVC system and voluntarily agreed to undergo examination. The average age of patients in group II was 41.2 ± 2.3 years ($p \leq 0.01$). There were 2 women (20.0%) and 8 men (80.0%).

Patients in group I were divided into the following subgroups depending on their previous treatment for thrombosis in the IVC system:

- Group I A – 8 (32.0%) patients who underwent open thromboectomy and incomplete mechanical cavaplication for IVC thrombosis;
- Group I B – 17 (68.0%) patients who received only conservative treatment for IVC thrombosis.

Laboratory and instrumental methods were used to examine patients, including ultrasound dopplerography and ultrasound duplex scanning, X-ray contrast phlebography, multispiral computed tomography (MSCT) with intravenous contrast, and radioisotope phleboscintigraphy.

Venous blood flow in the IVC was assessed in the immediate (up to 30 days after surgery), early (up to 1 year) and late (up to 10 years) postoperative periods.

Statistical processing of the study results was performed using Microsoft Excel 2010 computer software with the Statistica 5.0 for Windows application package. Comparisons of mean values and relative indicators were performed using the Mann-Whitney criteria and Pearson's parametric correlation analysis.

The study was conducted in accordance with the provisions of the World Medical Association's Declaration of Helsinki 'Ethical Principles for Medical Research Involving Human Subjects' (revised in 2008) and approved by the Bioethics Commission of the Medical Faculty of Uzhhorod National University. No violations of ethical standards were found during the research. All patients signed an informed consent form for participation in the research.

RESULTS

IVC thromboses were divided into tumour and non-tumour thromboses depending on the underlying cause. The cause of tumour thrombosis was the spread of implant thrombosis from the renal vein into the lumen of the IVC. Non-tumour IVC thrombosis was caused by the spread of thrombotic masses from the iliac venous segment towards the path of least resistance – in the direction of the right atrium. At the same time, vigorous blood flow through the renal and hepatic veins slowed the growth of thrombotic occlusion in the proximal direction, which was confirmed by a large number of infrarenal localisations of the apex of thrombotic masses among the examined patients in group I, in particular, infrarenal localisation of the apex of thrombotic masses was found in 18 (72.0%) of 25 patients. However, in 2 cases of non-tumour thrombosis and in all cases ($n=5$) of implantation thrombosis, thrombotic masses still caused a noticeable obstruction of blood flow from the renal and hepatic veins and contributed to the spread of the pathological process to the suprarenal section of the IVC.

In group I A, open thromboectomy from the IVC lumen and incomplete mechanical cavaplication were performed in 8 (32.0%) patients, including those with non-tumour ($n=3$) and tumour ($n=5$) thrombosis of the caval venous segment. When choosing the site for cavaplication, the infrarenal segment of the IVC directly under the renal veins prevailed in 7 (87.5%) patients, and in 1 (12.5%) patient, cavaplication was performed above the renal veins. The indications for cavaplication above the renal vein were old organised parietal layers in the infrarenal segment of the IVC, which could not be removed. A distinctive feature of tumour implantation thrombosis is that the 'thrombotic' masses in the IVC are morphologically tumour tissue, and anticoagulant therapy has no therapeutic effect. Therefore, the only way to combat IVC implantation thrombosis is thromboectomy from the IVC.

Group I B included 17 (68.0%) patients with diagnosed non-tumour IVC thrombosis who underwent conservative treatment.

Conservative treatment of IVC thrombosis in group I involved the administration of heparin at the maximum daily dose subcutaneously or intravenously continuously using an infusion pump, infusion-spasmolytic therapy, phlebotropic agents, and elastic hosiery. To prevent heparin-induced thrombocytopenia, the duration of heparin therapy averaged 9.3 ± 0.7 days. Subsequently, patients were switched to new oral anticoagulants at therapeutic doses. The duration of their administration, depending on the cause of thrombosis and the intensity of recanalisation of the veins of the IVC basin, ranged

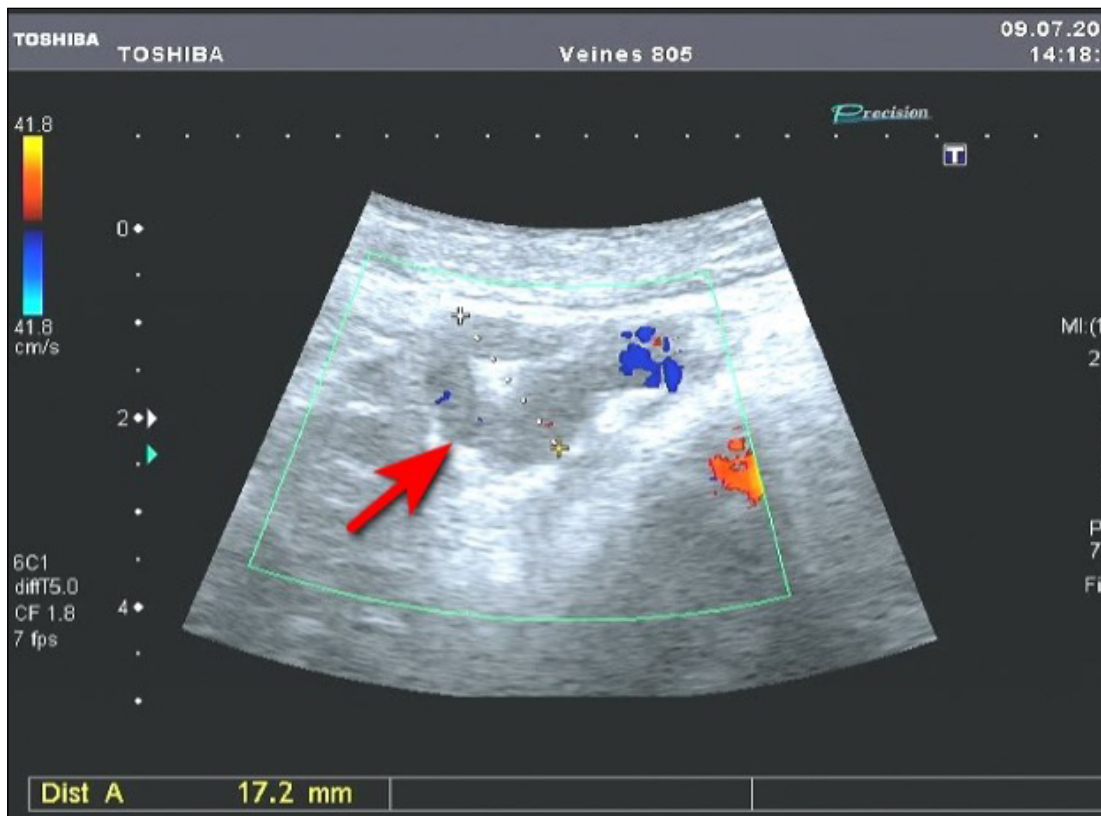


Fig. 1. Ultrasound examination: IVC in the plication area 6 months after surgery: IVC lumen is intact (the arrow indicates the plication area with two formed channels)

Picture taken by the authors

Table 1. Central haemodynamic parameters in the examined patients

Indicators*	I A group			I B group		II group
	Before surgery	After surgery		Before treatment	36 – 60 months	
		12 months	36 – 60 months			
Left ventricular ejection fraction, %	60,50±3,72	65,50±3,52	56,30±5,27	61,23±4,55	57,21±3,82	57,43±2,55
Minute blood flow, l/min	4,83±2,32	5,71±2,10	5,43±3,22	4,79±1,91	5,23±2,78	5,54±2,35
Stroke volume, ml/m²	49,97±3,15	46,54±2,10	55,15±2,14	47,56±1,27	57,21±2,32	60,12±2,34
Cardiac index, l/(min×m²)	3,41±0,14	3,50±0,30	3,61±0,60	3,24±0,20	3,56±0,71	3,67±0,56
Systolic volume, ml	65,6±2,32	67,3±1,32	66,2±1,41	61,1±1,22	66,2±1,23	67,2±1,42
End-systolic volume index of the right ventricle, ml/m²	21,45±1,2	24,52±1,1	25,31±1,1	21,32±1,5	27,23±1,3	27,51±1,6
End-diastolic volume index of the right ventricle, ml/m²	60,77±2,2	61,50±1,7	65,21±1,3	61,02±1,7	67,12±0,9	67,23±1,1
Linear blood flow velocity, cm/sec	3,06±1,5	6,31±1,8	7,13±1,6	2,98±1,7	7,02±1,2	9,01±1,4
Blood flow volume, ml/sec	2,63±0,5	4,6±0,7	5,31±1,2	3,01±0,8	5,11±1,4	5,21±1,1
Average transport time of RP, sec	12,7±0,5	7,9±0,3	5,1±0,4	13,3±0,7	5,2±0,5	4,1±0,3
IVC pressure (mm Hg)	7,73±1,52	5,42±1,73	4,9±1,13	8,21±1,56	6,1±3,21	5,7±1,22
IVC collapse index, %	11,2±2,9	15,4±2,1	35,5±2,0	10,3±1,7	27,2±1,5	36,7±2,5
IVC diameter (infrarenal), mm	24,7±2,3	22,3±1,4	21,5±1,2	25,1±2,2	21,9±1,6	20,9±2,1
Diameter of the left gonadal vein, mm	11,2±2,1	7,5±1,9	6,7±2,3	10,9±2,1	7,4±1,8	3,4±1,2

* - $P \leq 0,05$

Source: compiled by the authors of this study

from 4–6 months to lifelong administration. The average duration of oral anticoagulants in therapeutic doses at the end of the study was 14.7 ± 3.5 months.

In group I A, after incomplete device-based cavaplication, no cases of PE were observed in any of the 8 patients in the early and late postoperative period. It should be noted that the absence of a foreign body in the lumen of the IVC contributed to early recanalisation and improved outflow from the IVC. Staple eruption and gradual restoration of the IVC lumen were observed after 10.2 ± 2.7 months. This is the main advantage of direct methods of PE prevention over indirect methods. The characteristic ultrasound image is shown below (Fig. 1).

To determine individual indicators of central haemodynamics in patients with IVC thrombosis, echocardiography, ultrasound examination and radioisotope phleboscintigraphy were performed in the preoperative and postoperative periods. In all patients of group I, during the manifestation of IVC thrombosis, changes in central haemodynamic parameters were noted, indicating the absence of adequate venous return to the heart (Table 1).

Thus, in patients of groups I A and I B, before the start of surgical or conservative treatment of IVC thrombosis, due to its thrombotic occlusion, an increase in the diameter of the IVC to 24.7 ± 2.3 mm ($p \leq 0.05$) and 25.1 ± 2.2 mm ($p \leq 0.05$), respectively, compared with the control group of 20.9 ± 2.1 mm ($p \leq 0.05$). At the same time, a sharp decrease in the IVC collapse index was observed, in particular $11.2 \pm 2.9\%$ ($p \leq 0.05$) in group I A and $10.3 \pm 1.7\%$ ($p \leq 0.05$) in group I B compared with the norm of $36.7 \pm 2.5\%$ ($p \leq 0.05$). One of the compensatory mechanisms for activating collateral blood flow in IVC thrombosis was an increase in the diameter of the left gonadal vein to 11.2 ± 2.1 mm ($p \leq 0.05$) in group I A and 10.9 ± 2.1 mm ($p \leq 0.05$) in group I B compared with the norm of 3.4 ± 1.2 mm ($p \leq 0.05$). In addition, ultrasound examination revealed compensatory dilation of the pelvic veins, which also indicated an increase in the volume of collateral venous blood flow in the IVC basin. At the same time, the pressure in the IVC practically did not exceed the upper limit of the norm and amounted to 7.73 ± 1.52 mm Hg ($p \leq 0.05$) in group I A and 8.21 ± 1.56 mm Hg ($p \leq 0.05$) in group I B.

Due to thrombotic occlusion of the IVC, a decrease in the main blood flow parameters was noted, in particular, the linear and volumetric blood flow velocity during ultrasound examination and the average radio-pharmaceutical (RP) transport time during radioisotope phleboscintigraphy. The linear blood flow velocity in the IVC above the apex of the thrombotic masses was reduced by almost three times compared to the control

group, in particular 3.06 ± 1.5 cm/sec ($p \leq 0.05$) in group I A and 2.98 ± 1.7 cm/sec ($p \leq 0.05$) in group I B at 9.01 ± 1.4 cm/sec ($p \leq 0.05$) in the control group. The volumetric blood flow velocity in the IVC above the apex of the thrombotic masses was reduced by half compared with the control group, namely 2.63 ± 0.5 ml/sec ($p \leq 0.05$) in group I A and 3.01 ± 0.8 ml/sec ($p \leq 0.05$) in group I B, compared to 5.21 ± 1.1 ml/sec ($p \leq 0.05$) in the control group.

The average RP transport time due to thrombotic occlusion of the IVC increased threefold compared to the control group, in particular 12.7 ± 0.5 sec ($p \leq 0.05$) in group I A and 13.3 ± 0.7 sec ($p \leq 0.05$) in group I B compared to 4.1 ± 0.3 sec ($p \leq 0.05$) in the control group.

During echocardiography, no significant changes in cardiac performance indicators such as left ventricular ejection fraction, minute blood flow volume, stroke and systolic volume, cardiac index, end-systolic and end-diastolic volumes of the right ventricle were observed. This is associated with the enormous compensatory capacity of collateral blood flow in the IVC basin.

Restoration of IVC lumen at the site of its thrombotic occlusion in patients of group I A after open thromboectomy allowed rapid improvement of central haemodynamic parameters. Return of blood flow parameters to normal values was observed only after staples were removed at the site of cavaplication and complete restoration of IVC lumen. Restoration of IVC lumen at the site of cavaplication in patients of group I A was noted during ultrasound examination after 1–1.5 years (14.3 ± 2.2 months ($p \leq 0.01$)). At the same time, thickening and rigidity of the IVC wall were noted in the cavaplication area (Fig. 2).

After thromboectomy, in the early postoperative period, there was also an improvement in regional haemodynamic parameters, in particular a decrease in the average RP transport time during radioisotope phleboscintigraphy from 12.7 ± 0.5 ($p \leq 0.05$) seconds to 7.9 ± 0.3 seconds ($p \leq 0.05$), and after restoration of IVC patency at the site of cavaplication, the mean RP transport time decreased to 5.1 ± 0.4 with values of 4.1 ± 0.3 sec ($p \leq 0.05$) in the control group. At the same time, at the site of cavaplication, with preserved IVC patency on phleboscintigrams, a slight delay of the RP was observed (Fig. 3). There were also no areas of venous stasis and dilated collateral veins (Fig. 4). The images of the IVC and contrasted iliac veins are clear, homogeneous, with no collateral outflow. The patency of the IVC and recanalisation of the distal bed, with preserved volumetric blood flow, allow us to predict satisfactory functional results of treatment in the long term.

Thus, the average RP transit time during IVC restoration was close to that of the control group (Fig. 5). Radioisotope phleboscintigraphy data confirmed the

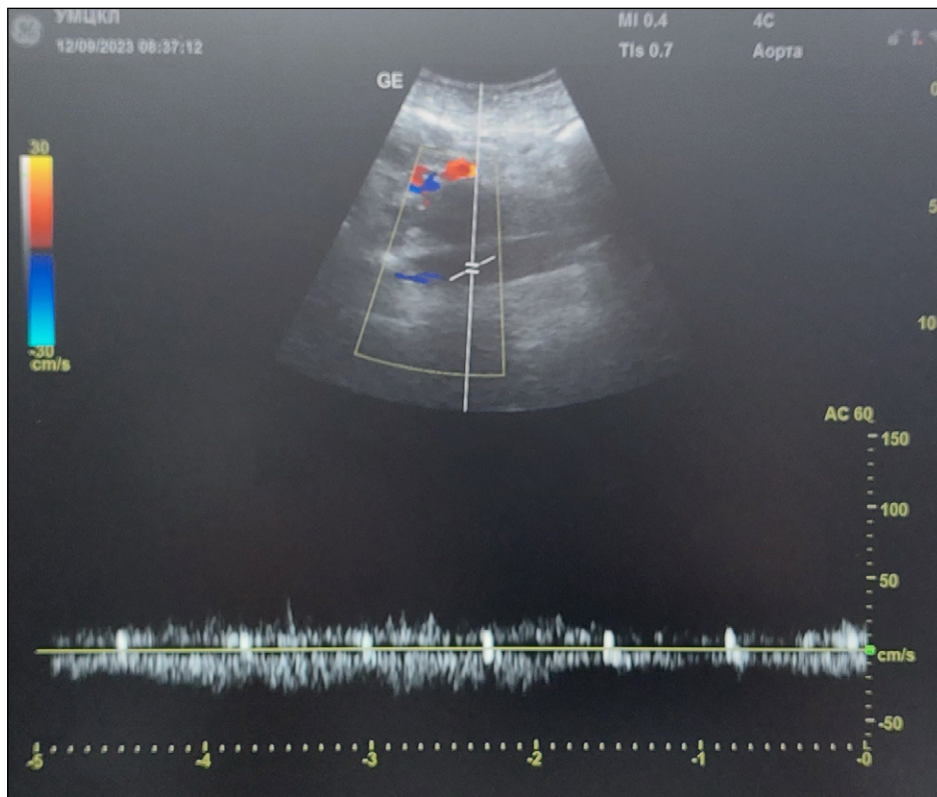


Fig. 2. Ultrasound examination: venous blood flow spectrum in the IVC 1.5 years after cavaplication is not disturbed
Picture taken by the authors

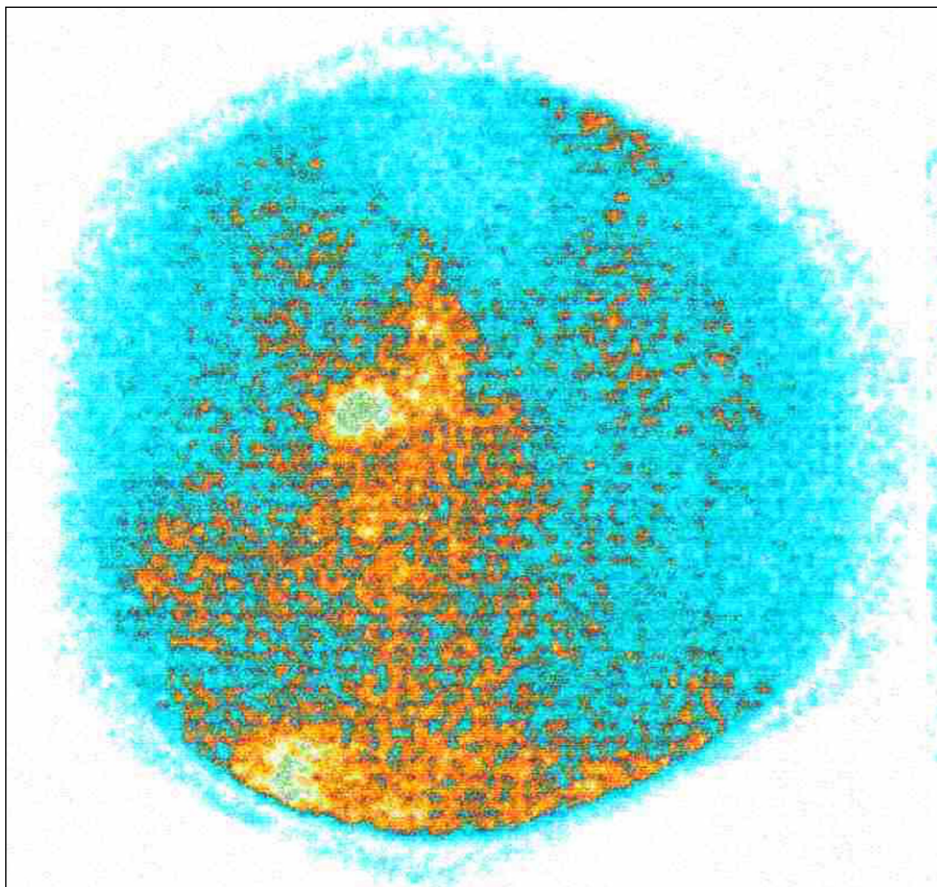


Fig. 3. Radioisotope phleboscintigraphy in a horizontal position: patent iliac-caval segment, slight delay in the evacuation of the radiopharmaceutical at the level of cavaplication
Picture taken by the authors

results of ultrasound and X-ray contrast studies in the long-term follow-up period (Fig. 6).

In group I, a gradual recovery of central and regional haemodynamic parameters was observed. This situa-

tion was associated with the processes of recanalisation of the IVC lumen against the background of prolonged anticoagulant therapy. The average recanalisation time with conservative treatment in group I B was 4.74 ± 2.35

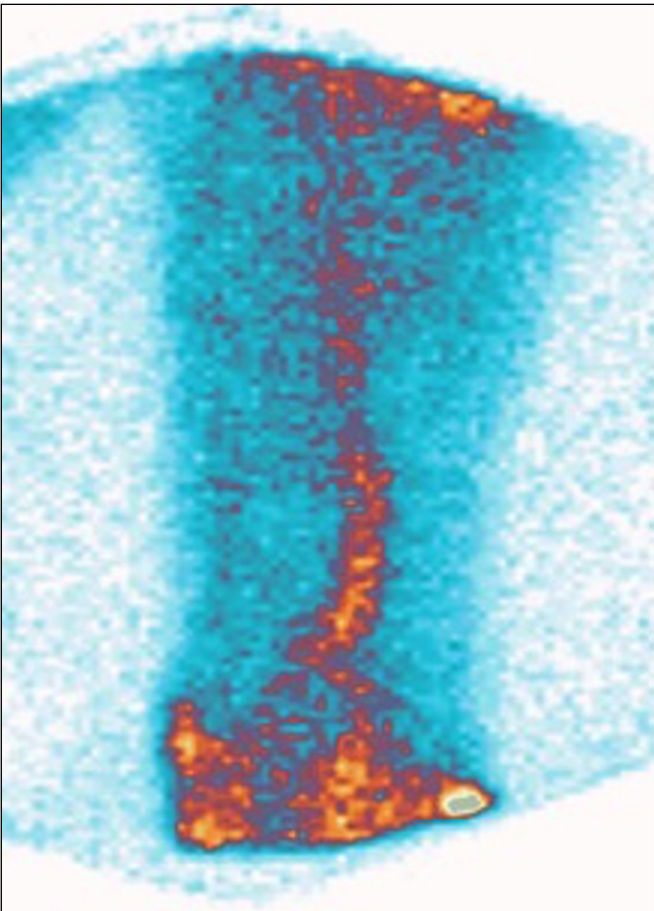


Fig. 4. Radioisotope phleboscintigraphy in a horizontal position: patent IVC after cavaplication
Picture taken by the authors

months ($p \leq 0.01$). Central haemodynamic parameters in group I B differed from blood flow parameters in patients in groups I A and II, which was caused by incomplete recanalisation and the occurrence of post-thrombotic changes in the IVC walls. Thus, the IVC diameter in patients of the I B group in the long term was 21.9 ± 1.6

mm ($p \leq 0.05$) compared to 21.5 ± 1.2 mm ($p \leq 0.05$) in the I A group and 20.9 ± 2.1 mm ($p \leq 0.05$) in the control group. The IVC collapse index increased gradually and amounted to $27.2 \pm 1.5\%$ ($p \leq 0.05$) and was still significantly lower than in group I A ($35.5 \pm 2.0\%$, $p \leq 0.05$) and the control group ($36.7 \pm 2.5\%$, $p \leq 0.05$), which was also associated with post-thrombotic changes in the IVC wall. The diameter of the left gonadal vein, even after IVC recanalisation, decreased insignificantly, which was due to its prolonged participation in the compensatory mechanisms of collateral venous blood flow. We observed preservation of varicose transformation of the left gonadal vein, in particular, its diameter was 7.4 ± 1.8 mm ($p \leq 0.05$) versus 6.7 ± 2.3 mm ($p \leq 0.05$) in group I A and 3.4 ± 1.2 mm ($p \leq 0.05$) in the control group. In addition, during ultrasound examination, varicose venous plexuses of the small pelvis and retroperitoneal space were visualised, and clinically, varicose superficial veins of the abdominal wall were detected in patients (Fig. 7).

IVC pressure in patients of group I B in the remote period was slightly higher (6.1 ± 3.21 mm Hg ($p \leq 0.05$)) compared to similar indicators in group I A (4.9 ± 1.13 mm Hg ($p \leq 0.05$)) and the control group (5.7 ± 1.22 mm Hg ($p \leq 0.05$)). The linear blood flow velocity in patients of the I B group after IVC recanalisation was 7.02 ± 1.2 cm/sec ($p \leq 0.05$) and practically did not differ from the indicators of the I A group (7.13 ± 1.6 cm/sec ($p \leq 0.05$)), although it was lower than that of the control group (9.01 ± 1.4 cm/sec ($p \leq 0.05$)). At the same time, the volumetric blood flow velocity in all groups was practically the same, in particular 5.11 ± 1.4 ml/sec ($p \leq 0.05$) in patients of the I B group compared to 5.31 ± 1.2 ml/sec ($p \leq 0.05$) in patients of the I A group and 5.21 ± 1.1 ml/sec ($p \leq 0.05$) in the control group. The average RP transport time during radioisotope phleboscintigraphy in groups I B (5.2 ± 0.5 sec ($p \leq 0.05$)) and I A (5.1 ± 0.4 sec

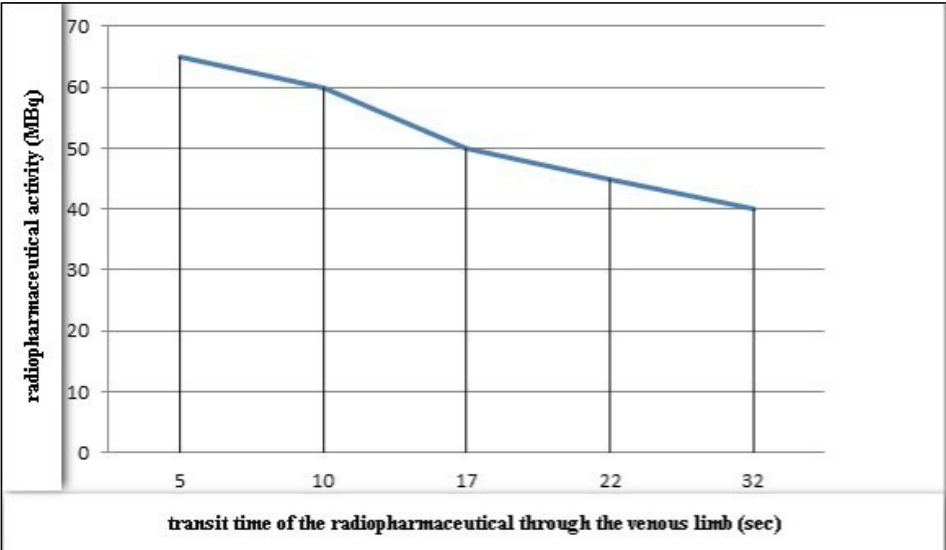


Fig. 5. Graph showing the dependence of the transport time of the radiopharmaceutical Tc-99 (70–40 MBq) on IVC 1 year after cavaplication
Picture taken by the authors



Fig. 6. X-ray contrast cavography: preservation of the patency of the inferior vena cava 3 years after plication
Picture taken by the authors



Fig. 7. Patient X: varicose veins of the anterior abdominal wall in post-thrombotic syndrome of the inferior vena cava
Picture taken by the authors

($p \leq 0.05$)) increased to almost the same values, although it was lower than that of the control group (4.1 ± 0.3 sec ($p \leq 0.05$)).

During echocardiography, no significant changes in cardiac function were observed in patients of group I B compared to patients of groups I A and II.

DISCUSSION

Thrombosis of the IVC significantly remodels venous return to the heart, changing central haemodynamic parameters during ultrasound examination of the heart. Compensation of venous return to the heart from the lower half of the body in IVC thrombosis is provided by venous collaterals, in particular the lumbar venous plexus, ascending lumbar, gonadal, diaphragmatic, unpaired and semi-unpaired veins [17, 18]. At the same time, the principles of diagnosis and treatment of DVT are mainly based on morphological criteria, and changes in peripheral and central venous haemodynamics are practically not assessed [19]. According to studies by Antignani P.L. et al. (2020), venous pressure in individuals with chronic lower limb vein disease is significantly higher in superficial and deep veins com-

pared to healthy individuals [20]. In post-thrombotic syndrome, pressure in superficial and deep veins reaches the highest possible values, causing severe pain [20]. At the same time, deep venous hypertension is more pronounced than superficial hypertension, with pressure rising to 130–140 mm Hg [20]. The authors note that venous pressure values do not always correspond to the severity of the disease [20].

An important parameter of central haemodynamics is central venous pressure or right atrial pressure, which requires mainly invasive examination [21]. At the same time, the invasive method of measuring central venous pressure is dangerous due to catheter-induced thrombosis, arrhythmia and infectious complications [21]. Therefore, in clinical practice, preference is given to non-invasive methods of assessing central venous pressure [21]. According to the recommendations of the American Society of Echocardiography (2015), the maximum diameter of the IVC should be measured along its axis approximately 1–2 cm caudal to the junction of the IVC and the right atrial appendage [22]. Ciozda W. et al. (2015), based on an analysis of 21 prospective studies involving 1,430 patients, found a direct relationship between central venous pressure and IVC diameter [23].

The difficulty of measuring central venous haemodynamic parameters in vivo led to the study of haemodynamics in an experimental model of the inferior vena cava, which revealed peak blood flow velocities ranging from 4.9 cm/s to 27 cm/s at rest and during physical exertion, respectively [24]. Raju S. et al. (2020) proved that there is no evidence of inspiratory compression of the central veins of the abdominal cavity and refuted the haemodynamic theory of the abdominal pump [25]. Instead, with an increase in the volume of inspiration, an increase in the diameter of the IVC by 32% and a simultaneous decrease in pressure in it were observed [25].

Based on 7 studies involving 395 spontaneously breathing patients, the concept of the IVC collapse index (sensitivity 71%; specificity 81%) was proposed, which involves the ratio of the diameter of the IVC during the respiratory or ventilation cycle during ultrasound examination. specificity 81%), which is the ratio of the IVC diameter during the respiratory or ventilation cycle during ultrasound examination. Similar data were obtained in 9 studies involving 284 patients on artificial ventilation, where the sensitivity and specificity of the IVC collapse index were 75% and 82%, respectively. The IVC collapse index indirectly indicates right atrial pressure and circulating blood volume [26–28]. At the same time, other researchers believe that ultrasound examination of the IVC may be limited by factors affecting the diameter or collapse of the IVC and should take into account the clinical situation [29].

We have not found any studies in the available literature that evaluate changes in venous haemodynamics depending on the treatment of venous thrombosis in the IVC. However, our data suggest that open thromboectomy from the lumen of the IVC combined with incomplete mechanical cavaplication in floating thromboses not only restores the lumen of the venous trunk, prevent the development of PE, but also quickly normalise the parameters of central and regional venous

haemodynamics. Analysis of blood flow parameters in the early and late postoperative periods allows us to conclude that partial mechanical cavaplication does not impair venous return to the heart, and open thromboectomy from the IVC lumen prevents the development of post-thrombotic changes in the walls of the venous trunk. Conservative treatment of IVC thrombosis significantly accelerates recanalisation processes compared to the natural course of thrombosis, but during this time, natural venous collaterals arise, which ensure venous outflow from the lower half of the body and remain active even after restoration of the IVC lumen.

CONCLUSIONS

1. Open thromboectomy from the inferior vena cava allows restoration of the lumen and ensures effective main venous blood flow, and is the only effective treatment for implant thrombosis. The introduction of incomplete mechanical cavaplication after thromboectomy from the lumen of the inferior vena cava prevents venous thromboembolic complications.
2. The advantage of incomplete mechanical cavaplication is the independent gradual restoration of the lumen of the inferior vena cava within 14.3 ± 2.2 months ($p \leq 0.01$).
3. Cavaplication not only does not disturb central and regional venous haemodynamics, but also leads to an increase in linear and volumetric blood flow velocities in the inferior vena cava, which prevents recurrence of thrombosis.
4. Open thromboectomy from the lumen of the inferior vena cava, compared with conservative treatment, prevents the development of post-thrombotic syndrome with chronic venous insufficiency and prevent the development of venous collaterals with subsequent remodelling of venous blood flow in the lower hollow vein basin.

REFERENCES

1. Del Pozo MM, Asenjo MM, Moreno FAI et al. Long-term monitoring and treatment of venous thromboembolic disease: recommendations of the Thromboembolic Disease Group of the Spanish Society of Internal Medicine 2024. *Rev Clin Esp* 2024;224(10):652-63. doi:10.1016/j.rceng.2024.10.004. DOI
2. Shah NG, Wible BC, Paulisin JA et al. Management of inferior vena cava thrombosis with the FlowTrier and ClotTrier systems. *J Vasc Surg* 2021;9(3):615-20. doi:10.1016/j.jvsv.2020.09.008. DOI
3. Sildiroglu O, Ozer H, Turba CU. Management of the thrombosed filter-bearing inferior vena cava. *Semin Intervent Radiol*. 2012;29:57-63. doi:10.1055/s-0032-1302453. DOI
4. Girard P, Meyer G, Parent F et al. Medical literature, vena cava filters and evidence of efficacy. A descriptive review. *Thromb Haemost*. 2014;111:761-9. doi:10.1160/TH13-07-0601. DOI
5. Klein-Weigel PF, Elitok S, Ruttloff A et al. Inferior vena cava-syndrome. *Vasa*. 2021;50(4):250-64. doi:10.1024/0301-1526/a000919. DOI
6. Alkhouli M, Morad M, Narins CR et al. Inferior vena cava thrombosis. *JACC Cardiovasc Interv*. 2016;9(7):629-43. doi:10.1016/j.jcin.2015.12/268. DOI

7. Shi W, Dowell JD. Etiology and treatment of acute inferior vena cava thrombosis. *Thromb Res.* 2017;149:9–16. doi:10.1016/j.thromres.2016.07.010. [DOI](#)
8. McAree BJ, O'Donnell ME, Fitzmaurice GJ et al. Inferior vena cava thrombosis: a review of current practice. *Vasc Med.* 2013;18:32–43. doi:10.1177/1358863X12471967. [DOI](#)
9. Qi Yu-H, Wang T, Wang J et al. Inferior vena cava filter reduces pulmonary embolism but does not increase deep venous thrombosis: A systematic review and metaanalysis. *Asian J of Surg.* 2022;45(1):592–3. doi:10.1016/j.asjsur.2021.10.046. [DOI](#)
10. King RW, Wooster MD, Veeraswamy RK et al. Contemporary rates of inferior vena cava filter thrombosis and risk factors. *J Vasc Surg.* 2022;10(2):313–24. doi:10.1016/j.jvsv.2021.07.016. [DOI](#)
11. Van Ha TG. Complications of inferior vena caval filters. *Semin Intervent Radiol.* 2006;23:150–155. doi: 10.1055/s-2006-941445. [DOI](#)
12. Kalva SP. Complications of inferior vena cava filters. *Cardiovasc Diagn Ther.* 2016;6:632–41. doi:10.21037/cdt.2016.09.08. [DOI](#)
13. Friedman T, Quencer KB, Kishore SA et al. Malignant venous obstruction: superior vena cava syndrome and beyond. *Semin Intervent Radiol.* 2017;34:398–408. doi:10.1055/s-0037-1608863. [DOI](#)
14. Teter K, Schrem E, Ranganath N et al. Presentation and Management of Inferior Vena Cava Thrombosis. *Ann Vasc Surg.* 2019;56:17–23. doi:10.1016/j.avsg.2018.08.082. [DOI](#)
15. Popovych YaM, Korsak VV, Boldizhar PO et al. Khirurhichna profilaktyka tromboembolichnykh uskladnen pry transfastsialnomu trombozi [Surgical Prevention of Thromboembolic Complications in Transfascial Thrombosis]. *Ukrainskyi zhurnal sertsevo-sudynnoi khirurhii.* 2023;31(1):66–73. doi:10.30702/ujcv/23.31(01)/PK002-6673. (Ukrainian) [DOI](#)
16. Popovich YaM, Rosul MV, Sich PR et al. Thrombolysis in Pulmonary Embolism Treatment. *Wiad Lek.* 2023;71(3):604–9. doi:10.36740/WLek202303123. [DOI](#)
17. Meyer S, Poryo M. Inferior vena cava thrombosis-rope ladder sign. *Wien Med Wochenschr.* 2023;173:159–160. doi:10.1007/s10354-021-00886-y. [DOI](#)
18. Popovych YaM. Otsinka stanu hemodynamiky u patsientiv z trombozamy systemy nyzhnoi porozhnystoi veny zalezno vid sposobu likuvannia [Estimation of hemodynamic parameters in patients with thrombosis inferior vena cava system depends on the treatment method]. *Khirurgiia Ukrainy* 2018;1(65):55–61. doi:10.30978/SU2018155. (Ukrainian) [DOI](#)
19. Franceschi C. Measurement of venous pressure by Doppler: food for thought. *Acta Phlebologica.* 2022;23(3):95–6. doi:10.23736/S1593-232X.22.00545-8. [DOI](#)
20. Antignani PL, Peruzzi G, Spina T. The measurement of venous pressure by Doppler: is it a hemodynamic evaluation? *J of Theoret App Vascul Res.* 2020;5(2). doi:10.24019/jtavr.114. [DOI](#)
21. Beigel R, Cercek B, Luo H et al. Noninvasive evaluation of right atrial pressure. *J Am Soc Echocardiogr.* 2013;26:1033–42. doi:10.1016/j.echo.2013.06.004. [DOI](#)
22. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1–39. doi:10.1016/j.echo.2014.10.003. [DOI](#)
23. Ciozda W, Kedan I, Kehl DW et al. The efficacy of sonographic measurement of inferior vena cava diameter as an estimate of central venous pressure. *Cardiovasc Ultrasound* 2015;14(33). doi:10.1186/s12947-016-0076-1. [DOI](#)
24. Gallagher MB, Aycock KI, Craven BA et al. Manning Steady Flow in a Patient-Averaged Inferior Vena Cava—Part I: Particle Image Velocimetry Measurements at Rest and Exercise Conditions. *Cardiovasc Eng Technol.* 2018;9(4):641–53. doi:10.1007/s13239-018-00390-2. [DOI](#)
25. Raju S, Walker W, Noel C et al. An alternative explanation for the phasic variations in venous flow. *J Vasc Surg Venous Lymphat Disord.* 2021;9(4):977–986. doi:10.1016/j.jvsv.2020.11.018. [DOI](#)
26. Si X, Cao D, Xu H, Guan X. Meta-analysis of ventilated versus spontaneously breathing patients in predicting fluid responsiveness by inferior vena cava variation. *Int J Clin Med.* 2018;9:760–777. doi:10.4236/ijcm.2018.910063. [DOI](#)
27. Preau S, Bortolotti P, Colling D et al. Diagnostic accuracy of the inferior vena cava collapsibility to predict fluid responsiveness in spontaneously breathing patients with Sepsis and acute Circulatory failure. *Crit Care Med.* 2017;45(3):e290–e297. doi:10.4236/ijcm.2018.910063. [DOI](#)
28. Corl KA, George NR, Romanoff J et al. Inferior vena cava collapsibility detects fluid responsiveness among spontaneously breathing critically-ill patients. *J Crit Care.* 2017;41:130–137. doi:10.1016/j.jcrc.2017.05.008. [DOI](#)
29. Kaptein MJ, Kaptein EM. Inferior Vena Cava Collapsibility Index: Clinical Validation and Application for Assessment of Relative Intravascular Volume. *Adv Chronic Kidney Dis.* 2021;28(3):218–226. doi:10.1053/j.ackd.2021.02.003. [DOI](#)

The work was carried out within the framework of the research topic of the Department of Surgical Diseases «Occlusive diseases of arteries and veins in metabolic disorders» (State Registration No. 0120U100405). Implementation period: 2025 – 2029.

CONFLICT OF INTEREST

The Author declare no conflict of interest

CORRESPONDING AUTHOR

Yaroslav M. Popovych

Uzhhorod National University

1 Narodna Sqr., 88000 Uzhhorod, Ukraine

e-mail: yaroslav.popovych@uzhnu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Yaroslav M. Popovych: 0000-0002-8908-8541 **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: 18.04.2025

ACCEPTED: 27.08.2025



Cytomorphological characteristics of the Nasopharyngeal zone mucosa in children with Covid-19

Olesya M. Horlenko, Khrystyna A. Hechko, Mykhaylo M. Hechko, Fedir V. Horlenko, Olga A. Pushkarenko
UZHGOROD NATIONAL UNIVERSITY, UZHGOROD, UKRAINE

ABSTRACT

Aim: To investigate cytomorphological presentations of the mucous membrane damage of the nasopharyngeal zone in Coronavirus disease in children.

Materials and Methods: A epithelium scraping from the surface of the Pharyngeal tonsils was performed with the following double fixation: the samples were fixed in a 2% solution of glutaraldehyde (25% Glutaraldehyde E. M. Grade Polysciences Inc.) in 0.1M cacodylate buffer (Cacodylic acid Sodium salt. Fluka) at pH 7.2 for 2–2.5 hours in the cold. Washing (2 times) in cacodylate buffer was performed. The next stage was additional fixation of the samples in a 1.5% solution of OsO₄ (Osmium Tetroxide. SPI – CHEM USA) in 0.1 M sodium cacodylate solution at pH 7.2 for 2 hours in the cold with subsequent washing (2 times) in buffer. Sections are made on an UMTF-6M ultramicrotome using a diamond knife (DIATOM). Sections were viewed using a TEM-100 transmission electron microscope (Ukraine).

Results: Based on the electronic presentation, we can observe all the processes of inflammation and their consequences. We will consider the pathogenetic processes which were monitored in our studies. Inflammation consists of three main types of tissue disorders, which include: alteration, exudation, proliferation. Presentation of a section of the Palatine Tonsil epithelial cell is marked by increased focal hemorrhage and degenerative changes in the membrane of papillary structures, reactive-degenerative changes in the stroma and increased hemorrhages in the vessels, partial sclerosis and microcalcification of the Tonsil epithelial cell tissue, pronounced sclerotic changes in the epithelial cell and partial destruction of the cell membrane were also visualized, as a result of which the semiconductivity in the cell is disturbed.

Conclusions: Cytological changes in the studied material of Nasopharyngeal zone in the children with Coronavirus disease can be considered as nonspecific common violation. These changes were characterized by the presence of diffuse inflammatory polymorpho-cellular infiltration, impaired hemodynamics and diffuse desquamative, dystrophic, sclerotic changes in epithelial cells, which are consistent with numerous data of scientists.

KEY WORDS: Covid-19, changes in the mucous membrane of the nasopharyngeal zone, cytological examination, children

Wiad Lek. 2025;78(9):1741-1745. doi: 10.36740/WLek/212502 DOI

INTRODUCTION

Mucosal tolerance is essential and provides a robust barrier and suppressive mechanism in response to respiration, food, and ingestion. Development during the neonatal period is essential for this function, when the presence of the epithelial barrier is vulnerable due to their poor development [1]. At the beginning of 2020 y., the discovery of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) marked the start of the COVID-19 pandemic [2]. The nasal cavity serves as a point of entry, and the elevated viral load observed in this area as the primary site of SARS-CoV-2 infection and subsequent immune response [3-5].

AIM

To investigate cytomorphological presentations of the mucous membrane damage of the nasopharyngeal zone in Coronavirus disease in children

MATERIALS AND METHODS

A epithelium scraping from the surface of the Pharyngeal tonsils was performed with the following double fixation: the samples were fixed in a 2% solution of glutaraldehyde (25% Glutaraldehyde E. M. Grade Polysciences Inc.) in 0.1M cacodylate buffer (Cacodylic acid Sodium salt. Fluka) at pH 7.2 for 2–2.5 hours in the cold. Washing (2 times) in cacodylate buffer was performed. The next stage was additional fixation of the samples in a 1.5% solution of OsO₄ (Osmium Tetroxide. SPI – CHEM USA) in 0.1 M sodium cacodylate solution at pH 7.2 for 2 hours in the cold with subsequent washing (2 times) in buffer. Sections are made on an UMTF-6M ultramicrotome using a diamond knife (DIATOM). Contrasting of sections is carried out in 1% uranyl acetate solution and in Reynolds lead contrast medium [6, 7]. Sections were viewed using a TEM-100 transmission electron microscope (Ukraine).

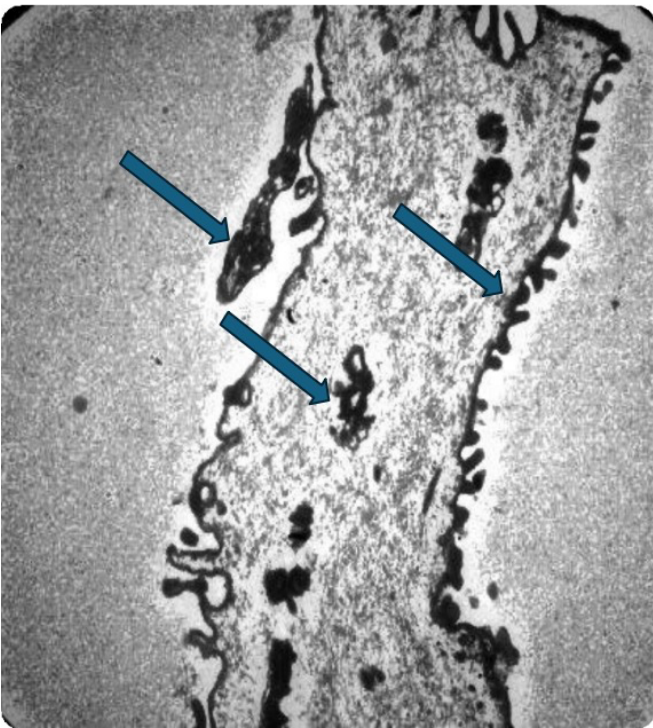


Fig. 1. Electronic photograph (magnification x10000). Section of an Palatine Tonsil epithelial cell in which focal hemorrhage and degenerative changes in the membrane of papillary structures are observed
Picture taken by the authors

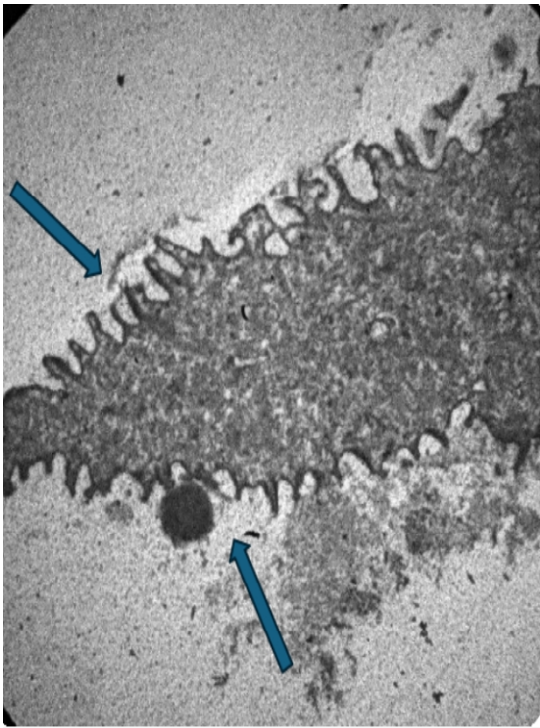


Fig. 2. Electronic photograph (magnification x10000). Papillary structures (lacunae) located on the basement membrane during Phagocytosis (active phase of inflammation)
Picture taken by the authors

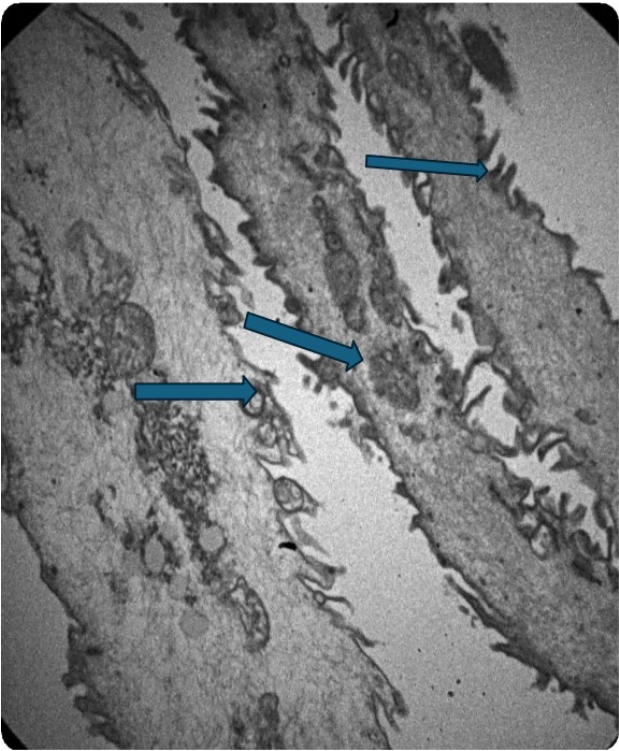


Fig. 3. Electronic photograph (magnification x10000). Palatine Tonsil with reactive-degenerative changes in the stroma and increased hemorrhages in the vessels
Picture taken by the authors

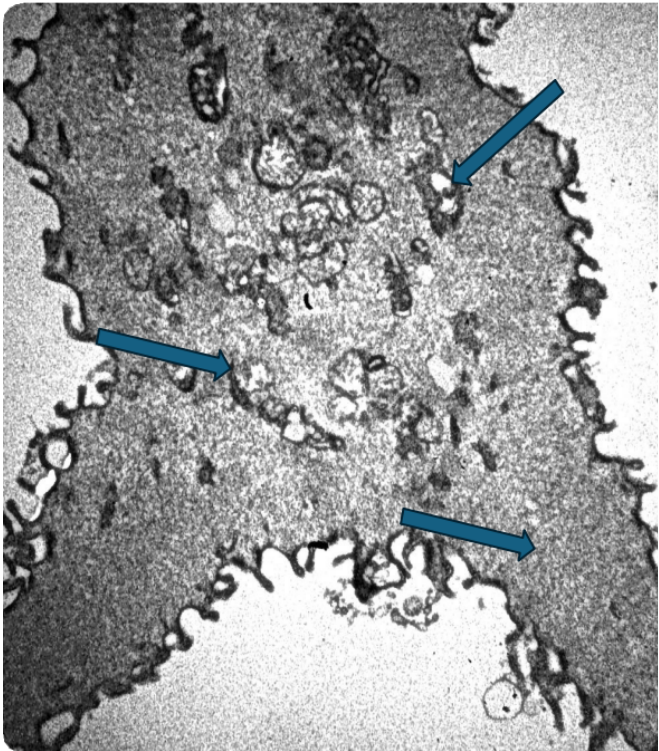


Fig. 4. Electronic photograph (magnification x10000). Partial sclerosis and microcalcification of the Tonsil epithelial tissue
Picture taken by the authors

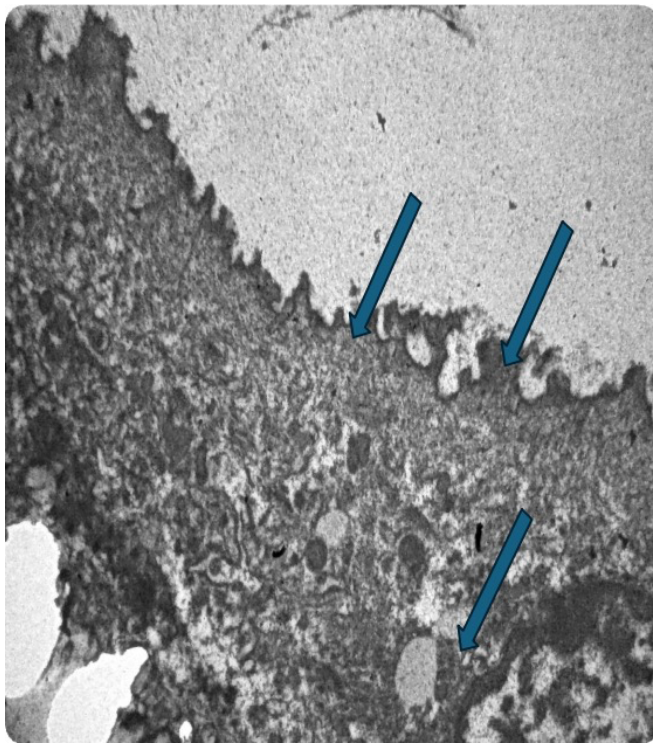


Fig. 5. Electronic photograph (magnification x10000). Pronounced sclerotic changes in the epithelial cell and partial destruction of the cell membrane, resulting in impaired semiconductivity in the cell
Picture taken by the authors

RESULTS

The S protein of SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) protease as a receptor for entry into human cells, which is facilitated by other proteases such as TMPRSS2 [8, 9]. SARS-CoV-2 has the potential to limit the innate immune response by weakening the Interferon response in epithelial cells after Coronavirus successful entry [10].

Virus-induced inflammation of the mucosa occurs, in which Neutrophils and Macrophages (CD68+ cells) circulate, with subsequent infiltration and increased Cytokine levels [11, 12]. When epithelial cells of the upper and lower Respiratory tract are affected, symptoms of Acute Rhinopharyngitis may develop at the onset of the disease. At the same time, in a significant number of cases this period may remain without manifestation, and a significant part of infected people endure this stage of the disease in an erased form, creating the main pool of latent infection [12].

The nasopharyngeal mucosa contains a moderate amount of mucosa-associated Lymphoid tissue (MALT), which is conveniently located for immunological sampling but also creates vulnerability to pathogens. In recent years, the Nasopharyngeal location has been implicated in the pathogenesis of important human

diseases (COVID-19), but this tissue has never been described in detail in any species. The oral cavity is an accessible and predominant environment for the interaction of SARS-CoV-2 with the Mucosal Immune system and target cells; also, direct exposure to the virus impairs the antiviral inflammatory response and causes oral disorders, particularly in association with Immunodeficiency states and Autoimmunity [13]. The most typical electronic photographs of changes in the nasopharyngeal mucosa in children with diagnosed Coronavirus infection are presented (Fig. 1, Fig.2, Fig.3, Fig.4, Fig.5). The clinical manifestation was represented by complaints from the upper Respiratory tract on the background of fever (body temperature was 38-39° C).

Pathological processes were detected in the mucous membrane of the Nasopharyngeal zone, which were characterized as polymorphic-cellular infiltration and presented by an active phase of inflammation, in the structure of the lacuna on the basement membrane of the cell during phagocytosis, according to the results of electron microscopy. Presentation of a section of the Palatine Tonsil epithelial cell is marked by increased focal hemorrhage and degenerative changes in the membrane of papillary structures. The Palatine Tonsil with reactive-degenerative changes in the stroma and increased hemorrhages in the vessels indicates degenerative changes that accompany the Acute infectious process, caused by Covid-19. Partial sclerosis and microcalcification of the Tonsil epithelial cell tissue, pronounced sclerotic changes in the epithelial cell and partial destruction of the cell membrane were also visualized, as a result of which the semiconductivity in the cell is disturbed.

Based on the electronic presentation, we can observe all the processes of inflammation and their consequences. We will consider the pathogenetic processes which were monitored in our studies. Inflammation consists of three main types of tissue disorders, which include: alteration, exudation, proliferation [14]:

1) alteration is the occurrence of damage under the influence of an inflammatory factor, in our case the Covid-19 virus and presented by the active phase of inflammation of papillary structures (lacunae) located on the basement membrane during phagocytosis;

2) changes in microcirculation, vascular wall permeability, exudation;

- a section of an epithelial cell of the Palatine Tonsil in which focal hemorrhage and degenerative changes in the membrane of papillary structures are observed.

- a Palatine Tonsil reactive-degenerative changes in the stroma and increased hemorrhages in the vessels;

3) proliferation;

- pronounced sclerotic changes in the epithelial cell and partial destruction of the cell membrane, resulting in impaired semiconductivity in the cell,

- partial sclerosis and microcalcification of the tonsil epithelial cell tissue.

DISCUSSION

Necrotic inflammation may develop in the case of predominance of alteration process, which is manifested by mucosal epithelium damage, its desquamation and exposure of the basement membrane [15], which were observed in the review of our presentations.

The membrane structure damage caused by the effects of physical and chemical factors, free radicals, the complement system, etc. This pathological process leads to cell necrosis, but local damage can be restored, however, with partially loss of membrane [15]. This date were also noted in our studies.

SARS-CoV-2 infection usually begins in the Nasopharynx and cytological and molecular correlates are not sufficiently characterized. Cytological analysis documented that glandular cells infected with SARS-CoV-2 showed marked degeneration with ciliocytophtory; viral inclusions were not detected. Co-expression analysis showed that virus-infected cells had increased apoptosis, as indicated by strong expression of activated *Caspase* [16].

Cytology studies performed in Sudan also did not reveal significant cytological and pathological changes. Examination of Nasopharyngeal swabs revealed an abnormally high number of Lymphocytes (Lymphocytosis), a large number of inflammatory cells. A thorough search failed to detect any viral inclusions due to the absence of squamous cells. This suggests that the claim of viral inclusions with COVID-19 disease may rather represent a non-specific cytopathic effect in Nasopharyngeal swabs, such as lymphocytosis [17,18].

CONCLUSIONS

Cytological changes in the studied material of the Nasopharyngeal zone with common changes in glandular cells can be considered as nonspecific. We founded the same type of morphological changes, by electron microscopy using of the mucous membrane investigation in the patients with COVID-19. These changes were characterized by the presence of diffuse inflammatory polymorpho-cellular infiltration, impaired hemodynamics and diffuse desquamative, dystrophic, sclerotic changes in epithelial cells, which are consistent with numerous data of scientists.

REFERENCES

1. Conti MG, Mortari EP, Nenna R et al. SARS-CoV-2-specific mucosal immune response in vaccinated versus infected children. Brief research report. *Front. Cell. Infect. Microbiol.* 2024;14:1-7. doi:10.3389/fcimb.2024.1231697. DOI
2. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020;5(4):536-544. doi: 10.1038/s41564-020-0695-z. DOI
3. Wang W, Xu Y, Gao R et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA.* 2020;323:1843-4. doi: 10.1001/jama.2020.3786. DOI
4. Zou L, Ruan F, Huang M et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N. Engl. J. Med.* 2020;382:1177-9. doi: 10.1056/NEJMc2001737. DOI
5. Gallo O, Locatello LG, Mazzoni A et al. The central role of the nasal microenvironment in the transmission, modulation, and clinical progression of SARS-CoV-2 infection. *Mucosal Immunol.* 2021;14:305-316. doi: 10.1038/s41385-020-00359-2. DOI
6. Reynolds ES, The use of lead citrate at high pH as an electronopaque stain in electron microscopy. *J Cell Biol.* 1963;17(1):208-12. doi: 10.1083/jcb.17.1.208. DOI
7. Weakley BS. A beginner's handbook in biological transmission electron microscopy. 2nd edition. Paperback: Churchill Livingstone. 1981, p.252.
8. Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020;181:271-80.e8. doi: 10.1016/j.cell.2020.02.052. DOI
9. Cantuti-Castelvetri L, Ojha R, Pedro LD et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* 2020;370:856-60. doi: 10.1126/science.abd2985. DOI
10. Hatton CF, Botting RA, Dueñas ME et al. Delayed induction of type I and III interferons mediates nasal epithelial cell permissiveness to SARS-CoV-2. *Nat. Commun.* 2021;12:7092. doi: 10.1038/s41467-021-27318-0. DOI
11. Chen S, Wang S. The immune mechanism of the nasal epithelium in COVID-19-related olfactory dysfunction. *Front. Immunol.* 2023;14:1045009. doi: 10.3389/fimmu.2023.1045009. DOI
12. Drozdziak A, Drozdziak M. Oral Pathology in COVID-19 and SARS-CoV-2 Infection-Molecular Aspects. *Int J Mol Sci.* 2022;23(3):1431. doi: 10.3390/ijms23031431. DOI
13. Zarrilli G, Angerilli V, Businello G et al. The Immunopathological and Histological Landscape of COVID-19-Mediated Lung Injury. *Int J Mol Sci.* 2021;22(2):974. doi: 10.3390/ijms22020974. DOI

14. Nuovo GJ, Magro C, Mikhail A. Cytologic and molecular correlates of SARS-CoV-2 infection of the nasopharynx. *Ann Diagn Pathol*. 2020;48:151565. doi: 10.1016/j.anndiagpath.2020.151565. DOI 
15. Mujahed MMA, Khalid IO, Seedahmed Mohamed AA et al. The Detection of Nasopharyngeal Cytological smears Among Positive COVID-19 Test Patients in Omdurman Medical Military Hospital (Sudan). *International Journal of Academic Health and Medical Research (IJAHMR)*. 2023;7(2):67-72.
16. Tamiya J, Sakaguchi W, Nakagawa K et al. Detection of SARS-CoV-2 and Its Related Factors on the Mucosal Epithelium of the Tongue. *Acta Histochem Cytochem*. 2023;56(2):29-37. doi: 10.1267/ahc.22-00089. DOI 
17. Li H., Kuga K, Ito K. Infection Dynamics of SARS-CoV-2 in Mucus Layer of the Human Nasal Cavity – Nasopharynx. *E3S Web of Conferences*. 2022;356:05021. doi:10.1051/e3sconf/202235605021. DOI 
18. Popovic M, Martin JH, Head RJ. COVID infection in 4 steps: Thermodynamic considerations reveal how viral mucosal diffusion, target receptor affinity and furin cleavage act in concert to drive the nature and degree of infection in human COVID-19 disease. *Heliyon*. 2023;9(6):e17174. doi:10.1016/j.heliyon.2023.e17174. DOI 

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Olesya M. Horlenko

Uzhhorod National University

14 Universytetska St, 88000 Uzhhorod, Ukraine

e-mail:ohorlenko@gmail.com

ORCID AND CONTRIBUTIONSHIP

Olesya M.Horlenko: 0000-0002-2210-5503    

Khrystyna A. Hechko: 0000-0003-4989-7659   

Mykhaylo Hechko: 0000-0003-2793-5044   

Fedir V. Horlenko: 0000-0002-0496-2069   

Olga A. Pushkarenko: 0000-0002-7143-029X   

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 19.04.2025

ACCEPTED: 22.08.2025



Use of high-intensity laser for prevention and treatment of osteomyelitic complications in patients with traumatic disease

Stepan S. Filip, Rudolf M. Slivka, Yuriy P. Skrypynets, Petro P. Popyurkanych, Andrii M. Bratasiuk
UZHGOROD NATIONAL UNIVERSITY, UZHGOROD, UKRAINE

ABSTRACT

Aim: To improve the results of treatment of patients with osteomyelitis on the background of traumatic disease.

Materials and Methods: A retrospective evaluation of the treatment of 29 patients with chronic post-traumatic osteomyelitis of the bones of the lower extremities on the background of a traumatic disease.

Results: As a result of the treatment, an acceleration of the dynamics of the wound process was observed in patients of the second group, which was manifested in a reduction in the healing time of fistulas. Radiologically, reparative changes and acceleration of bone regeneration were noted on the 22nd-23rd day after the injury, the formation of a primary bone callus in patients of the control group occurred on the 32nd-35th day after the injury.

Conclusions: The use of methods for the prevention and treatment of osteomyelitic complications in long bone fractures, using high-intensity laser radiation against the background of regional intra-arterial infusions, with correction of the state of "chronic stress", allows accelerating the dynamics of the wound process and bone regeneration, and achieving rapid restoration of working capacity in most patients.

KEY WORDS: traumatic disease, chronic stress, chronic post-traumatic osteomyelitis, clinical course, immunity

Wiad Lek. 2025;78(9):1746-1750. doi: 10.36740/WLek/212505 DOI

INTRODUCTION

Current events that are taking place in Ukraine today formulate special requests both to medical science in general and to the tactics of treating certain traumatic injuries in particular, especially in traumatic disease. Traumatic disease greatly affects the outcome of the injury, determines the prognosis for the course of the pathological process, the results of treatment and work capacity. Of great importance are changes in the psycho-emotional sphere, metabolic and homeostatic processes, the state of the immune system, the functioning of the heart, lungs, digestive organs and the central nervous system [1-4].

The traumatic agent of today (mine and explosive injury), having a large mass and significant acceleration, leads to massive damage to soft tissues and bones not only at the site of direct contact, but also at a considerable distance. Another significant factor that affects the results of treatment of these patients is bacterial contamination of wounds during trauma.

Due to the increase in the proportion of trauma in the overall structure of morbidity, against the background of the evolution of purulent infection towards new antibiotic-resistant strains and the weakening of the human body's resistance, the proportion of

postoperative osteomyelitis after osteosynthesis of closed fractures does not decrease. The widespread use of surgical methods to align bone fragments by metal osteosynthesis has led to an increase in the number of operations, and this has led to an increase in the proportion of osteomyelitic complications from up to 8-10% [5,6,7,8].

Osteomyelitis occupies one of the most dramatic pages of world medicine. Early, compared with other pathologies, disability defines the problem of osteomyelitis as one of the main priorities of national health care systems. In persons with open fractures of the long bones of the lower extremities, the frequency of osteomyelitis is 10.3-20.4% and tends to increase, while in 15-30% of patients the process passes into a chronic stage. In the overall structure of disability due to musculoskeletal injuries, the share of osteomyelitis is 15% [9-12].

Despite scientific and practical achievements and successes in the prevention and treatment of this serious bone pathology, relapses are observed in 10-40% of cases. Long-term disability of this category of patients and high disability rates give the problem of medical and social importance [13,14].

The search for early measures for the prevention and treatment of osteomyelitic complications, which

would be combined with bone-plastic reconstructive operations, is justified. In particular, the use of minimally invasive sanitizing laser measures makes it possible to prevent the development of infectious complications and avoid prolonged antibiotic therapy in the treatment of patients exhausted by «traumatic stress.»

AIM

To improve the results of treatment of patients with osteomyelitis on the background of traumatic disease.

MATERIALS AND METHODS

On the basis of the surgical department of the KNP «Uzhgorod City Multidisciplinary Clinical Hospital» of the Uzhgorod City Council of the SE «Clinical Hospital of Planned Treatment» for the period from 2022 to 2025, 29 patients with chronic post-traumatic osteomyelitis of the bones of the lower extremities on the background of a traumatic disease were treated. In 13 (44.8%) patients in the treatment complex, along with the regional administration of bone-tropic antibacterial, vasodilator, analgesic, and immunostimulating drugs, minimally invasive surgical interventions (treatment of fistula passages, treatment of sequestral cavities, sequestrectomy, sequestrotomy) using high-intensity laser radiation were used.

The age of the patients ranged from 25 to 65 years; there were 23 men (79.3%), 6 women (20.7%). In 25 (86.2%) patients, chronic post-traumatic osteomyelitis of the tibia was diagnosed, and in 4 (13.8%) – of the femur.

The patients were divided into two groups. The first group included 16 (55.2%) patients who received standard treatment, which consisted of sanitation of the focus of the purulent-necrotic process, antibacterial, detoxification and vascular therapy, which was carried out intravenously and intramuscularly.

In the treatment of the second, main group of patients, 13 (44.8%) patients, the method of regional administration of antibacterial and vascular drugs by intraarterial puncture (through the femoral artery) was used. Antibacterial therapy was carried out taking into account the sensitivity of microorganisms; preference was given to osteotropic drugs.

It should be noted that the dominant pathogen was *Staphylococcus aureus*, which was detected in 14.2% of cases as a monoculture and in 85.8% in association with other pathogens, *Escherichia coli* was present in 27.6% of cases, *Pseudomonas aeruginosa* – 17.2%, *Proteus* – 12.6%, *Streptococcus* – 10.4%. In 63.5% of cases, mixed flora was sown.

The aim of the surgical intervention was to eliminate the osteomyelitic focus without the use of large traumatic surgical accesses using a source of high-intensity infrared laser radiation «Lika-hirug» and a quartz-polymer monofiber light guide inserted through the skin or fistula passage under the control of X-ray examination methods, during which laser treatment of fistula passages, sequestral cavities, vaporization of individual sequestrs and the surgical wound with high-intensity laser radiation was performed using a source with a power of up to 10 W and a wavelength of 940 nm. When installing the appropriate metal fixators, careful processing was performed, both the edges of the bone fragments and the entire surgical wound.

For the purpose of fixing bone fragments, rod-type external fixation devices (Ex Fix) were used.

During the study, the dynamics of the wound process, radiological dynamics, endogenous intoxication indicators by the level of medium molecular peptides (MMP), indicators of the body's immune defense by the ratio of T-helpers to T-suppressors, indicators of humoral immunity by the level of circulating immune complexes (CICs) were evaluated. The results obtained were compared with a group of clinically healthy people who were matched by age and gender.

Patients in the second group were treated with anti-stress drugs, adaptogens, and medications that correct the level of cortisol in the body, which is an integral part of immunotherapy.

The effectiveness of treatment was assessed by the degree of severity of general and local signs of inflammatory reaction, the dynamics of bone wound healing and soft tissue lesions, the nature of reparative processes, and functional capabilities, based on the analysis of the terms of restoration of limb function and working capacity.

RESULTS

As a result of the treatment, an acceleration of the dynamics of the wound process was observed in patients of the second group, which was manifested in a reduction in the healing time of fistulas (their cleansing, the appearance of granulations and the beginning of epithelialization) (Fig. 1). Radiologically, reparative changes and acceleration of bone regeneration were noted on the 22-23rd day after the injury (Fig. 2). Along with this, the formation of primary bone callus in patients of the control group, according to radiological dynamics, occurred on the 32-35th day after the injury.

The level of endotoxemia was assessed by the content in the blood of SMP, which are endogenous



Fig. 1. Patient K., Post-traumatic osteomyelitis of the bones of the left tibia. Scalped wound of the left tibia. Dynamics of the wound process
Picture taken by the authors

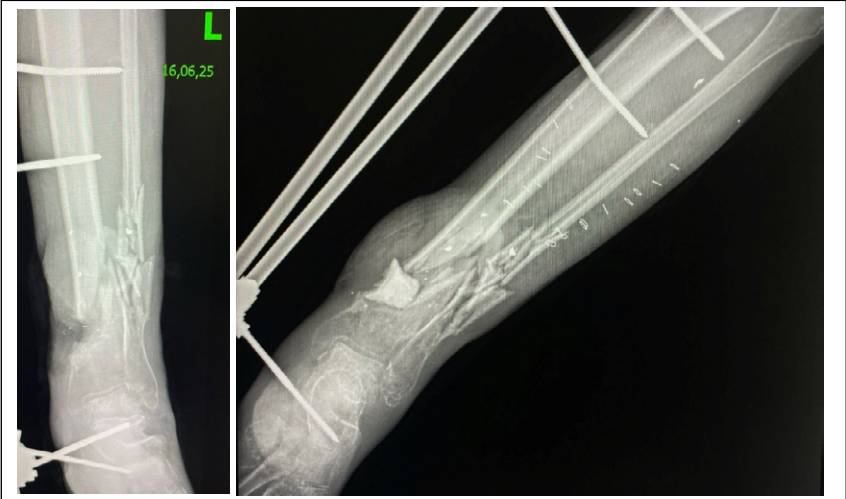


Fig. 2. Patient K., Post-traumatic osteomyelitis of the bones of the left tibia. Scalped wound of the left tibia. X-ray dynamics
Picture taken by the authors

compounds with an average molecular weight of 500 to 5000 d, the content of which increases with the increase in intoxication syndrome.

In patients with post-traumatic osteomyelitis, with increasing intoxication in the blood, the level of SMP sharply increased, mainly due to the pool, which is determined at a wavelength of 254 nm and

characterizes the toxic properties of the blood – up to 0.442 ± 0.05 in patients of the first (control) group and 0.445 ± 0.06 in the second (main) group; in healthy people – 0.333 ± 0.04 .

In patients with post-traumatic osteomyelitis, against the background of a decrease in the total number of lymphocytes (up to 21.6 ± 0.64 , in healthy

subjects – 44.4 ± 0.79), there was a sharp decrease in the number of Tx with a moderate decrease in Tc and a corresponding decrease in their ratio (Tx/Tc) to 1.02 ± 0.14 in patients of the first group and 1.04 ± 0.15 in the second (main) group (in healthy subjects 1.34 ± 0.12). The level of CIC in the blood increases to 32.46 ± 1.64 in patients of the first group and 34.76 ± 1.84 in the second (main) group; in healthy subjects 16.17 ± 0.53 .

After treatment, there is a tendency to normalize the ratio Th/Ts to 1.20 ± 0.12 in patients of the first group and to 1.24 ± 0.14 in the second (main) group. The level of CIC in the blood decreases – to 27.86 ± 2.02 in patients of the first group and 24.88 ± 1.94 – in the main group, but these indicators do not reach the indicators of healthy people.

DISCUSSION

Chronic or “prolonged traumatic” stress worsens the results of treatment of traumatic injuries, contributing to the development of inflammatory processes, worsening of wound healing and even increasing the likelihood of infectious complications. Chronic stress leads to an imbalance in the immune response, reduces the activity of cells responsible for protecting the body from infections and contributes to the chronicity of inflammatory processes [7]. In conditions of traumatic disease, this leads to a slowdown in healing and an increased risk of developing infectious-inflammatory complications, such as sepsis or osteomyelitis. Statistical data show that 30–40% of patients who experience severe injuries against the background of chronic stress have a higher risk of developing infectious-inflammatory complications, namely wound infections, impaired healing. Osteomyelitis is the most significant purulent-necrotic complication that affects reparative osteogenesis, which especially needs to be taken into account in traumatic disease. Regeneration

in this case should be considered as the most complex manifestation of life in extreme conditions. Since a bone fracture involves a violation of the integrity of the muscles, ligaments, skin and blood vessels, which in turn is a significant obstacle to regenerative mechanisms. That is why careful correction of regeneration processes in bone fractures against the background of a traumatic disease has important socio-economic significance, as it will significantly reduce the level of disability and loss of work capacity [5].

In the treatment of post-traumatic osteomyelitis of the long bones of the lower extremities, the use of regional infusion and the application of high-intensity laser radiation, along with monitoring and correction of chronic stress, allows stopping the progression of the purulent-necrotic process in the bone and soft tissues, allows achieving rapid sanitation of fistula passages and foci of purulent-necrotic process, accelerating the dynamics of the wound process and reparative processes in the bone, reducing the level of endotoxemia, activating immune defense, significantly reducing treatment times, reducing course doses of medications and achieving restoration of working capacity in the vast majority of patients. The effectiveness of the proposed treatment method has been proven, which allows avoiding disabling operations and restoring the function of the damaged limb more quickly.

CONCLUSIONS

The use of the method of prevention and treatment of osteomyelitic complications in long bone fractures, using high-intensity laser radiation against the background of regional intraarterial infusions, with correction of the state of «chronic stress», allows to accelerate the dynamics of the wound process and bone regeneration, shorten the treatment period, reduce the course doses of medications and achieve faster restoration of working capacity in most patients.

REFERENCES

1. Hofmann SR, Schnabel A, Rosen-Wolff A et al. Chronic nonbacterial osteomyelitis: pathophysiological concepts and current treatment strategies. *J. Rheumatol.* 2016;43:1956–64. doi: 10.3899/jrheum.160256. DOI
2. Schnabel A, Range U, Hahn G et al. Unexpectedly high incidences of chronic non-bacterial as compared to bacterial osteomyelitis in children. *Rheumatol. Int.* 2016;36:1737–45. doi: 10.1007/s00296-016-3572-6. DOI
3. Ferguson PJL. Autoinflammatory Bone Disorders. In: Petty L, Lindsley, Wedderburn, editor. *Textbook of Pediatric Rheumatology*. 7th Edition. Elsevier, Philadelphia. 2016, pp. 627–41.
4. Hofmann SR, Böttger F, Range U et al. Serum Interleukin-6 and CCL11/Eotaxin May Be Suitable Biomarkers for the Diagnosis of Chronic Nonbacterial Osteomyelitis. *Front Pediatr.* 2017;5:256. doi: 10.3389/fped.2017.00256. DOI
5. Schnabel A, Range U, Hahn G et al. Unexpectedly high incidences of chronic non-bacterial as compared to bacterial osteomyelitis in children. *Rheumatol. Int.* 2016;36:1737–1745. doi: 10.1007/s00296-016-3572-6. DOI
6. Hofmann SR, Kubasch AS, Ioannidis C et al. Altered expression of IL-10 family cytokines in monocytes from CRMO patients result in enhanced IL-1 β expression and release. *Clin. Immunol.* 2015;161:300–307. doi: 10.1016/j.clim.2015.09.013. DOI

7. Hedrich CM, Beresford MW, Dedeoglu F et al. Gathering expert consensus to inform a proposed trial in chronic nonbacterial osteomyelitis (CNO). *Clin Immunol.* 2023;251:109344. doi: 10.1016/j.clim.2023.109344. [DOI](#)
8. Hofmann SR, Kubasch AS, Range U et al. Serum biomarkers for the diagnosis and monitoring of chronic recurrent multifocal osteomyelitis (CRMO). *Rheumatol. Int.* 2016;36:769–79. doi: 10.1007/s00296-016-3466-7. [DOI](#)
9. Hofmann SR, Schnabel A, Rösen-Wolff A et al. Chronic nonbacterial osteomyelitis: Pathophysiological concepts and current treatment strategies. *Journal of Rheumatology.* 2016;43(11):1956–1964. doi: 10.3899/jrheum.160256. [DOI](#)
10. Hofmann C, Wurm M, Schwarz T et al. A standardized clinical and radiological follow-up of patients with chronic non-bacterial osteomyelitis treated with pamidronate. *Clin Exp Rheumatol.* 2014;32(4):604–9.
11. Chou PH, Lin HH, Su YP et al. Staged protocol for the treatment of chronic femoral shaft osteomyelitis with Ilizarov's technique followed by the use of intramedullary locked nail. *Journal of the Chinese Medical Association.* 2017;80(6):376–382. doi: 10.1016/j.jcma.2017.01.001. [DOI](#)
12. Fang CH, Tsai PI, Huang SW et al. Magnetic hyperthermia enhance the treatment efficacy of peri-implant osteomyelitis. *BMC Infectious Diseases.* 2017;17(516):1–12. doi: 10.1186/s12879-017-2621-4. [DOI](#)
13. McNally MA, Ferguson JY, Lau ACK et al. Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite. *Bone Joint J.* 2016;98(9):1289–1296. doi: 10.1302/0301-620X.98B9.38057. [DOI](#)
14. Lu V, Zhang J, Zhou A, Krkovic M. Management of post-traumatic femoral defects with a monorail external fixator over an intramedullary nail. *Eur. J. Orthop. Surg. Traumatol.* 2022;32(6):9–1126. doi: 10.1007/s00590-021-03082-1. [DOI](#)
15. Chan JKK, Ferguson JY, Scarborough M et al. Management of Post-Traumatic Osteomyelitis in the Lower Limb: Current State of the Art. *Indian J. Plast. Surg.* 2019;52(1):62–72. doi: 10.1055/s-0039-1687920. [DOI](#)

The work was carried out in the framework of research work 0124U002167 «Monitoring of traumatic disease against the background of chronic stress».

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Stepan S. Filip

Uzhgorod National University

71 Minayska St, 88000 Uzhgorod, Ukraine

e-mail: filip.uz@i.ua

ORCID AND CONTRIBUTIONSHIP

Stepan S. Filip: 0000-0002-6549-3892 [A](#) [E](#) [F](#)

Rudolf M. Slyvka: 0000-0002-0187-2711 [A](#) [C](#) [D](#)

Yuriy P. Skripinets: 0000-0002-9741-4175 [B](#) [C](#)

Petro P. Popyrkanych: 0000-0002-4809-2640 [C](#) [E](#)

Andriy M. Bratasyuk: 0000-0003-4390-2357 [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: 10.04.2025

ACCEPTED: 21.08.2025



Prediction of abdominal compartment syndrome in patients with severe acute pancreatitis

Olexii I. Dronov, Inna O. Kovalska, Andrii I. Horlach, Ivanna A. Shchyhel, Vitaliy R. Balyak, Vadym O. Kostiukevich
BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: To identify factors associated with the risk of developing abdominal compartment syndrome (ACS) in patients with severe acute pancreatitis (SAP).

Materials and Methods: A retrospective single-center cohort study of 106 patients with SAP, complicated by ACS (n=32) and without the given complication (n=74). The first stage included an intergroup comparison of 28 clinical-laboratory indicators recorded during the early stages of the disease. The second and third stages consisted of univariate and multivariate logistic regression analyses of the variables selected over the first stage, developing a prediction model, and evaluating its characteristics.

Results: Statistically significant difference between the groups was found for the following 14 indicators: BMI, Glasgow Coma Scale score, visceral obesity index, CRP level, radiological signs of paresis, pleural effusion, fluid collections in the retroperitoneal space, daily fluid balance, pain intensity according to the NPRS scale, the total score on the Marshall and BISAP scales, early persistent SIRS, APP and RFG levels ($p < 0.05$). The given factors were identified as independent risk factors for ACS development: daily fluid balance, pain intensity (NPRS), retroperitoneal fluid collections, early persistent SIRS, and elevated WHR. The developed logistic model demonstrated high discriminatory ability: AUC = 0.92, sensitivity – 94%, specificity – 81%.

Conclusions: The developed model can enable patient stratification and targeted correction of potentially modifiable ACS risk factors in the early stages of SAP.

KEY WORDS: acute severe pancreatitis, abdominal compartment syndrome, early prediction, logistic regression

Wiad Lek. 2025;78(9):1751-1757. doi: 10.36740/WLek/212506 DOI

INTRODUCTION

Abdominal compartment syndrome (ACS) is characterized by sustained intra-abdominal pressure (IAP) exceeding 20 mmHg and organ failure (OF). Regardless of the etiology, it requires prompt decision-making, intensive therapy and urgent surgical intervention when conservative methods are ineffective [1]. Acute pancreatitis (AP) is accompanied by intra-abdominal hypertension (IAH) in 50-60% of cases, and in 15-30% of these cases, it progresses to ACS [2, 3]. The systemic and local manifestations of severe acute pancreatitis (SAP) worsen with the development of ACS, a rare complication that significantly worsens the course and prognosis, with mortality rates increasing to 75% [4, 5].

The course, management, and prevention of intra-abdominal hypertension (IAH) progression in severe acute pancreatitis (SAP) are actively being researched. However, knowledge on the risk factors for ACS in SAP still remains limited [6-9]. Hence, the critically important need for the review of approaches to patient stratification in SAP and IAH, depending on the response to complex therapeutic measures, within the concept of preventing

irreversible ACS outcomes [10, 11]. In the given study, we analyzed information from medical records of SAP patients to study the risk factors for ACS development, followed by the systematization of prediction.

AIM

To identify factors associated with the risk of developing abdominal compartment syndrome in patients with severe acute pancreatitis.

MATERIALS AND METHODS

A retrospective non-randomized single-center cohort study was conducted among 106 patients treated at the General Surgery Department No. 1 of Bogomolets National Medical University, between 2018 and 2024, with a diagnosis of SAP (K-85). Patients were divided into two groups:

- Group A – Patients with SAP complicated by ACS, n=32;
- Group B – Patients with SAP not complicated by ACS, n=74.

The diagnosis and severity of AP were established based on the revised Atlanta criteria (2012). The modified

Table 1. Intergroup comparison of variables (First stage of the study)

Nº	Variable, units of measurement	Group A (SAP + ACS) N = 32	Group B (SAP - ACS) N = 74	p-value
1.	Sex	Male 21(65.6%)	Male 52(71.6%)	0.653 ^X
2.	Age, years	52.84 ± 9.79	55.01 ± 9.33	0.283 ^T
3.	BMI, kg/m ²	31.28 ± 2.99	26.64 ± 2.64	<0.001 ^T
4.	Onset, hours	6(5 - 7)	5(5 - 6)	0.159 ^U
5.	Etiology	A - 13(40.6%)	23(31.1%)	0.824 ^F
		B - 12(37.5%)	27(36.5%)	
		H - 3(9.4%)	9 (12.2%)	
		P - 1(3.1%)	4(5.4%)	
		I - 3(9.4%)	11(14.9%)	
6.	Charlson Index, points	2(1 - 3)	2(1 - 3)	0.725 ^U
7.	Glasgow Coma Scale, points	14(13 - 14)	15(14 - 15)	<0.001 ^U
8.	Waist-to-Hip Ratio, %	96(90.5 - 100)	92.5(87 - 97)	0.01 ^U
9.	Platelets, 10 ⁹ /l	269.5 ± 66.15	273.7 ± 71.97	0.780 ^T
10.	Amylase, U	969.9 ± 532.6	1025 ± 495	0.611 ^T
11.	C-reactive protein, mg/l	102(93 - 124)	98(88 - 104)	0.03 ^U
12.	Albumin, g/l	30.75 ± 4.32	30.9 ± 3.68	0.865 ^T
13.	AST, U/l	44.3(29.4 - 54.35)	49.65(31.2-62.1)	0.184 ^U
14.	Creatinine, µmol/l	89.28 ± 12.65	93.97 ± 13.67	0.1 ^T
15.	Glucose, mmol/l	8.1(6.65 - 9.4)	8(6.8 - 9.5)	0.880 ^U
16.	Radiological signs of paresis	Yes - 18(56.3%)	Yes - 20(27.8%)	0.007 ^X
17.	Pleural effusion	Yes - 21(65.6%)	Yes - 29(39.2%)	0.02 ^X
18.	Inferior vena cava	19.2 ± 3.84	18.9 ± 3.5	0.742 ^T
19.	Retroperitoneal fluid collections	Yes - 20(62.5%)	Yes - 28(37.8%)	0.03 ^X
20.	Daily fluid balance, l	2.76 ± 0.45	2.35 ± 0.38	<0,001 ^T
21.	Diuresis, l	1.2(0.95 - 1.4)	1.25(1.05 - 1.45)	0.364 ^U
22.	NPRS scale, max points	8.3 ± 0.99	7.1 ± 1.1	<0.001 ^T
23.	BISAP, points	3.3 ± 0.73	2.9 ± 0.86	0.04 ^T
24.	Marshall, points	2.2±0.81	1.9±0.75	0.02 ^T
25.	Early persistent SIRS	Yes - 21 (65.6%)	Yes - 31 (41.9%)	0.03 ^F
26.	MAP, mmHg	93.59±5.58	94.43±5.98	0.498 ^T
27.	APP, mmHg (3rd day)	77.79±5.18	82.14±6.9	<0.001 ^T
28.	RFG, mmHg (3rd day)	61.99±5.1	69.84±8.1	<0.001 ^T

T - Student's t-test, U - Mann-Whitney U test, X - Chi-square (χ^2), F - Fisher's Exact Test

Source: compiled by the authors of this study

Marshall score was used to assess the severity of organ failure (OF), [12, 13]. ACS was diagnosed with IAP ≥ 20 mmHg and progression of organ failure occurred.

Inclusion Criteria:

- Persistent organ failure (>48 hours) and local complications of SAP;
- Hospitalization to the intensive care unit (ICU) within the first 72 hours from the onset of symptoms;
- Written informed consent for data processing.

Demographic, epidemiological, and clinical-laboratory data from the first seven days of hospitalization or less (for deceased patients) were collected from the

medical records. The study included sex, age, body mass index (BMI), and the time in hours from the onset of symptoms. Upon admission, data on the etiology of AP, Charlson comorbidity index, Glasgow Coma Scale score, and Bedside Index of Severity in Acute Pancreatitis (BISAP) score [14] were collected. On the first day of hospitalization, all patients underwent anthropometric measurement of visceral obesity index using the Waist-to-Hip Ratio (WHR) method – waist circumference (cm) divided by hip circumference (cm) – with the result recorded in percentages for convenience in calculations.

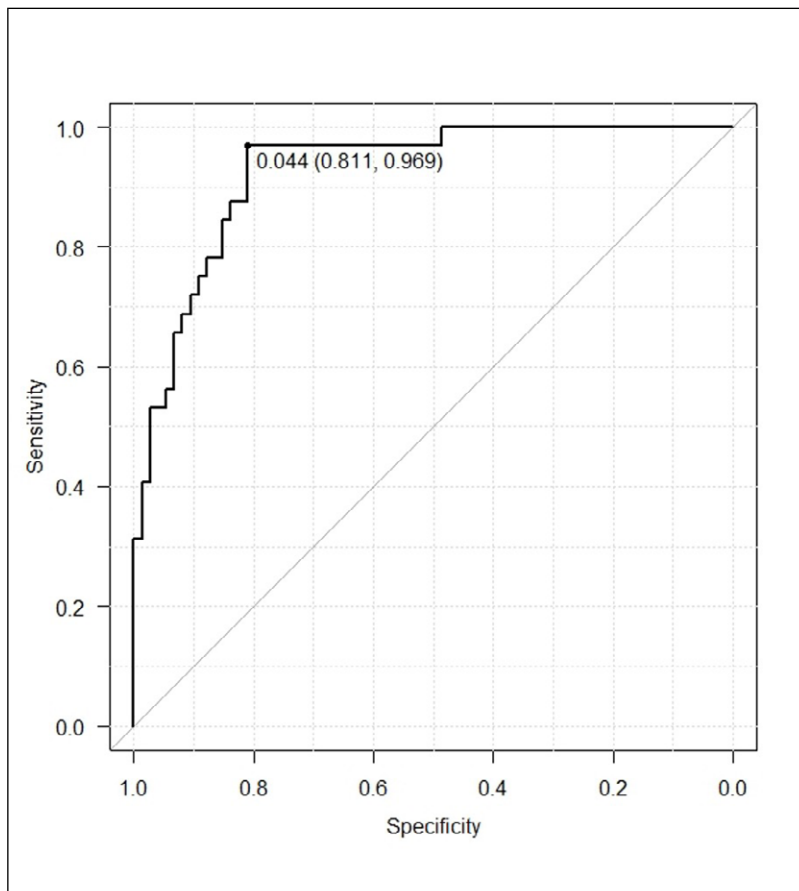


Fig. 1. ROC curve for predicting the risk of ACS in patients with SAP

Picture taken by the authors

The laboratory indicators selected for the first day included the following: platelet count, serum amylase, C-reactive protein (CRP) level, albumin, aspartate aminotransferase (AST) level, creatinine, and venous blood glucose level.

After visual patient's examination over the first day, the following signs were also recorded: evidence of paresis (marked pneumatosis or the presence of single horizontal fluid levels) on abdominal radiography and pleural effusion detected during ultrasound (US) examination. The maximum diameter of the inferior vena cava (IVC) during ultrasound examination of the abdominal organs and the presence of retroperitoneal fluid collections were noted during the first two days after hospitalization.

After one day of treatment, daily fluid balance and diuresis (in liters) were recorded. Pain intensity, assessed by the patient using the Numeric Pain Rating Scale (NPRS), a simplified version of the Visual Analog Scale, was also recorded. For calculations, the maximum score obtained during the first day of hospitalization was used. Data on daily intra-abdominal pressure (IAP) measurements via transurethral catheter in mmHg, mean arterial pressure (MAP), abdominal perfusion pressure (APP), and renal filtration gradient (RFG) were also recorded. The presence of persistent early systemic inflammatory response syndrome (SIRS) diagnosed within the first 24 hours and lasting for more than 24 hours was included in the study.

For presenting quantitative data, the mean $\pm$ standard deviation was used for normal distribution, while for non-normal distribution it was, the median and interquartile range (IQR) were presented. For categorical data, the absolute number and percentage were provided. Continuous variables were compared using the Student's t-test and the Mann-Whitney U test, while categorical data were analyzed using Fisher's exact test and the chi-square test. A univariate logistic regression analysis was conducted to evaluate the association of selected variables with the development of ACS. Odds ratios with 95% confidence intervals were calculated. Variables showing statistical significance were considered potential predictors and were included in the multivariate analysis. To assess the discriminatory ability of the constructed multivariate logistic model, the area under the ROC curve (AUC) was used. Results were considered statistically significant with $p < 0.05$. Data were processed using the standard Microsoft Excel 365 package. For calculations and analysis, MedStat v.5.2 and EZR (R-statistics) [15] were used.

RESULTS

In Group A, there were 21 male patients (65.6%), with an average age of 52.84 ± 9.79 years, and 25 (78%) patients, who died due to complications of the primary disease.

Table 2. Results of univariate regression analysis

Nº	Variable, units	OR (95% CI)	p-value
1.	BMI, kg/m ²	3.32 (1.94 - 5.68)	<0.001
2	Glasgow Coma Scale, points	0.21 (0.10 - 0.44)	<0.001
3.	Waist-to-Hip Ratio, %	1.08 (1.01 - 1.16)	0.01
4.	C-reactive protein, mg/l	1.03 (1.01 - 1.06)	0.001
5.	Radiological signs of paresis	3.47 (1.46 - 8.26)	0.005
6.	Pleural effusion	13.2 (4.9 - 35.5)	<0.001
7.	Retroperitoneal fluid collections	2.74 (1.16 - 6.45)	0.02
8.	Daily fluid balance, ml	12.4 (3.5 - 44.1)	<0.001
9.	Max NPRS scale, points	2.77 (1.72 - 4.46)	<0.001
10.	BISAP, first day, points	1.66 (0.99 - 2.76)	0.05
11.	Marshall, first day, points	1.82 (1.05 - 3.16)	0.03
12.	Early persistent SIRS	2.65 (1.12 - 6.28)	0.02
13.	APP on the 3rd day, mmHg	0.9 (0.83 - 0.96)	0.003
14.	RFG on the 3rd day, mmHg	0.85 (0.78 - 0.92)	<0.001

Source: compiled by the authors of this study

Table 3. Coefficients of the final model for predicting ACS risk in patients with SAP – five independent predictors

Variable	Coefficient, b ± mb	p-value	OR (95% CI)
Const	-31.42 ± 6.86	<0.001	-
Fluid balance, day 1	2.4 ± 0.91	0.008	11.1 (2.0 - 62.1)
Max NPRS, day 1	1.24 ± 0.35	<0.001	3.5 (1.82 - 6.73)
Retroperitoneal fluid collections	1.98 ± 0.74	0.007	7.65 (1.88 - 31.2)
Early persistent SIRS	2.34 ± 0.83	0.004	11.1 (2.33 - 53.2)
Waist-to-Hip Ratio, %	0.11 ± 0.04	0.01	1.13 (1.03 - 1.23)

Source: compiled by the authors of this study

In Group B, there were 52 male patients (71.6%), with an average age of 55.01 ± 9.33 years, and 28 (38%), patients who died. The patients did not differ in age, sex, time from the onset of symptoms, comorbidities, or etiology ($p > 0.05$). When performing the first stage of intergroup comparison of selected variables, a statistically significant difference was found among 14 indicators (Table 1).

In the second stage, a series of univariate regression analyses was conducted for the variables that showed statistically significant differences in the intergroup comparison. In the univariate logistic regression analysis, all 14 variables demonstrated statistically significant relevance (Table 2). When selecting variables for the third stage, the potential modifiability of the variables was considered, and variables with multicollinearity or a high risk of overfitting the predictive model were excluded.

In the third stage of the study, a multivariate logistic regression model was constructed using the variables selected during the previous stage. The analysis re-

vealed a relationship between the risk of developing ACS and five factor characteristics: fluid balance, maximum NPRS score during the first day of treatment, presence of retroperitoneal fluid collections during the first 48 hours of observation, early persistent SIRS, and the visceral obesity index WHR. The model assessment coefficients are presented in Table 3.

The obtained mathematical model for predicting the risk of abdominal compartment syndrome can be expressed by the following formula:

$$\text{logit}(P) = -31.42 + 2.4X_1 + 1.24X_2 + 1.98X_3 + 2.34X_4 + 0.11X_5,$$

- logit(p) = $p / (1-p)$ – the log odds of ACS development;
- X_1 – fluid balance during the first day of treatment, l;
- X_2 – maximum NPRS score during the first day of treatment;
- X_3 – presence of retroperitoneal fluid accumulation (0/1);
- X_4 – presence of early persistent SIRS (0/1);
- X_5 – visceral obesity index using the Waist-to-Hip Ratio method, percentage.

The suggested test allows to predict the risk of ACS with AUC = 0.92 (95% CI 0.88 – 0.97) (Fig. 1). To choose

the optimal threshold value for the test, the Youden Index calculation method was used. The optimal decision threshold was $P_m = 0.044$: for a patient with SAP, if the value is equal to or greater than P_m , the risk of ACS is predicted, and for a patient with a value below P_m , the risk of ACS is not indicated. At this decision threshold, the sensitivity of the test was 94% (95% CI 79-99), the specificity of the test was 81% (95% CI 70-89), the positive predictive value (PPV) of the test was 68% (95% CI 52-81), and the negative predictive value (NPV) of the test was 97% (95% CI 88-99).

DISCUSSION

In the given study, we developed and analyzed a predictive model for the risk of ACS in patients with SAP. The proposed model includes five available clinical factors that showed a statistically significant association with the development of this complication. Among these five predictors, at least three – infusion load, pain control, and modification of the systemic inflammatory response – can be actively corrected in the early days of the disease.

The risks of fluid overload during infusion therapy in AP are associated with the development and progression of intra-abdominal hypertension (IAH) [16-20]. Aggressive infusion has logical justifications. However, it can exacerbate the movement of intravascular fluid into the third space, initiated by the action of pro-inflammatory cytokines, which potentiates IAH. On the other hand, positive fluid balance in the early period is limited by diuresis and can be explained by excretory capacity, which is often compromised in SAP [21, 22].

Pain intensity on the NPRS scale during the first day was included in our study as a potentially modifiable predictor of ACS. A systematic review and meta-analysis on pain management in the early stages of SAP (2024) evaluated the effect of seven drugs based on dynamics using the visual analog scale, and in our study a simplified derivative was used [23].

The role of pathological pressure increase in the retroperitoneal space initiated by SAP was considered, highlighting retroperitoneal fluid collections as an independent predictor of ACS. The updated definitions of the World Society of Abdominal Compartment Syndrome (WSACS) emphasized the complexity of ACS mechanisms, referring to the retroperitoneum, pelvis,

and omentum as additional compartments among the four main compartments involved in polycompartment syndrome [24]. In previous studies based on a limited sample, we examined the relationship between IAH and the volume of necrosis [25].

Systemic Inflammatory Response Syndrome (SIRS) has been established as an independent predictor of the severity of AP [26] and is utilized as a component of prognostic scales [27, 28]. The duration of SIRS precedes organ failure (OF), and when present, it increases the risk of progression to OF and death [29, 30]. SIRS during the first day is capable of predicting the severity of the course of AP [31].

In 2024, a retrospective study of more than a million patients with AP was published, identifying obesity and blood transfusions as independent risk factors for ACS [32]. Obese patients with AP have been proven to have a worse prognosis [33]. Visceral obesity significantly impacted the outcomes and severity of hypertriglyceridemic pancreatitis [34, 35]. A high level of visceral adipose tissue is an independent negative prognostic marker of AP [36].

CONCLUSIONS

1. The group of patients with severe acute pancreatitis and abdominal compartment syndrome in the studied sample exhibited worse clinical-laboratory indicators compared to the group with reversible or absent intra-abdominal hypertension.
2. In the studied sample of patients with severe acute pancreatitis, the development of abdominal compartment syndrome was associated with the following five independent risk factors: daily fluid balance, pain intensity on the NPRS scale, retroperitoneal fluid collections, early persistent SIRS, and high visceral obesity index (WHR).
3. The developed logistic model demonstrated high discriminatory ability with a decision threshold for predicting the event at 0.044: AUC = 0.92 (95% CI 0.88–0.97), sensitivity 94%, specificity 81%.
4. The practical value of the model lies in the ability to stratify patients and target the correction of potentially modifiable risk factors in the early stage of the disease.
5. Further external validation on independent samples is required to assess universal degree of the model.

REFERENCES

1. Kirkpatrick AW, Roberts DJ, De Waele J et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med.* 2013;39(7):1190-1206. doi:10.1007/s00134-013-2906-z. DOI 

2. DeWaele JJ, Ejike JC, Leppäniemi A et al. Intra-abdominal hypertension and abdominal compartment syndrome in pancreatitis, paediatrics, and trauma. *Anaesthesiol Intensive Ther.* 2015;47(3):219-227. doi:10.5603/AIT.a2015.0027. DOI 
3. Zarnescu NO, Dumitrascu I, Zarnescu EC, Costea R. Abdominal Compartment Syndrome in Acute Pancreatitis: A Narrative Review. *Diagnostics (Basel).* 2022;13(1):1. doi:10.3390/diagnostics13010001. DOI 
4. Jena A, Singh AK, Kochhar R. Intra-abdominal hypertension and abdominal compartment syndrome in acute pancreatitis. *Indian J Gastroenterol.* 2023;42(4):455-466. doi:10.1007/s12664-023-01407-y. DOI 
5. Smit M, Buddingh KT, Bosma B et al. Abdominal Compartment Syndrome and Intra-abdominal Ischemia in Patients with Severe Acute Pancreatitis. *World J Surg.* 2016;40(6):1454-1461. doi:10.1007/s00268-015-3388-7. DOI 
6. Mancilla Asencio C, Berger Fleiszig Z. Intra-Abdominal Hypertension: A Systemic Complication of Severe Acute Pancreatitis. *Medicina (Kaunas).* 2022;58(6):785. doi:10.3390/medicina58060785. DOI 
7. Mancilla Asencio C, Berger Fleiszig Z. Intra-Abdominal Hypertension: A Systemic Complication of Severe Acute Pancreatitis. *Medicina (Kaunas).* 2022;58(6):785. doi:10.3390/medicina58060785. DOI 
8. Holodinsky JK, Roberts DJ, Ball CG et al. Risk factors for intra-abdominal hypertension and abdominal compartment syndrome among adult intensive care unit patients: a systematic review and meta-analysis. *Crit Care.* 2013;17(5):R249. doi:10.1186/cc13075. DOI 
9. Malbrain ML, Chiumello D, Pelosi P et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Crit Care Med.* 2005;33(2):315-322. doi:10.1097/01.ccm.0000153408.09806.1b. DOI 
10. Rajasurya V, Surani S. Abdominal compartment syndrome: Often overlooked conditions in medical intensive care units. *World J Gastroenterol.* 2020;26(3):266-278. doi:10.3748/wjg.v26.i3.266. DOI 
11. Łągosz P, Sokolski M, Biegus J et al. Elevated intra-abdominal pressure: A review of current knowledge. *World J Clin Cases.* 2022;10(10):3005-3013. doi:10.12998/wjcc.v10.i10.3005. DOI 
12. Marshall JC, Cook DJ, Christou NV et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med.* 1995;23(10):1638-1652. doi:10.1097/00003246-199510000-00007. DOI 
13. Banks PA, Bollen TL, Dervenis C et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013;62(1):102-111. doi:10.1136/gutjnl-2012-302779. DOI 
14. Chandra S, Murali A, Bansal R et al. The Bedside Index for Severity in Acute Pancreatitis: a systematic review of prospective studies to determine predictive performance. *J Community Hosp Intern Med Perspect.* 2017;7(4):208-213. doi:10.1080/20009666.2017.1361292. DOI 
15. Kanda Y. Investigation of the freely available easy-to-use software for medical statistics. *Bone Marrow Transplant.* 2013;48(3):452-458. doi:10.1038/bmt.2012.244. DOI 
16. Ke L, Ni HB, Sun JK et al. Risk factors and outcome of intra-abdominal hypertension in patients with severe acute pancreatitis. *World J Surg.* 2012;36(1):171-178. doi:10.1007/s00268-011-1295-0. DOI 
17. Crosignani A, Spina S, Marrazzo F et al. Intravenous fluid therapy in patients with severe acute pancreatitis admitted to the intensive care unit: a narrative review. *Ann Intensive Care.* 2022;12(1):98. doi:10.1186/s13613-022-01072-y. DOI 
18. Evans D, Hajibandeh S, Hajibandeh S et al. Meta-analysis and trial sequential analysis of randomized controlled trials comparing aggressive versus non-aggressive intravenous fluid therapy in acute pancreatitis: an insight into the existence of type 2 error. *J Gastroenterol Hepatol.* 2024. doi:10.1111/jgh.16648. DOI 
19. He K, Gao L, Yang Z et al. Aggressive versus controlled fluid resuscitation in acute pancreatitis: A systematic review and meta-analysis of randomized controlled trials. *Chin Med J (Engl).* 2023;136(10):1166-1173. doi:10.1097/CM9.0000000000002684. DOI 
20. Szeliga J, Jagielski M, Sobocki J et al. Diagnostic and therapeutic management of severe acute pancreatitis. Evidence based medicine (EBM) clinical practice guidelines. *Wideochir Inne Tech Maloinwazyjne.* 2025;20(1):1-29. doi:10.20452/wiitm.2025.17941. DOI 
21. Nassar TI, Qunibi WY. AKI Associated with Acute Pancreatitis. *Clin J Am Soc Nephrol.* 2019;14(7):1106-1115. doi:10.2215/CJN.13191118. DOI 
22. Sandhu G, Mankal P, Gupta I et al. Pathophysiology and management of acute kidney injury in the setting of abdominal compartment syndrome. *Am J Ther.* 2014;21(3):211-216. doi:10.1097/MJT.0b013e318235f1cf. DOI 
23. Thavanesan N, White S, Lee S et al. Analgesia in the Initial Management of Acute Pancreatitis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *World J Surg.* 2022;46(4):878-890. doi:10.1007/s00268-021-06420-w. DOI 
24. Nasa P, Wise RD, Smit M et al. International cross-sectional survey on current and updated definitions of intra-abdominal hypertension and abdominal compartment syndrome. *World J Emerg Surg.* 2024;19(1):39. doi:10.1186/s13017-024-00564-5. DOI 
25. Dronov OI, Kovalska IO, Horlach AI et al. Intra-abdominal hypertension and pancreatic destruction in patients with acute necrotizing pancreatitis. *Wiad Lek.* 2024;77(10):1871-1876. doi:10.36740/WLek/195128. DOI 
26. Barrera Gutierrez JC, Greenburg I, Shah J et al. Severe Acute Pancreatitis Prediction: A Model Derived From a Prospective Registry Cohort. *Cureus.* 2023;15(10):e46809. doi:10.7759/cureus.46809. DOI 

27. Szeliga J, Jagielski M, Sobocki J et al. Diagnostic and therapeutic management of severe acute pancreatitis. Evidence based medicine (EBM) clinical practice guidelines. *Wideochir Inne Tech Maloinwazyjne*. 2025;20(1):1-29. doi:10.20452/wiitm.2025.17941. DOI 
28. Tenner S, Vege SS, Sheth SG et al. American College of Gastroenterology Guidelines: Management of Acute Pancreatitis. *Am J Gastroenterol*. 2024;119(3):419-437. doi:10.14309/ajg.0000000000002645. DOI 
29. Mofidi R, Duff MD, Wigmore SJ et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Br J Surg*. 2006;93(6):738-744. doi:10.1002/bjs.5290. DOI 
30. Forsmark CE, Vege SS, Wilcox CM. Acute Pancreatitis. *N Engl J Med*. 2016;375(20):1972-1981. doi:10.1056/NEJMra1505202. DOI 
31. Oppenlander KE, Chadwick C, Carman K. Acute Pancreatitis: Rapid Evidence Review. *Am Fam Physician*. 2022;106(1):44-50.
32. Jaan A, Sarfraz Z, Farooq U et al. Incidence, implications and predictors of abdominal compartment syndrome in acute pancreatitis: A nationwide analysis. *Pancreatol*. 2024;24(3):370-377. doi:10.1016/j.pan.2024.02.010. DOI 
33. Ince AT, Seven G, Koçhan K et al. The course of acute pancreatitis in patients with different BMI groups. *Pancreatol*. 2022;22(3):348-355. doi:10.1016/j.pan.2022.03.009. DOI 
34. Zhu Y, Huang Y, Sun H et al. Novel anthropometric indicators of visceral obesity predict the severity of hyperlipidemic acute pancreatitis. *Lipids Health Dis*. 2024;23(1):120. doi:10.1186/s12944-024-02112-1. DOI 
35. Xia W, Yu H, Huang Y et al. The visceral adiposity index predicts the severity of hyperlipidaemic acute pancreatitis. *Intern Emerg Med*. 2022;17(2):417-422. doi:10.1007/s11739-021-02819-4. DOI 
36. Xie J, Xu L, Pan Y et al. Impact of visceral adiposity on severity of acute pancreatitis: a propensity score-matched analysis. *BMC Gastroenterol*. 2019;19(1):87. doi:10.1186/s12876-019-1015-z. DOI 

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Ivanna A. Shchyhel

Bogomolets National Medical University
59B Holosiivskii Avenue, 01001 Kyiv, Ukraine
e-mail : ringoo3110@gmail.com

ORCID AND CONTRIBUTIONSHIP

Olexii I. Dronov: 0000-0003-4033-3195  
Inna O. Kovalska: 0000-0002-6264-2928 
Andrii I. Horlach: 0000-0003-4330-4904   
Ivanna A. Shchyhel: 0000-0002-1672-8149    
Vitaliy R. Balyak: 0009-0009-5415-2361   
Vadym O. Kostiukevich: 0009-0005-9263-9032  

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 06.04.2025

ACCEPTED: 25.08.2025



Development of a methodology and study of the stress-strain state of the biomechanical system “jaw-implant”

Olha S. Musiienko¹, Vitalii V. Parii², Oleksii I. Morhun¹ Ihor G. Diadik²

¹NATIONAL TECHNICAL UNIVERSITY OF UKRAINE “IGOR SIKORSKY KYIV POLYTECHNIC INSTITUTE”, KYIV, UKRAINE

²BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

Aim: To investigate the stress-strain state of the “jaw-implant” system under static loading using finite element analysis (FEA) and experimental photoelastic methods, with a focus on different implant placement angles.

Materials and Methods: The study combined numerical and experimental approaches. Samples made of epoxy resin were tested using a polariscope to observe stress distributions, while FEA was performed in SolidWorks 2021 and Ansys 2019 R2. Implant placement angles of 0°, 7°, 15°, and 22° were analyzed under a load of 20 N.

Results: Both experimental and numerical methods revealed stress concentration patterns dependent on implant placement angles. Maximum stress values were observed at larger angles, and the FEA results showed satisfactory agreement with the experimental data.

Conclusions: The developed methodology effectively predicts the stress-strain state of the “jaw-implant” system. The findings demonstrate the importance of optimizing implant placement angles to minimize stress and improve implant longevity. The integration of FEA and photoelastic methods provides a robust tool for enhancing dental implant design and placement strategies.

KEY WORDS: Stress-strain state, jaw-implant system, finite element analysis, photoelastic analysis, biomechanics, implant placement angle

Wiad Lek. 2025;78(9):1758-1764. doi: 10.36740/WLek/212507 DOI

INTRODUCTION

The biomechanical interaction between the jaw and dental implants is a critical area of research in biomedical engineering, particularly given the increasing prevalence of dental implant procedures. Understanding the stress-strain state of the “jaw-implant” system is essential for optimizing implant design and ensuring long-term success [1, 2].

The intricate relationship between biomechanical systems and their structural integrity is pivotal in the field of biomedical engineering, particularly in the design and assessment of dental implants [3].

One of the most critical interfaces in this realm is that of the jaw-implant system, where the mechanical performance and biological compatibility determine the success of implant therapies. Understanding the stress-strain state of this system is essential, as it directly affects the stability of the implant and the surrounding bone. Research has shown that the mechanical interactions between the jawbone and the implant can significantly impact clinical outcomes, making it imperative to investigate these dynamics comprehensively [4, 5].

The implications of this research extend beyond theoretical modeling; they hold significant potential for improving the design of dental implants, optimizing surgical procedures, and ultimately enhancing patient care [6]. By systematically exploring the stress-strain distribution within the jaw-implant system, we aim to identify critical failure mechanisms and suggest design modifications that could lead to more resilient and effective implant solutions. Studies [7] highlight the importance of load distribution in the jaw-implant system, noting that uneven stress can lead to complications such as bone resorption and implant failure. Moreover, the work [8] emphasizes the role of mechanical loading in osseointegration, suggesting that a thorough understanding of stress patterns is vital for improving implant design and surgical techniques.

Furthermore, the work [8] underscores the necessity of integrating biological factors into mechanical assessments. Our methodology not only evaluates mechanical stress but also considers the biological responses that occur at the implant interface, thereby providing a more holistic understanding of the system's

performance. Recent advancements in computational modeling, particularly finite element analysis (FEA), offer powerful tools for simulating the mechanical behavior of the jaw-implant interface. As demonstrated by [9], FEA enables researchers to assess how varying loads affect the stress distribution and strain responses within the system, providing insights that are crucial for optimizing implant performance [2, 10].

This article aims to delve into the stress-strain state of the jaw-implant biomechanical system, building on existing literature while presenting new findings from our analyses. By examining the mechanical interactions and their implications for clinical practice, we seek to contribute to the ongoing development of more effective and resilient dental implants, ultimately enhancing patient care in implant dentistry. By systematically exploring the stress-strain distribution within the jaw-implant system, we aim to identify critical failure mechanisms and suggest design modifications that could lead to more resilient and effective implant solutions.

AIM

To investigate the stress-strain state of the “jaw-implant” system under static loading using the finite element analysis and experimental method of photoelastic analysis as a validation.

MATERIALS AND METHODS

Experimental study [11]. Using a metal matrix with dimensions of 90x35x9 mm, a silicone mold was made, which allows for easy removal of samples without damage. The samples were made of a transparent material in which the implant was placed. The jewelry epoxy resin MagicCrystal 3D was used as the specimen material. To determine the mechanical properties of the epoxy resin, a specimen was made in the form of a straight cylinder with a height of 30 mm and a diameter of 20 mm. For this purpose, a plastic matrix was printed on a 3D printer. After that, the matrix was processed to reduce its roughness and a silicone mold was made. Since the properties of epoxy resin vary each time and also change over time, it is necessary to simultaneously produce both specimens for the photoelasticity test and specimens for determining the mechanical properties of the epoxy resin. It is also necessary to test the specimens on the same day for better accuracy of the results.

The compression tests were carried out using an UTM TIRATEST-2151.

The deformation rate was 5 mm/min. The specimen was placed on the test bench and subjected to an axial

compressive load. At the same time, the diagram was recorded.

To place the specimen and conduct experiments using the photoelasticity method, a specially designed device, a polariscope, is used. A polariscope consists of a light source, a polarizer, and an analyzer.

The specimen is placed between the polarizer and the analyzer. The analyzer, for its part, transmits only horizontal projections of the light vectors. Thus, the light passing through the analyzer will be horizontally polarized.

As light passes through the sample, its polarization changes due to the distribution of stresses and strains. With a polarizer changes in light polarization can be observed and analyzed, which allows you to determine the stress and strain distribution fields in the specimen.

The load on the implant was transmitted through a steel ball with a diameter of 5 mm using a universal testing machine TIRATEST-2151.

Before starting the tests, a photo of an unloaded specimen was taken to ensure that there were no stresses on the models. After that, the axial load was consistently increased. During the test, extraneous light sources should be turned off in the room.

When certain load values are reached, the specimen is photographed to record the stress distribution in it.

At the end of the experiment, all the photos were analyzed to check the direction and intensity of the stresses. In this case, the higher the order of the stripes and the number of stripes, the greater the stress intensity. In addition, the closer the stripes are to each other, the higher the stress concentration.

Numerical modeling. The SolidWorks 2021 software package was used to build the simulation model. We considered 4 options for implant placement: at angles of 0°, 7°, 15°, and 22° (Fig. 1). The simulation model was made without a thread, the diameter of the model corresponds to the outer diameter of the thread.

Ansys 2019 R2 software package was used to analyze the simulation model. The model is considered in a plane stress-strain state.

Boundary conditions: a force of 20 N was applied vertically (parallel to the side faces of the resin model) to the implant model and lower edge of epoxy resin. The mechanical properties of the materials of the computational model are shown in Table 1.

RESULTS

The results of this study are presented in three successive parts to ensure a comprehensive understanding of the stress-strain state of the jaw-implant system. First, the mechanical properties of the epoxy resin used as

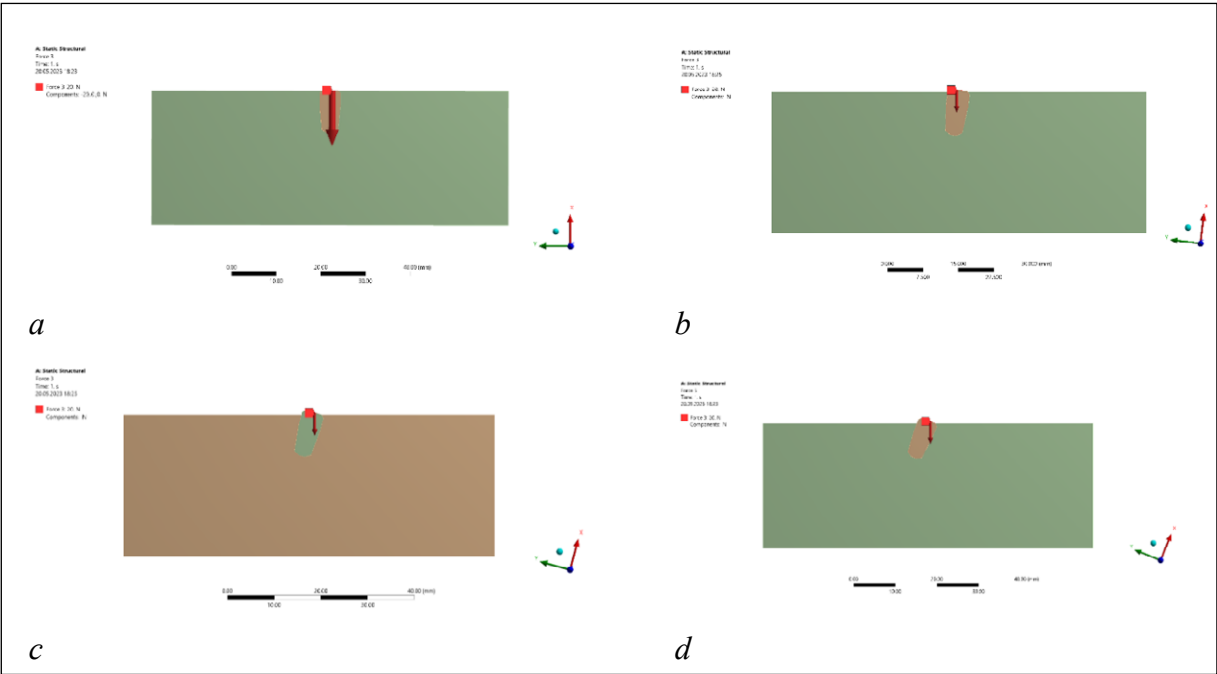


Fig. 1. Installed implant model with inclination angles: (a) 0°, (b) 7°, (c) 15°, (d) 22°
Picture taken by the authors

Table 1. Mechanical properties of materials of the computational model

Object	Material	E, MPa	μ
Implant	Titanium alloy Ti-6Al-4V	111,2·10 ³	0,3387
Epoxy resin		7,327	0,3

Source: compiled by the authors of this study

a model material were determined, since these values were required for both experimental interpretation and numerical simulations. Second, photoelastic analysis was employed to visualize stress distribution fields under different loading and inclination conditions. Finally, the findings from finite element modeling were obtained and compared with the experimental observations to validate the numerical approach and quantify the influence of implant inclination on peri-implant stress concentrations.

Compression tests revealed distinct time-dependent variations in the mechanical behavior of the epoxy resin. The stress–strain curves (Fig. 2) obtained from cylindrical specimens demonstrated that samples tested 7 days after curing exhibited significantly higher stiffness compared to those tested 6 months post-curing. The calculated elastic modulus averaged $E = 7.327$ MPa with Poisson's ratio $\nu = 0.30$, values which were subsequently used for finite element simulations.

Photoelastic experiments provided a detailed visualization of stress distribution around the implant under axial loading. In the unloaded state (Fig. 3a), the specimens exhibited no stress-induced birefringence.

Under a 20 N vertical load at 0° inclination (Fig. 3b), concentric isochromatic fringes appeared at the implant neck, confirming the presence of localized stress concentrations. Increasing the load to 200 N at 0° (Fig. 3c) led to a marked increase in fringe density, reflecting nonlinear growth of stress intensity.

When the implant was inclined at 15° under 20 N load (Fig. 3d), asymmetric fringe patterns were observed. The isochromes became denser on the side opposite to the direction of inclination, indicating higher tensile stresses and less favorable load distribution. This confirmed that implant tilting introduces significant biomechanical asymmetry in stress transfer.

Numerical modeling was performed for the presented systems and stress distribution fields were obtained (Fig. 4). Finite element analysis was performed for implant inclinations of 0°, 7°, 15°, and 22°. The obtained stress distribution fields (Fig. 4) demonstrated a progressive increase in both the magnitude and localization of stress concentrations as the inclination angle increased.

For the 0° inclination model, the stress distribution exhibited axial symmetry with the highest von Mises stresses localized in the cervical peri-implant region.

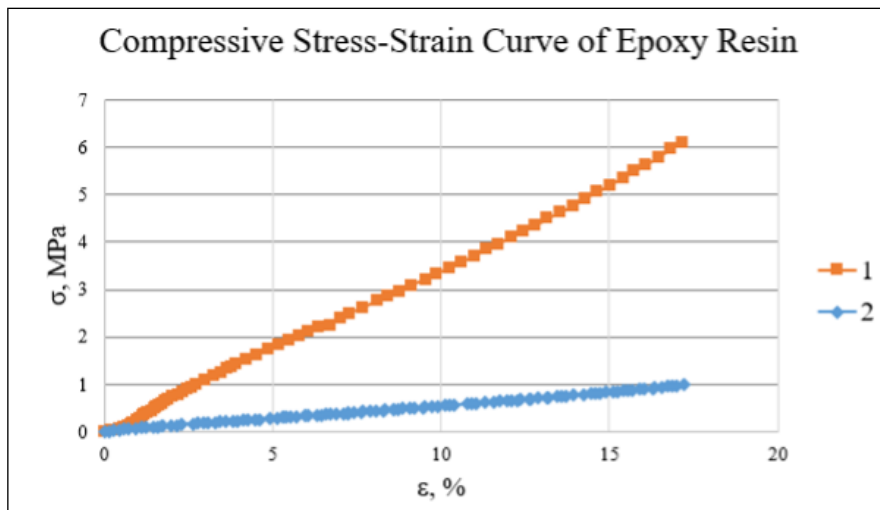


Fig. 2. Mechanical properties of epoxy resin: (1) 6 months after curing; (2) 7 days after curing
Picture taken by the authors

Peak values were concentrated at the implant neck, gradually diminishing along the apical direction. This configuration corresponded to favorable load transfer and minimal shear components.

At an inclination of 7°, the stress field showed distinct asymmetry relative to the implant axis. Maximum stresses shifted toward the cortical region on the side opposite to the loading vector, accompanied by an approximately 12% increase in peak von Mises stress compared to the vertical model. The stress gradients indicated an onset of unfavorable load redistribution.

In the 15° model, stress redistribution became more pronounced. High-intensity zones extended from the cervical margin into the apical third of the implant–resin interface. Peak stresses increased by approximately 25–27% relative to the 0° configuration, and the stress field revealed broader areas of critical concentration, which is biomechanically unfavorable for osseointegration.

The 22° inclination model exhibited the most unfavorable conditions, with stress maxima simultaneously localized at the cervical and apical implant regions. The von Mises stresses at this angle exceeded the threshold values considered biomechanically tolerable for peri-implant bone ($\sigma_{\max} > 30$ MPa in the simulated resin analogue, extrapolated to cortical bone properties). Such conditions are likely to accelerate peri-implant bone resorption and compromise implant stability.

The simulated stress distribution patterns corresponded well with the photoelastic fringe orders obtained experimentally. In particular, the densification of isochromatic fringes at increasing tilt angles was consistent with the numerical prediction of elevated von Mises stresses. The highest degree of correlation was observed for the 0° and 15° models, confirming the adequacy of the finite element model as a predictive tool for clinical implant biomechanics.

DISCUSSION

Our review of the literature has shown the relevance of studies devoted to the determination of the stress-strain state of jaw-implant systems, which is discussed in [12–14]. In the cited works, the authors use the finite element method as a tool for determining the stress-strain state of the jaw and the implant installed in it. However, the above-mentioned works did not validate the numerical model by means of analytical calculations or experimental studies. We have developed a methodology for validating a numerical model of the jaw-implant system based on the method of photoelasticity at different implant angles.

In contrast to this research, we carried out a study on axial loads applied through a ball that simulated a food lump during the chewing cycle. This scientific work aimed to determine how the distribution of these loads depends on the diameter of the implant [15].

This scientific research studied the distribution of loads in short implants with different types of abutment fixation to the implant. In contrast to this research, we studied an implant that had a connection with an abutment featuring an internal cone of 11 degrees [16].

The use of photoelastic analysis as a methodology for verifying numerical modeling of experimental work provides a powerful impetus for studying the stress-strain states that occur in the jawbone during chewing loads. However, there is a challenge related to the differing densities of the cortical and spongy layers of bone tissue. In numerical modeling, we account for these differences, but in full-scale experiments, this issue remains unresolved because the resin we use is homogeneous. Therefore, the development and search for a filler that can closely mimic the cortical and spongy layers is an urgent task for scientific research.

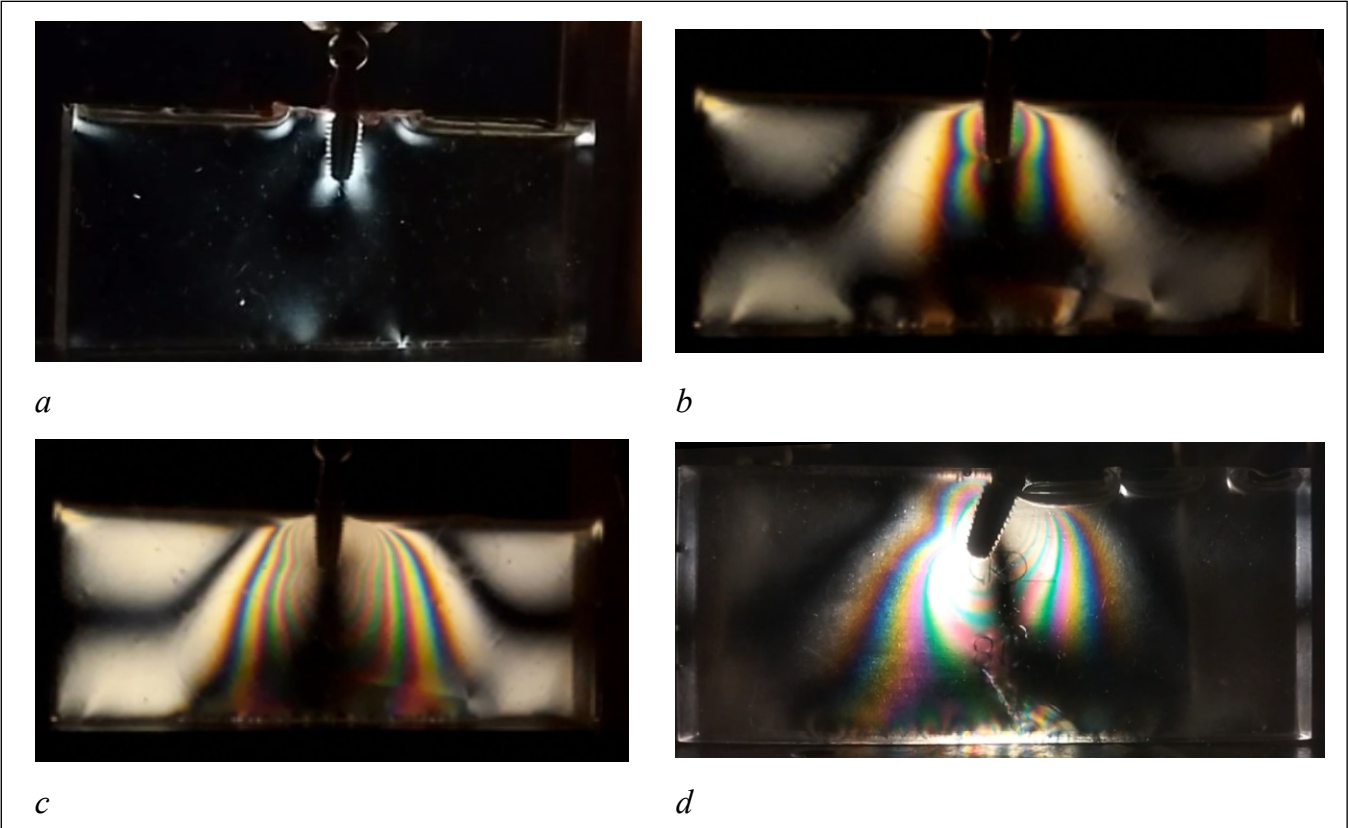


Fig. 3. (a) Unloaded specimen in the polarizer; (b) Stress distribution in a specimen under a force of 20N with an inclination of 0° ; (c) Stress distribution in a specimen under a force of 200N with an inclination of 0° ; (d) Stress distribution in a specimen under a force of 20N with an inclination of 15°
Picture taken by the authors

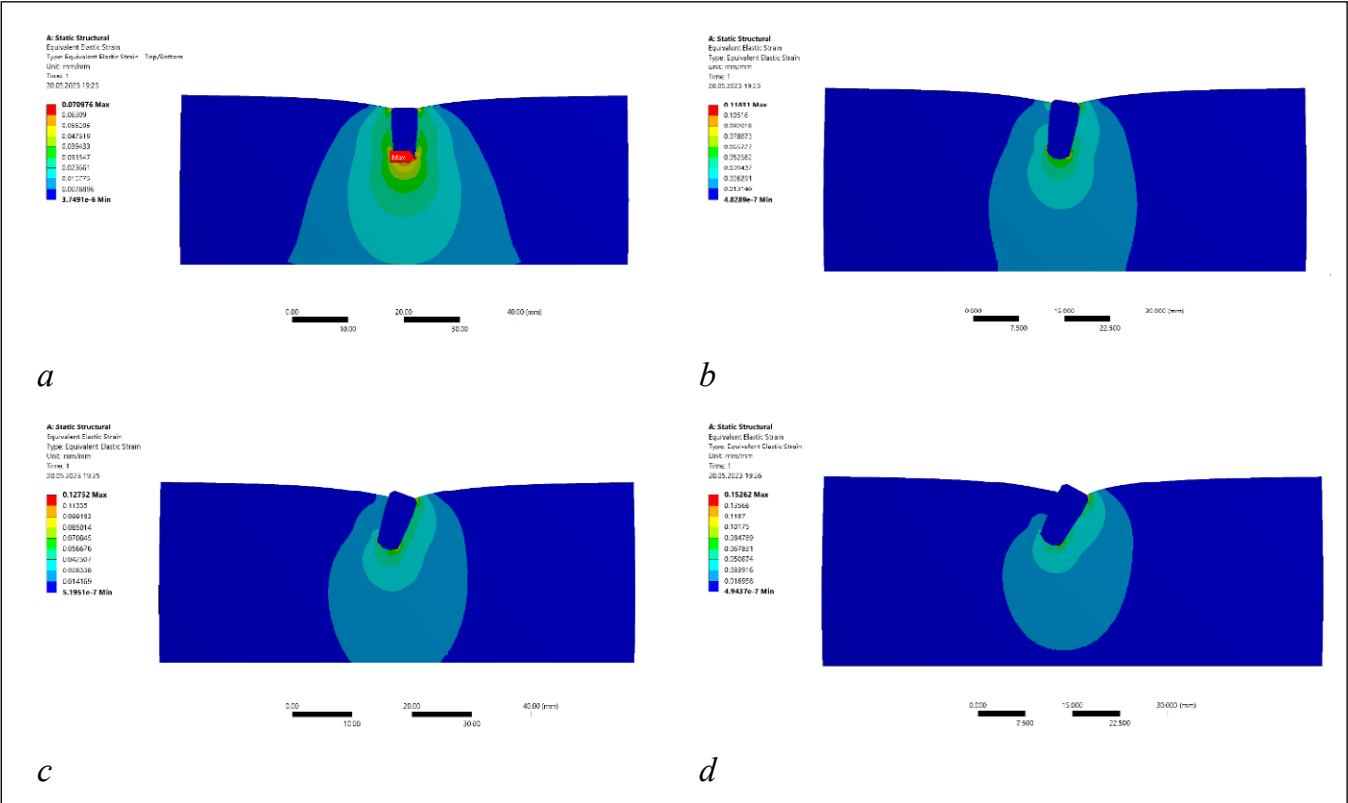


Fig. 4. Stress-strain state of the computational model at a load of 20N with implant tilt angles (a) 0° , (b) 7° , (c) 15° , (d) 22°
Picture taken by the authors

CONCLUSIONS

The created numerical model showed satisfactory results. As a result, it can be used to analyze the behavior of the implant in the human jaw and to predict the allowable angles of implant placement if it is impossible to place it at a right angle. The photoelasticity method has also proven to be one of the methods for validating numerical solutions.

Based on the results of the study, the stress distribution fields were obtained and the maximum stresses in the system were determined. The dependence of the stresses on the angle of implant placement was revealed. It was also proved that the maximum stresses do not exceed

the allowable ones. Thus, the use of these data will help in choosing the optimal implant placement angle.

This experimental study is important because having an understanding of the load distribution in the superstructure-implant-bone system, which occurs when they are installed at different angles, allows us to plan dental implantation in such a way as to minimize the risk of potential biomechanical complications. The application of digital technologies and navigational methods in implantology enables predictable implant placement at angles that will reduce the risk of biomechanical complications during the functioning of the orthopedic structure supported by dental implants.

REFERENCES

1. Cheng HC, Peng BY, Chen MS et al. Influence of deformation and stress between bone and implant from various bite forces by numerical simulation analysis. *Biomed Res Int*. 2017;2017:2827953. doi:10.1155/2017/2827953. DOI
2. Baggi L, Cappelloni I, Di Girolamo M et al. The influence of implant diameter and length on stress distribution of osseointegrated implants related to crestal bone geometry: A three-dimensional finite element analysis. *J Prosthet Dent*. 2008;100(6):422-431. doi:10.1016/s0022-3913(08)60259-0. DOI
3. Lahoti K, Pathrabe A, Gade J. Stress analysis at bone-implant interface of single- and two-implant-retained mandibular overdenture using three-dimensional finite element analysis. *Indian J Dent Res*. 2016;27(6):597-603. doi:10.4103/0970-9290.199587. DOI
4. Alsrouji MS, Ahmad R, Abdul Razak NH et al. Premaxilla stress distribution and bone resorption induced by implant overdenture and conventional denture. *J Prosthodont*. 2019;28(2): e764-e770. doi:10.1111/jopr.12954. DOI
5. Pham DQ, Sulyma O, Musiienko O et al. Development of a finite element model for optimization of the bone fixator design. *Procedia Struct Integr*. 2023;47:945-951. doi:10.1016/j.prostr.2023.07.026. DOI
6. Coskunses FM, Tak O. Clinical performance of narrow-diameter titanium–zirconium implants in immediately loaded fixed full-arch prostheses: a 2-year clinical study. *Int J Implant Dent*. 2021;7(1):51. doi:10.1186/s40729-021-00312-3. DOI
7. Meijer HJA, Slagter KW, Gareb B et al. Immediate single-tooth implant placement in bony defect sites: A 10-year randomized controlled trial. *J Periodontol*. 2024;95(8):1002-1013. doi:10.1002/JPER.24-0251. DOI
8. Misch CE. Single-tooth implant restoration. In: Misch CE, ed. *Dental Implant Prosthetics*. St. Louis: Elsevier; 2015:499-552. doi:10.1016/B978-0-323-07845-0.00029-4. DOI
9. Li G, Keyes KM, Huang X. Respond. *Am J Public Health*. 2018;108(10):e2. doi:10.2105/AJPH.2018.304672. DOI
10. Doroshenko OM, Sirenko OF. Prediction of biomechanical complications in patients with implant supported fixed dental prostheses in different terms of functional loading. *Zaporozhye Med J*. 2017;(4):482-487. doi:10.14739/2310-1210.2017.4.104923. DOI
11. Herráez-Galindo C, Torres-Lagares D, Martínez-González AJ et al. A comparison of photoelastic and finite elements analysis in internal connection and bone level dental implants. *Metals (Basel)*. 2020;10(5):648. doi:10.3390/met10050648. DOI
12. Thomková B, Marcián P, Borák L et al. Biomechanical performance of dental implants inserted in different mandible locations and at different angles: A finite element study. *J Prosthet Dent*. 2023;130(6):925-934. doi:10.1016/j.prosdent.2023.10.012. DOI
13. De Stefano M, Lanza A, Faia E, Ruggiero A. A novel ultrashort dental implant design for the reduction of the bone stress/strain: A comparative numerical investigation. *Biomed Eng Adv*. 2023;5:100077. doi:10.1016/j.bea.2023.100077. DOI
14. Akbas O, Greuling A, Stiesch M. The effects of different grading approaches in additively manufactured dental implants on peri-implant bone stress: A finite element analysis. *J Mech Behav Biomed Mater*. 2024;154:106530. doi:10.1016/j.jmbbm.2024.106530. DOI
15. Goiato MC. Photoelastic stress analysis in prosthetic implants of different diameters: mini, narrow, standard or wide. *J Clin Diagn Res*. 2014;8(5):268-272. doi:10.7860/jcdr/2014/8489.4902. DOI
16. Sotto-Maior BS, Senna PM, Silva-Neto JP et al. Influence of crown-to-implant ratio on stress around single short-wide implants: a photoelastic stress analysis. *J Prosthodont*. 2015;24(1):52-56. doi:10.1111/jopr.12171. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Vitalii V. Parii

Bogomolets National Medical University.
34 Beresteisky Avenue, 88000 Kyiv, Ukraine
e-mail: vitaliy-pariy@ukr.net

ORCID AND CONTRIBUTIONSHIP

Olha S. Musiienko: 0000-0001-8255-3909 **A** **B** **D** **E** **F**
Vitalii V. Parii: 0009-0005-2207-5307 **A** **C** **E** **F**
Oleksii I. Morhun: 0009-0000-9611-1829 **B** **D**
Ihor G. Diadik: 0009-0006-2962-2155 **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: 06.04.2025
ACCEPTED: 22.08.2025



Dynamics of gut microbiota in qualified female boxers

Anastasiia M. Kaliga¹, Oksana L. Palladina¹, Olena A. Dulo², Svitlana A. Burmei^{2,3}, Dmytro V. Shtanagei¹, Nadiya V. Boyko^{2,3}

¹NATIONAL UNIVERSITY OF UKRAINE ON PHYSICAL EDUCATION AND SPORT, KYIV, UKRAINE

²UZHGOROD NATIONAL UNIVERSITY, UZHGOROD, UKRAINE

³EDIENS LLC, VELYKI LAZY, UKRAINE

ABSTRACT

Aim: To analyze changes in the gut microbiota of qualified female boxers at different stages of the training cycle, influenced by physical activity of different intensity.

Materials and Methods: The study involved nine qualified female boxers, who performed high-intensity training sessions. The study of changes in the state of the microbiota, namely its diversity, was carried out in two phases of the training cycle. A microbiological quantitative method was used, in-depth with species identification and detection of anaerobes, the unit of measurement of which was colony-forming units per gram (CFU/g). The quantitative assessment of microorganisms was performed using arithmetic mean values expressed and log-transformed values ($\log_{10}$ CFU/g).

Results: High-intensity training loads were associated with microbiota changes indicative of dysbiosis. It is noticeable that the concentration of typical pathogenic genera (*Candida albicans*, *Klebsiella pneumoniae*, *Streptococcus*) significantly increased during the post-competition period. At the same time, classic "beneficial" bacteria (*Lactobacillus* and *Bifidobacterium*) remained within normal limits, although *Bifidobacterium* showed some growth. Notably, *Escherichia coli* (a normal representative of the microbiome) exceeded the norm during the post-competition period.

Conclusions: Increased training intensity in qualified female boxers resulted in alterations in gut microbiota composition, most notably a significant rise in *Escherichia coli* and other opportunistic microbes, while the levels of beneficial *Lactobacillus* and *Bifidobacteria* species remained relatively stable. These changes suggest early signs of dysbiosis, consistent with current evidence on the impact of extreme physical exertion on microbial health.

KEY WORDS: microbiota profile, high-intensity training, female athletes

Wiad Lek. 2025;78(9):1765-1770. doi: 10.36740/WLek/212509 DOI

INTRODUCTION

Recent studies have demonstrated a complex, dose-dependent effect of exercise on gut microbiota composition and function. A meta-analysis of 25 studies including 1044 participants showed that exercise significantly increased gut microbiota alpha diversity, including the Shannon index [1]. A systematic review of 28 studies confirmed that moderate- or vigorous-intensity physical activity performed for 30–90 min, more than 3 times per week (or 150–270 min weekly) for a period of 8 weeks can induce changes in the gut microbiota [2]. Intensive physical activity has been associated with an increase in butyrate- and succinate-producing bacteria, which affects the metabolic homeostasis of the host and has a potentially positive effect on the state of the immune system [4]. Professional soccer players have been shown to have an increased diversity of gut microbiota compared to amateurs, particularly during periods of intensive training.

A study of professional martial artists revealed a significant pattern: higher-level athletes exhibit significantly greater gut microbiota diversity compared to lower-level athletes [5]. Shannon ($p = 0.019$) and Simpson ($p = 0.001$) indices were significantly higher in highly skilled athletes [5]. This is particularly important for female boxers, as increased microbial diversity correlates with better immunity, reduced susceptibility to respiratory infections, and lower BMI values [6]. Gender is an important modulator of the microbiota response to physical exercise. Women tend to show greater changes in Shannon index and observed operational taxonomic units [5].

The gut microbiota may significantly influence the physical performance of female boxers through multiple mechanisms, from energy metabolism to immune regulation. Increased microbial diversity, enrichment with specific beneficial taxa, and optimized microbial function are positively correlated with athletic performance [7].

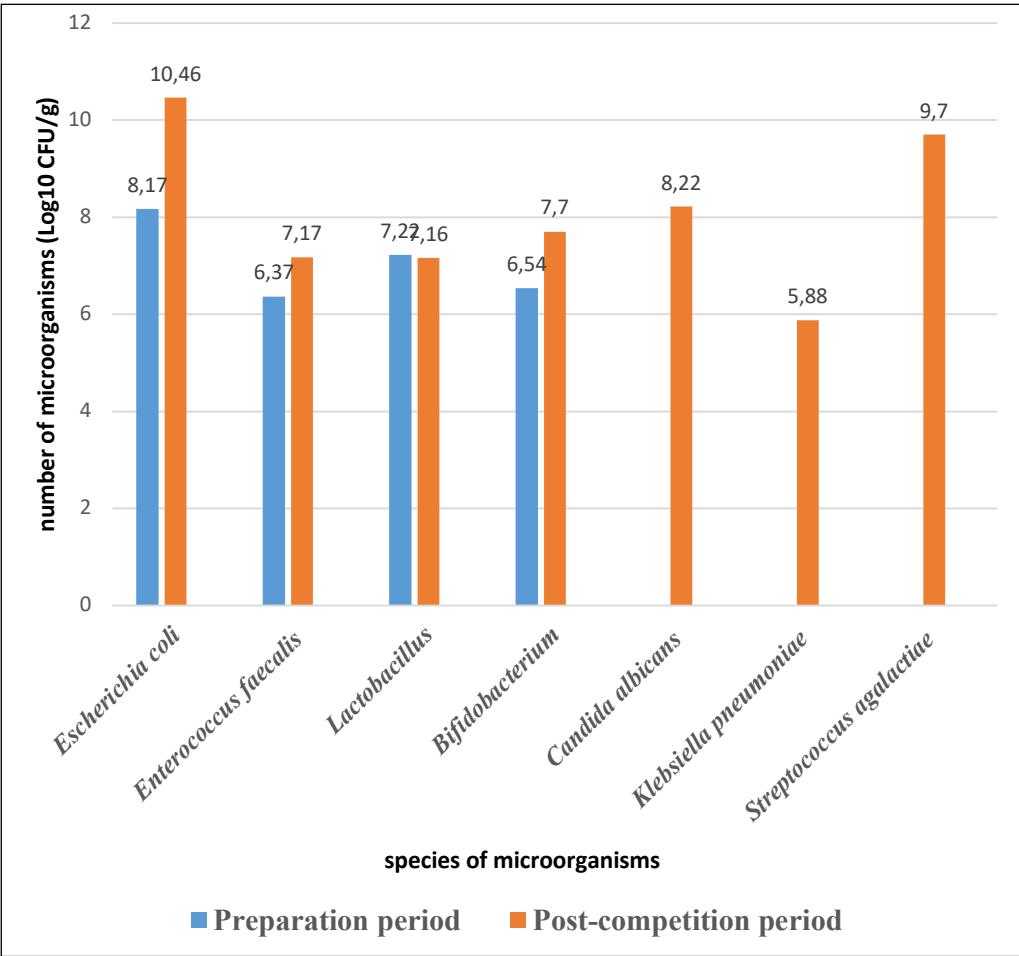


Fig. 1. Average Log10 CFU/g of the main microorganisms in the microbiota of qualified female-boxers
Picture taken by the authors

Although direct studies linking gut microbiota to performance outcomes such as win rate in female boxers are lacking, existing evidence suggests that optimizing microbial health can be an important factor in improving athletic performance and achievement in this sport. Moreover, microbiota profiling may become a tool for predicting athletic performance.

AIM

The aim was to analyze changes in the gut microbiota of qualified female boxers at different stages of the training cycle, influenced by physical activity of different intensity.

MATERIALS AND METHODS

The study involved nine qualified female boxers from the Kyiv City School of Higher Sports Mastery (Kyiv, Ukraine), a specialized sports training center. The average age of the boxers was 22.00 ± 0.89 years. The study was conducted during the preparation period and immediately after the competitive period (post-competition period), during which the athletes

performed high-intensity training sessions lasting 90 minutes, 6 times per week [8]. During the scientific study, all recommendations to ethics committee recommendations on biomedical research were followed. All participants provided written informed consent for the use of their data in scientific research. To effectively address the goal of the scientific study, a combination of sport science, microbiological, and medical methods was applied: microbiota research, leukocyte formula analysis to verify the inflammatory process; methods of mathematical statistics. To study the features and diversity of the intestinal microflora in female boxers, an in-depth study of the state of the intestinal microbiota was conducted with the identification of commensal and opportunistic microorganisms to the species with the determination of the diagnostic ratio. For this purpose, a microbiological quantitative method was used, in-depth with species identification (biochemical automated test systems) and detection of anaerobes, the unit of measurement of which was colony-forming units per gram (CFU/g). The quantitative assessment of microorganisms was performed using arithmetic mean values (M±m) expressed and log-transformed values (log₁₀ CFU/g). Statistical significance of differences was

Table 1. Gut microbiota profile of trained female boxers by training intensity, n=9 (M±m), Log₁₀

Microorganism	Preparation period		Post-competition period		Reference range
	Concentration of CFU/g				
	M±m CFU/g	log ₁₀ CFU/g	M±m CFU/g	log ₁₀ CFU/g	
<i>Escherichia coli, lac+(n=9)</i>	(1,48±0,98)×10 ⁸	8,17±1,20	(2,86±1,55)×10 ¹⁰	10,46±1,17	10 ⁶ – 10 ⁸
t-test	1,84				
P	> 0,05				
<i>Enterococcus faecalis (n=9)</i>	(2,36±1,32)×10 ⁶	6,37±1,32	(1,47±0,14)×10 ⁷	7,17±0,51	10 ⁵ – 10 ⁸
t-test	6,41				
P	< 0,01				
<i>Lactobacillus spp (n=8)</i>	(1,66±1,14)×10 ⁷	7,22±1,39	(1,43±0,14)×10 ⁷	7,16±0,58	10 ⁶ – 10 ⁸
t-test	0,2				
P	> 0,05				
<i>Bifidobacterium spp (n=9)</i>	(3,49±1.48)×10 ⁶	6,54±1,05	(5,03±2,22)×10 ⁷	7,70±0,62	10 ⁷ – 10 ⁸
t-test	2,23				
P	< 0,05				
<i>Candida albicans (n=6)</i>	10 ⁶	-	(1,67±0,192)×10 ⁸	8,22±0,91	<10 ⁴
<i>Klebsiella pneumoniae (n=4)</i>	10 ⁴	-	(7,53±2,47)×10 ⁵	5,88±0,50	<10 ⁴
<i>Streptococcus agalactiae (n=2)</i>	10 ⁶	-	(5,00±5,00)×10 ⁹	9,70±3,0	<10 ⁴

Note: t – Student's test;

p – significance of the difference in different periods of the training cycle

Source: compiled by the authors of this study

determined using Student's t-test. Data analysis was carried out with Statistical 10.0 Software (StatSoft, Inc., USA) and Microsoft Excel.

RESULTS

The study of changes in the state of the microbiota, namely its diversity, was carried out in two phases. The first one was during the preparatory period, during which the athletes engaged in moderate-intensity physical activity. In order to monitor whether changes occur in the microbiota profile during high-intensity training, a follow-up analysis was conducted conducted after 8 weeks, in the post-competition period. The obtained test results are presented in Table 1 and Fig. 1. In the preparation period, the average value of *Escherichia coli* was (1.48 ± 0.98)×10⁸ CFU/g (log₁₀ 8.17 ± 1.20), and in the post-competition period – (2.86 ± 1.55)×10¹⁰ CFU/g (log₁₀ 10.46 ± 1.17). Thus, the concentration of *E. coli* in the post-competition period increased nearly 200-fold. The log₁₀ value also increased, but the difference did not reach statistical significance (p > 0.05). Both average values exceed the upper limit of the norm (10⁸ CFU/g), suggesting excessive coloni-

zation – potentially a sign of intestinal dysbiosis due to intense training load.

Enterococcus faecalis increased approximately 6-fold during the post-competition period. According to the t-test, this increase was statistically significant (t=6.41, p < 0.01). Specifically its concentration rose from (2.36 ± 1.32)×10⁶ CFU/g (log₁₀ 6.37 ± 1.32), and in the post-competition period the concentration was (1.47 ± 0.14)×10⁷ CFU/g (log₁₀ 7.17 ± 0.51). Both values are within the physiological norm. Notably, the decrease in standard error (±0.51 vs ±1.32) indicates a more stable level in the post-competition period. This may reflect an adaptive intestinal response to changes in metabolism or diet during and after the competition.

The concentration of *Lactobacillus spp* was (1.66 ± 1.14)×10⁷ CFU/g (log₁₀ 7.22 ± 1.39) during the preparation period and (1.43 ± 0.14)×10⁷ CFU/g (log₁₀ 7.16 ± 0.58) after competition. A slight decrease of approximately 0.2×10⁷ is observed, but this change is statistically insignificant (t=0.2, p > 0.05). Such a minor reduction during intense training may be a typical sign of dysbiosis, but remained within the normal range and lacked statistical relevance.

Regarding the concentration of *Bifidobacterium spp* in the preparation period the observed value

was $(3.49 \pm 1.48) \times 10^6$ CFU/g ($\log_{10}$ 6.54 ± 1.05), and in the post-competition period it increased to $(5.03 \pm 2.22) \times 10^7$ CFU/g ($\log_{10}$ 7.70 ± 0.62). The content of bifidobacteria in the post-competition period increased approximately 15 times. The difference is statistically significant ($p < 0.05$). The reference range is approximately $(10^7 - 10^8)$ CFU/g, so the values of the preparation period were somewhat underestimated, and in the post-competition period they approached the lower threshold of the reference range. Bifidobacteria are commensal intestinal microorganisms with known anti-inflammatory properties. Their increased abundance following intense physical activity may reflect a beneficial adaptive response.

In the preparation period, a level of 10^6 CFU/g (i.e., which is close to the detection limit) for *Candida albicans* was detected, in the post-competition period it was $(1.67 \pm 0.192) \times 10^8$ CFU/g ($\log_{10}$ 8.22 ± 0.91). The normal upper limit for *Candida albicans* is $<10^4$ CFU/g, indicating a pathologically elevated level in the post-competition period. No statistical comparison was performed (it was present in the preparation period in only 1 athlete), but the fact that it appeared in 6 out of 9 people with such a high concentration indicates a significant disturbance of the microbiota.

The presence of *Klebsiella pneumoniae* 10^4 CFU/g in the microbiota of the examined female boxers in the preparation period is also noteworthy. However, in the post-competition period, the level significantly exceeded the normal range $(7.53 \pm 2.47) \times 10^5$ CFU/g ($\log_{10}$ 5.88 ± 0.50). *Klebsiella pneumoniae* is a facultative pathogen; its appearance in 4 out of 9 female athletes in significant quantities indicates the presence of dysbiosis. Also, in two female athletes, we observed the appearance of *Streptococcus agalactiae* during the post-competition period $(5.00 \pm 5.00) \times 10^9$ CFU/g ($\log_{10}$ 9.70 ± 3.0) and between competitions 10^6 CFU/g, with an approximate norm of $<10^4$ CFU/g, which represents an unfavorable finding, since *Streptococcus agalactiae* is a potentially pathogenic species, the presence of which indicates the presence of dysbiosis.

High-intensity training loads were associated with microbiota changes indicative of dysbiosis. It is noticeable that the concentration of typical pathogenic genera (*Candida albicans*, *Klebsiella pneumoniae*, *Streptococcus*) significantly increased during the post-competition period. This is consistent with the observations that high physiological tension and stress can reduce the barrier functions of the intestine and promote the excessive growth of opportunistic microorganisms. At the same time, classic "beneficial" bacteria (*Lactobacillus* and *Bifidobacterium*) remained within normal limits, although *Bifidobacterium* showed some growth. Notably, *Esche-*

richia coli (a normal representative of the microbiome) exceeded the norm during the post-competition period. Taken together, these findings indicate a shift in the gut microbiota balance: on the one hand, the number of commensals increased, while on the other, atypical pathogens emerged, a combination that is characteristic of excessive physiological stress. These findings align with previous studies reporting that excessive or extreme physical exertion may lead to a decrease in beneficial barrier bacteria and an overgrowth of potentially pathogenic species, i.e., dysbiosis, reflecting the adverse effects of overly intensive athletic training.

DISCUSSION

A critical consideration in this context is the distinction between moderate and intense physical activity, as they have different effects on the gut microbiota, Clauss M. et al. [3].

Moderate exercise has been associated with reduced inflammation, improved body composition, and favorable changes in gut microbial diversity and composition. In contrast, high-intensity exercise may increase the permeability of the gastrointestinal epithelial barrier and reduce the thickness of the intestinal mucus layer, potentially allowing pathogens to enter the bloodstream and contributing to increased inflammation [3]. In a study of military personnel undergoing intense physical training, intestinal permeability increased by $62 \pm 57\%$, accompanied by alterations in the gut microbiota including increased alpha-diversity and changes in the relative abundance of over 50% of identified genera, Grosicki, G. J. et al. [9]. These findings suggest that sustained physical stress negatively affects intestinal barrier integrity while simultaneously altering microbial composition. Similarly, Barton W. et al. studying elite athletes revealed specific functional adaptations of the gut microbiota. In particular, in marathon runners after the race, an increase in the relative abundance of *Veillonella atypica*, a bacterium capable of metabolizing lactate as its sole carbon source, was observed [10]. Experimental administration of this strain to mice significantly prolonged treadmill running time to exhaustion, which demonstrates a direct relationship between specific microbes and sports performance. A pivotal discovery was the identification of *Veillonella* as a bacterium that enhances endurance through a metabolic conversion of exercise-induced lactate into propionate [10]. A study using radiolabeled isotopes showed that serum lactate crosses the epithelial barrier into the intestinal lumen, and intrarectal administration of propionate is sufficient to reproduce increased endurance performance by 133% and reduce muscle fatigue [10].

Short-chain fatty acids (SCFAs) such as propionate, acetate and butyrate are key metabolites that link the gut microbiota to host metabolism. Athletes typically exhibit increased microbial diversity and a compositional shift towards bacterial taxa involved in amino acid biosynthesis and carbohydrate/fiber metabolism, which leads to enhanced SCFA production, Clauss M. et al. [3].

According to Bonomini-Gnutzmann et al., excessively intense or prolonged physical activity can lead to increased intestinal permeability, contributing to exercise-induced gastrointestinal disturbances and systemic inflammation [11]. Paradoxically, among elite athletes, despite a modest increase in diversity, in some cases a decrease in microbiota diversity is observed, compared to individuals performing moderate physical activity Li Y. et al. [12]. However, elite athletes still have high levels of fecal SCFA, which play a crucial role in host energy metabolism. A multi-cohort study of 543 samples from athletes participating in various sports disciplines (aerobics, wrestling, rowing) revealed the presence of sport-specific gut microbiota profiles [12]. Through the application of Latent Dirichlet Allocation (LDA), 10 microbial subgroups were identified and were associated with specific inflammation markers, dietary patterns, and anaerobic performance indicators.

A review of the current literature reveals inconsistent findings regarding the impact of moderate-intensity and vigorous-intensity exercise on gut microbiota diversity and composition. Some studies have reported negative effects of aerobic exercise on gut microbiota, such as elevated intestinal fatty acid-binding protein I-FABP, gastrointestinal discomfort and adverse microbial shifts [11, 13]. However, the majority of evidence supports beneficial outcomes of endurance training on gut microbiota, including increased microbial diversity.

Current research demonstrates a complex, non-linear relationship between exercise intensity and gut microbiota. The “inverted U-curve” model best describes this association: low exercise frequency and duration result in minimal changes, moderate exercise (30-90 minutes 3-5 times a week) causes the greatest positive changes, whereas excessively intense exercise (>90 minutes, >5 times a week) may elicit detrimental effects.

The clinical significance of these findings lies in the possibility of developing personalized training programs that incorporate individual microbiota profiles. Such approaches may not only enhance athletic performance but also support the long-term health of athletes.

Future research should aim to elucidate the mechanisms underlying the bidirectional interactions between physical activity and the gut microbiota. Moreover, standardized methodologies and longitudinal study designs are needed to better understand the sustained effects of various training modalities on microbial health.

CONCLUSIONS

Increased training intensity in qualified female boxers resulted in alterations in gut microbiota composition, most notably a significant rise in *Escherichia coli* and other opportunistic microbes, while the levels of beneficial *Lactobacillus* and *Bifidobacteria* species remained relatively stable. These changes suggest early signs of dysbiosis, consistent with current evidence on the impact of extreme physical exertion on microbial health. To enhance athletes' physical performance and improve competitive outcomes, future interventions may consider probiotic supplementation and the development of personalized nutritional strategies based on individual microbial profiles.

REFERENCES

1. Min L, Ablitip A, Wang R, Luciana T, Wei M, Ma X. Effects of Exercise on Gut Microbiota of Adults: A Systematic Review and Meta-Analysis. *Nutrients*. 2024;16(7):1070. doi: 10.3390/nu16071070. [DOI](#)
2. Boytar AN, Skinner TL, Wallen RE et al. The Effect of Exercise Prescription on the Human Gut Microbiota and Comparison between Clinical and Apparently Healthy Populations: A Systematic Review. *Nutrients*. 2023;15(6):1534. doi: 10.3390/nu15061534. [DOI](#)
3. Clauss M, Gérard P, Mosca A, Leclerc M. Interplay Between Exercise and Gut Microbiome in the Context of Human Health and Performance. *Front Nutr*. 2021;8:637010. doi: 10.3389/fnut.2021.637010. [DOI](#)
4. Urban S, Chmura O, Vator J et al. Intense physical activity induces changes in the composition of intestinal and oral microbiota. *Sci Rep*. 2024;14:20858. doi: 10.1038/s41598-024-71684-w. [DOI](#)
5. Liang R, Zhang S, Peng X et al. Characteristics of the gut microbiota in professional martial arts athletes: A comparison between different competition levels. *PLoS One*. 2019;14(12):e0226240. doi: 10.1371/journal.pone.0226240. [DOI](#)
6. Di Dio M, Calella P, Pelullo CP et al. Effects of probiotic supplementation on athletic performance and performance-related outcomes in athletes: a systematic review. *Int J Environ Res Public Health*. 2023;20(3):2226. doi: 10.3390/ijerph20032226. [DOI](#)
7. Shalmon G, Ibrahim R, Israel-Elgali I et al. Gut Microbiota Composition Positively Correlates with Sports Performance in Competitive Non-Professional Female and Male Runners. *Life (Basel)*. 2024;14(11):1397. doi: 10.3390/life14111397. [DOI](#)

8. Ost'yanov VN, Antonov SA, Komisarenko HI et al. Boks: navchal'na prohrama dlya dytyacho-yunats'kykh sportyvnykh shkil, spetsializovnykh dytyacho-yunats'kykh shkil olimpiys'koho rezervu, shkil vyshchoyi sportyvnoyi maysternosti [Boxing: a curriculum for children and youth sports schools, specialized children and youth schools of the Olympic reserve, schools of higher sports mastery]. Kyiv. 2004, p.95. (Ukrainian)
9. Grosicki GJ, Langan JP, Bagley JR et al. Gut Check: Detecting the Effects of Acute Exercise on the Gut Microbiota. *Experimental Physiology*. 2023;108:1466–1480. doi:10.1113/EP091446. DOI 
10. Barton W, Penney NC, Cronin O et al. The microbiome of professional athletes differs from that of people who lead a more sedentary lifestyle, in composition and especially at the functional-metabolic level. *Gut*. 2018;67:625–633. doi: 10.1136/gutjnl-2016-313627. DOI 
11. Bonomini-Gnutzmann R, Plaza-Díaz J, Jorquera-Aguilera C et al. Effect of Intensity and Duration of Exercise on Gut Microbiota in Humans: A Systematic Review. *Int J Environ Res Public Health*. 2022;19(15):9518. doi: 10.3390/ijerph19159518. DOI 
12. Li Y, Cheng M, Zha Y et al. Gut microbiota and inflammation patterns for specialized athletes: a multi-cohort study across different types of sports. *mSystems*. 2023;8(4):e0025923. doi: 10.1128/msystems.00259-23. DOI 
13. Jarrett H, Medlin S, Moren JK. The role of the gut microbiome and probiotics in athletic performance: an updated systematic review. *Nutrients*. 2025;17:690. doi:10.3390/nu17040690. DOI 

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Olena Dulo

Uzhhorod National University;

3 Narodna Square, 88000 Uzhhorod, Ukraine

e-mail:olena.dulo@uzhnu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Anastasiia Kaliga: 0009-0001-7987-0142    

Oksana Palladina: 0000-0001-7133-0072    

Olena Dulo: 0000-0003-0473-5605    

Svitlana Burmei: 0000-0002-8157-4262  

Dmytro Shtanagei: 0000-0001-5675-5582  

Nadiya Boyko: 0000-0002-2467-7513    

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 10.04.2025

ACCEPTED: 20.08.2025



The influence of implant channel preparation technique on the mechanical and radiological properties of bone during the dental mini-implants placement (*ex-vivo* experimental study)

Bohdan G. Mykhajlychenko¹, Vladyslav O. Humeniuk¹, Iurii O. Mochalov², Ihor V. Tukalo²,
Tetiana M. Vakhrusheva³, Ihor O. Bilichenko³, Oleksandr O. Mochalov³

¹NATIONAL UNIVERSITY OF HEALTH CARE OF UKRAINE NAMED BY P. L. SHUPIK, KYIV, UKRAINE

²UZHGOROD NATIONAL UNIVERSITY, UZHGOROD, UKRAINE

³OBUKHIV CITY DENTAL POLYCLINIC, OBUKHIV, UKRAINE

ABSTRACT

Aim: To compare the mechanical and radiological properties of animal bone after preparation with different surgical protocols (including tissue compaction/densification).

Materials and Methods: Samples of animal bone tissue (porcine ribs) were prepared according to 4 protocols: osteotomic, compaction with a bone condenser, slow (50 rpm) and osteocondensation without special burrs. After preparation, the torque was measured and relative radiological density of the bone was examined using CBCT.

Results: The torque when using the slow protocol (50 rpm) was $35.82 \pm 5.10 \text{ N}\times\text{cm}$ ($M = 36.48$), with the standard osteotomic technique – $37.27 \pm 2.14 \text{ N}\times\text{cm}$ ($M = 37.40$), with the bone condensers – $46.57 \pm 2.72 \text{ N}\times\text{cm}$ ($M = 46.75$) and with osteodensification – $50.61 \pm 6.77 \text{ N}\times\text{cm}$ ($M = 50.16$). The lowest relative x-ray density of the walls of the implantation channel was when using the osteotomy protocol (1000 rpm) – $372.85 \pm 181.01 \text{ dHU}$ ($M = 374.00$), with the slow protocol – $538.75 \pm 167.82 \text{ dHU}$ ($M = 522.50$). Slightly higher values were obtained with the use of bone condensers – $602.18 \pm 263.42 \text{ dHU}$ ($M = 549.00$), and the highest was with osteodensification technique – $877.75 \pm 226.25 \text{ dHU}$ ($M = 862.50$).

Conclusions: The use of bone condensers and osteodensification techniques (even without special burrs) during the preparation of the implantation channel for mini-implants leads to progressive improvement of bone tissue.

KEY WORDS: dental implantation, preparation protocol, bone, x-ray, torque

Wiad Lek. 2025;78(9):1771-1776. doi: 10.36740/WLek/212511 DOI

INTRODUCTION

Bone compaction techniques for implant channel preparation are relatively new and innovative techniques that can be used, including when installing mini-implants. Since the purpose of such bone processing techniques is to increase its density, which has a positive effect on the primary stabilization of the installed implants. Unlike traditional preparation (osteotomic preparation technique), in which bone fragments are removed and, accordingly, the mechanical properties of bone tissue in the area of operation may decrease, during densification, bone hardness increases, and its volume is also preserved [1-3]. The vast majority of manufacturers of mini-implant systems do not focus the user's attention on the osteodensification technique when using their products. Although from the very beginning, the surgical kits include surgical

burs for osteotomy bone preparation, as well as bone condensers or taps, which partially work according to the bone densification technique [4-6].

When using the osteodensification technique to prepare the channel for mini-implants, several advantages may be identified and to be achieved in the clinic. The first advantage is better primary stability, and this is the most important advantage. By densifying the bone, osteodensification provides a tighter fit of the implant, which leads to higher insertion torque values and reduced micromovement of the product. For mini-implants, the functioning of which is often highly dependent on primary stability due to their smaller diameter, this is a critical condition for successful osseointegration. Another advantage of densifying the wall of the implant channel is improved bone-implant contact. These techniques increase direct bone-implant

contact, which is important for the long-term success of the implantation [7,8].

Also, osteodensificative techniques can locally improve the quality of bone tissue, especially in areas with low density (for example, the distal parts of the maxilla, where there is a high risk of osteoplasia). This technique can make it possible to place a dental implant in areas that, with the classic osteotomy technique of bone bed preparation, would require more extensive procedures and prior bone grafting. Another advantage of densification techniques is the achievement of a slight widening of the alveolar ridge. These techniques can contribute to the widening of narrow alveolar ridges (which is a "pleasant" side effect). This modification of the alveolar ridge allows for the placement of wider mini-implants or even conventional implants in affected areas, without resorting to the more invasive technique of lateral bone augmentation. An additional advantage of the above treatment is the higher potential for accelerated healing and immediate loading of the superstructure. Better primary stability could potentially allow for earlier or even immediate loading of mini-implants, reducing the patient's rehabilitation period. Another advantage of densification techniques is the preservation of bone tissue. By densifying rather than removing bone, the patient's existing bone tissue is preserved, which is a significant advantage in cases where available bone is limited [6,9,10].

AIM

The aim of the study was to compare the mechanical and radiological properties of animal bone after its preparation using different surgical protocols (including tissue compaction).

MATERIALS AND METHODS

To perform this study, 6 samples of animal bone tissue (pork ribs) were used. Bones were purchased from a retail chain (the animals for this experiment were not slaughtered in a planned manner, but ready-made food products produced by industrial livestock were used). The bone tissue was skeletonized mechanically and cleaned using metal spatulas and disposable scalpel blades. Subsequently, the ribs were fixed in a vice, as perpendicular as possible to the ground surface. On the upper edge, at a distance of 1.5-2.0 cm from each other, marks were made using the XFD1135 pilot drill from the SlimOneBody XIFS dental implant surgical set (Dentium). Further, according to the markings, the implantation channel was prepared to a depth of 10.0 mm for mini-implants with a diameter

of 2.5 mm with the following options for speed, direction and type of instrument:

No 1 (standard protocol) – at a speed of 1000 rpm, clockwise with a maximum torque up to 35 N×cm, using surgical burs XFD1635 and XFD2135;

No 2 (compaction) – at a speed of 100 rpm, clockwise with a maximum torque up to 50 N×cm, using osteocondensers (crest expanders) RS201036R and RS251036R;

No 3 (slow) – at a speed of 50 rpm, clockwise with a maximum torque up to 50 N×cm, using surgical burs XFD1635 and XFD2135;

No 4 (osteodensification) – at a speed of 100 rpm, counterclockwise with a maximum torque up to 50 N×cm, using XFD1635 and XFD2135.

Before using the final surgical burs, all canals were prepared to a depth of 10.0 mm using the pilot bur XFD1635. After preparation using the XHDHT hand driver, XRA3917 adapter and XRCA1 ratchet wrench, IUS251510 dental mini-implants were inserted into the prepared canals. After insertion, the torque (primary stabilization) was measured using an XNTW torque wrench (maximum value – 70 N×cm. Each measurement was performed 6 times and then entered into spreadsheets. In spreadsheets, descriptive and comparative statistics methods were used to establish a significant difference between groups of values. After measurements, mini-implants were removed from the implantation channels, and bone tissue samples after applying metal tags were stored in a refrigerator at a temperature of 4-6°C.

Subsequently, cone-beam computed tomography (CBCT) studies of the samples were performed in CBCT scanner "ACTEON X-MIND prime 3D" (France). The results of the study were analyzed in the "ACTEON® Imaging Suite 3D" software (based on the Obukhiv City Dental Clinic, Kyiv reg., Ukraine), in which the conditional radiographic density of the bone tissue of the walls of the implant channel was determined. channel in dHU. Measurements around each channel were carried out 10 times, the results were entered into spreadsheets, where statistical data processing was performed. Statistical analysis of the obtained data was performed by using the Microsoft Excel 2016 in the form of simple table analysis, descriptive statistics, and comparative statistics (t-test by Student). The level of significance was established at a value of 0.05.

RESULTS

RESULTS OF MEASURING THE LEVEL OF PRIMARY STABILIZATION OF MINI-IMPLANTS WITH DIFFERENT PREPARATION PROTOCOLS

The measurements showed that different methods of preparation of the implant canal on the jaw

Table 1. Torque indicators of the installed mini-implant with different implant channel preparation protocols, N×cm

	1000 rpm	Condensing	50 rpm	Osseodensification
Average	37.27	46.57	35.82	50.61
Standard deviation, ±	2.14	2.72	5.10	6.77
Median	37.40	46.75	36.48	50.16
Min.	33.55	41.80	26.22	42.75
Max.	41.25	50.60	49.02	68.69

Source: compiled by the authors of this study

Table 2. Relative bone density indicators of the implant channel margins for a mini-implant with different preparation protocols, dHU

	1000 rpm	Condensing	50 rpm	Osseodensification
Average	372.85	602.18	538.75	877.75
Standard deviation, ±	181.01	263.42	167.82	226.25
Median	374.00	549.00	522.50	862.50
Min.	77.00	89.00	163.00	418.00
Max.	805.00	1332.00	908.00	1483.00

Source: compiled by the authors of this study

bone model at the final stage of mini-implant installation showed different torque force, which was directly proportional to the possible level of primary stabilization of the dental implant. Thus, the lowest level of torque was determined when using the slow preparation protocol (50 rpm) – 35.82 ± 5.10 N×cm ($M = 36.48$), the minimum value was 26.22 N×cm, and the maximum – 49.02 N×cm. With the standard preparation method (1000 rpm), the torque force was slightly higher – 37.27 ± 2.14 N×cm ($M = 37.40$). The minimum value was 33.55 N×cm, and the maximum – 41.25 N×cm. When using the bone condenser from the surgical kit, the torque values of the installed implant increased significantly. The average value was 46.57 ± 2.72 N×cm ($M = 46.75$). Also, the minimum and maximum values changed in the direction of increase – 41.80 N×cm and 50.60 N×cm, respectively (Table 1). The highest torque values on the bone tissue model were obtained when using the fourth bone canal preparation protocol (osteodensification). The average value was 50.61 ± 6.77 N×cm ($M = 50.16$) with a minimum of 42.75 N×cm and a maximum of 68.69 N×cm (almost the upper limit of the torque wrench measurement).

The results of the statistical calculations showed that there was a statistically significant difference ($p < 0.05$) in the torque values during implant insertion between protocols 1 and 2, protocols 1 and 4, protocols 2 and 3, protocols 2 and 4, and protocols 3 and 4. There was no statistically significant difference in the torque levels after the use of protocols 1 and 3. That is, both osteotomic techniques – both high-speed (1000 rpm) and slow (50 rpm) – did not lead to a real difference

in the torque force during the installation of a dental mini-implant.

RESULTS OF MEASUREMENT OF RELATIVE RADIOGRAPHIC BONE DENSITY IN DHU

The performed measurements showed more heterogeneous results than were obtained at the previous stage of the study. Indeed, different protocols for preparing the implant channel caused different changes in the structure of the bone tissue, which could be registered during the performance of the CBCT and the corresponding image analysis in the software. Thus, the lowest level of relative density of the walls of the implant channel was when using the standard high-speed osteotomy protocol (1000 rpm). It was 372.85 ± 181.01 dHU ($M = 374.00$), the minimum value was 77.00 dHU, and the maximum was 805.00 dHU. In the conditional second place in terms of relative radiographic tissue density were the channels prepared using the slow osteotomy protocol (No 3). The average value was 538.75 ± 167.82 dHU ($M = 522.50$). The minimum was 163.00 dHU, and the maximum was 908.00 dHU. Slightly higher values were found in the canal walls prepared using bone sealers (protocol No 2). Here, the average value was 602.18 ± 263.42 dHU ($M = 549.00$), the minimum value was 89.00 dHU, and the maximum was 1332.00 dHU. Finally, the highest values of the conditional radiographic density of the walls of the implant canals were achieved when using the fourth preparation protocol (osteodensification). In such zones, the average bone density was 877.75 ± 226.25 dHU ($M =$

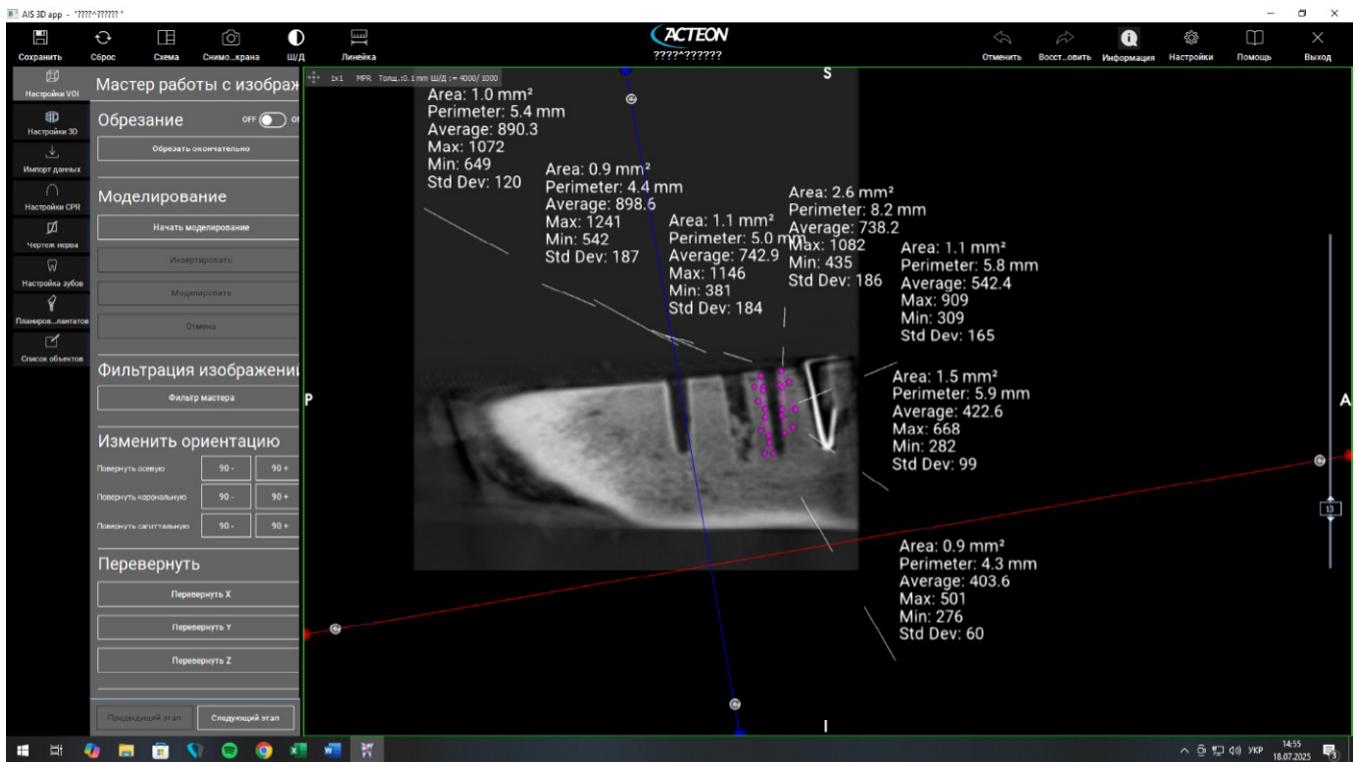


Fig. 1. Determination of the relative radiographic density of the walls of implant channels in the AIS 3D Acteon program environment
Picture taken by the authors

862.50); the minimum value was 418.00 dHU, and the maximum was 1483.00 dHU (Table 2)

The results of statistical calculations showed that the difference in the values between different protocols was significant ($p < 0.05$) in such compared pairs as Protocol 1/ Protocol 2, Protocol 1/Protocol 3, Protocol 1/Protocol 4, Protocol 2/Protocol 4 and Protocol 3/Protocol 4. The difference was insignificant in the relative radiological density of the walls of the implantation channel after the use of Protocol 2 and Protocol 3. That is, the level of bone density on the CBCT when using special sealants and the slow osteotomy protocol was similar. It is important to note that almost all preparation methods modified bone density to varying degrees (Fig. 1).

DISCUSSION

The data we obtained show that the use of bone condensers and osteodensification techniques leads to a progressive change in bone tissue in the area of the future implant canal. It is these two methods of preparation that allow a significant increase in the torque during the installation of a dental mini-implant, as well as an increase in the relative radiographic density of the prepared tissue. It is worth noting that a progressive change in the properties of bone tissue was achieved without the use of special

osteodensification burs. But only by changing the direction and speed of tissue preparation using a conventional bur for osteotomy preparation. As the results of similar studies show, bone densification itself is, in fact, a polishing process that redistributes material on the surface by plastic deformation. Counterclockwise rotation of the bur causes the edges to slide along the bone surface with a compressive force less than the ultimate strength of the bone. Since fresh, hydrated trabecular bone is a plastic material, it has a good capacity for plastic deformation. The irrigation fluid and the tissue fluid content of the bone itself assist this process by creating a lubricating film between the two surfaces to reduce friction and more evenly distribute compressive forces [11,12].

Morphological studies of the results of the osseodensification technique show that the most peculiar feature of the bone healing pattern is observed at the level of the more coronal cortical walls, where the bone acquires an unusual granular appearance. In these areas, osteoid tissue strands, osteons, and newly formed bone become visible. Also, the bone trabeculae in the treatment area demonstrate a specific granular appearance also in the inner part, while lamellar bone layers are visible on the outer side. It is believed that these bone trabeculae thicken due to the inclusion of autogenous bone fragments in the regenerate during the healing process. The granules in the trabeculae appear as nuclei of mineralization. Next

to these granules, interwoven bone areas are observed, mixed with lamellar bone [13,14].

The percentage of the bone surface lined with osteoid bands in the coronal region is much higher than in other areas around the implant canal. The increase in bone density is especially noticeable in the most coronal region. Along with this, bone chips and resorption of newly formed trabeculae are observed. It has been established that active bone remodeling is directed more towards bone attachment and increasing bone density than towards bone resorption. And such detected phenomena may indicate that in the long term, bone can still increase its density [7,13,14].

CONCLUSIONS

Thus, the use of bone condensers and osteodensification techniques in the preparation of the implant channel for mini-implants leads to a progressive change in the bone tissue in the area of future implantation, even without the use of special osteodensification burs. These preparation methods allow to increase the torque during the installation of a dental mini-implant (by 25% when using bone condensers and by 34% when using the osseodensification technique), and also increase the relative radiological density of the prepared tissue under the control of CBCT (by 47% and 130% in dHU, respectively).

REFERENCES

1. Huwais S, Meyer E. A novel osseous densification approach in implant osteotomy preparation to increase biomechanical primary stability, bone mineral density, and bone-to-implant contact. *Int J Oral Maxillofac Implants*. 2017;32:27–36. doi: 10.11607/jomi.4817. DOI
2. Frizzera F, Spin-Neto R, Padilha V. Effect of osseodensification on the increase in ridge thickness and the prevention of buccal peri-implant defects: an in vitro randomized split mouth pilot study. *BMC Oral Health*. 2022;22(1): 233. doi:10.1186/s1290302202242x. DOI
3. Tsuperiak SS, Mochalov IO. Pokaznyky renthenohrafichnoyi shchil'nosti kistkovoyi tkanyiny pislya vykorystannya riznykh khirurhichnykh protokoliv dental'noyi implantatsiyi. [The Indicators of X-ray Density of Bone Tissue after using the Different Surgical Protocols of Dental Implantation]. *Suchasna stomatolohiya*. 2023;1–2: 46–54. doi: 10.33295/1992576X20231246. (Ukrainian) DOI
4. Pellegrino G, Zaccheroni Z, Tayeb S et al. Flapless Mini Implants Immediately Loaded for Full-Arch Overdenture Rehabilitation: An Up-To-15-Year Retrospective Study. *Clin Oral Implants Res*. 2025. doi: 10.1111/clr.70017. DOI
5. Duraisamy R, Ganapathy DM, Rajeshkumar S, Ashok V. Mini-Implants in Dentistry – A Review. *J Long Term Eff Med Implants*. 2022;32(3):29–37. doi: 10.1615/JLongTermEffMedImplants.2022041814. DOI
6. Khubchandani SR, Dahane T, Dubey SA. Osseodensification: An Innovative Technique With Manifold Gains. *Cureus*. 2024;16(5):e60255. doi: 10.7759/cureus.60255. DOI
7. Bandela V, Shetty N, Munagapati B et al. Comparative Evaluation of Osseodensification Versus Conventional Osteotomy Technique on Dental Implant Primary Stability: An Ex Vivo Study. *Cureus*. 2022;14(10): e30843. doi: 10.7759/cureus.30843. DOI
8. Cáceres F, Troncoso C, Silva R, Pinto N. Effects of osseodensification protocol on insertion, removal torques, and resonance frequency analysis of BioHorizons® conical implants. An ex vivo study. *J Oral Biol Craniofac Res*. 2020;10(4):625–628. doi: 10.1016/j.jobcr.2020.08.019. DOI
9. Jarikian S, Jaafar MH, Al-Nerabieah Z. Clinical Evaluation of Two Techniques for Narrow Alveolar Ridge Expansion: Clinical Study. *Int. J. Dent. Oral Sci*. 2021;8:1047–1052. doi: 10.19070/2377-8075-21000264. DOI
10. Oliveira PGFP, Bergamo ETP, Neiva R et al. Osseodensification Outperforms Conventional Implant Subtractive Instrumentation: A study in sheep. *Mater. Sci. Eng. C Mater. Biol. Appl*. 2018;90:300–307. doi: 10.1016/j.msec.2018.04.051. DOI
11. Vaddamanu SK, Saini RS, Vyas R et al. A comparative study on bone density before and after implant placement using osseodensification technique: a clinical evaluation. *Int J Implant Dent*. 2024;10(1):56. doi: 10.1186/s40729-024-00565-8. DOI
12. Gayathri S. Osseodensification Technique – A Novel Bone Preservation Method to Enhance Implant Stability. *Acta Scientific Dental Sciences*. 2018;2(12):17–22.
13. Balasaheb S, Vidyapeeth MB, Lulla S et al. Enhancing Implant Stability With Osseodensification – A Review. *International Journal of Current Medical and Pharmaceutical Research*. 2019;5:4280–4284. doi: 10.24327/23956429.ijcmpr201906675. DOI
14. Slete FB, Olin P, Prasad H. Histomorphometric Comparison of 3 osteotomy techniques. *Implant. Dent*. 2018;27:424–428. doi: 10.1097/ID.000000000000076. DOI

Title and number of scientific project (grant): "The improvement and clinical evaluation of methods for the diagnosis, treatment and prevention of dental diseases in adults and children" (state registration number 0123U100414).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Iurii O. Mochalov

Uzhhorod National University
16A Universytetska St., 88015 Uzhhorod, Ukraine
e-mail: yuriy.mochalov@uzhnu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Bohdan G. Mykhajlychenko: 0009-0007-0001-1921 **B C D**
Vladyslav O. Humeniuk: 0009-0001-9384-678X **B C D**
Iurii O. Mochalov: 0000-0002-5654-1725 **A E F**
Ihor V. Tukalo: 0000-0002-8431-8133 **B C D**
Tetiana M. Vakhrusheva: 0009-0008-1212-5034 **B C E**
Ihor O. Bilichenko: 0009-0004-9225-8515 **B C E**
Oleksandr O. Mochalov: 0009-0003-1326-0717 **B 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: 09.04.2025
ACCEPTED: 28.08.2025



Medical and social substantiation of early detection and prevention of visual forms of cervical cancer

Iryna A. Holovanova¹, Orest Ya. Vovk², Tetiana P. Mats¹, Valentina L. Filatova¹, Olena V. Filatova¹, Alla M. Podvin¹, Maksim V. Khorosh¹

¹POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

²MUNICIPAL ENTERPRISE "POLTAVA REGIONAL CLINICAL ONCOLOGY DISPENSARY OF THE POLTAVA REGIONAL COUNCIL", MUNICIPAL ENTERPRISE "POLTAVA REGIONAL CLINICAL ONCOLOGY DISPENSARY OF THE POLTAVA REGIONAL COUNCIL", POLTAVA, UKRAINE

ABSTRACT

Aim: The purpose of the study was to provide a comprehensive medical and social justification for the feasibility and necessity of timely detection of pathology, taking into account existing risk factors, barriers to access to health care services, and the potential for public influence to increase participation in screening.

Materials and Methods: The following research methods were used in the study: sociological; systematic approach and analysis; monitoring and evaluation of indicators of the model implementation process; expert assessments.

The focus is on the aspects of early detection and prevention of visual forms of cervical cancer. Women's health indicators – incidence, prevalence and mortality from cervical cancer – are studied. Data from the State Statistics Service of Ukraine, the National Cancer Registry of Ukraine, the Center for Medical Statistics of the Ministry of Health of Ukraine, and the Department of Health of the Poltava Region for 2010–2021. Legislative acts and regulatory documents governing the organization of medical, physical, psychological, and social assistance to women with cervical cancer in Ukraine. Results of a sociological survey – 140 questionnaires.

Results: The functional and organizational model of early detection and prevention of visual forms of cervical cancer is proposed, which allows a woman to undergo a preventive examination in two ways: through non-admission to work or voluntarily, when a woman becomes a subject of her own health, and her husband and relatives can support her on the way to the doctor.

Conclusions: In the proposed model of early detection and prevention of cervical cancer, a woman is seen as an element of the ecosystem, which makes it possible to involve her family and friends in preventive examinations and provide support.

KEY WORDS: cervical cancer, visual forms, prevention, early detection, functional and organizational model

Wiad Lek. 2025;78(9):1777-1788. doi: 10.36740/WLek/212513 DOI

INTRODUCTION

Cervical cancer remains one of the leading causes of morbidity and mortality among women worldwide, especially in low- and middle-income countries. Despite the availability of effective prevention and screening methods, a significant proportion of cases are diagnosed at late stages, which significantly reduces the chances of successful treatment [1].

As of 2022-2024, cervical cancer remains a serious medical and social problem in Ukraine. According to the National Cancer Registry, in 2023, 2962 new cases of cervical cancer were registered, of which 1075 were fatal.

In 2022, there was a 20% decrease in the number of new cases of cervical cancer compared to previous years, which may be due to the impact of the war and limited access to healthcare services.

As for the prevalence of cervical cancer in the regions, the highest incidence rates were recorded in Dnipropetrovsk and Lvivska oblasts and the city of Kyiv. A significant number of cases were also detected in Odesa, Kyiv, Khmelnytsky, Poltava, Ivano-Frankivsk, and Zakarpattia regions.

In total, at the end of 2024, 58,419 women diagnosed with cervical cancer were registered in Ukraine. The distribution by stage of the disease was as follows: Stage I – 31.5%, Stage II – 26.0%, Stage III – 25.3%, Stage IV – 10.7%.

These data emphasize the need to strengthen preventive measures, including screening and vaccination against human papillomavirus, which is the main etiological factor in the development of cervical cancer. On January 1, 2025, the Procedure for Screening and Early Diagnosis of Cervical Cancer and Monitoring the Health

Status of Patients at Risk came into force in Ukraine, which aims to reduce morbidity and mortality from this disease.

The World Health Organization identifies two key strategies for combating cancer: early diagnosis of symptomatic cases and population screening among apparently healthy individuals [2,3]. At the same time, the effectiveness of these measures is complicated by a number of medical and social factors, such as insufficient public awareness, economic barriers, lifestyle influences, and limited involvement of men in women's health. In this context, special attention should be paid to the importance of early detection of visual forms of cervical cancer, which are relatively easy to diagnose in the initial stages but often remain untreated due to low motivation for preventive examinations.

AIM

The purpose of the study was to provide a comprehensive medical and social justification for the feasibility and necessity of timely detection of pathology, taking into account existing risk factors, barriers to access to health care services, and the potential for public influence to increase participation in screening.

Objectives:

1) to substantiate the functional and organizational model of early detection and prevention of cervical cancer; 2) to identify modern innovations that form the basis of the functional and organizational model of early detection and prevention of cervical cancer; 3) to define the role of public health professionals.

MATERIALS AND METHODS

The following research methods were used in the study:

- sociological – to survey women on the issue of cervical cancer and determine the role of men in early detection and prevention of the disease (Appendix 1);
- systematic approach and analysis – used at all stages of the work to study and analyze aspects of the organization of early detection and prevention of cervical cancer;
- monitoring and evaluation of indicators of the model implementation process;
- expert assessments – to determine the feasibility of applying the proposed model in institutions that provide early detection and prevention of cervical cancer.

The focus is on the aspects of early detection and prevention of visual forms of cervical cancer. Women's health indicators – incidence, prevalence and mortality from cervical cancer – are studied.

Data from the State Statistics Service of Ukraine, the National Cancer Registry of Ukraine, the Center for

Medical Statistics of the Ministry of Health of Ukraine, and the Department of Health of the Poltava Region for 2010–2021.

Legislative acts and regulatory documents governing the organization of medical, physical, psychological, and social assistance to women with cervical cancer in Ukraine.

Results of a sociological survey – 140 questionnaires.

RESULTS

The World Health Organization has identified two distinct but interrelated strategies to promote early detection of cancer and early diagnosis, i.e., recognition of symptomatic cancer at an early stage; and screening, i.e., detection of asymptomatic disease among a target group of apparently healthy people [2].

The main components that determine the need for early detection of visual forms of cervical cancer are epidemiological; risk factors (behavioral risk factors, poor financial situation, risk factors); awareness of cervical cancer (women may have barriers to screening, men may have rejection of a woman who has lost her femininity, doctors may have no experience in diagnosis); lack of appropriate early diagnosis programs at the state level.

In the modern scientific environment, a logical model for early detection and prevention of cervical cancer has been developed, based on human papillomavirus vaccination and periodic medical examinations [4].

Nevertheless, despite the developed strategy for prevention and early detection, the epidemiological factor of the ratio of cervical cancer mortality to morbidity remains high.

The main risk factors for cervical cancer are: urban residence, poor financial situation, childlessness, smoking, history of abortion, use of oral contraceptives, lack of diet, eating red meat three or more times a week, while eating fish and fruit 1-2 times a week.

We found that women are often not sufficiently aware of the issue of cervical cancer, and also point to existing barriers to screening.

A small proportion of men were convinced that prevention and early detection is a woman's personal business.

Awareness of primary care physicians was studied by Majid E et al and Qazi OA et al [5, 6]. The participants were 144 (41.5%) nurses and 203 (58.5%) doctors. Overall, 239 (68.8%) were well aware that the Pap smear is a screening test; 85 (24.5%) were aware of the current recommendations for repeating the test; 152 (43.8%) had an understanding of the exact application of the acetic acid visual examination; 61 (17.6%) had had a Pap smear;

and 156 (45%) believed they were at risk for cervical cancer. The common risk factors identified were multiple sexual partners 254 (73.2%), age at first intercourse 160 (46%), smoking 131 (37.8%), smelly discharge 221 (63.7%), and postcoital bleeding 231 (66.6%) [6].

The study of the legal framework showed that there are no programs for early detection and prevention of cervical cancer, and as a result, there is a lack of appropriate financial support.

Today, prevention and early detection of cervical cancer in Ukraine is clearly justified by the requirements of the Medical Guarantees Program 2025. If a healthcare facility has a contract with the National Health Service of Ukraine for the package "Prevention, diagnosis, monitoring and treatment on an outpatient basis," women can receive appropriate care without a referral from their family doctor.

The patient's route for early detection and prevention of cervical cancer is as follows: a woman can visit a gynecologist for an examination without a family doctor's referral, or with a referral. If we consider early detection and prevention as a model with established stages of its implementation and actors, in our case, two pairs: a woman and a gynecologist, a woman and a first aid doctor, then this model appears as an autonomous system. Unfortunately, this model does not meet the needs of the actors in the course of value creation – prevention and early detection of cervical cancer, when – in the first case – a woman does not get sick, and in the second – detection at an early stage of the disease will restore the lost health.

If early detection and prevention of cervical cancer were a separate innovation, it would involve only medical professionals: a gynecologist, a first-aid doctor, on the one hand, as service providers, and a woman, as a consumer, on the other. But a woman is in a personal environment, which may consist of her own and her parents' family, her team at work, friends, relatives. In turn, a doctor is in the health care system, performing his or her medical functions. Thus, the system is failing, and it needs new elements – participants in the process of early detection and prevention of cervical cancer. Such a community of interconnected actors, for which the network of connections is the determining factor, will be an ecosystem [7].

Ecosystems are inherently interdependent. We cannot consider early detection and prevention of cervical cancer as an autonomous innovation, but only as an ecosystem. To make this transition from an autonomous innovation to an ecosystem, it is necessary to see the so-called management blind spots.

The health of the woman in this ecosystem is at the center and she is the consumer of the services provided

by the health care system. Do all women go to the doctor for a preventive examination? Our research has shown that they do not. Women who are aware of early detection and prevention are more likely to go for a preventive examination. In this case, they play a major role in the ecosystem they have created. In this case, a woman's concern about her health does not require additional efforts and time for educational work aimed at herself, and the medical examination will be successful in terms of timeliness and frequency. In this case, a woman acts from the position of accepting the rules of the ecosystem in which she is and chooses the position of being healthy, and only then the means and sequence of events that will contribute to her early solution of the problem – an appointment with a gynecologist.

Unfortunately, prevention and early detection are not enough for the ecosystem if only a part of strong-willed and motivated women solve their health problems. The uninformed are left out of the picture, as they will visit a doctor at a certain stage of the disease, or even with an inoperable form.

The role of the "arbiter" of values – a woman's health and safety – is played by her family, her husband as a partner with whom she shares responsibility and duties for the family, possibly minor children, when innovations depend on these partners and their processes need to be changed. Men should be involved in prevention, as they can provide a completely different level of support than a specialist. The formation of a future woman's health culture begins in childhood, when a great responsibility is placed on parents who visit doctors with their child on time and instill behavioral factors that would promote a healthy lifestyle.

The information world has changed. The circle of communication has expanded with the help of social networks, including those filled with advertising about women's health. Thus, in our proposed ecosystem, the following participants and elements are represented on the woman's side: husband, parents, social networks, schools.

The healthcare system is represented by a primary care physician and a gynecologist, with the National Health Service of Ukraine as an external financial partner and the registry, which operates through the latest E-health network, as an internal element. The material and technical base of the gynecological service is being improved annually, and the human potential of the service cannot keep up with its innovations.

In general, if we consider the health care system, which has undergone reforms since 1991, with the introduction of E-health, the strategy aimed at improving women's health care should have changed

accordingly. But, as the results of our research show, this did not happen, because the risk of joint innovation and the risk in the chain of change approval are hidden in the blind spot of the traditional strategy. The risk in the chain of change approval is a product of the struggle between innovation and the status quo.

Under the old model, the doctor used paper records that contained the results of laboratory tests and medical examinations of the woman. These data were entered into an outpatient card, which was either stored in the clinic or with the patient. When E-health was introduced, it was expected that the data entered into this system would be available to all healthcare facilities and all doctors. However, experience shows that this did not happen, as each healthcare facility chose and implemented its own provider, thus limiting doctors' access to women's health indicators.

At the same time, the introduction of the function of interaction between health care facilities through the E-health network would lead to new opportunities for interaction between a general practitioner and a gynecologist. If a woman uses a specialized E-health application, she can track her health indicators. In this case, she becomes an active participant in the ecosystem we offer.

In the early detection and prevention of cervical cancer, the participation of primary care physicians is undeniable, as they refer women for preventive cancer examinations.

The National Health Service of Ukraine is an undoubted external actor, which currently provides guaranteed packages for examinations when concluding contracts with health care facilities, while the logistics and its updating are the responsibility of local communities.

When all the elements of the ecosystem in which a woman is involved are involved, it is necessary to establish a chain of approval for changes with each element of the system so that early detection and prevention of cervical cancer can be effective. That is why we take a structured approach to implementing innovations in ecosystems.

As already mentioned, there are a number of intermediaries between the doctor and the patient: parents who once taught them to take care of their health, teachers who taught them to pay attention to changes in the body, a husband, a family where a woman has her responsibilities.

Functional elements include accessibility, awareness of the need for preventive examinations, and knowledge of the route to the doctor. Awareness is based on a woman's values about her own health as a consumer of the service. In our proposed ecosystem, each participant has its own value and benefit.

In order for a woman to seek early detection and prevention of cervical cancer, it is necessary that all elements of the ecosystem in the chain of change approval are focused on the woman's health values:

1. Family: proper upbringing, support of the husband.
2. Psychological: fear of examination, fears of a fatal diagnosis, uncertainty at the thought of going to the doctor, feeling of shame.
3. Economic: knowledge that the service is free.
4. Accessibility: availability of a gynecologist whom a woman would trust.
5. Awareness: orientation about the route to the doctor and about the health care facilities that provide services.

Then, the risk in the chain of approval of changes on the part of a woman regarding the prevention and early detection of cervical cancer is as follows: at the stage of childhood and adolescence, under the influence of upbringing by parents, teachers, and health care workers, a girl's worldview of a healthy lifestyle is formed, which continues to be formed in adulthood under the influence of her own family, husband, and environment (team, employer, friends). A risk or blind spot in this chain is when a woman has not received adequate knowledge or support, and then she does not visit a doctor. Involving women in tracking the Helthy app with a reminder function and entering data into the medical information system by a doctor will help women pay attention to the need to see a doctor, in addition to monitoring the results of clinical tests and instrumental research methods, would allow them to manage their health status independently, including both prevention and early detection.

The point of early detection and prevention of cervical cancer is a preventive examination of a woman who has visited a gynecologist. A preventive examination will be effective if all possible risks in the chain of approval of changes by the woman's health care system are taken into account. First of all, it is a high-quality staffing of doctors, both primary care and specialized medical care, and the possibility of training.

A general practitioner of family medicine and a gynecologist of any health care facility should be connected through a medical information system, where they could see the results of the examination, test data, and instrumental methods of examining a woman, which would allow them to draw up an individual portrait of the patient and make decisions about her further treatment. Since the doctor is engaged in personal prevention, early detection and treatment of women, the state of women's health at the community level remains out of his or her attention. We propose to solve this problem with the help of public health specialists, who should

have information on community health indicators. The medical information system should be built in such a way that a separate module for a public health specialist is opened, where information about patients would be depersonalized. Then, through the medical information system, he or she would be able to communicate with doctors, both general practitioners and gynecologists, which would allow for health information education of the entire community. Conducting a sample survey of the population by the Public Health Centers on risk factors and access to medical care would provide an opportunity to get feedback. All these predictable and unpredictable issues would be discussed at joint conferences of doctors and public health professionals, where oncologists would be invited to gain a deeper understanding of the situation. Such an event would allow identifying blind spots in the chain of change approval and actively managing them.

The inclusion of external partners in our proposed ecosystem – the National Health Service of Ukraine and local governments – will allow us to provide preventive examinations with a logistical component. To do this, the National Health Service of Ukraine should conclude an agreement with health care institutions, and local governments should inform them about the need to purchase or improve modern medical equipment, such as an ultrasound diagnostic device, colposcope, which should be available to any gynecologist. Every gynecological office should have such a set of material and technical resources. The results of the examination are entered into the E-health database available to other doctors, which in turn helps the GP to monitor the woman's health. In this case, when all the chains in the chain of early detection and prevention are coordinated, an effective preventive examination will take place.

So much depends on the chain of approval for change. And to understand this interdependence, it is necessary to identify stakeholders in women's health, because in today's interdependent world, a successful innovator must treat each partner as a consumer.

Each partner or intermediary mentioned above, who is part of the ecosystem, should see their own benefit from a woman's timely and regular medical check-up.

Family members of a girl – parents, and women – husband, children have the most to gain from a woman's health. Parents do not spend extra time, money, or effort on treatment, and manage their child's health with lesser expenses, such as preventive examinations. For her husband and children, a healthy woman is a person who fulfills her marital and household responsibilities to the fullest.

There is a benefit for the territorial community, which is seen as a set of people who ensure the economic

stability of the region and the country as a whole. Due to the high incidence of cervical cancer among women, women's reproductive health is deteriorating, which affects the birth rate and deepens the demographic crisis. This situation is not conducive to economic development and destabilizes the labor market (shortage of personnel).

Timely and regular preventive examinations reduce the workload of a general practitioner in terms of medical work, improve the quality of the doctor's work, as timely examinations reduce the number of women with advanced cancer and increase the number of women satisfied with the quality of medical care.

Women's activity in taking care of their health, their desire to have information about their own health status will affect the work of the electronic healthcare system, which will allow the developers of the medical information system to successfully pass tenders in procurement, trying to improve their system, and will have advantages in competition.

A healthy woman in the workplace is the key to a well-coordinated workflow at any production facility and to creating a healthy psychological atmosphere in the team

Risk can be proactively managed if it is recognized in advance. From the perspective of the ecosystem, the biggest beneficiary is a woman – a patient who, when seeking help, receives the greatest value – her own health. The blind spot in this chain is the patient's own visit to the doctor, which will need to be taken into account when creating a functional and organizational model for the early detection and prevention of visual forms of cancer. A gynecologist is the most motivated subject in the process of success – the implementation of a preventive examination, as this is the quintessence, the essence of his or her professional purpose. The gynecologist's interests are represented by the director of the healthcare facility, who is directly interested in the availability of patients.

However, in practice, the most interested parties do not notice the intentions and motivation of intermediaries with whom they are not directly connected. Untrained healthcare professionals are more likely to make a false diagnosis of cancer. Thus, the importance of both systemic and patient-related delays should not be underestimated [8]. Lack of quality communication between participants in a woman's reproductive health reduces to zero the efforts of doctors aimed at early detection and prevention.

In order to address these gaps, it is necessary to coordinate changes with all participants in the process through communication in the form of meetings where a public health specialist would act as a coordinator.

When women go to the doctor for a checkup, the chain of approval of changes is transformed accordingly. The following elements of the process of providing a woman with a preventive examination appear: logistical support for the process – the actual preventive examination, the doctor's level of knowledge – category, sanitary conditions, a registrar who guides and explains her actions to the patient.

The functional and organizational aspect of women's health care management is included in the list of problems that require immediate and systemic solutions, especially during hostilities, when changes in the population occur due to high mortality rates and mechanical movement – emigration, which can lead to a demographic crisis. We took visual forms of cancer in women – cervical cancer, as a unit of detection and prevention, bearing in mind that during one visit to the gynecologist she will be fully examined: palpation of the mammary glands, screening from the cervical canal – cytological smear according to Papanicolaou (Pap test). Strict hierarchy and accountability will allow us to coordinate and implement the model in such a way that the goal – covering as many women as possible with preventive examinations – would be achieved. At the top of our pyramid is the Cabinet of Ministers of Ukraine, which, due to the recognition of the priority of maternal and child health care – coordinates the work between the ministries – health care and social policy. In the first case, the Cabinet of Ministers of Ukraine approves the National Program for Early Detection and Prevention of Cervical Cancer, which would include vaccination against human papillomavirus. This program would become a guide for our model. The Ministry of Education and Science assigns responsibility for creating a regulatory framework for including the prevention and early detection of cervical cancer in the training program for doctors to higher medical institutions. The National Health Service of Ukraine provides opportunities for creating communications between users of the medical information system, which would include all participants in the process: a general practitioner of family medicine, a gynecologist, a public health specialist, and the woman herself.

At the top of our pyramid is the Cabinet of Ministers of Ukraine, which, recognizing the priority of maternal and child health, coordinates the work between the ministries of health and social policy. In the first case, the Cabinet of Ministers of Ukraine approves the National Program for Early Detection and Prevention of Cervical Cancer, which would include vaccination against human papillomavirus. This program would become a guideline for our model. The Ministry of Education and Science is responsible for creating a regulatory

framework to include cervical cancer prevention and early detection in the curriculum of medical schools. The National Health Service of Ukraine provides opportunities to create communications between users of the medical information system, which would include all participants in the process: a general practitioner, a gynecologist, a public health specialist, and the woman herself.

The legal justification for recommending that employers not allow women who have not undergone a preventive examination to work is a peremptory, economic approach that would force women to go for a preventive examination. In contrast to this governmental approach, under the Ministry of Health program, a public health center would motivate women by promoting the need for preventive screening through health education for both women and men and at all age levels, working with educators. The next stage is a visit to a doctor, who informs the woman about the need for a preventive examination and refers her to a gynecologist. The specialized level – a visit to a gynecologist – is where early detection and secondary prevention actually take place. Specific prevention in the form of vaccination against human papillomavirus is the responsibility of an infectious disease specialist at a children's clinic, where parents and their child are referred by a pediatrician. While early detection is the prerogative of the gynecologist and specific prevention is the responsibility of the infectious disease specialist, the public health center should be responsible for general primary prevention as part of the Ministry of Health program. They are responsible for both sanitary and educational work and the coverage of women's health indicators by the medical information system.

Thus, the first stage of information collection will allow the public health specialist to monitor and evaluate women's health indicators at the population level, identifying the determinants that indirectly affect the occurrence of cervical cancer.

The proposed model was implemented sequentially, according to a preliminary plan. To this end, we have built a logical model for the implementation of a functional and organizational model for the early detection and prevention of visual forms of cervical cancer malignancies (Fig. 1).

Thus, our model allows a woman to get a preventive examination in two ways: mandatory – through not being allowed to work and voluntary, when a woman becomes the subject of her own health and can track it through the application of a medical information system, and her husband and relatives can support her on the way to the doctor.

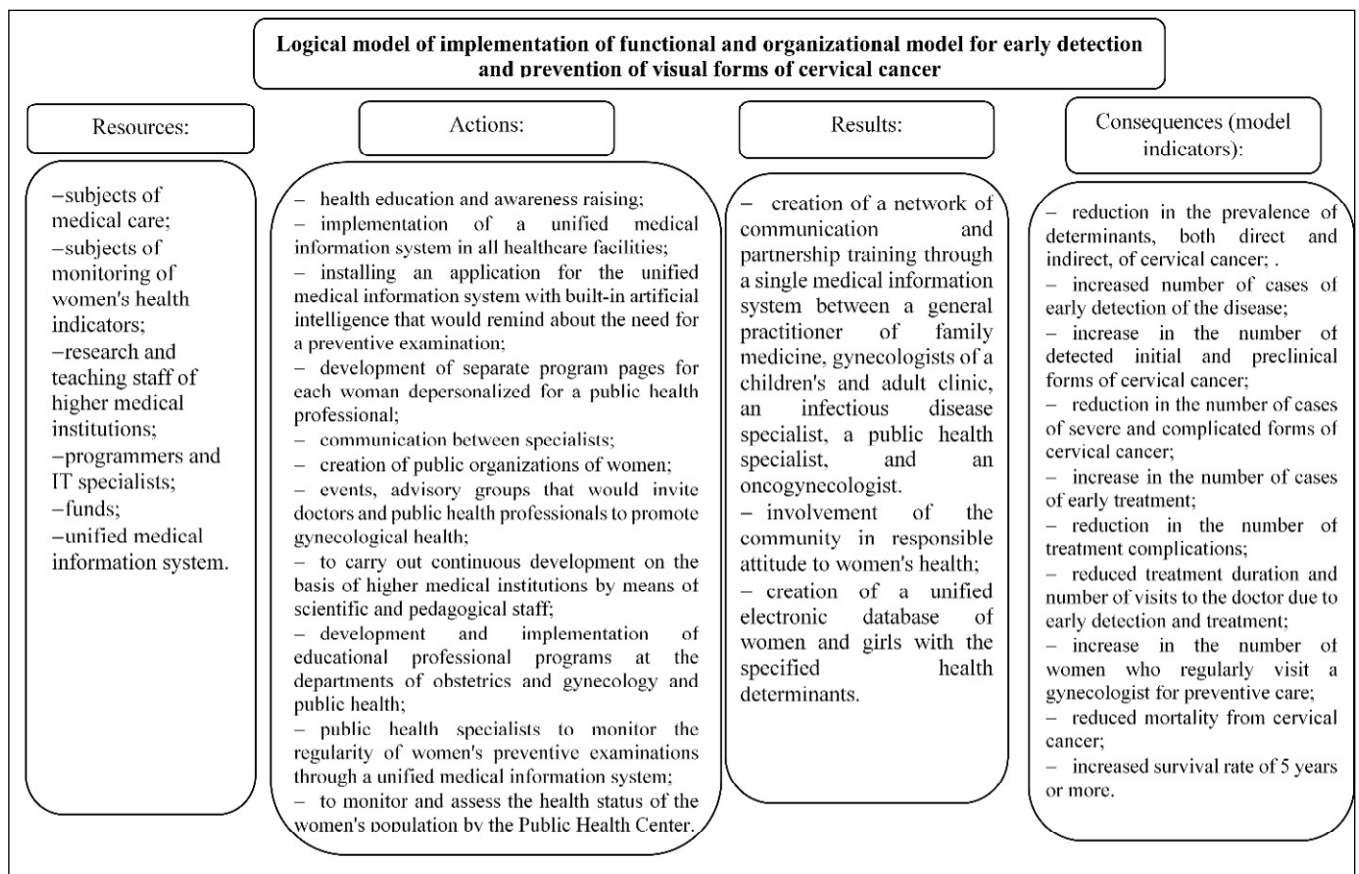


Fig. 1. Logical model of implementation of functional and organizational model for early detection and prevention of visual forms of cervical cancer

Source: compiled by the authors of this study

DISCUSSION

Cervical cancer (CC) remains a pressing public health problem, especially in low- and middle-income countries, including Ukraine. Despite the fact that the disease is among the visually identifiable oncopathologies, it is often diagnosed at late stages, which significantly worsens the prognosis and increases mortality. Visual forms of SCC – those that can be detected by simple cervical examination with acetic acid and Lugol's solution – have a high potential for early detection and prevention.

In terms of medical and social feasibility, early declaration (early diagnosis and public awareness) of visual forms of RSM is closely related to the level of health literacy of women, the availability of screening programs, and the cultural and social characteristics of the region. Studies show that programs focusing on visual inspection with acetic acid (VIA) are an effective and cost-effective alternative to cytology screening in resource-limited settings [9].

Health and social aspects of prevention also include vaccination against human papillomavirus (HPV), which is a major etiologic factor of RSM. According to a meta-analysis by Drolet et al. (2019), the introduction

of HPV vaccination in national programs demonstrates a reduction in the incidence of HPV-associated precancerous lesions and visually prominent forms of RSM within 5-10 years of program initiation [10].

Thus, early declaration and prevention of visually visible forms of RSM should be based on a multidisciplinary approach that includes education, vaccination, accessible screening, and social support. Timely implementation of these interventions in the Ukrainian health care system will contribute to reducing the disease burden and improving women's health indicators.

CONCLUSIONS

The functional and organizational model of early detection and prevention of visual forms of cervical cancer is based on modern innovations: a medical information system, involvement of the public health system.

The role of a public health specialist is defined, who, thanks to a unified medical information system for all health care facilities, will be able to monitor and evaluate women's health indicators through the

analysis of women's surveys, health indicators that will be detected during preventive examinations.

In our proposed functional and organizational model of early detection and prevention of cervical cancer, a

woman is considered as an element of the ecosystem, so that it becomes possible to involve close and supportive family members of women in preventive examinations.

REFERENCES

1. Osnytska Y, Martin LR, Goodman A. Cervical cancer prevention Challenges and barriers to cervical cancer screening and HPV vaccinations in Ukraine and eastern Europe. *Health*. 2023;15(06):525–43. doi:10.4236/health.2023.156036. DOI
2. Ginsburg O, Yip C, Brooks A, Cabanes A et al. Breast Cancer Early Detection: A Phased Approach to Implementation. *Cancer*. 2020;126(S10):2379–93. doi:10.1002/cncr.32887. DOI
3. Wilm J, Schüler-Toprak S, Ortmann O. Krebsfrüherkennung des Zervix- und des Mammakarzinoms. *Der Pathologe*. 2016;37(5):477–89. doi:10.1007/s00292-016-0228-y. DOI
4. The Global Breast Cancer Initiative (GBCI). <https://www.who.int/publications/m/item/the-global-breast-cancer-initiative-gbci>. [Accessed 14 April 2025]
5. Akhtar O, Qazi O, Yasmin NDrH et al. Frequency of HIV among patients seeking antenatal care at a tertiary care hospital, Karachi. *Journal of the Pakistan Medical Association*. 2022. doi:10.47391/jpma.1816. DOI
6. Majek O, Danes J, Skovajsova M et al. Breast cancer screening in the Czech Republic: time trends in performance indicators during the first seven years of the organised programme. *BMC Public Health*. 2011;11(1). doi:10.1186/1471-2458-11-288. DOI
7. Soldak M. Industrial ecosystems and technological development. *Economy of Industry*. 2019;4(88):75–91. doi:10.15407/econindustry2019.04.075. DOI
8. Mwaka AD, Orach CG, Were EM et al. Awareness of cervical cancer risk factors and symptoms: cross-sectional community survey in post-conflict northern Uganda. *Health Expectations*. 2015;19(4):854–67. doi:10.1111/hex.12382. DOI
9. Denny L, Kuhn L, De Souza M et al. Screen-and-Treat Approaches for Cervical Cancer Prevention in Low-Resource Settings. *JAMA*. 2005;294(17):2173. doi:10.1001/jama.294.17.2173. DOI
10. Drolet M, Bénard É, Pérez N et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *The Lancet*. 2019;394(10197):497–509. doi:10.1016/s0140-6736(19)30298-3. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Tetiana P. Mats

Poltava State Medical University
24 Shevchenko st., 36000 Poltava, Ukraine,
e-mail: tetiana.mats.p@gmail.com

ORCID AND CONTRIBUTIONSHIP

Iryna A. Holovanova: 0000-0002-8114-8319 A F

Orest Ya. Vovk: 0000-0003-4364-5493 E

Tetiana P. Mats: 0000-0001-6793-0892 B C D

Valentina L. Filatova: 0000-0001-5247-1144 E

Olena V. Filatova: 0000-0001-6264-570X B C D

Alla M. Podvin: 0009-0008-5946-7621 B C D

Maksim V. Khorosh: 0000-0002-2083-1333 B 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: 30.04.2025

ACCEPTED: 29.08.2025



APPENDIX 1

QUESTIONNAIRE ON AWARENESS OF CERVICAL CANCER

This questionnaire is intended for academic research and is designed to identify barriers that affect cervical cancer screening among women in Poltava. Your answers will be kept confidential, and all information will be presented as aggregate data. Therefore, you are not required to write your name. There are no wrong or right answers. This is just to find out your opinion on this issue. Please check the appropriate boxes or write your opinion in the open-ended questions. We would appreciate it if you could answer all the questions as best you can. Thank you.

SECTION A: SOCIO-DEMOGRAPHIC DATA

1. Please indicate your age _____ years old.
2. Occupation _____.
3. Education

☐ Secondary	☐ Higher
☐ Secondary specialized	☐ Academic degree
4. Religious beliefs

☐ Christian	☐ Buddhist
☐ Muslim	☐ Other _____
5. Marital status

☐ Married	☐ Widowed
☐ Single	☐ Informal marriage
☐ Divorced	
6. Number of children born _____
7. Family history of cervical cancer

☐ Yes	☐ No
------------------------------	-----------------------------
8. Are you a healthcare professional?

☐ Yes	☐ No
------------------------------	-----------------------------

SECTION B: AWARENESS OF CERVICAL CANCER

9. Have you heard anything about cervical cancer?

☐ Yes	☐ No
------------------------------	-----------------------------
10. Who first told you about cervical cancer?

☐ Never heard of it until today	☐ From school staff
☐ From a family member	☐ From radio, television, magazine
☐ From a friend	☐ I don't remember
☐ From a doctor/nurse	☐ Other sources _____

APPENDIX 1 cont.

11. Is cervical cancer a sexually transmitted disease?

- ☐ Yes ☐ No ☐ Difficult to answer

12. Can cervical cancer be prevented?

- ☐ Yes ☐ No ☐ Difficult to answer

13. Cervical cancer can be prevented by vaccinating young girls.

- ☐ Yes ☐ No ☐ Difficult to answer

14. Is cervical cancer curable in hospitals if diagnosed early?

- ☐ Yes ☐ No ☐ Difficult to answer

15. Please indicate the risk factors for cervical cancer.

- | | |
|---|--|
| ☐ Early onset of sexual activity | ☐ Cigarette/tobacco smoking |
| ☐ Sexually transmitted infection (HPV) | ☐ Large number of sexual partners, promiscuous sexual behavior. |
| ☐ Multiple male sexual partners | ☐ Use of contraceptives |

16. Please indicate the symptoms of cervical cancer.

- | | |
|--|---|
| ☐ Intermenstrual vaginal bleeding | ☐ Excessive vaginal discharge, often with an unpleasant odor |
| ☐ Vaginal bleeding during menopause | ☐ Pain in the lower abdomen |
| ☐ Vaginal bleeding | ☐ Pain in the genitals during sexual intercourse. |
| ☐ Vaginal bleeding after sexual intercourse | |

17. Have you heard of cervical cancer screening (examination and smear test)?

- ☐ Yes ☐ No

18. Have you ever been screened for cervical cancer (examination and smear test)?

- ☐ Yes ☐ No

19. If yes, when was your last screening?

20. How often do you go for screening?

- | | |
|--|--|
| ☐ Once a year | ☐ Every 2-5 years |
| ☐ Less than every 5 years | ☐ Difficult to answer |

21. Are you interested in participating in cervical cancer screening?

- ☐ Yes ☐ No

APPENDIX 1 cont.

SECTION C: PERCEPTIONS ABOUT THE RISK OF CERVICAL CANCER

Which of the following issues would prevent you from participating in cervical cancer screening?

22. Does the thought of cervical cancer scare you?

- ☐ Yes ☐ No ☐ Difficult to answer

23. Do you think you are at risk for cervical cancer?

- ☐ Yes ☐ No ☐ Difficult to answer

24. Are you afraid of a bad diagnosis?

- ☐ Yes ☐ No ☐ Difficult to answer

SECTION D: WHAT ARE THE BENEFITS OF CERVICAL CANCER SCREENING?

25. Do you think cervical cancer screening is important?

- ☐ Yes ☐ No ☐ Difficult to answer

26. Do you believe that cervical cancer can be cured?

- ☐ Yes ☐ No ☐ Difficult to answer

SECTION E: BARRIERS TO CERVICAL CANCER SCREENING

Psychosocial barriers to cervical screening.

Which of the following questions would prevent you from participating in cervical cancer screening?

27. Do you consider cervical screening to be painful?

- ☐ Yes ☐ No ☐ Difficult to answer

28. Do you consider cervical screening to be inconvenient?

- ☐ Yes ☐ No ☐ Difficult to answer

29. Do you believe that cervical cancer is a curse from the gods?

- ☐ Yes ☐ No ☐ Difficult to answer

30. Does your religion have anything against cervical screening?

- ☐ Yes ☐ No ☐ Difficult to answer

31. Is cervical screening prohibited in your culture?

- ☐ Yes ☐ No ☐ Difficult to answer

Socio-economic barriers to screening.

Which of the following questions would prevent you from participating in cervical cancer screening?

32. Do you know that cervical cancer screening (examination and smear test) is free and does not require a referral?

- ☐ Yes ☐ No ☐ Difficult to answer

33. Is it easy to get to the medical facility where the examination will take place?

- ☐ Yes ☐ No ☐ Difficult to answer

34. Do you have time for cervical screening?

APPENDIX 1 cont.

☐ Yes ☐ No ☐ Difficult to answer

Barriers from the healthcare system.

Which of the following questions would prevent you from participating in cervical cancer screening?

35. Do you know of any health care facilities that offer cervical cancer screening services?

☐ Yes ☐ No ☐ Difficult to answer

36. Are you comfortable with male health care personnel providing screening services?

☐ Yes ☐ No ☐ Difficult to answer

37. Is there a long wait at the medical facility (queue to see a doctor)?

☐ Yes ☐ No ☐ Difficult to answer

38. Is it difficult to communicate with medical staff?

☐ Yes ☐ No ☐ Difficult to answer

SECTION F: RECOMMENDATIONS FOR ACTION

39. Do you think that the availability of screening from early in the morning (e.g., 7:00 a.m.) and late in the evening (e.g., 8:00 p.m.) for working patients would increase their adherence to screening?

☐ Yes ☐ No ☐ Difficult to answer

40. Do you think that improving patients' awareness of how cervical screening is performed would increase their willingness to undergo screening?

☐ Yes ☐ No ☐ Difficult to answer

41. Would the use of female medical staff to provide screening services encourage you to undergo screening?

☐ Yes ☐ No ☐ Difficult to answer

Thank you for your answers.

Management of damage control surgery and resuscitation at different stages of evacuation. Tough lesson from the frontier of Russian–Ukrainian war

Dmytro O. Samofalov¹, Dmytro Androshchuk², Igor Korpusov³, Leonid Kopus³, Nataliya Izhytska⁴

¹DEPARTMENT OF THE MINISTRY OF DEFENCE OF UKRAINE, KYIV, UKRAINE

²FORCES OF THE UKRAINIAN ARMED FORCES, KYIV, UKRAINE

³PULSE, KYIV, UKRAINE

⁴DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Aim: To provide analyzes of practical implementation of Prolonged Casualty Care (PCC) and Damage Control Surgery (DCS) principles in Ukrainian frontline medical settings (MEDEVAC, Role I and Role II) under prolonged evacuation conditions during 2022–2024.

Materials and Methods: Clinical data were collected from multiple combat zones, focusing on indications for DCS, surgical interventions, postoperative complications, and patient outcomes.

Results: Among all casualties treated at Role II facilities, 43% underwent DCS procedures, often dictated more by tactical constraints than by medical necessity. The mortality rate in the DCS group was 5.9%, comparable to that of patients undergoing Early Total Care, definitive surgery on day of admission. The most frequent complications included intestinal anastomotic leaks, hernias, pneumonia (9.2%), acute kidney injury (10.4%), and anemia requiring transfusion (7.2%). Challenges in timely evacuation due to hostile drone activity, attacks on medical personnel, and terrain limitations led to a critical shift in trauma care paradigms.

Conclusions: Modern war dictate wider implementation of PCC and DCS.

KEY WORDS: damage control surgery, military medicine, blood transfusion, whole blood, hemorrhage management, tourniquet application, abdominal injuries, forward surgical teams

Wiad Lek. 2025;78(9):1789-1797. doi: 10.36740/WLek/211346 DOI

DISCLAIMER

Taking into account the moments and precautions related to the military situation in Ukraine and National Security, all data and indicators are presented in relative values. Locations of Medical Treatment Facility (MTF) not disclosed. Current article is not official position of Ministry of Defence of Ukraine, just private point of view of authors.

INTRODUCTION

From the beginning of full-scale military invasion of Ukraine by the Russian Federation it was observed changes in the nature of military force. From the winter of 2022 both armies used standard doctrines and available weapons. But in the summer of 2023, the wide use of reconnaissance and strike drones, which were connected in a system of situational awareness.

That made the battlefield transparent. And this gives unlimited opportunities for highly accurate strikes on the tactical level. Thus, due to absolute transparency, a 10-15 kilometer zone of continuous death was formed in front of the front line [1]. From the 2023 one can observe changes in structure of injuries. Before that maximum losses in the personnel of the armed forces were during accentuated offensive actions aimed at concentrating the enemy's main efforts in the main defense zone, as well as when counterattacks are carried out by the Defense Forces [2]. From the summer 2023 a lot of wounded were registered in more or less safe zones. What leads to increase of wounds and injuries of live critical organs, because in this zones military personnel rarely wear body armor. Also a lot of attacks on civilian infrastructure was observed. Lot of civilian medics were wounded and killed. In this group injuries were different from those which were seen in military personnel [3,4].

Another peculiarity of medical help during full scale aggression was inability of medical forces of armed forces of Ukraine to provide treatment to all injured, because of lack of armored evacuation vehicles; shortage of personnel, in particular certain categories of doctors and nurses. Thus it was created single medical space aim to establish cooperation at the level of each type of military and a certain (or group of) medical institutions under one commander [2,5].

In conditions when lot of Medical Treatment Facilities (MTF) with different levels were involved and continuous work of forward surgical teams (FST) in conditions of mass casualty incident (MASCAL), led to the necessity for strict restrictions on each level of medical care. For this, guiding documents were created that standardized and unified the scope of assistance and the organization of medical support. These documents took into account vertical and horizontal connections and were agreed upon at all levels of the military and civilian link of assistance. Which was extremely important, since the conduct of various types of military operations involves close interaction between different branches and types of troops [6].

In 2023, the Ministry of Defense of Ukraine approved by order the scope of medical care at the pre-hospital stage, clearly defining the necessary operations and manipulations that must be performed at each stage of providing assistance to the wounded [7].

AIM

The aim of the work is to provide analyzes of practical implementation of Prolonged Casualty Care (PCC) and Damage Control Surgery (DCS) principles in Ukrainian frontline medical settings (MEDEVAC, Role I and Role II) under prolonged evacuation conditions during 2022–2024.

MATERIALS AND METHODS

This is a retrospective descriptive study based on data collected from 2022 to 2024. Data were gathered on CASEVAC, MEDEVAC, Role I and Role II (all types), on different parts of the Ukrainian frontline. Another important question was the consequences of DCS on Role II. Complications and survival rate on hospital level. Complications reported included pneumonia, cardiac arrest, acute kidney injury, postoperative hernias, anemia requiring transfusion, chimerism, wound infections, peritonitis, leakage of anastomosis and sepsis. Finally, intraoperative administration of blood products was reported including direct donor to casualty transfusion (walkin blood bank), whole blood, packed red blood

cells (pRBC), Freeze dried plasma (FDP) and fresh frozen plasma (FFP). It was observed in separate cases of platelet infusion. Preparation and storage is too complicative for usage on Role I and Role II. The use of Cryoprecipitate and Antihemorrhagics containing a combination of blood clotting factors was sporadic and did not affect the overall picture in any way. All patients who were in 3 hours after injury got 2 ml. of tranexamic acid. Also all wounded get antitetanus and antibiotic prophylaxis in order to resent laws of Ukraine.

The obtained quantitative data were processed using descriptive statistics and graphical interpretation. The combination of different research methods provided a comprehensive assessment of the current situation.

Thus, the research design can be characterized as a descriptive case study, focused on evaluating a specific innovation in a specific context, using mixed methods to increase the reliability of the conclusions.

For reasons of national security, the location of the MTF is not disclosed, and all data is given in relative values.

RESULTS

The studied population was mostly homogeneous and consisted of male servicemen aged 27 to 55 years who were wounded as a result of combat operations. The average age was 44.3 ± 12.1 . At the same time, all age and gender categories were represented among civilians. Youngest patient with DCS was an 11 years old boy, who was wounded during the shelling of a peaceful city with cassette bombs. He was in the car with father and his younger brother. He got multiple wounds of head, brain, chest, abdomen and extremities. The patient dies two days after surgery. The oldest patient was 72 years. He had abdominal wounds with massive injury to the liver. Heart arrest during the surgery. Non successful resuscitation.

The condition of patients in time of their delivery at the Role II was very serious, so we can not evaluate concomitant diseases, which can affect surgical treatment. (Fig. 1).

In most cases the only device to stop the bleeding on Role I was tourniquet. It was used in nearly 60% of all injuries. Other methods of massive hemorrhage management in the condition of MEDEVAC were the REBOA system and Abdominal Aortic and Junctional Tourniquet (AAJT). Dmytro Androshchuk [31] reported six cases of successful management of battlefield traumatic cardiac arrest using the AAJT. Four cases succeeded in surviving the patient, one patient died due to prolonged evacuation time and one after 10 days on the Role 3 because severe damage of thoraco-abdominal injuries.

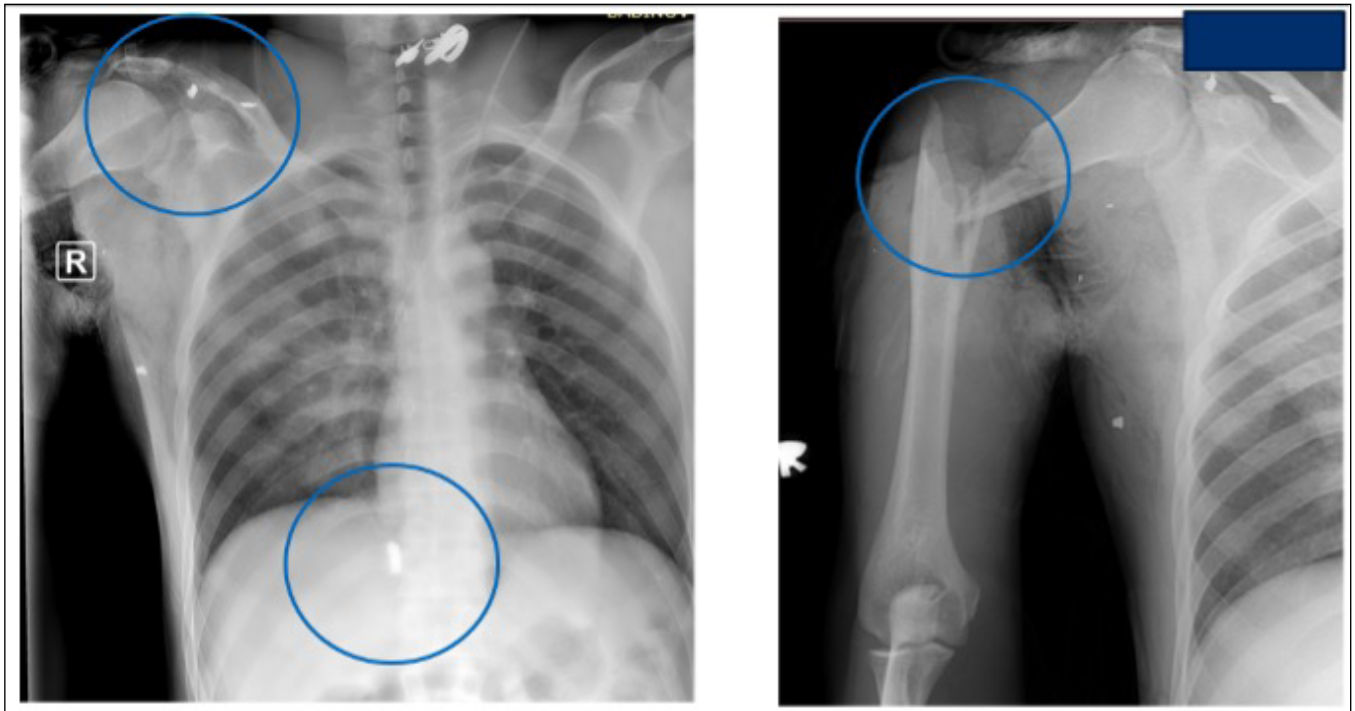


Fig. 1. Multiple life-threatening injuries

Picture taken by the authors

I.A.Lourin and authors in the abstract [8] shows the difference in the effectiveness of AAJT, Reboa and aortic clamping, emphasizing the appropriateness of each of these methods at a certain stage of care.

In contrast, Dmytro Samofalov reported a comparable number of traditional management techniques, including emergency thoracotomy with aortic clamping. Just 25% of cases achieved the restoration of rhythm, with exitus letalis in a further ten days. On delivery to FST all wounded undergo trauma assessment with laboratory and instrumental check up according to the defined algorithm. Also, vascular access was established to all patients. In definite cases central lines (jugular vein) with ultrasound control. All casualties undergo vital signs check, blood samples, X-ray and extended Focused Assessment with Sonography in Trauma (eFAST). Patients with unstable hemodynamics, signs of shock and positive eFAST immediately were transported to operative theatre for laparotomy in rare cases thoracotomy as well. Stable patients who have uncertain eFAST undergo additional tests. Among the patients with penetrating abdominal wounds it was injuries of small intestine (28,2 %), colon (26.2%), liver (19.7%), and spleen (13.6%). This was similar to other series reports from Ukrainian battleline [9,10]. In FST we provided DCS – 56 %, Early Total Care (ETC) (definitive surgery on day of admission) – 35%. At 9% just exploratory laparotomy was provided. During explorative laparotomy shrapnel was found or in greater momentum or separate in the abdominal cavity.

DISTRIBUTION OF INJURIES

In general, the distribution of wounded who were delivered to FST is shown in Table 1.

Most of the patients on FST were moderate and needed just primary surgical care for their wounds. Up to 13% were severe and needed advanced surgeries, such as laparotomy, thoracotomy, external fixation of bones, amputations, fasciotomies, temporary shunting of great vessels Etc. The distribution of patients who underwent advanced surgery is shown in Table 2.

As shown in Table 2. The total number of surgeries is greater than 100%, which is due to the necessity to conduct two and more surgeries in patients with multiple injuries. Most often a combination was laparotomy and pleural drainage. Rarely we provided laparotomy with thoracotomy, or laparotomy and greater vessels temporary shunting. Also for safe transportation to the next level we used provision tourniquet to renal pedicle. In case if bleeding, from a packed kidney, renews during the transportation of the patient, one can just tighten a tourniquet to achieve hemorrhage control.

During laparotomies, the most common procedures performed were abdominal packing (14%), obstructive resection of the small intestine (7%), and colon (21%).

Among the patients in DCS group were those with high Injury Severity Score (ISS) with average score 32 (23-37). To compared with patients who undergo early total care (ECT) ISS was 15 (11-17). One of the important

Table 1. Structure of wounds in patients who were delivered to the advanced surgical group Role 2

	Head	Thorax	Abdomen	Extremities	Multiple
2022	8,5 %	6,3 %	1,1 %	29,0 %	45,2 %
2023	8,8 %	6,9 %	2,9 %	39,2 %	42,2 %
2024	11,7 %	7,5 %	3,6 %	52,9 %	24,3 %

Source: compiled by the authors of this study

Table 2. Advanced surgeries

Laparotomy	Thoracotomy	Pleural drainage	External fixation of bones	Surgery on graeate vessels	Extremities amputation
31,1 %	4,4 %	16,2 %	35,5 %	14,6 %	15,5 %

Source: compiled by the authors of this study



Fig. 2. Vacuum-assisted temporary closure of laparotomy wound
Picture taken by the authors

indicators for choosing surgical tactics was the injury isolated or multiple. All patients with multiple injuries of the intestine were operated on in DCS approach. During explorative laparotomy we find few injuries of pancreas (%). In all cases at the FST pancreas was packed, and the abdominal wall was temporarily closed. Other indications for DCS were: level of consciousness (stunning, sopor, coma), body temperature less than 35 °C, blood saturation less than 85%, liquid (blood) in abdominal cavity during eFAST. We didn`y use Algover`s shock index as it was not informative in condition of permanent combat stress.

For temporary closure of abdominal wall in contaminated cavity without signs of hemorrhage we used vacuum assisted closure (VAC). (Fig. 2)

In risk of hemorrhage, temporary sutures or Bogota bag (Fig. 3).

Mandatory yarly administration of tranexamic acid (TXA), which was shown in the CRASH-2 trial to reduce

mortality, has been applied in combat situations. But due to delayed evacuation it was used rarely.

A blood transfusion as a routine medical procedure was started before or parallel with surgical intrusion, and lasted up to stabilisation and evacuation of the patient to the next Role. In some cases we continued hemotransfusion in evacuation vehicles.

From the middle of 2023, the amount of blood transfusions during MEDEVAC increased significantly. This was largely facilitated by the provision of the necessary equipment and training among the personnel of evacuation teams. Training for providers operating in prehospital settings (Role 1 stabilisation points) is conducted by charitable organisation jointly with Ukrainian Transplant coordination centre and in accordance with the Ministry of Health of Ukraine roadmap. It integrates compliance with national standards and best practices from the Trauma Hemostasis & Oxygenation Research (THOR) network`s



Fig. 3. Temporary closure of laparotomy wound: plastic interface shields the bowel, then loose sutures are added

Picture taken by the authors

field transfusion course. A critical component of this program is realistic simulation-based education.

Also important role in this increase played legal regulation of the right (if necessary) to transfuse blood to the wounded during their evacuation from the battlefield by military personnel without medical education after completing the relevant courses [11].

Thus the amount of MTF Roll II, which uses no blood at all, was still high. Whole blood (WB) (O(I) Rh-) – was used at 32% from all the stabilisation units (Role 2). The whole picture was:

- WB (O(I) Rh-), and Packed red blood cells (pRBC) – 4%;
- WB (O(I) Rh-), Fresh frozen plasma (FFP) – 8%;
- WB (O(I) Rh-), pRBC, FFP – 4%;
- WB (O(I) Rh-), pRBC, FFP, Freeze-dried plasma (FDP) – 4%;
- WB (O(I) Rh-), pRBC, FFP, FDP, Cryoprecipitate Anti-hemophilic factor (AHF) – 2%;
- Only pRBC – 2%;
- pRBC, FDP – 2%;
- pRBC, FFP, AHF, FDP – 2%;
- FFP, AHF – 3%;
- 34% used no blood transfusions at all.

PATIENT OUTCOMES

Among all patients who undergo DCS and DCR case fatality rate (CFR) was 5,9 %. In 1,8 %, cases of death were severe extraabdominal injuries. Injuries of the abdomen which lead to death were 3,6 %. In most cases multiple injuries of abdominal organs involving pancreas and duodenum.

In the ETC group we observed failure of intestinal anastomosis sutures and early postoperative hernias.

Among general complications most common were pneumonia (9.2%), anemia requiring transfusion (7.2%), cardiac arrest (6.4%) and acute kidney injury (10.4%).

DISCUSSION

John Chovanec et al. notes that philosophy DCS and DCR is to save patient's life at any costs [12]. Higa G et al. on the other hand insists, that DCS is used much more often than has a reasonable need [13]. Jiong Hao Tan et al. showed that in Borderline patients with polytrauma being adequately resuscitated may be treated with ETC [14]. However data from those studies are related to civilian trauma. And as discussed in a number of studies based on data from the modern russian-Ukrainian war (both its full-scale phase and in the conditions of the Anti-Terrorist Operation), indications for damage control are primarily determined by the tactical situation, and only secondarily by medical indications [15,16]. It is important that Role2 is situated near battle zone and always work in condition of conditional MASCAL. Even if in exact moment it is no delivery of multiple casualties group is still in permanent awaiting mode. Changes in tactical situation can be immediate and unpredictable. That's why time of surgery can't be longer than 90 min. That is the reason why we used DCS over the ETC. for maximum release of medical personnel. Regulated by the Order of the Ministry of Health of Ukraine dated March 8, 2022 № 431. Classically it is distinguished five

critical stages of DCS and DCR: I, patient selection and decision to perform damage control; II, operation and intraoperative hemorrhage management and prevention of contamination; III, resuscitation in the intensive care unit; IV, definitive surgery after returning to the operating room; and V, reconstruction and rehabilitation [17,18].

For battlefield injury it is highly reasonable to add one more Phase 0 of DCS, termed «Damage Control Ground Zero» [19].

In military conditions, time before getting professional surgical care can be quite prolonged.

In 2022 the average evacuation time was 134 min. And ranged from 15 minutes after injury to a maximum of 12 hours. In 2023, evacuation time was significantly increased due to prolonged waiting for evacuation. The average indicators were not representative, as they can be in range from a few hours to a few days. Maximum awaiting time of evacuation (47 days). Evacuation itself in this case, took less than two hours. Nowadays it is less than 10% of wounded who are delivered to the Role II during the Golden hour. It can be due to water barriers, drones, and heavy shelling [20]. The most important in Phase 0 was hemorrhage management, blood transfusion and prevention of hypothermia.

TOURNIQUET APPLICATION

Lipsky et al. stands for that wide implementation of tourniquets, which decreased mortality from extremity hemorrhage by 85% [21]. And for the last years in Ukraine, the same as in the whole other world, tourniquets have become a standard piece of equipment for soldiers and officers on the field. But in the beginning of full scale aggression it was a problem to get enough tourniquets for the Ukrainian army, because a lot of civilians joined it. So the need for tourniquets reached more than two million. So a lot of poor quality tourniquets reached the soldiers. Also, overuse of tourniquets can be observed. Holcomb et al. note that, “recently the proper application of tourniquets for extremity hemorrhage has been increasingly underscored by experiences in Ukraine. With delay in evacuation (upward of 6 h), complications of limb ischemia from prolonged tourniquet applications have been observed” [22] Vladyslav Yatsun notifies that tourniquet application was appropriate in 24.6% of the wounded with tourniquets [23].

From all the wounded, who were transported to Role II 1,19% had tourniquet syndrome, which led to amputation. (64% from all cases of tourniquet syndrome) and in 46% to complicative vascular surgeries or/and fasciotomies. On other direction of battle line it was 5,3% amputations from the total number of casualties.

And tourniquet syndrome enriched 18,8% from the total amount of casualties.

In total, if to compare amount amputations due to tourniquet syndrome to amputations due to complicated extremities injuries it was $42\pm 3\%$ and $58\pm 3\%$ respectfully. Also we should mention $22\pm 4\%$ fasciotomies stipulated by long staying tourniquets.

This data corresponds with other studies. When evacuation was delayed more then for 3 hours in 20% of cases it was conversion of tourniquets by battle medics, in 26,7% conversion by FST, in all other cases no conversions at all. 34% of all cases extremities were amputated after release of tourniquets. 20% fasciotomies, 14% were in need of hemodialysis. Total mortality in this group was 14% (7% with hemodialysis and 7% with fasciotomy).

BLOOD TRANSFUSION IN PROLONGED CASUALTY CARE AND PROLONGED EVACUATION

Still it is no satisfactory fluid therapy for use during prolonged transport, but the whole blood or its components. Current evidence show benefits of the implementation of whole blood transfusion in prehospital services. It was problems with platelet concentrates. In multiple studies it was shown that it usage fresh whole blood and cold-stored whole blood to patient care in austere environments is beneficial and leads to better survival rate [24,25].

Despite this in Ukraine up to middle of 2023 it was illegal for military stuff with out degree in medicine. Just in summer of 2023 the proper order was published by ministry of health. From that time amount of blood transfusions during prolonged casualty care (PCC) and prolonged evacuation increased several dozen times. For example all brigades of The Ukrainian Marine Corps were trained in blood transfusion and all necessary equipment was given to them [26]. It played important role in saving lives in situations when evacuation was seriously delayed or prolonged. During Krynky operation we observed that more than 70% of patient who received additional blood transfusions during the initial resuscitation phase – survived. There was less then 2% of cases of a minor adverse reaction that could be attributed to prehospital transfusion.

Based on the study conducted by Ukrainian military doctors about the thermal properties of blood, it can be concluded that the temperature range of $+37-42^{\circ}\text{C}$ is optimal for heating blood in terms of safety, with a temperature of $+42^{\circ}\text{C}$ demonstrating the best coagulation parameters and effectiveness in preventing hypothermia.

The rationale for this conclusion is provided below, considering key aspects:

1. Safety (Absence of Hemolysis)

•The study data indicate that at temperatures of +37–42°C, no hemolysis was observed in samples from groups A and B (0 damaged erythrocytes), confirming the safety of this range. Hemolysis begins at +43°C (0–1 erythrocytes in group B) and significantly increases at +44–45°C (2–3 erythrocytes in group A, 6–10 in group B).

2. Prevention of Hypothermia

•Heating to +37–42°C effectively prevents hypothermia, which is associated with coagulopathy due to reduced activity of coagulation factors and platelet adhesion.

3. Coagulation Parameters

•Coagulogram data show that from +37 to +42°C, there is an acceleration of coagulation (reduction of PT to 11.0–11.2 s, APTT to 23.0–26.1 s, $p < 0.05$), consistent with increased enzyme activity. D-dimer levels remain within normal limits (0.28–0.29 ng/mL), indicating no fibrinolysis.

•At +44–45°C, group B exhibits significant acceleration of coagulation (PT 11.0 s, APTT 37.2 s, $p < 0.01$) and a decrease in fibrinogen (from 2.9 to 2.4 g/L), suggesting hypercoagulation due to hemolysis and a risk of DIC (Bouchama et al., 2002). In group A at +44°C, prolongation of PT (14.3 s) and APTT (34.6 s) is observed, along with an increase in D-dimers (0.33 ng/mL), indicating the onset of coagulation disturbances.

DCS IN ABDOMINAL AND THORACIC INJURIES

A significant cause of combat deaths is from noncompressible torso hemorrhage. There are just two methods that can reduce intra abdominal bleeding in severe abdominal injury: REBOA system and AAJT. REBOA system showed good results [27], but it is not easy to mount it in a field environment. On other hand AAJT easy to apply [28], and showed good results in controlled swine studies, healthy human volunteer and mannikin study [29,30]. But reports on the use of AAJT in combat conditions are began to appear only last year in limited reports of Ukrainian military doctors. They have good results but are limited in use by trauma to the pelvis, lower extremities, and aorta zone 3.

As it was shown, we often used DCS not just due to life threatening hemorrhage but also due to tactical condition and severe contamination of the abdominal cavity. That gives the opportunity to compare the DCS and ETC groups results.

Among the observed patients CFR, after 5 days of treatment was comparable among both groups. What can be explained by the bigger number of patients who undergo DCS not due to medical, but to tactical indications. Postoperative mortality, in the 7 day period

following surgery, was slightly higher in the DCS group.

Most common organs to be injured, were momentum and small bowel. If we find nothing but momentum injuries, we just finished in ETC approach, leaving control drainage in case of hidden hemorrhage not noticed by surgeon. In injury of the small intestine, we used both ETC and DCS. In case of DCS mostly at first stage it was obstructive resection and anastomosis the next day on the next level. No abdominal complication or mortality observed in these two groups.

Among all patients after DCS worst results were observed in those patients who have injuries of pancreas and duodenum. This patient has abdominal adhesions, postoperative hernias and even one lethal case after two months of treatment.

CONCLUSIONS

The evolving nature of the Russian-Ukrainian war, especially with the introduction of integrated drone reconnaissance-strike systems, has significantly altered the pattern of injuries and the demands on military medical support. The resulting «zone of continuous death» and delayed evacuation due to tactical conditions have necessitated widespread use of Damage Control Surgery (DCS) and Damage Control Resuscitation (DCR), even in scenarios where Early Total Care (ETC) might be preferable under peacetime or civilian trauma settings.

This study confirms the effectiveness of DCS/DCR approaches under MASCAL conditions at Role II facilities, particularly in the context of delayed evacuation, hypovolemia, and resource scarcity. While DCS resulted in a slightly higher complication and postoperative mortality rate compared to ETC, it was indispensable for patients with high Injury Severity Scores (ISS), unstable vitals, and multiple organ injuries, particularly involving the pancreas or duodenum.

Additionally, innovations in field resuscitation, such as the deployment of whole blood transfusion during MEDEVAC and the use of AAJT devices, have contributed to increased survival rates. The integration of these practices into a single medical space—standardized across civilian and military systems—ensured coordinated and timely care despite logistical limitations.

However, the data also highlights critical challenges, including overuse and complications from tourniquets, inconsistent access to blood products, and the need for better triage and surgical timing protocols. The formalization of Phase 0 in the DCS framework—focused on hemorrhage control, hypothermia prevention, and blood transfusion at the point of injury—has proven essential in this conflict and may serve as a valuable model for future high-intensity warfare settings.

In conclusion, this experience emphasizes that surgical decision-making in modern warfare is often dictated more by tactical realities than purely by medical criteria. The find-

ings support continued refinement of DCS/DCR protocols, greater investment in evacuation capabilities, and expansion of prehospital transfusion training for combat medics.

REFERENCES

1. Zaluzhnyi V. Evolyutsiya kharakteru voyennykh diy pereosmyslyla fundamental'ni pryntsyipy hlobal'noyi bezpeky: dosvid Ukrayiny ta svitovyy poryadok, shcho formuyet'sya. [The evolving nature of warfare has redefined the fundamental principles of global security: the Ukrainian experience and the emerging world order]. *Ukrainska Pravda*. 2025. <https://www.pravda.com.ua/eng/columns/2025/04/25/7509135/>. [Accessed 30 May 2025] (Ukrainian)
2. Verba AV, Ostashchenko TM, Plis IB et al. Experience of using consolidated medical units as part of a forward hospital base in conditions of high intensity armed conflict. *Ukrainian Journal of Military Medicine*. 2023;4(1):13-20. doi:10.46847/ujmm.2023.1(4)-013. DOI
3. UN Human Rights Monitoring Mission in Ukraine. 2024. <https://ukraine.ohchr.org/en> [Accessed 30 May 2025]
4. Khotsianivska A. Safari na liudei. Rosiiski viiskovi navmysne poliuiut dronamy za tsyvilnymy na Khersonshchyni. [Safari on people. Russian troops deliberately policing drones behind civilians in Kherson]. *Radio Svoboda*. 2024. <https://www.radiosvoboda.org/a/rosiys%CA%B9kiy-viys%CA%B9kovi-masovo-atakuyut%CA%B9-dronamy-myryne-naselennya-khersona-ta-oblasti/33219523.html> [Accessed 30 May 2025] (Ukrainian)
5. Shostak SL. Funktsionuvannya Medychnykh Syl V Konteksti Stvorennia Yedynoho Medychnoho Prostoru Ukrayiny Zadlya Zdorov' yazberezhennia Natsiyi. [Functioning Of Medical Forces In The Context Of Creating A Single Medical Space Of Ukraine For The Purpose Of Protecting The Nation's Health]. *Vcheni zapysky TNU imeni V.I. Vernads'koho. Seriya: Publichne upravlinnya ta administruvannya*. 2023;74(2):96-100. doi: 10.32782/TNU-2663-6468/2023.2/16. (Ukrainian) DOI
6. Zhakhovskiy VO, Livinskiy VH. Pravovi ta doktrynal'ni zasady viys'kovoyi okhorony zdorov'ya ta medychnoho zabezpechennia Zbroynykh Syl Ukrayiny. [Legal and doctrinal principles of military health care and medical support of the Armed Forces of Ukraine]. *Nauka i oborona*. 2024;(3):18-28. doi: 10.33099/2618-1614-2024-26-3-18-28. (Ukrainian) DOI
7. Pro zatverdzhennia Obsiahiv nadannia medychnoi dopomohy na dohospitalnomu etapi, yaki nadaiutsia pid chas vedennia boiovykh dii ta pidhotovky syl bezpeky i syl oborony za pryznachenniam u taktychnykh umovakh [On approval of the Scope of medical care at the pre-hospital stage, which is provided during combat operations and training of security forces and defense forces for their intended purpose in tactical conditions.]. *Ofitsiyniy vebportal parlamentu Ukrainy*. <https://zakon.rada.gov.ua/laws/show/z1359-24#Text> [Accessed 30 May 2025] (Ukrainian)
8. Lurin IA, Khoroshun EM, Panasenko SI et al. Tymchasove zdavlennia aorty pry boyoviy khirurhichniy travmi. [Temporary compression of the aorta in combat surgical trauma]. *Svit medytsyny ta biolohiyi*. 2024;20(90):088-92. (Ukrainian)
9. Gumeniuk KV, Marcinkovsky IP, Bogush GL, Verdesch VG. Results of surgical treatment of fire wounds of colon. *Kharkiv Surgical School*. 2021;(5-6):52-6. DOI:10.37699/2308-7005.5-6.2021.11.
10. Khoroshun EM, Lurin IA, Shipilov SA et al. The use of surgical damage control tactics in the treatment of severely wounded with combat abdominal trauma in modern warfare. *The Ukrainian Journal of Clinical Surgery*. 2024;91(3):47-53. doi: 10.26779/2786-832X.2024.3.47. DOI
11. Uriad dozvoliv boiovym medykom perelyvati krov na dohospitalnomu etapi [The institution allowing combat medics to transfuse blood at the prehospital stage]. *Armyinform.com.ua*. 2023. <https://armyinform.com.ua/2023/09/05/uryad-dozvoliv-boiovym-medykam-perelyvati-krov-na-dogospitalnomu-etapi/> [Accessed 30 May 2025] (Ukrainian)
12. Chovanes J, Cannon JW, Nunez TC. The Evolution of Damage Control Surgery. *Surgical Clinics of North America*. 2012;92(4):859-75. doi: 10.1016/j.suc.2012.04.002. DOI
13. Higa G, Friese R, O'Keeffe T et al. Damage control laparotomy: a vital tool once overused. *J Trauma* 2010;69(1):53. doi: 10.1097/TA.0b013e3181e293b4. DOI
14. Tan JH, Wu TY, Tan JYH et al. Definitive Surgery Is Safe in Borderline Patients Who Respond to Resuscitation. *J Orthop Trauma*. 2021;35(7):e234-e240. doi: 10.1097/BOT.0000000000001999. DOI
15. Herasymenko OS. Khirurhichne likuvannya boiovykh uskodzhen zhyvota u raioni provedennia antyterorystychnoi operatsii. [Surgical treatment of combat ear wounds of animals in the area of anti-terrorist operations]. *Odeskyi medychnyi zhurnal*. 2017 (3):34-7. (Ukrainian)
16. Remondelli MH, Rhee J, Barzanji NK et al. Advancements in Prehospital, En-Route, and Damage Control Casualty Care and Areas of Future Research for Large-Scale Combat Operations. *Current Trauma Reports*. 2025;11(1).
17. Moore EE. Orr Memorial Lecture. Staged laparotomy for hypothermia, acidosis, and coagulopathy syndrome. *Am J Surg*. 1996;172(5):405-10. doi: 10.1016/s0002-9610(96)00216-4. DOI
18. Johnson JW, Gracias VH, Schwab CW et al. Evolution in damage control for exsanguinating penetrating abdominal injury. *J Trauma*. 2001;51(2):261-9. doi: 10.1097/00005373-200108000-00007. DOI

19. Meléndez-Lugo JJ, Caicedo Y, Guzmán-Rodríguez M et al. Prehospital Damage Control: The Management of Volume, Temperature... and Bleeding! Colomb Med (Cali). 2020;51(4):e4024486. doi: 10.25100/cm.v51i4.4486. DOI 
20. Specifics of providing emergency pre-medical and evacuation assistance in water operations Generalization of military experience of operations in 2022-2024 [Internet]. [cited 2025 May 30]. <https://cbacenter.ngo/storage/documents/9f5d76a6-b995-4997-9973-187de29b0576/72fe6047635d8f7bbb865c78045b58f8c249e3d7.pdf> [Accessed 30 May 2025]
21. Lipsky AM, Ganor O, Abramovich A et al. Walking between the drops: Israeli defense forces' fluid resuscitation protocol. J Emerg Med. 2013;44:790–5. doi: 10.1016/j.jemermed.2012.08.029. DOI 
22. Holcomb JB, Dorlac WC, Drew BG et al. Rethinking limb tourniquet conversion in the prehospital environment. J Trauma Acute Care Surg. 2023;95(6):e54–60. doi: 10.1097/TA.0000000000004134. DOI 
23. Yatsun V. Application of Hemostatic Tourniquet on Wounded Extremities in Modern “Trench” Warfare: The View of a Vascular Surgeon. Military Medicine. 2024;189(1-2):332–336. doi: 10.1093/milmed/usac208. DOI 
24. Barkana Y, Stein M, Maor R et al. Prehospital Blood Transfusion in Prolonged Evacuation. J Trauma. 1999;46(1):176–80. doi: 10.1097/00005373-199901000-00030. DOI 
25. Strandenes G, De Pasquale M, Cap AP et al. Emergency whole-blood use in the field: a simplified protocol for collection and transfusion. Shock. 2014;41(1):76–83. doi: 10.1097/SHK.0000000000000114. DOI 
26. Three Brigades of the OC South Trained and Equipped for Blood Transfusions. PULSE . 2025. <https://www.pulse.charity/en/post/three-brigades-of-the-oc-south-trained-and-equipped-for-blood-transfusions> [Accessed 30 May 2025]
27. Smith SA, McAlister VC. A novel REBOA system: prototype and proof of concept. Can J Surg. 2018;61:S188–94. doi: 10.1503/cjs.015718. DOI 
28. Smith TN, Beaven A, Handford C et al. Abdominal Aortic Junctional Tourniquet – Stabilized (AAJTS) can be applied both successfully and rapidly by Combat Medical Technicians (CMTs). BMJ Mil Health. 2023;169:493–498. doi: 10.1136/bmjilitary-2021-001881. DOI 
29. Rall JM, Ross JD, Clemens MS et al. Hemodynamic effects of the abdominal aortic and junctional tourniquet in a hemorrhagic swine model. J Surg Res. 2017;212:159–66. doi: 10.1016/j.jss.2017.01.020. DOI 
30. Kheirabadi BS, Terrazas IB, Miranda N et al. Physiological consequences of abdominal aortic and junctional tourniquet (AAJT) application to control hemorrhage in a swine model. Shock. 2016;46:160–6. doi: 10.1097/SHK.0000000000000651. DOI 
31. Androshchuk D, Verba A. Successful Management of Battlefield traumatic Cardiac Arrest Using the Abdominal Aortic and Junctional Tourniquet (AAJT): A Case Series. J Spec Oper Med. 2025;25(1):65–69. doi: 10.55460/7FEV-3ZRK. DOI 

No funding was provided for this work. This work was supported by the Department of Health of Ministry of Defence of Ukraine.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Dmytro O. Samofalov

Ministry of Defence of Ukraine

23/3 Lesi Ukrainky Av., Odesa, Ukraine

e-mail: dr.samofalov@gmail.com

ORCID AND CONTRIBUTIONSHIP

Dmytro O. Samofalov: 0000-0001-7850-5365      

Nataliya Izhytska: 0000-0002-7089-5810    

Dmytro Androshchuk: 0009-0008-5431-9574   

Igor Korpusov: 0009-0005-8851-3883  

Leonid Kopus: 0009-0000-7740-9056  

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 10.06.2025

ACCEPTED: 29.08.2025



Self-assessment of the quality of life by Ukrainians during martial law and ways to improve it

Grygoriy P. Griban¹, Natalia A. Lyakhova², Inna O. Asauliuk³, Oleksandra Yu. Brezdeniuk³, Oksana V. Zeleniuk⁴, Valentin P. Golub⁴, Nataliya A. Prudyvus³

¹ZHYTOMYR IVAN FRANKO STATE UNIVERSITY, ZHYTOMYR, UKRAINE

²POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

³VINNYTSIA MYKHAILO KOTSIUBYNSKYI STATE PEDAGOGICAL UNIVERSITY, VINNYTSIA, UKRAINE

⁴KYIV NATIONAL UNIVERSITY OF TECHNOLOGY AND DESIGN, KYIV, UKRAINE

ABSTRACT

Aim: To study the quality of life in Ukraine during martial law and identify priority areas for its improvement.

Materials and Methods: The research was conducted in 2023–2024. It involved 159 respondents of different genders and age. Research methods: bibliographic, self-assessment of quality of life (survey), medical, and statistical. The author's questionnaire consists of 6 blocks and contains 77 questions.

Results: It has been established that 51.6 % of the respondents are dissatisfied with their health, 65.4 % – with the health care system in Ukraine, 52.2 % – with the education system; housing conditions during the war deteriorated by 34.6 %; the number of those satisfied with their financial situation decreased from 52.8 % to 37.7 %, with their place of work – from 83.0 % to 67.3 %; the level of satisfaction with the quality of life decreased from 76.1 % to 31.5 %. Priority areas for improving the quality of life of Ukrainians in the postwar period have been identified: maintaining public health, improving the quality of medical services, providing housing and employment, increasing access to and quality of education, improving the environmental situation, increasing incomes, social assistance, modernizing infrastructure, stabilizing the socio-political situation, etc.

Conclusions: It has been found that during the war, there were significant negative changes in the quality of life of the Ukrainian population. The findings should be considered when public health experts develop practical recommendations for improving the quality of life of the Ukrainian population during and after the war.

KEY WORDS: quality of life, war, martial law, population of Ukraine

Wiad Lek. 2025;78(9):1798–1804. doi: 10.36740/WLek/212517 DOI

INTRODUCTION

In modern research [1, 2], there is no single approach to assessing the quality of life; each of the developed approaches is based on the objectives of the research being conducted and the specifics of the research object (country, region, locality, etc.). The concept of “quality of life” characterizes both material human benefits (welfare, prosperity, housing conditions, etc.) and intangible ones (social, economic, environmental, socio-political living conditions, health, education, security, participation in public life, leisure, etc. [1, 3].

Scientists [4] believe that “quality of life” includes such structural elements as the quality of the population (demographic characteristics, health status of the population, level of education, etc.), quality of the environment (natural and environmental conditions, economic development of territories, development of social infrastructure, level of personal safety), quality of

activity (quality of work, recreation, domestic, spiritual, cultural and socio-political spheres of life).

The quality of life varies significantly around the world. It depends on many factors, including the natural, social, economic, and socio-political environment in which the population lives, health status, level of education, satisfaction with the profession, housing conditions, etc. [5] Today, the quality of life in Ukraine is low compared to economically developed countries. According to international studies, Ukraine ranks 77th among 191 countries regarding quality of life (human development index) and 92nd in happiness among 150 countries [6, 7].

According to the results of studies [8], the quality of life of the population of Ukraine is assessed by statistical data on the quality of the natural, social, economic, and socio-political environment, as well as by the level of satisfaction of each member of society with the goods

that are valuable to them – material wealth, place of work, health status, living conditions, environmental situation, personal safety, social well-being, etc. At the same time, the issue of assessing the quality of life of the Ukrainian population during wartime and finding ways to improve it remains insufficiently researched.

AIM

The aim is to study the quality of life in Ukraine during martial law and identify priority areas for its improvement.

MATERIALS AND METHODS

The research was conducted in 2023-2024. It involved 159 respondents of different genders belonging to various age groups – from 18 to 75 years old. The 18-25, 26-35, and 46-65 age categories are represented in approximately the same ratio – up to 30 %; the respondents under 18 – 2.5 %, 66-75 – 1.3 %. 97.5 % of the respondents live in Ukraine, 2.5 % live abroad. Among the surveyed respondents, 61.0 % are married, 39.0 % are single. The research results were processed at the Department of Physical Education and Sport Improvement of Zhytomyr Ivan Franko State University (Zhytomyr, Ukraine).

Research methods: bibliosemantic, self-assessment of quality of life (according to the author's questionnaire), medical and statistical. The bibliosemantic method was used to study the literature on the chosen topic (18 sources from PubMed, Scopus, Web of Science, Index Copernicus, and other databases were analyzed). The method of self-assessment of the quality of life was used to survey the population of Ukraine using the author's questionnaire to determine the level of satisfaction of the population with various aspects of their lives; the author's questionnaire consisted of six blocks of questions: Block 1. General Information About Respondents (8 questions); Block 2. Natural Environment (8 questions); Block 3. Social Environment (20 questions); Block 4. Economic Environment (14 questions); Block 5. Socio-Political Environment (25 questions); Block 6. Ways to Improve the Quality of Life in Ukraine (2 questions). In total, the questionnaire contains 77 questions. The questionnaire was anonymous without any references to the authors of the article in the answers. The results were used for scientific purposes only. Questionnaire was assessed by the experts in this field (1 professor and 3 associate professors) and was approved by the Academic Council of Zhytomyr Ivan Franko State University (Protocol No. 9 dated 10.02.2023). The medical and statistical method was used to process the experimental data obtained during the research.

Data collection, processing, and analysis of the research results were performed on a personal computer using MS Excel, a software package that allows statistical data processing methods. Consent to voluntary participation in the survey was obtained from all the respondents involved in the study. This research followed the regulations of the World Medical Association Declaration of Helsinki – ethical principles for medical research involving human subjects.

RESULTS

When analyzing the answers to the questions in Block 1 of the questionnaire, it was found that the majority of the respondents have higher education (44.6 %), one-third have completed secondary education (34.6 %), and the rest have specialized pre-university education (20.8 %). Among the respondents, the largest groups of professions were represented by military personnel (30.2 %), healthcare workers (18.9 %), students (17.0 %), and employees of educational institutions (11.9 %). Most respondents live in urban areas (60.4 %), while the rest (39.6 %) live in rural areas. The residents of Zhytomyr, Vinnytsia, and Kyiv oblasts accounted for 69.2 %, Poland – 1.3 %, Slovakia, and the United States – 0.6 % each. The remaining 28.3 % of the respondents live in Ternopil, Khmelnytskyi, Lviv, Sumy, Kharkiv, Kirovohrad, and Donetsk oblasts of Ukraine. All settlements where the respondents live are located in the territory controlled by Ukraine.

The answers to the questions in Block 2 of the questionnaire (Natural Environment) showed that 77.4 % of the respondents are not satisfied with the environment in Ukraine, and 86.8 % are convinced that the environmental situation in the country has deteriorated during the full-scale war. Among the main environmental problems that worsen the state of the environment, the respondents mentioned: ecological pollution from industrial enterprises and factories (52.2 %); air pollution due to a large number of vehicles (46.5 %); the presence of landfills near housing (37.1 %); environmental pollution due to enemy bombing (30.2 %); water pollution (18.9 %); radiation emissions (10.1 %); and mining plants (1.9 %).

The analysis of the questions in Block 3 (Social Environment) revealed that 65.4 % of the respondents are dissatisfied with the health care system in Ukraine, and only one-third of the respondents (34.6 %) are satisfied. At the same time, 51.6 % of the respondents are dissatisfied with their health. This is quite understandable since only 31.4 % of the respondents adhere to a healthy lifestyle. Less than half of the respondents (47.8 %) are satisfied with the education system in

Ukraine. Most of the respondents (79.2 %) are quite confident with their education level. It was found that before the war, 96.9 % of the respondents had adequate living conditions, while during the war, living conditions deteriorated for 34.6 % of the respondents and did not change for 60.4 %. It was found that the frequency of attending cultural and entertainment events during the war decreased from 81.7 % to 32.0 %. The number of respondents who regularly engage in physical exercises and sports decreased from 54.1 % before the war to 30.8 % during the war; those who could afford a resort vacation decreased from 64.8 % to 17.0 %. Before the war, the respondents' satisfaction with the work of transportation in Ukraine was 76.2 %, and during the war, it was 56.6 %.

The analysis of the questions in Block 4 (Economic Environment) revealed that 52.8 % of the respondents were satisfied with their financial situation before and 37.7 % during the war. Before the war, 83.0 % of the respondents were satisfied with their jobs, while during the war – 67.3 %. Before the war, 44.0 % of the respondents were satisfied with their financial income (salary, pension, scholarship), while during the war – 41.5 %. 6.3 % of the respondents lost their property and housing during the war. Before the war, 47.2 % of the respondents assessed the cost of utilities as high, while it was 81.1 % during the war. Before the war, 10.1 % of the respondents reported poor quality food, and during the war – 26.4 %. It is worth noting that the surveyed population of Ukraine is trying to improve their financial situation by working at several jobs – 22.6 %; help from relatives – 16.4 %; and social benefits – 10.1 %. Before the war, 86.2 % of the respondents considered their standard of living satisfactory, 8.8 % – high; during the war, satisfactory – 71.1 %, high – 4.4 %.

The analysis of the questions in Block 5 (Socio-Political Environment) revealed the level of satisfaction of the Ukrainian population with the socio-political situation in the country before the war: yes – 10.7 %; not quite – 67.9 %; no – 21.4 %. During the war, the share of the respondents who were dissatisfied with the socio-political situation in the country increased to 51.6 %, while those who were satisfied decreased to 5.1 %. During the war, the number of respondents who considered themselves to have low income increased from 16.4 % to 23.3 %.

It is important to note that before the war, 86.8 % of the respondents spoke Ukrainian, and 9.4 % spoke russian; during the war, the share of the population speaking Ukrainian increased to 91.8 %, while the share of russian decreased to 2.5 %. A study of the respondents' opinions on the quality of their family relationships revealed a decrease in satisfaction with them during the war in 63.5 % of the respondents, compared to 84.9 %

in the pre-war period. In 0.6 % of the respondents, dissatisfaction with family relationships is related to the forced residence of the family outside of Ukraine.

It has been found that 32.1 % of the respondents are currently dissatisfied with healthcare reforms and 34.0 % with the education system. Most respondents believe that Ukraine had a high level of corruption (78.0 %) and bribery (65.4 %) before the war. 74.8 % of the respondents expressed the opinion that the level of corruption in the country has increased even more in the current situation; the same applies to domestic bribery (63.5 %).

A group of the following questions studied the population's level of personal and social well-being. It has been found that during the war, the respondents lost a sense of security (68.6 %), mental health (62.9 %), the ability to relax (50.3 %), friends (39.6 %), physical health (35.2 %), income (26.4 %), etc. The respondents also identified the most important indicators of life satisfaction for them: peace in the country (89.9 %); good health (59.1 %); personal security (49.1 %); love of family members (48.4 %); well-paid job (47.2 %); opportunity to relax (42.8 %); opportunity to receive necessary medical care (42.1 %). When assessing the level of satisfaction with their lives, the respondents said that before the war, 76.1 % were satisfied with their lives. Now, only 31.5 % were satisfied with it (Fig. 1).

According to the questions of Block 6, we investigated the respondents' opinions on the priority areas for improving the quality of life in Ukraine during the war and in the postwar period. According to the results of the analysis of the respondents' answers, the respondents primarily associate the improvement of the quality of life during the war with the following areas: help to the front (59.7 %); maintaining the moral and psychological state of the population (53.5 %); compliance with the law (49.7 %); quality and accessibility of medical care (49.7 %); stabilization of the socio-political situation in the country (47.2 %); the environmental situation in the country (45.3 %); job security (44.0 %); maintaining public health (40.9 %); increasing income levels (39.6 %); collective and personal security (37.7 %); housing security (36.5 %); care for vulnerable groups of the population, social assistance (33.3 %).

According to the respondents, after the war ends, the following quality of life indicators will become a priority for the population: job security (55.3 %); housing security (54.7 %); increase in income (50.3 %); the environmental situation in the country (50.3 %); maintaining public health (49.7 %); stabilization of the socio-political situation in the country (49.1 %); maintaining the moral and psychological state of the population (48.4 %); quality and accessibility of medical care (45.3 %); compliance

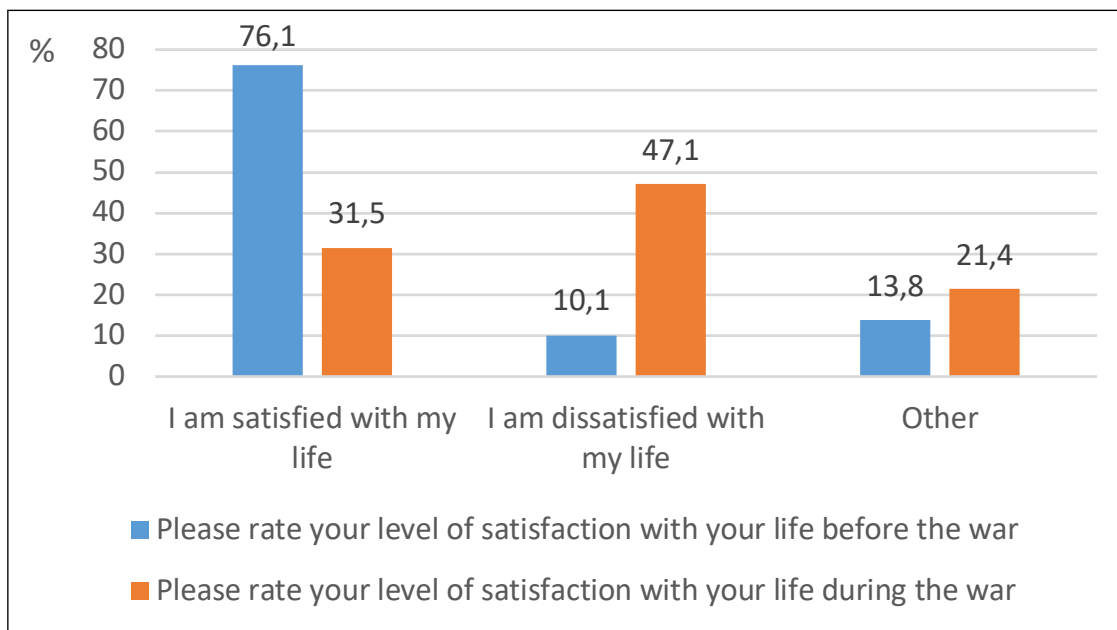


Fig. 1. The respondent's level of satisfaction with their lives before and during the war (n = 159)
Picture taken by the authors

with the law (44.7 %); collective and personal security (37.7 %); social assistance (37.7 %).

DISCUSSION

Modern research on the quality of life is based on the fundamental scientific support of many scientists [5, 9, 10]. Quality of life as a multidimensional concept refers to all spheres of human existence – health, including mental health, well-being, education, medical care, living conditions (housing, material, environmental, socio-political), extends to different levels of society – personal, family, professional and public, consists of objective and subjective components, which are described by various indices (indicators) and is determined by the level of realization of human needs [9, 11].

Based on the results of research by many scientists [1, 3, 8, 12], we have identified the most important problems of the quality of life of the Ukrainian population in wartime compared to peacetime:

- Demographic: the country's population has decreased, and the aging rate and mortality rate have increased;

- Public health and quality of medical services: a significant number of healthcare facilities in Ukraine were destroyed or damaged, which reduced the ability to receive quality medical services; due to constant stressors, the health status of the country's population has deteriorated significantly, a significant part of the population has turned to bad habits; the share of the population in need of rehabilitation measures has increased substantially;

- Security: the level of life safety has significantly decreased for all categories of citizens of the country in the context of war;

- Economy and incomes: since the beginning of the war, 77 % of the surveyed population has seen a decrease in income; 47 % of the employed are unsure of their future; a large number of skilled workers have been lost (due to the mobilization of citizens of working age and those who left the country); financial capabilities of businesses are being exhausted; despite the increase in the subsistence level per person of the minimum wage and pension, as well as state social assistance to people with disabilities, in 2022-2024, the level of real wages decreased by 17.7%; the economic situation of families worsened significantly;

- Education: a large number of educational institutions have been destroyed; the mental health of students, teachers, and lecturers has deteriorated; a significant number of institutions are not equipped with bomb shelters; due to the blackout, there is no uninterrupted power supply and stable access to the Internet; students abroad cannot receive full educational services due to the language barrier or are forced to study remotely under the Ukrainian program;

- Ecology: the state of the environment has deteriorated significantly; from the beginning of the war to the end of 2022, more than 2,200 crimes against the environment were recorded; the hostilities caused significant environmental pollution – air, drinking water, and soil; ecotourism facilities were destroyed, and the diversity of flora and fauna decreased; material damage from air pollution is over UAH 927 billion;

- Labor and working conditions: in 2022, the number of vacancies registered with the State Employment Service decreased by 48 %; the share of employees in the shadow economy increased, and working conditions worsened (over 41 %);

- Housing: a large share of the population lost their homes; a significant number of homes were destroyed; living conditions deteriorated;

- Purchasing power of the population: the cost of food increased by 32.7 %, clothing and footwear by 6.8 %, housing, and utilities by 5.6 %, household appliances and household items by 25.5 %, healthcare services by 17.6 %, transportation by 39.3 %, education by 9.8 %, and communication services by 11 %;

- Civil liberties, leisure, and life satisfaction: the population of Ukraine has lost the ability to move freely around the country and travel abroad, and the ratio between working time and leisure time has been disturbed; the level of life satisfaction has decreased.

It is established that the main directions of the State policy to improve the quality of life of the population of Ukraine are stimulation of economic growth, decentralization of budgetary funds distribution, development of the labor market, improvement of pension provision, improvement of the social support mechanism, development of small and medium-sized enterprises, creation of a system of integration of services, reform of the health care system and housing and communal services [13].

These strategic directions of improving the quality of life of the population of Ukraine are the basis of the country's regional policy, which covers such areas of life as demographic processes, health, social and environmental safety, development of educational and cultural spheres, increase in employment and labor protection, provision of housing, modernization of housing and communal services, strengthening of social integration, participation of the population of the region in the socio-economic, political and cultural life of society, increase in the level of social and personal consciousness [14, 15].

To improve the quality of life of the population, Ukraine develops and implements State targeted social programs, namely: affordable housing for such categories of the population as military personnel, medical workers, and educators – “E-Home”; “Youth of Ukraine”; national-patriotic education; combating human trafficking; childbirth assistance, baby packages; rehabilitation and health improvement programs for children with disabilities and from low-income families – “E-Health Care”; a social program for psychological support of the population of 150 communities of Ukraine referred to as “Resilience Center”; medical programs named “Affordable Medicines”, “Help for Joints”, “I See”, etc. At the level of territorial communities, there are also regional targeted social programs, such as “Preventing and Counteracting Domestic Violence and/or Gender-based Violence”, “Safe City”, etc.

However, according to experts [16], the measures currently being taken in Ukraine to improve the population's lives are insufficient. Given the profound consequences of the war for the economy, environment, health, medical and educational spheres of life, security, civil liberties, etc., measures to improve the quality of life of the population at the level of the state, society, each family and individual require fundamental changes. Taking into account the results of our research and based on the conclusions of scientists in this field [2, 4, 11, 17, 18], we have identified priority areas for improving the quality of life of the population of Ukraine during the war and, especially after its end:

- in the postwar period, housing problems of the population can be solved by repairing the partially destroyed property, subsidizing rental housing, and rebuilding the country's housing stock;

- given the growing volume of environmental pollution in the country, in the postwar period, it will be necessary to improve existing and develop new standards for emissions and discharges using international grants and loans;

- promising areas of the country's recovery in the area of “population income” are economic development and bringing the levels of minimum and real wages closer to the standards of remuneration in the EU countries; increasing the purchasing power of the population; minimizing the risk of poverty and social exclusion of the weakest categories of the population; preventing poverty and social exclusion among internally displaced persons;

- the country's infrastructure and digital network, which was destroyed by the war, needs to be restored and modernized;

- the state's priority task is to rebuild healthcare facilities, improve the quality of service provision and simplify access to specialized medical care; master new modern methods of laboratory diagnosis, treatment, rehabilitation, and prevention; further develop the digitalization of the medical industry, including the spread of contemporary health monitoring applications, the introduction of electronic prescriptions, etc.;

- an important area of improving the quality of life in Ukraine is the creation of a safe environment and the involvement of the population in a healthy lifestyle;

- it is necessary to create and fund a psychological rehabilitation service for the military and civilians;

- improving the accessibility and quality of education is a priority for the state in the postwar period. The younger generation needs modern, competitive educational programs that are unified with programs from other countries, which will create the necessary conditions for international academic mobility of students and academic staff.

CONCLUSIONS

It has been established that the quality of life of the Ukrainian population has significantly decreased as a result of hostilities. The environmental situation has deteriorated dramatically (86.8 %). The population is particularly concerned about environmental pollution from industrial facilities, a large number of vehicles, landfills near housing; destruction of nature due to enemy bombing, reduced water quality due to the destruction of the Kakhovka hydroelectric power plant, emissions from the Zaporizhzhia nuclear power plant, etc. 51.6 % of the respondents are dissatisfied with their health, but only 31.4 % adhere to a healthy lifestyle. More than half of the respondents are dissatisfied with the education system in Ukraine, and more than 20 % of them are unable to access education because of the war. The living conditions of the population have deteriorated significantly during the war. Before the war, only 3.1 % were dissatisfied with them; now, it is a third of the respondents. The share of people attending cultural and sporting events during the war has significantly decreased. The number of people satisfied with their financial situation has decreased (from 52.8 % to 37.7 %), as well as with their place of work (from 83.0 % to 67.3 %). Only 5.8 % are satisfied with the socio-political situation in the country. The share of the population belonging to the lower class in terms of income

has increased (from 16.4 % to 23.3 %). During the war, the number of Ukrainian citizens who speak Ukrainian has increased (from 86.8 % to 91.8 %). According to the respondents, the level of corruption (74.8 %) and bribery (63.5 %) in Ukraine has increased during the full-scale war. During the full-scale war, the respondents lost their sense of happiness, peace, joy, optimism, security, mental health, and relaxation. Feelings of fatigue, exhaustion, depression, and caution replaced this.

During the war, life satisfaction decreased from 76.1 % to 31.5 %. To improve the quality of life in a state of war, the respondents suggest that the state authorities should pay attention to priority areas such as providing the population with housing and employment, improving the environmental situation in the country, maintaining public health, increasing incomes, social assistance, and stabilizing the socio-political situation in the country. The importance of these quality-of-life indicators should increase in the postwar period.

PROSPECTS FOR FURTHER RESEARCH

A comparative analysis of the quality of life of the Ukrainian population living in urban and rural areas during the war is planned.

REFERENCES

1. Buchcik J, Kovach V, Adedeji A. Mental health outcomes and quality of life of Ukrainian refugees in Germany. *Health Qual Life Outcomes*. 2023;21(1):23. doi:10.1186/s12955-023-02101-5. DOI
2. Kiro L, Urbanovych A, Zak M. Intervention impact on quality of life in Ukrainians with post-traumatic stress disorder. *BMC Psychol*. 2024;12(1):601. doi:10.1186/s40359-024-02109-6. DOI
3. Wang S, Barrett E, Hicks MH et al. Associations between mental health symptoms, trauma, quality of life and coping in adults living in Ukraine: A cross-sectional study a year after the 2022 Russian invasion. *Psychiatry Res*. 2024;339:116056. doi:10.1016/j.psychres.2024.116056. DOI
4. Panzini RG, Mosqueiro BP, Zimpel RR et al. Quality-of-life and spirituality. *Int Rev Psychiatry*. 2017;29(3):263-282. doi:10.1080/09540261.2017.1285553. DOI
5. Haraldstad K, Wahl A, Andenæs R et al. A systematic review of quality of life research in medicine and health sciences. *Qual Life Res*. 2019;28(10):2641-2650. doi:10.1007/s11136-019-02214-9. DOI
6. Anjum G, Aziz M, Hamid HK. Life and mental health in limbo of the Ukraine war: How can helpers assist civilians, asylum seekers and refugees affected by the war?. *Front Psychol*. 2023;14:1129299. doi:10.3389/fpsyg.2023.1129299. DOI
7. Pavlenko V, Kurapov A, Drozdov A et al. War impact on Ukrainian university women: Does location status effect depression and quality of life factors? *Health Care Women Int*. 2024;45(2):164-168. doi:10.1080/07399332.2023.2289428. DOI
8. Slaba O, Sadova-Chuba Z, Hrushkovska D, Hurka O. Comparative analysis of the quality of life of women who left the territory of Ukraine during the ongoing Russia – Ukraine war and women who stayed at their homes. *Wiad Lek*. 2024;77(1):42-46. doi:10.36740/WLek202401106. DOI
9. Rakhshani T, Saeedi P, Kashfi SM et al. The relationship between spiritual health, quality of life, stress, anxiety and depression in working women. *Front Public Health*. 2024;12:1366230. doi:10.3389/fpubh.2024.1366230. DOI
10. Fumincelli L, Mazzo A, Martins JCA, Mendes IAC. Quality of life and ethics: A concept analysis. *Nurs Ethics*. 2019;26(1):61-70. doi:10.1177/0969733016689815. DOI
11. Goto R, Pinchuk I, Kolodezhny O et al. Mental Health of Adolescents Exposed to the War in Ukraine. *JAMA Pediatr*. 2024;178(5):480-488. doi:10.1001/jamapediatrics.2024.0295. DOI

12. Baker MS, Baker J, Burkle FM Jr. Russia's Hybrid Warfare in Ukraine Threatens Both Healthcare & Health Protections Provided by International Law. *Ann Glob Health*. 2023;89(1):3. doi:10.5334/aogh.4022. DOI 
13. Tsybuliak N, Kolomiets U, Lopatina H et al. Anxiety among Ukrainian academic staff during wartime. *Sci Rep*. 2024;14(1):27152. doi:10.1038/s41598-024-78052-8. DOI 
14. Hryhorczuk D, Levy BS, Prodanchuk M et al. The environmental health impacts of Russia's war on Ukraine. *J Occup Med Toxicol*. 2024;19(1):1. doi:10.1186/s12995-023-00398-y. DOI 
15. Barten DG, Tin D, Granholm F et al. Attacks on Ukrainian healthcare facilities during the first year of the full-scale Russian invasion of Ukraine. *Confl Health*. 2023;17(1):57. doi:10.1186/s13031-023-00557-2. DOI 
16. Pinchuk I, Solonskyi A, Yachnik Y et al. Dobrostan psychiczny ukraińskich studentów trzy miesiące po wybuchu wojny na pełną skalę. [Psychological well-being of Ukrainian students three months after the emerge of full-scale war]. *Psychiatr Pol*. 2024;58(1):121-151. doi:10.12740/PP/177073. (Polish) DOI 
17. Dubenko A, Morelli R, Cross JH et al. Mental health and quality of life of individuals with epilepsy during the war in Ukraine. *Epilepsia*. 2024;65(9):2718-2727. doi:10.1111/epi.18052. DOI 
18. Kurapov A, Danyliuk I, Loboda A, et al. Six months into the war: a first-wave study of stress, anxiety, and depression among in Ukraine. *Front Psychiatry*. 2023;14:1190465. doi:10.3389/fpsy.2023.1190465. DOI 

The study was carried out according to the plan of the research work of Zhytomyr Ivan Franko State University for 2014-2024 on the theme of "Theoretical and methodological bases of improving the educational process of physical education at higher educational institutions" (state registration number 0114U003978).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Natalia A. Lyakhova

Poltava State Medical University

24 Shevchenko st, 36000 Poltava, Ukraine.

e-mail: natanew2017@ukr.net

ORCID AND CONTRIBUTIONSHIP

Grygoriy P. Griban: 0000-0002-9049-1485  **A**

Natalia A. Lyakhova: 0000-0003-0503-9935  **E**

Inna O. Asauliuk: 0000-0001-8119-2726  **A**  **B**

Oleksandra Yu. Brezdeniuk: 0000-0003-0844-8777  **B**  **D**

Oksana V. Zeleniuk: 0000-0001-9183-7807  **B**  **C**

Valentin P. Golub: 0009-0009-1122-6033  **B**  **D**

Nataliya A. Prudyvus: 0009-0003-1761-9467  **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: 18.04.2025

ACCEPTED: 27.08.2025



Analysis of the association of rs1333049-polymorphic variants of the *ANRIL* gene with the development of clear cell renal cell carcinoma in Ukrainian population

Yelizaveta Stroi¹, Andriy Volkohon², Olha Obukhova¹

¹SUMY STATE UNIVERSITY, SUMY, UKRAINE

²SUMY REGIONAL CLINICAL ONCOLOGY CENTER, SUMY, UKRAINE

ABSTRACT

Aim: The study aimed to assess the association between rs1333049 polymorphic variants of the *ANRIL* gene and the development of clear cell renal cell carcinoma in the Ukrainian population.

Materials and Methods: Venous blood from 201 individuals was analyzed, including 101 ccRCC patients (42 women, 59 men) and 100 cancer-free controls (34 women, 66 men). *ANRIL* rs1333049 genotyping was performed using real-time PCR, with statistical analysis conducted via Prism (v10.4.1) and R (v4.4.2).

Results: The rs1333049 genotype distribution in ccRCC patients was GG – 16 (15.8%), GC – 50 (49.5%), CC – 35 (34.7%); in controls: 28 (28%), 49 (49%), 23 (23%) ($P=0.0561$). The C allele was more frequent in ccRCC patients ($P=0.0167$). In the dominant model, GC+CC carriers had a 2.066-fold higher risk than GG homozygotes ($P=0.0392$). No genotype differences were found between sexes in controls ($P=0.39$), but allele distribution differed in male and female ccRCC patients ($P=0.0105$). In the recessive model, males with CC had a 2.5-fold higher ccRCC risk ($P=0.02$). Kaplan-Meier analysis found no effect of rs1333049 on overall survival.

Conclusions: The rs1333049 polymorphism of the *ANRIL* gene increases ccRCC risk. GC and CC genotypes raise risk 2.07-fold ($P=0.0392$), up to 3.1-fold ($P=0.040$) after adjustments. In males, CC genotype increases risk 2.5-fold ($P=0.02$) and 3.12-fold ($P=0.05$) after adjustments. No link to overall survival was found ($P=0.4321$).

KEY WORDS: gene polymorphism, long non-coding RNA, *ANRIL*, clear cell renal cell carcinoma (ccRCC)

Wiad Lek. 2025;78(9):1805-1812. doi: 10.36740/WLek/204031 DOI

INTRODUCTION

According to the International Agency for Research on Cancer (IARC), approximately one in five men or women will develop cancer in their lifetime, and approximately one in nine men and one in 12 women will die from it. Given demographic projections, the number of new cancer cases is expected to reach 35 million by 2050 [1].

Regarding statistical data for Ukraine, in the overall structure of malignant diseases among men, kidney cancer ranks 7th (5.6%) and among women – 9th (2.9%) [2]. Clear cell renal cell carcinoma (ccRCC) accounts for approximately 95% of all cases of malignant kidney tumors [3]. Therefore, the development of methods for accurate diagnosis, individual treatment, and early prevention of ccRCC is an important direction of modern fundamental and applied medical science.

Today, several genetic factors are known that are predictors of the development of ccRCC [4, 5], includ-

ing single nucleotide polymorphisms (SNPs) of genes involved in the processes of cell division and differentiation. As shown by numerous experimental studies, long noncoding RNAs (lncRNAs) play a crucial role in the occurrence and progression of tumors of various localization, providing molecular regulation of cell division and transformation [6,7]. Given this, lncRNAs are not only promising markers for early diagnosis of cancer diseases, but also important factors in targeted therapy [8-10].

Special attention in the study of the pathogenesis of malignant tumors is currently given to lncRNA *ANRIL* (Antisense Non-coding RNA in the INK4 Locus). *ANRIL* is transcribed from the antisense strand of the INK4b-ARF-INK4a gene cluster (chromosome 9, region p21.3). This gene cluster encodes three important tumor suppressors – p14ARF, p15INK4b, and p16INK4a – which play a crucial role in cell cycle arrest.

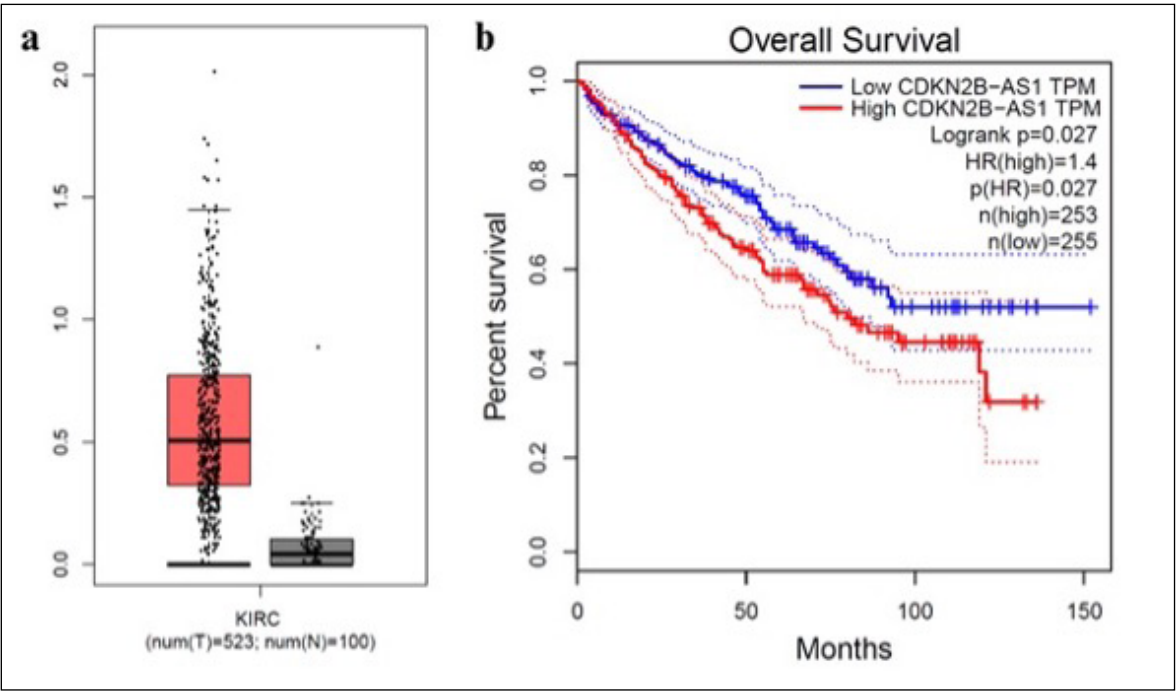


Fig. 1. *ANRIL* expression levels in kidney tumors compared to the control group based on GEPIA data
Picture taken by the authors

Although the primary molecular mechanism by which *ANRIL* increases the risk of cancer progression remains unclear, it is believed that this risk is associated with high levels of gene expression. Studies have shown that excessive expression of *ANRIL* suppresses the activity of p14ARF, p15INK4b, and p16INK4a, leading to genomic instability and promoting tumor progression [11].

Recent experimental research has confirmed *ANRIL*'s involvement in the development of various malignant tumors [9], including gastric cancer [12], bladder cancer [13, 15], prostate cancer [14], esophageal cancer [16], hepatocellular carcinoma [17], breast cancer [18], and lung cancer [19].

Using GEPIA (<http://gepia.cancer-pku.cn/>), an application that analyzes available gene expression data, we found that *ANRIL* levels are significantly higher in kidney tumors compared to controls (Fig. 1a). Furthermore, elevated *ANRIL* expression is associated with poorer patient survival (Fig. 1b), confirming a potential link between *ANRIL* and kidney tumor progression.

Regarding the role of *ANRIL* gene polymorphic variants in kidney cancer development, research remains limited. Notably, studies indicate that males carrying the AG genotype of the rs4977574 polymorphism have a higher risk of developing clear cell renal carcinoma (ccRCC) compared to individuals with AA or GG genotypes [20]. However, no data currently exist on the association of the rs1333049 polymorphism with oncological diseases of the urinary system.

AIM

The aim of our study was to study the possible association between the rs1333049 polymorphism of the *ANRIL* gene and the development of clear cell renal cell carcinoma in the Ukrainian population.

MATERIALS AND METHODS

The study included 201 participants, consisting of 101 patients with clear cell renal carcinoma (ccRCC) (42 women and 59 men) and 100 individuals without an oncological history (34 women and 66 men). The clinical characteristics of the patients and control group are presented in Table 1.

The final morphological diagnosis of ccRCC was verified in accordance with the European Association of Urology Guidelines (EAU) [21]. All patients were diagnosed with Stage II cancer, according to the TNM classification of malignant tumors, based on histological examination or MRI results. Individuals with tumors of other locations, hereditary diseases, or conditions of unknown etiology were excluded from the study group.

The study protocol was approved by the Bioethics Committee of the Educational and Scientific Medical Institute of Sumy State University (No. 5/07.2022) and complies with Order No.690 of the Ministry of Health of Ukraine (dated September 23, 2009) [22] as well as the Declaration of Helsinki on ethical principles for medical research involving human subjects. All participants provided written informed consent for personal data processing, blood sampling, and genetic analysis.

Table 1. General clinical characteristics of patients with ccRCC and control group individuals

Characteristics	ccRCC	Control group	P
Age, years	61.62	77.38	<0.000001
Body weight, kg	78.49	74.31	0.021181
Height, cm	170.7	165.8	0.000561
Body mass index	27.01	27.13	0.851827
Blood glucose, mmol/l	54.99	52.68	0.238665
Gender, f/m	42/59	34/66	0.3093
Smokers (%)	49 (48.5)	27 (27.0)	0.0022
Obesity (%)	30 (29.7)	18 (18.0)	0.0683

Note: ccRCC – clear cell renal cell carcinoma, n – number of patients; f – women; m – men; P – statistical significance of differences. Categorical variables were compared using the χ^2 -test, quantitative vari

Source: compiled by the authors of this study

Table 2. Frequencies of alleles and genotypes according to the rs1333049 polymorphism of the *ANRIL* gene in patients with ccRCC and individuals of the control group

	ccRCC		Control group		P (χ^2)
	n	%	n	%	
Genotypes					
GG	16	15.8	28	28	0.0561 (5.761)
GC	50	49.5	49	49	
CC	35	34.7	23	23	
Alleles					
G	82	40.6	105	52.5	0.0167 (5.726)
C	120	59.4	95	47.5	

Note: ccRCC – clear cell renal cell carcinoma, n – number of patients; P – Pearson's χ^2 test for significance of differences

Source: compiled by the authors of this study

To investigate the rs1333049 polymorphism of the *ANRIL* gene, venous blood was collected under sterile conditions into 2.7 ml Monovette tubes containing potassium salt of ethylenediaminetetraacetic acid (EDTA, 11.7 mM) as an anticoagulant ("Sarstedt," Germany). Blood samples were frozen and stored at -20°C. DNA extraction from whole blood leukocytes was performed using the GeneJET Whole Blood Genomic DNA Purification Mini Kit ("Thermo Fisher Scientific," USA). Genotyping of the rs1333049 polymorphic locus of the *ANRIL* gene was carried out at the Scientific Laboratory of Molecular-Genetic Research of Sumy State University using the real-time polymerase chain reaction (Real-time PCR) method on a Quant Studio 5 DX Real-Time system ("Applied Biosystems," USA). The study utilized TaqMan assays (TaqMan® SNP Assay C__1754666_10) and a PCR Real-Time reagent kit ("Thermo Fisher Scientific," USA). Amplification conditions included an initial denaturation at 95°C for 10 minutes, followed by 45 cycles consisting of 15 seconds at 95°C and 30 seconds at 60°C. The generated amplification curves were analyzed using the software provided with Quant Studio 5 DX Real-Time.

Statistical analysis of the obtained data was performed using Prism software (version 10.4.1) and R software (version 4.4.2). The distribution of rs1333049 genotypes between groups was assessed using Pearson's chi-square (χ^2) test. Hardy-Weinberg equilibrium (HWE) was tested using the Equilibrium WpCalc online resource (<https://wpcalc.com/en/equilibrium-hardy-weinberg/>). The risk of developing ccRCC depending on the rs1333049 genotype was calculated using logistic regression, considering different inheritance models: Dominant model (GG vs. GC+CC), Recessive model (GG+GC vs. CC), Overdominant model (GG+CC vs. GC). To assess the association of rs1333049 polymorphic variants with ccRCC risk, adjusting for gender, age, body mass index (BMI), and smoking status, a multivariable logistic regression model was applied. Overall survival analysis was conducted using the Kaplan-Meier method. All statistical tests were two-tailed, and p-values <0.05 were considered statistically significant.

RESULTS

As a result of the study, the distribution of genotypes and alleles for the rs1333049 polymorphism of the

Table 3. Analysis of the association of the rs1333049 polymorphism of the *ANRIL* gene with ccRCC considering different inheritance models

Model	P _{obs}	OR _{obs} (95 % CI)	P _{adj}	OR _{adj} (95 % CI)
Dominant	0.0392	2.066 (1.04 - 4.11)	0.040	3.1 (1.05 - 9.18)
Recessive	0.0698	1.770 (0.95 - 3.301)	0.065	2.36 (0.94 - 5.89)
Over dominant	0.9430	1.020 (0.587 - 1.77)	0.990	0.996 (0.437 - 2.27)

Note: ccRCC – clear cell renal cell carcinoma, 95% CI – 95% confidence interval; P_{obs} – observed P value (without adjustment for covariates); ORobs – observed odds ratio; Padj – P value after adjustment for age, sex, smoking habit and BMI; ORadj – odds ratio after adjustment for covariates

Source: compiled by the authors of this study

Table 4. Frequency of alleles and genotypes according to the rs1333049 polymorphism of the *ANRIL* gene in patients with ccRCC and control group individuals of different genders

Group	Genotypes						P ₁
	GG		GC		CC		
	n	%	n	%	n	%	
Male							
ccRCC	25	42.4	24	40.7	10	16.9	0.275 (2.577)
Control	19	28.8	32	48.5	15	22.7	
Female							
ccRCC	6	14.3	26	61.9	10	23.8	0.39 (1.885)
Control	9	26.5	17	50.0	8	23.5	
P ₂ = 0.0105 (9.122); P ₃ = 0.97 (0.0598)							

Note: ccRCC – clear cell renal cell carcinoma, n – number of patients; P₁ – significance level of differences between patients with SCRC and controls, P₂ – significance level of differences between patients of different sexes; P₃ – significance level of differences between individuals of the control group of different sexes (Pearson's χ^2 -test).

Source: compiled by the authors of this study

ANRIL gene was examined in patients with clear cell renal cell carcinoma (ccRCC) and individuals from the control group (Table 2). It was shown that the minor C allele was more frequently detected in ccRCC patients compared to the control group ($P = 0.0167$; $\chi^2 = 5.726$). The genotype distribution for this polymorphism in the ccRCC group was as follows: GG – 16 (15.8%), GC – 50 (49.5%), CC – 35 (34.7%). In the control group, the distribution was GG – 28 (28%), GC – 49 (49%), CC – 23 (23%). The P-value, calculated using Pearson's χ^2 test, was close to statistical significance ($P = 0.0561$).

The association between the rs1333049 polymorphism of the *ANRIL* gene and ccRCC was analyzed using binary and multivariable logistic regression under different inheritance models (Table 3). According to the dominant model, carriers of the minor allele (GC+CC) had a 2.066-fold increased risk of developing the disease compared to homozygotes for the major allele (GG) ($P = 0.0392$). After adjusting for age, sex, smoking status, and BMI, the association remained statistically significant, with the risk increasing to 3.1 times ($P = 0.040$).

The next step in the analysis was to examine the sex-specific differences in the association of the rs1333049 polymorphism of the *ANRIL* gene with

ccRCC. Table 4 presents the genotype frequency distribution for the rs1333049 locus in male and female ccRCC patients and control individuals. Among male ccRCC patients, the genotype distribution was GG – 25 (42.4%), GC – 24 (40.7%), CC – 10 (16.9%), while in the male control group, it was GG – 19 (28.8%), GC – 32 (48.5%), CC – 15 (22.7%) ($P = 0.275$). Among female patients, the genotype distribution was GG – 6 (14.3%), GC – 26 (61.9%), CC – 10 (23.8%), whereas in the female control group, it was GG – 9 (26.5%), GC – 17 (50.0%), CC – 8 (23.5%). No significant differences in genotype distribution were found between control group individuals of different sexes ($P = 0.39$). However, the allelic distribution of rs1333049 differed significantly between male and female ccRCC patients ($P = 0.0105$).

Table 5 shows the results of the regression analysis of the association of the rs1333049 polymorphism of the *ANRIL* gene with the development of ccRCC separately in the groups of women and men with ccRCC. In the group of women, no genotype-dependent increase in the risk of developing ccRCC was detected in any inheritance model.

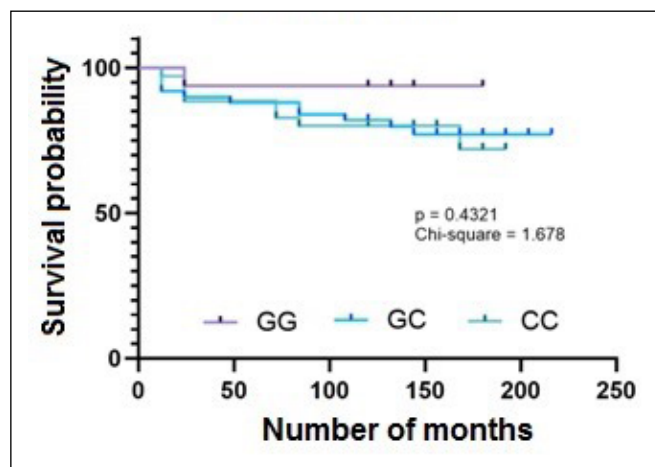
However, according to the recessive inheritance model, the risk of developing ccRCC in males with the CC genotype is 2.5 times higher than in carriers of the GG

Table 5. Analysis of the association of the rs1333049 polymorphism of the *ANRIL* gene with the development of ccRCC in individuals of different sexes, considering different inheritance models

Model	P _{obs}	OR _{obs}	P _{adj}	OR _{adj}
Male				
Dominant	0.12	0.5 (0.21 – 1.19)	0.49	0.64 (0.18 – 2.25)
Recessive	0.02	2.5 (1.15 – 5.42)	0.05	3.12 (1.0 – 9.75)
Over dominant	0.38	0.73 (0.36 – 1.48)	0.20	0.5 (0.17 – 1.43)
Female				
Dominant	0.19	0.46 (0.15 – 1.46)	0.055	0.145(0.02 – 1.04)
Recessive	0.98	1.01 (0.35 – 2.94)	0.33	2.46 (0.4 – 15.6)
Over dominant	0.3	1.62 (0.65 – 4.06)	0.14	3.6 (0.65 – 19.7)

Note: ccRCC – clear cell renal cell carcinoma; 95% CI – 95% confidence interval; P_{obs} – observed P value (without adjustment for covariates); OR_{obs} – observed odds ratio; P_{adj} – P value after adjustment for age, sex, smoking habit and BMI; OR_{adj} – odds ratio after adjustment for covariates

Source: compiled by the authors of this study

**Fig. 2.** Overall Survival of Patients with ccRCC Depending on Genotype
Picture taken by the authors

and GC genotypes ($P = 0.02$). After adjusting for age, sex, smoking habit and BMI, the risk increased to 3.12 times ($P = 0.05$).

To assess the impact of the rs1333049 polymorphism of the *ANRIL* gene on the overall survival of patients with ccRCC, a survival analysis was performed using the Kaplan-Meier method (Fig.2).

In the group of GG-genotype carriers, 1 fatal case was recorded, among GC carriers – 11, and among CC carriers – 8. Statistical analysis did not reveal a significant relationship between the genotype according to the rs1333049 polymorphism of the *ANRIL* gene and overall survival ($P=0.4321$).

DISCUSSIONS

The first studies on the role of long non-coding RNAs in the development of pathological processes and diseases were devoted to the pathology of the cardiovascular system, including in the Ukrainian population [23-25]. Later, given the great importance of long noncoding

RNAs in the regulation of cell division and transformation [26], the efforts of scientists were directed to studying the role of these molecules as possible markers of the development of malignant tumors and their malignancy [27-29].

In normal cells, elevated levels of *ANRIL* transcripts play an important role in suppressing the formation of tumor suppressors p14ARF, p15INK4b, and p16INK4a and DNA repair. However, in cancer cells, overexpression of *ANRIL* has negative consequences – it causes genome instability and promotes tumor development [30]. D. Meseure et al. explained the mechanism of action of the long non-coding RNA *ANRIL* [31]. The authors proved that the interaction of *ANRIL* with *CBX7*, which is a component of the PRC1 (Polycomb repressive complex 1) repressor complex, inhibits the transcription of p16INK4a. In the laboratory of Zhao J., it was found that *ANRIL* affects the proliferation of cancer cells through inhibition of the TGF β /Smad signaling cascade [31]. However, the exact molecular mechanisms by which *ANRIL* interacts with TGF β 1 still remain unclear.

The long non-coding RNA *ANRIL* (also known by its official name *CDKN2BAS1*) is encoded by a gene consisting of 21 exons and 20 introns. This gene is located on the short arm of chromosome 9, in the 9p21.3 region, within the INK4b-ARF-INK4a gene cluster. According to the National Center for Biotechnology Information (NCBI), as of early 2025, 52,654 polymorphic sites have been identified in the *ANRIL* gene (<https://www.ncbi.nlm.nih.gov/snp/?term=CDKN2B-AS1+homo+sapience>). Based on the GRCh38/hg38 genome assembly, the single nucleotide polymorphism (SNP) rs1333049 (G/C) of *ANRIL* is located at position 22,125,504 within the 3'-untranslated region (3'-UTR) of the gene.

The number of studies investigating the role of the rs1333049 polymorphism in the long non-coding RNA *ANRIL* gene in tumor development is limited. Research

by S. Seifi et al. has shown that carriers of the minor CC and CG alleles have an increased risk of developing breast cancer compared to individuals with the GG genotype [33]. Additionally, the rs1333049 polymorphism has been proven to play a role in the development of gastric cancer [34]. Studies have also revealed that this polymorphism is associated with an increased risk of breast cancer and mortality in patients with diabetes [35]. Furthermore, it has been demonstrated that the CC genotype is linked to reduced overall survival in patients with esophageal squamous cell carcinoma [36]. Moreover, research by Y. Chen et al. found that lung cancer patients with the CC genotype at rs1333049 in the *ANRIL* gene undergoing platinum-based chemotherapy had a lower risk of cancer progression and significantly longer progression-free survival compared to patients with the GG and GC genotypes [35].

Our study demonstrated an association between the rs1333049 polymorphism and the development of clear cell renal cell carcinoma (ccRCC) in the Ukrainian population. Specifically, individuals carrying the minor allele exhibited a higher risk of developing the disease compared to those who were homozygous for the major allele ($P = 0.0392$). However, no significant effect on overall survival in ccRCC patients was observed.

Currently, there is no additional data on the association between the rs1333049 polymorphic locus of the *ANRIL* gene and tumor development in the urinary system in both the Ukrainian and other populations. Given the critical role of *ANRIL* in cell differentiation and division, study-

ing its single nucleotide polymorphisms (SNPs) remains a highly relevant direction in identifying genetic markers for cancer diagnostics and personalized treatment.

CONCLUSIONS

An association of the rs1333049 polymorphism of the *ANRIL* gene with the development of clear cell renal cell carcinoma was found in the Ukrainian population: carriers of the minor allele (GC+CC) had a higher risk of developing the disease than homozygotes for the major allele (GG) (according to binary logistic regression, 2.066 times ($P=0.0392$); according to multivariable logistic regression, after adjusting for age, sex, smoking habit and BMI, – 3.1 times ($P=0.040$).

It has been proven that in males with the CC genotype, the risk of developing ccRCC is 2.5 times higher than in carriers of the GG and GC genotypes ($P=0.02$). Considering the adjustment for age, sex, smoking habit and BMI, the risk increases to 3.12 times ($P=0.05$).

No significant association between the genotype of the rs1333049 polymorphism of the *ANRIL* gene and overall survival of patients with ccRCC ($P=0.4321$).

PROSPECTS FOR FURTHER RESEARCH

To investigate the association of polymorphisms of other long non-coding RNAs in the development of clear cell renal cell carcinoma in order to predict the risk of developing the disease.

REFERENCES

1. Bray F, Laversanne M, Sung H et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229–63. doi: 10.3322/caac.21834. DOI
2. Rak v Ukraini, 2022–2023. Zakhvoriuvanist, smertnist, pokaznyky diialnosti onkologichnoi sluzhby [Cancer in Ukraine, 2022–2023. Incidence, mortality, indicators of oncological service activity]. Byuleten' Natsional'noho byuro onkologichnoho reyestru Ukrainy. 2024;25:132. http://www.ncru.inf.ua/publications/BULL_25/PDF/BULL_25.pdf [Accessed 15 March 2025] (Ukrainian)
3. Bahadoram S, Davoodi M, Hassanzadeh S et al. Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment. *G Ital Nefrol.* 2022;39(3):2022–vol3.
4. Mendhiratta N, Muraki P, Sisk AE Jr, Shuch B. Papillary renal cell carcinoma: Review. *Urol Oncol.* 2021;39(6):327–37. doi: 10.1016/j.urolonc.2021.04.013. DOI
5. Bui TO, Dao VT, Nguyen VT et al. Genomics of clear-cell renal cell carcinoma: a systematic review and meta-analysis. *Eur Urol.* 2022;81(4):349–61. doi: 10.1016/j.eururo.2021.12.010. DOI
6. Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. *Cancer Cell.* 2016;29(4):452–63. doi: 10.1016/j.ccell.2016.03.010. DOI
7. Liu Y, Liu X, Lin C et al. Noncoding RNAs regulate alternative splicing in Cancer. *J Exp Clin Cancer Res.* 2021;40:11. doi: 10.1186/s13046-020-01798-2. DOI
8. Todén S, Zumwalt TJ, Goel A. Non-coding RNAs and potential therapeutic targeting in cancer. *Biochim Biophys Acta Rev Cancer.* 2021;1875(1):188491. doi: 10.1016/j.bbcan.2020.188491. DOI
9. Yang X, Wei L, Wu S et al. Potential links between ANRIL and MiRNAs in various cancers. *Comb Chem High Throughput Screen.* 2024. doi: 10.2174/0113862073294838240523035706. DOI
10. Chen Y, Li Z, Chen X, Zhang S. Long non-coding RNAs: From disease code to drug role. *Acta Pharm Sin B.* 2021;11(2):340–54. doi: 10.1016/j.apsb.2020.10.001. DOI

11. Liu Y, Zhu L, Zhao W et al. High expression of ANRIL correlated with the poor prognosis in patients with cancer: A meta-analysis. *Medicine* (Baltimore). 2022;101(36):e30531. doi: 10.1097/MD.00000000000030531. DOI
12. Hu X, Lou T, Yuan C et al. Effects of lncRNA ANRIL-knockdown on the proliferation, apoptosis and cell cycle of gastric cancer cells. *Oncol Lett*. 2021;22(2):621. doi: 10.3892/ol.2021.12882. DOI
13. Volkohon AD, Chumachenko YaD, Harbuzova VYu, Ataman OV. Doslidzhennya asotsiatsiyi polimorfnoho lokusu rs4977574 hena dovhoyi nekoduyuchoyi RNK ANRIL iz rozvytkom raku sechovoho mikhura. [Analysis of association between long non-coding RNA ANRIL gene rs4977574 polymorphism and bladder cancer development]. *Fiziologichnyi Zhurnal*. 2020;66(2-3):13-20. (Ukrainian)
14. Zhao B, Lu YL, Yang Y et al. Overexpression of lncRNA ANRIL promoted the proliferation and migration of prostate cancer cells via regulating let-7a/TGF- β 1/Smad signaling pathway. *Cancer Biomark*. 2018;21(3):613-20. doi: 10.3233/CBM-170683. DOI
15. Zhu H, Li X, Song Y et al. Long non-coding RNA ANRIL is up-regulated in bladder cancer and regulates bladder cancer cell proliferation and apoptosis through the intrinsic pathway. *Biochem Biophys Res Commun*. 2015;467(2):223-8. doi: 10.1016/j.bbrc.2015.10.002. DOI
16. Fanelli GN, Gasparini P, Coati I et al. LONG-NONCODING RNAs in gastroesophageal cancers. *Noncoding RNA Res*. 2018;3(4):195-212. doi: 10.1016/j.ncrna.2018.10.001. DOI
17. Du Z, Zhang F, Liu L et al. lncRNA ANRIL promotes HR repair through regulating PARP1 expression by sponging miR-7-5p in lung cancer. *BMC Cancer*. 2023;23:130. doi: 10.1186/s12885-023-10593-z. DOI
18. Alkhatami AG, Hadi A, Alfaifi M et al. Serum-Based lncRNA ANRIL, TUG1, UCA1, and HIT Expressions in Breast Cancer Patients. *Dis Markers*. 2022;2022:9997212. doi: 10.1155/2022/9997212. DOI
19. Gupta S, Hashimoto RF. Dynamical Analysis of a Boolean Network Model of the Oncogene Role of lncRNA ANRIL and lncRNA UFC1 in Non-Small Cell Lung Cancer. *Biomolecules*. 2022;12(3):420. doi: 10.3390/biom12030420. DOI
20. Volkogon AD, Harbuzova VY, Ataman AV. Analysis of ANRIL gene polymorphism rs4977574 association with kidney cancer development in Ukrainian population. *Med. perspekt*. 2020;25(2):60-5. doi: 10.26641/2307-0404.2020.2.206360. DOI
21. Powles T, Albiges L, Staehler M et al. Updated European Association of Urology Guidelines: Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. *Eur Urol*. 2018;73(3):311-5. doi: 10.1016/j.eururo.2017.11.016. DOI
22. Pro zatverdzhennia poriadku provedennia klinichnykh vyprobuvan likarskykh zasobiv ta ekspertyzy materialiv klinichnykh vyprobuvan i tyпового polozhennia pro komisii z pytan etyky [About the Approving of Conducting of Medicines Clinical Trials Procedure and Expertise of Clinical Trials Materials, and the Model Regulations on Ethics Committees]: Order of the Ministry of Health of Ukraine № 690; 2009 Sept 23. <https://zakon.rada.gov.ua/laws/show/z1010-09#Text> [Accessed 15 March 2025] (Ukrainian)
23. Kniazkova PV, Harbuzova V Yu. Analiz zv'yazku rs4977574-polimorfnykh variantiv hena ANRIL iz rozvytkom hostroho koronarnoho syndromu v osib z riznym indeksom masy tila v ukrayins'kiy populyatsiyi. [Association between MALAT1 rs4102217-polymorphic variant and ischemic atherothrombotic stroke development in people with increased body mass inde. *EUMJ*. 2022;10(2):147-54. doi: 10.21272/eumj.2022;10(2):147-154. (Ukrainian) DOI
24. Moiseienko KA, Harbuzova VYu, Obukhova OA. Zv'yazok mizh polimorfnykh variantom MALAT1 rs4102217 ta rozvytkom ishemichnoho aterotrombotychnoho insul'tu u lyudey z pidvyshchenym indeksom masy tila. [Association between MALAT1 rs4102217-polymorphic variant and ischemic atherothrombotic stroke development in people with in-creased body mass index]. *EUMJ*. 2022;10(2):131-7. doi: 10.21272/eumj.2022;10(2):131-137. (Ukrainian) DOI
25. Kniazkova PV, Harbuzova VYu, Pokhmura VV. The Link between ANRIL Gene RS4977574 Polymorphism and Common Atherosclerosis Cardiovascular Complications: A Hospital-Based Case-Control Study in Ukrainian Population. *Biomed Res Int*. 2022;2022:8468202. doi: 10.1155/2022/8468202. DOI
26. Sanchez Calle A, Kawamura Y, Yamamoto Y et al. Emerging roles of long non-coding RNA in cancer. *Cancer Sci*. 2018;109(7):2093-100. doi: 10.1111/cas.13642. DOI
27. Volkohon AD, Kolnoguz, AV, Chumachenko YD, Harbuzova VY, Tsyndrenko NL. Association analysis between HOTAIR RS1899663 single nucleotide polymorphism and clear cell renal cell carcinoma development in Ukrainian population. *Wiad lek*. 2020;73(1):12-6.
28. Aguilo F, Di Cecilia S, Walsh MJ. Long Non-coding RNA ANRIL and Polycomb in Human Cancers and Cardiovascular Disease. *Curr Top Microbiol Immunol*. 2016;394:29-39. doi: 10.1007/82_2015_455. DOI
29. Meseure D, Vacher S, Alsibai KD et al. Expression of ANRIL-Polycomb Complexes-CDKN2A/B/ARF Genes in Breast Tumors: Identification of a Two-Gene (EZH2/CBX7) Signature with Independent Prognostic Value. *Mol Cancer Res*. 2016;14(7):623-33. doi: 10.1158/1541-7786.MCR-15-0418. DOI
30. Zhao JJ, Hao S, Wang LL et al. Long non-coding RNA ANRIL promotes the invasion and metastasis of thyroid cancer cells through TGF- β /Smad signaling pathway. *Oncotarget*. 2016;7:57903-18. doi: 10.18632/oncotarget.11087. DOI
31. Seifi S, Pouya F, Rahmani M et al. Association of cyclin-dependent kinase inhibitor 2A/B with increased risk of developing breast cancer. *J Cell Physiol*. 2020;235(6):5141-5. doi: 10.1002/jcp.29388. DOI
32. Hasani S, Pourfarzi F, Mazani M et al. Association of ANRIL Gene Polymorphisms with Gastric Cancer Risk: A Case-Control Study. *Genet Test Mol Biomarkers*. 2024;28(11):445-51. doi: 10.1089/gtmb.2024.0302. DOI

33. Parada HJr, Cleveland RJ, North KE et al. Genetic polymorphisms of diabetes-related genes, their interaction with diabetes status, and breast cancer incidence and mortality: The Long Island Breast Cancer Study Project. *Mol Carcinog.* 2019;58(3):436-46. doi: 10.1002/mc.22940. 
34. Ghobadi N, Mehramiz M, ShahidSales S et al. A genetic variant in CDKN2A/2B locus was associated with poor prognosis in patients with esophageal squamous cell carcinoma. *J Cell Physiol.* 2019;234(4):5070-6. doi: 10.1002/jcp.27310. 
35. Chen YX, Chen J, Yin JY et al. Non-Coding RNA Polymorphisms (rs2910164 and rs1333049) Associated With Prognosis of Lung Cancer Under Platinum-Based Chemotherapy. *Front Pharmacol.* 2021;12:709528. doi: 10.3389/fphar.2021.709528. 

This research has been performed with the financial support provided by the Ministry of Education and Science of Ukraine: Grant №0123U101850.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Olha Obukhova

Sumy State University

116 Kharkivska St, 40000 Sumy, Ukraine

e-mail: o.obukhova@med.sumdu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Yelizaveta Stroi: 0000-0003-3366-8800  

Andriy Volkohon: 0000-0003-0835-0657 

Olha Obukhova: 0000-0002-2104-8412   

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 20.02.2025

ACCEPTED: 14.08.2025



Peculiarities of rehabilitation of patients with musculoskeletal disorders: what has changed during the war in Ukraine

Grygoriy Griban¹, Olha S. Zablotska², Inna O. Asauliuk³, Dmytro G. Oleniev⁴, Svitlana M. Dmytrenko³, Oleh L. Morin⁵, Nataliia O. Terentieva⁶

¹ZHYTOMYR IVAN FRANKO STATE UNIVERSITY, ZHYTOMYR, UKRAINE

²ZHYTOMYR MEDICAL INSTITUTE OF ZHYTOMYR REGIONAL COUNCIL, ZHYTOMYR, UKRAINE

³VINNYTSIA MYKHAILO KOTSIUBYNSKYI STATE PEDAGOGICAL UNIVERSITY, VINNYTSIA, UKRAINE

⁴NATIONAL DEFENCE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

⁵NATIONAL ACADEMY OF EDUCATIONAL SCIENCES OF UKRAINE, KYIV, UKRAINE

⁶NATIONAL UNIVERSITY OF LIFE AND ENVIRONMENTAL SCIENCES OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: The aim of the study was to investigate changes in the structure of musculoskeletal injuries in patients during the war in Ukraine and to determine the organizational and methodological features of the rehabilitation of patients with these injuries according to the conclusions of rehabilitation specialists.

Materials and Methods: The study was conducted in 2022-2024, 102 rehabilitation specialists participated in it. Scientific methods: analysis of sources of scientific information, questionnaires, statistical methods. The survey of rehabilitation specialists was conducted using the author's questionnaire, which contains 27 questions divided into 3 blocks.

Results: It was established that during the war years, significant changes occurred in the structure of appeals from patients with musculoskeletal diseases. The share of appeals for help for limb amputations increased to 23.6%, for injuries to joints, muscles and tendons – to 37.3%, for habitual dislocation of the patella – to 6.8%. Physiotherapists are convinced that the quality of rehabilitation services can be improved by using the latest equipment (35.3%), systematic advanced training of specialists (26.5%), expanding access to equipment (21.6%), and introducing the latest physiotherapy methods (13.7%).

Conclusions: Based on the conducted research, a system of exercise therapy tools for certain diseases of the musculoskeletal system and the sequence of their application were determined, and practical recommendations were developed for the rehabilitation of the population with musculoskeletal disorders, taking into account changes in their structure and the opinions of rehabilitation specialists who have experience working during the war in Ukraine.

KEY WORDS: physical therapy, musculoskeletal disorders, physical therapist, health, rehabilitation specialist

Wiad Lek. 2025;78(9):1813-1820. doi: 10.36740/WLek/206076 DOI

INTRODUCTION

According to the World Health Organization (WHO), more than 30 % of the world's population suffers from musculoskeletal disorders, such as osteochondrosis, osteoporosis, arthritis, etc. [1]. The 120 types of these disorders included in the International Classification of Diseases (ICD-10) are accompanied by acute or chronic pain, limit a person's motor activity, and often lead to disability [1]. Disorders of the musculoskeletal system can lead to a deterioration in health and a decrease in the ability to work, which has significant economic consequences for the state [2].

In the structure of the prevalence of diseases, the pathology of the musculoskeletal system has been ranked fourth in Ukraine over the past 25 years [3].

The proportion of musculoskeletal system diseases in the overall morbidity structure in Ukraine in 2014 averaged 4.74 ± 0.14 % and ranged from 4.53 to 5.01 %. In 2022, these indicators deteriorated: the proportion of diseases was 5.54 ± 0.14 %, ranging from 5.37 % to 5.89 %. The increase in morbidity is explained by this class's chronically progressive course of diseases and their accumulation in the population [4, 5].

Physical therapy is an effective method of restoring the health status of the population with musculoskeletal disorders [6]. The physical therapy method is based on the use of restorative physical exercises and the patient's active participation in the treatment process. The level of such activity is individual, considering the nature of the disease, the degree of functional impair-

ment, and the patient's general health, motivation, and readiness for physical activity [7]. The restoration of patients' health by physical therapy is carried out using kinesiotherapy (therapeutic physical education (TPE)), therapeutic massage, manual therapy, biomechanotherapy, Kinesio taping, etc. [8]. However, the importance of specific physical therapy means, and their system in improving the health of the population with musculoskeletal disorders has not been comprehensively addressed despite the particular relevance of physical therapy in wartime.

AIM

The aim of the study was to investigate changes in the structure of musculoskeletal injuries in patients during the war in Ukraine and to determine the organizational and methodological features of the rehabilitation of patients with these injuries according to the opinion of rehabilitation specialists.

OBJECTIVES

1) to compare the structure of musculoskeletal disorders of patients before the war (2022) and during the war in Ukraine (2022-2024); 2) to find out the opinion of rehabilitation specialists on measures that will help improve the quality of rehabilitation services; 3) to specify the organizational and methodological peculiarities of rehabilitation of patients with the most common disorders; 4) to develop practical recommendations for the rehabilitation of the population with musculoskeletal disorders through physical therapy.

MATERIALS AND METHODS

The research was conducted in 2022-2024 at Zhytomyr Medical Institute of Zhytomyr Regional Council and Zhytomyr Ivan Franko State University. It involved 102 rehabilitation therapists from Zhytomyr, Kyiv, Sumy and Vinnytsia regions of Ukraine. The formation of the sample for the survey involved the selection of only those rehabilitation therapists who have a diploma in the specialty "Physical Therapy, Occupational Therapy" and professional experience of at least 5 years or professional experience during the war in Ukraine with wounded and injured military personnel and civilians. Criteria such as gender, age, marital status, level of financial satisfaction, place of residence were not taken into account in the study. The participation of respondents in the survey was voluntary, only those rehabilitation therapists who signed the Informed consent to participate in the study were included.

The following scientific methods were used to achieve the aim of the research: analysis of scientific information sources, questionnaire, and statistical methods.

The analysis of scientific information sources was used to clarify the essence of physical therapy and the impact of its means on improving the health of the population with musculoskeletal disorders. 16 sources from PubMed, Scopus, Web of Science, Index Copernicus and other databases were analyzed. The main attention during the selection of literary sources was focused on clarifying the essence of physical therapy, its purpose, objectives, principles, means, types of musculoskeletal disorders, the use of physical therapy in the process of improving the health of the population with musculoskeletal disorders. The key words in the publications selected for our study were: physical therapy, rehabilitation, musculoskeletal disorders.

The survey of rehabilitation therapists was conducted to study the impact of physical therapy on improving the health of patients with various musculoskeletal disorders and to examine the importance of physical therapy in improving the health of the population with musculoskeletal disorders. The questionnaire was presented in 3 blocks. Block I ("Disorders of the musculoskeletal system and means of physical therapy") contains questions that studied the level of knowledge of respondents about types of disorders of the musculoskeletal system and means of physical therapy. Block II ("Physical therapy of patients with musculoskeletal disorders") includes questions that obtained information about specific means of physical therapy used by rehabilitation therapists to improve the health of the population with these disorders; frequency of their use; types of necessary equipment; the role of an individual approach to patients in the process of physical therapy; duration and intensity of the course of therapy; main difficulties that arise during rehabilitation; systematicity in improving the qualifications of rehabilitation therapists; possibilities of introducing technological and medical innovations into physical therapy; conditions for conducting physical therapy for patients with relevant disorders; ways to improve the quality of rehabilitation services. Questions of Block III ("Effectiveness of physical therapy methods for musculoskeletal disorders") aimed to study the most effective physical therapy methods for patients with the most common musculoskeletal disorders, and the problems of integrating physical therapy into the process of general rehabilitation of patients with musculoskeletal disorders. The survey of the rehabilitation therapists was conducted according to the author's questionnaire, which contains 27 questions. The survey was conducted remotely using the GOOGLE-FORMS tool.

The questionnaire was posted at the link: <https://docs.google.com/forms/d/1b3jUbQ8zib7XOM5ZpzL0LBCM-fNv2QM3B7x8vw0EMV3U/edit>. The questionnaire was anonymous without any references to the authors of the article in the answers. The results were used for scientific purposes only. The questionnaire was assessed by the experts in this field (2 professors and 5 associate professors). It was approved by the Academic Council of Zhytomyr Medical Institute of Zhytomyr Regional Council (Protocol No. 5 dated 03.10.2022).

The survey results were processed using a statistical method. All results of the rehabilitation therapist survey were presented in percentages. The research also determined the percentage difference in the frequency of visits to physical therapists for patients with musculoskeletal disorders at the beginning of the war (2022) and during the war (2022-2024). Data was calculated using the MS Excel software package on a personal computer.

Consent to voluntary participation in the survey was obtained from all the respondents involved in the study. This research followed the regulations of the World Medical Association Declaration of Helsinki – ethical principles for medical research involving human subjects.

RESULTS

Based on the study of many sources of scientific information [2, 3, 6, 7, 8], we found that the purpose of rehabilitation is to preserve, partially or completely restore, lost or weakened motor functions, further ensure the body's lifelong performance, and integrate the patient into society. Realizing the goal of rehabilitation is based on solving the following tasks: a) effective recovery (complete or compensation for insufficient recovery using physical therapy); b) adaptation of patients to everyday life using ergotherapy equipment. The main stages of the rehabilitation process are also defined: examination (determination of motor disorders and activity), planning (creation of a physical rehabilitation program), intervention (program implementation), and control (ensuring optimal functioning of the physical rehabilitation system).

Physical therapy is based on the following principles: 1) early initiation of therapeutic measures, which allows for quick recovery of body functions and prevention of complications; 2) continuity, phasing, and combination of alternation of different means; 3) individualization, i.e., the use of programs created for each patient: considering their characteristics regarding musculoskeletal disorders, age, gender, etc. Group therapeutic physical education sessions provide spiritual support and make patients feel like community members, which gives

them confidence in their abilities and helps them recover faster.

In the process of surveying the rehabilitation specialists, we found that the main musculoskeletal disorders of patients who sought medical care from physical therapists at the beginning of the war are scoliosis – 40.2 %, injuries of joints, muscles, and tendons – 26.5 %, osteoarthritis – 10.8 %, hip dysplasia – 8.8 %, osteoporosis – 5.9 % and other (arthritis, amputations and all of the above) – 7.8 % (Fig. 1).

According to rehabilitation specialists, there were significant changes in the structure of patients' visits with musculoskeletal disorders during the war years. The proportion of visits for help with limb amputations increased by 23.6 %, injuries of joints, muscles, and tendons by 37.3 %, habitual patellar dislocation by 6.8 %, osteochondrosis and arthritis by 6.8 % (Table 1).

It has been found that among the main methods of physical therapy used by physical therapists to improve the health of the musculoskeletal system of their patients are therapeutic massage – 42.2 %, TPE – 33.3 %, Kinesio taping – 14.7 %, manual therapy – 4.9 %, yoga – 4.9 %. At the same time, according to the rehabilitation therapists, the priority factors in drawing up an individual rehabilitation plan for patients with musculoskeletal disorders are type of disorder – 40.2 %, physical activity – 33.3 %, and patient's age – 20.6 %.

Assessment of rehabilitation therapists' opinions on effective means of physical therapy for patients depending on certain disorders of the musculoskeletal system shows that the most effective means are: for injuries of joints, muscles and tendons: 35.4 % – exercise therapy, 23.5 % – therapeutic massage, 22.7 % – Kinesio taping, 18.4 % – mechanotherapy; in case of amputations: 30.9 % – exercise therapy, 25.1 % – therapeutic massage, 23.6 % – Kinesio taping, 20.4 % – mechanotherapy; for scoliosis: 40.1 % – exercise therapy, 33.3 % – therapeutic massage, 11.7 % – yoga; for hip dysplasia: 45.1 % – exercise therapy, 25.5 % – therapeutic massage, 15.6 % – Kinesio taping, 13.8 % – mechanotherapy; for habitual patellar dislocation: 36.0 % – exercise therapy, 30.4 % – Kinesio taping, 18.6 % – therapeutic massage; for osteochondrosis: 46.1 % – exercise therapy, 16.7 % – therapeutic massage, 14.7 % – mechanotherapy, 13.7 % – Kinesio taping, 8.8 % – manual therapy; for osteoarthritis (arthrosis): 45.1 % – exercise therapy, 14.7 % – mechanotherapy, 13.7 % – therapeutic massage, 8.8 % – manual therapy; for osteoporosis: 41.2 % – exercise therapy, 25.5 % – therapeutic massage, 11.7 % – mechanical therapy. As we can see, the main means of physical therapy for most musculoskeletal disorders are exercise therapy, therapeutic massage, Kinesio taping, and mechanotherapy.

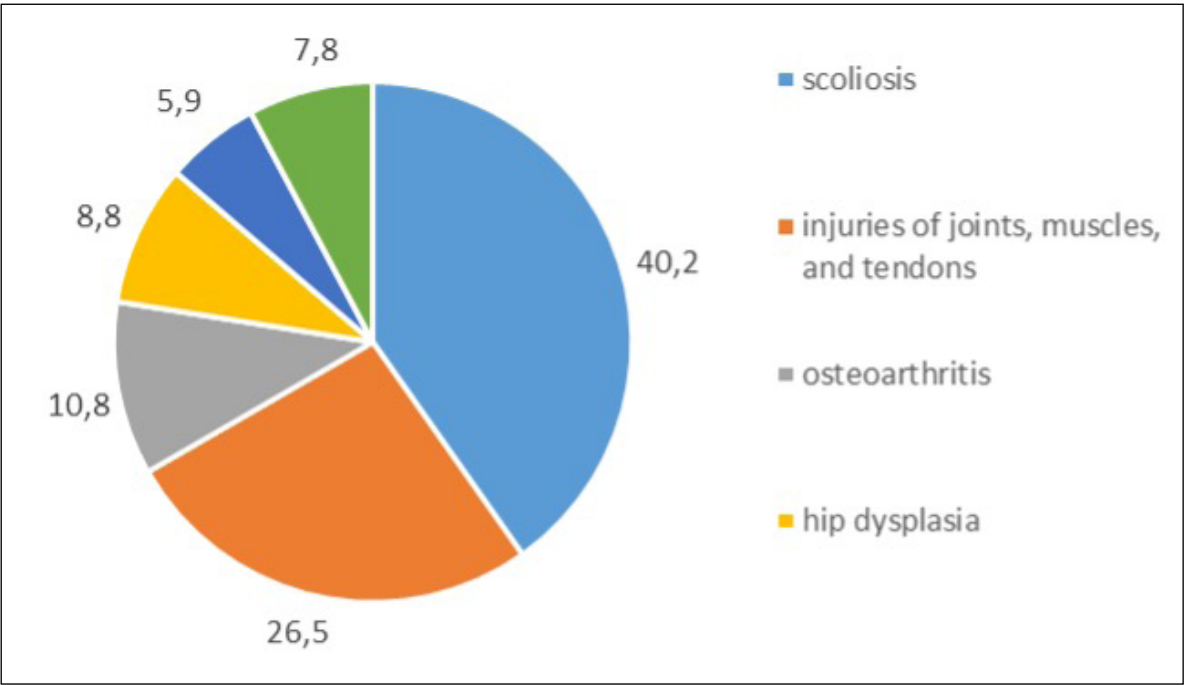


Fig. 1. The most common musculoskeletal disorders of patients at the beginning of the war
Picture taken by the authors

Table 1. Comparison of the frequency of visits to physical therapists for patients with musculoskeletal disorders at the beginning of the war (2022) and during the war (2022-2024), %

Type of disorder	Frequency of visits, %		Percentage difference, %
	2022 (at the beginning of the war)	2022-2024 (during the war)	
Scoliosis	40.2	12.7	- 27.5
Injuries to joints, muscles, and tendons	26.5	37.3	+ 10.8
Osteoarthritis	10.8	2.0	- 8.8
Hip dysplasia	8.8	8.8	0.0
Osteoporosis	5.9	2.0	- 3.9
Habitual patellar dislocation	2.0	6.8	+ 4.8
Amputations of limbs	1.0	23.6	+22.6
Osteochondrosis, arthritis	4.8	6.8	+ 2.0

Source: compiled by the authors of this study

Also, in the course of the survey, we have found that the physical therapists observe the following results in the health status of patients with musculoskeletal disorders as a result of physical therapy: 62.7 % – significant improvement, 31.4 % – moderate improvement, 5.9 % – no change or minimal improvement. At the same time, the rehabilitation therapists noted that they use physical therapy as an adjunct to the medical treatment of patients with musculoskeletal disorders: in most cases (64.7 %), always (23.5 %), rarely (11.8 %). According to the rehabilitation therapists, more intensive physical therapy may be required for patients with the following conditions: after injuries (62.7 %), chronic diseases (18.6 %), and postoperative conditions (13.7 %). It has

been found that the rehabilitation therapists determine the effectiveness of physical therapy for each patient according to the following criteria: 54.9 % – by the indicator of improvement of motor activity, 30.4 % – by changes in physical condition, 14.7 % – by the indicator of pain reduction.

The rehabilitation therapists indicated how they respond to a patient’s refusal to undergo physical therapy and how they try to convince them of its importance: 59.8 % look for an individual approach, 21.6 % explain the need for treatment in detail, and 9.8 % show examples of how physical therapy is used. It has been found that 76.5 % of the rehabilitation therapists determine the optimal duration and intensity of physical therapy

Table 2. Recommendations for the use of physical therapy means for various disorders of the musculoskeletal system

Disorder type	Kinesiotherapy	Therapeutic massage	Kinesio taping	Mechanical therapy	Manual therapy
Injuries to joints, muscles, and tendons	1	2	3	4	-
Amputations	1	2	3	4	-
Scoliosis	1	2	-	-	-
Dysplasia of the hip joints	1	2	3	4	-
Habitual dislocation of the patella	1	3	2	-	-
Osteochondrosis	1	2	4	3	5

Source: compiled by the authors of this study

for a particular patient based on an individual approach to each case, 18.6 % – taking into account medical indicators, and 4.9 % – according to standard treatment. It has been established that the main problems or difficulties faced by the rehabilitation therapists in the implementation of physical therapy in the rehabilitation process are 50.0 % – patients' refusal to participate in rehabilitation, 36.3 % – lack of equipment, lack of coordination between specialists – 8.8 %, lack of specialized knowledge – 4.9 %. It has been found that the surveyed rehabilitation specialists update their knowledge and skills in the field of physical therapy (advanced training, internships, etc.): 70.6 % – regularly, several times a year, 15.7 % – once a year, 10.8 % – every few years, 2.9 % – do not update their knowledge. The need for individualized approaches to patients when choosing physical therapy methods is determined by 66.7 % of the rehabilitation therapists based on individual medical indicators, 26.5 % – on the analysis of the patient's lifestyle and wishes, and 6.8 % – on the results of communication with other specialists.

Among the main problems of integrating physical therapy into general rehabilitation of patients with musculoskeletal disorders, the respondents believe 36.3 % – of limited resources, 35.3 % – of low patient motivation, and 28.4 % – a lack of coordination between specialists. At the same time, 56.8 % of the rehabilitation therapists consider family participation in physical therapy for patients with musculoskeletal disorders to be very important, 40.1 % – important. The physical therapists are convinced that the quality of rehabilitation services for patients with musculoskeletal disorders can be improved in the following ways: 35.3 % by using the latest equipment, 26.5 % by systematically improving the qualifications of specialists, 21.6 % by increasing access to appropriate equipment, and 13.7 % by introducing the latest methods of physical therapy.

Based on the research, a set of physical therapy means for certain musculoskeletal disorders has been specified, and practical recommendations have been developed to improve the health of the population

with musculoskeletal disorders through physical therapy (Table 2).

1. TPE (kinesiotherapy) effectively restores patients' health with scoliosis, hip dysplasia, arthritis, osteochondrosis, herniated discs, mechanical injuries, common patellar dislocations, muscle and tendon sprains, etc. We offer a set of exercises on S. M. Bubnovskyi's training devices that have proven effective. The exercises are divided into three blocks, which are part of the structure of each training session. They are prescribed and adjusted based on the intensity of low back pain, limiting factors, high blood pressure, heart pain, dizziness, headache, severe shortness of breath, excessive sweating, and leg and abdominal pain. If these factors appear, the exercise is stopped, and the patient consults with a doctor to determine whether or not to continue training.

The kinesiotherapy course consists of three cycles, each consisting of twelve training sessions. The first cycle is adaptation, the second is recovery and training, and the third is training.

When developing a rehabilitation program for patients, the following tasks are set: normalization of functional parameters of the patient's body; removal of fear of movement; restoration of the motor stereotype; elimination of spasms of the spinal muscles; improvement of spinal hemodynamics; normalization of posture; reduction of intensity or elimination of pain; prevention of recurrence of low back pain or reduction of their frequency and severity.

2. Therapeutic massage is used for osteochondrosis and scoliosis. The lower back massage focuses on several muscles, including the latissimus dorsi, the quadratus minor, and the spinal straightening muscle, located around the lower half of the spine. A variety of reasons can cause low back pain. The main cause of low back pain is muscle tension. A lower back massage helps warm up the muscles and improve blood and lymphatic circulation, encouraging the movement of beneficial nutrients through the body and eliminating large amounts of toxins. The

massage has the following objectives: to stimulate blood and lymph circulation in the extremities and spine; to reduce pain; to increase the tone of the hypotrophic muscles of the back of the thigh and lower leg, as well as the gluteal muscles; to minimize tension and tone of the long muscles of the back.

3. Kinesio taping is most effective for scoliosis, habitual patellar dislocations, and arthrosis. Taping is applying a type of elastic plaster (Kinesio tape) to painful areas of the body. Spinal taping relieves pain, supports back muscles, and corrects posture. Back Kinesio taping is used for chronic injuries, osteochondrosis, sprains, and pain during rehabilitation after injuries. The back taping increases blood and lymph flow and promotes a quick recovery without painkillers. During Kinesio taping, the patient should lean forward as much as possible. Then, the anchor is glued to the upper part of the gluteal region. Long strips are directed vertically upwards, parallel to the vertebrae on each side. Kinesio taping of the back is performed without tensioning the bandages.
4. Mechanotherapy (biomechanotherapy) is effective in herniated discs, scoliosis, osteochondrosis, arthrosis, habitual patellar dislocations, and hip dysplasia. Comprehensive treatment of patients is based on determining the cause of pain in the musculoskeletal system. Special exercises that work with muscles to eliminate the source of pain are used. Non-surgical treatment is performed under the supervision of a physical therapist. For a long time, with the above diseases, the muscles do not work physiologically: sometimes they spasm; sometimes, on the contrary, there is a lack of muscle tone and strength. Dr. Pavlenko developed the "Symmetry" training simulator so that it is possible to work out a single muscle or a group of muscles, expand it, or give a dynamic load. The simulator provides gentle conditions for the spine: no vertical load on the spinal column allows treating hernias and protrusions.
5. Manual therapy is an important component of the treatment of various diseases of the musculoskeletal system. It includes manipulations and mobilizations of joints and muscles aimed at reducing pain and improving the patient's mobility and functional status. Manual therapy can help with arthrosis, osteochondrosis, herniated discs, sprains, and strains.

DISCUSSION

The WHO definition of health focuses on its physical, mental, and social components [9]. A person who has all these aspects of well-being is healthy. When health is lost, therapy is required. Therapy is the treatment of

internal diseases using various methods. The method of physical therapy involves using such means as therapeutic physical education (TPE), manual therapy, mechanotherapy, Kinesio taping, therapeutic massage, etc. [10, 11].

These means are used to restore a person's immediate physical health, although they also improve their mental and social well-being to some extent. In this way, physical therapy differs from rehabilitation, which aims to restore a person's health comprehensively, return to the profession, and establish social ties [12]. Therefore, physical therapy is a part of rehabilitation that helps restore a person's physical health. This area of rehabilitation is also called "physical rehabilitation" (physical therapy) [13]. The physical therapy method is used in cases where the full functioning of the musculoskeletal system and the body's capacity is weakened or completely lost, which worsens the general state of human health [6].

According to experts [14], diseases of the musculoskeletal system rank third in the structure of primary disability among adults and the able-bodied population, behind only circulatory system diseases and cancer. Every year in Ukraine, more than 15 thousand adults become disabled because of musculoskeletal diseases, including more than 12 thousand people of working age (the working age population includes people aged 18 to retirement age). In addition, the category of patients with permanent disability is also significant [3, 5]. The proportion of newly registered musculoskeletal system diseases in the adult population during 2002-2022 was 5.54 ± 0.14 %. The proportion of primary disability due to peptic ulcer diseases of the musculoskeletal system was much higher and amounted to 10.85 ± 0.75 % with an upward trend [4]. During the war in Ukraine, the number of disabled people with musculoskeletal disorders increased significantly not only among military personnel, but also among the civilian population, but their statistical data is difficult to determine due to the ongoing hostilities.

According to scientists [15, 16], the main reasons for the increase in the level of disability due to diseases of the musculoskeletal system are: 1) patients are at late stages or do not receive full treatment due to the territorial inaccessibility of diagnosis and treatment, as well as the lack of financial capacity to pay for treatment and purchase of medicines; 2) late diagnosis of these diseases at the outpatient stage, lack of a comprehensive approach to the choice of treatment and correction of concomitant disorders leads to progression and complications of the disease. Although group III disabilities account for more than 80 % of disability due to musculoskeletal diseases, they have a very low probability

of recovering their ability to work, hence the constant increase in the number of disabled people in society.

The research results showed that significant changes took place during the war in the organization of the rehabilitation of patients with musculoskeletal disorders. Such changes are explained by the growing number of patients needing professional assistance, as well as the need to intensify their rehabilitation process. Organizational changes require specialists who can formulate comprehensive individual programs and carry out rehabilitation work with patients using a range of physical therapy tools, namely: doctors of physical and rehabilitation medicine, physical therapists, physical therapists' assistants, ergotherapists, and ergotherapists' assistants. These specialists are pushing out highly specialized professionals from the labor market, such as exercise therapy instructors, massage therapists, etc.

The results of the survey show that the intensification of rehabilitation of patients with musculoskeletal disorders and its effectiveness is possible only if comprehensive individual programs are developed and implemented, which include the use of a whole

range of physical therapy tools, including new ones (for example, Kinesio taping and the use of hardware technologies) and which clearly define the sequence of work with these tools. The results of our research confirm the findings of many scientists in this area and complement them.

CONCLUSIONS

Based on the conducted research, the system of physical therapy tools for certain diseases of the musculoskeletal system and the sequence of their application have been clarified, practical recommendations have been developed for the rehabilitation of the population with musculoskeletal disorders, taking into account changes in their structure and the opinions of rehabilitation specialists with experience working during the war in Ukraine.

PROSPECTS FOR FURTHER RESEARCH

The study of the effect of Kinesio taping on the recovery of spinal injuries and disorders in athletes is planned.

REFERENCES

1. Shevroja E, Reginster JY, Lamy O et al. Update on the clinical use of trabecular bone score (TBS) in the management of osteoporosis: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), and the International Osteoporosis Foundation (IOF) under the auspices of WHO Collaborating Center for Epidemiology of Musculoskeletal Health and Aging. *Osteoporos Int.* 2023;34(9):1501-1529. doi:10.1007/s00198-023-06817-4. DOI
2. Cibulka MT, Bloom NJ, Ensey KR et al. Hip Pain and Mobility Deficits-Hip Osteoarthritis: Revision 2017. *J Orthop Sports Phys Ther.* 2017;47(6):A1-A37. doi:10.2519/jospt.2017.0301. DOI
3. Doskaliuk B, Zimba O, Yatsyshyn R, Kovalenko V. Rheumatology in Ukraine. *Rheumatol Int.* 2020;40(2):175-182. doi:10.1007/s00296-019-04504-4. DOI
4. Selezneva S, Sinyachenko O, Zabara A. Features of the treatment of the spine in rheumatoid arthritis. *Georgian Med News.* 2017;(262):33-38.
5. Fedorchenko Y, Zimba O, Yatsyshyn R et al. The interplay between rheumatic diseases and pulmonary health. *Rheumatol Int.* 2024;44(7):1179-1184. doi:10.1007/s00296-024-05565-w. DOI
6. Carvalho GF, Schwarz A, Szikszay TM et al. Physical therapy and migraine: musculoskeletal and balance dysfunctions and their relevance for clinical practice. *Braz J Phys Ther.* 2020;24(4):306-317. doi:10.1016/j.bjpt.2019.11.001. DOI
7. Ho E, Tran J, Fateri C et al. Work-related musculoskeletal disorders affecting diagnostic radiologists and prophylactic physical therapy regimen. *Curr Probl Diagn Radiol.* 2024;53(4):527-532. doi:10.1067/j.cpradiol.2024.03.008. DOI
8. Critchley CJC. Physical Therapy Is an Important Component of Postpartum Care in the Fourth Trimester. *Phys Ther.* 2022;102(5):pzac021. doi:10.1093/ptj/pzac021. DOI
9. Nobile M. The WHO definition of health: a critical reading. *Med Law.* 2014;33(2):33-40.
10. Cornwell L, Doyle H, Stohner M, Hazle C. Work-related musculoskeletal disorders in physical therapists attributable to manual therapy. *J Man Manip Ther.* 2021;29(2):92-98. doi:10.1080/10669817.2020.1793470. DOI
11. Bervoets DC, Luijsterburg PA, Alessie JJ et al. Massage therapy has short-term benefits for people with common musculoskeletal disorders compared to no treatment: a systematic review. *J Physiother.* 2015;61(3):106-116. doi:10.1016/j.jphys.2015.05.018. DOI
12. Beutler A. Musculoskeletal Therapies: Adjunctive Physical Therapy. *FP Essent.* 2018;470:16-20.
13. Fan LJ, Liu S, Jin T et al. Ergonomic risk factors and work-related musculoskeletal disorders in clinical physiotherapy. *Front Public Health.* 2022;10:1083609. doi:10.3389/fpubh.2022.1083609. DOI
14. Mourad F, Giudice A, Maritati G et al. A guide to identify cervical autonomic dysfunctions (and associated conditions) in patients with musculoskeletal disorders in physical therapy practice. *Braz J Phys Ther.* 2023;27(2):100495. doi:10.1016/j.bjpt.2023.100495. DOI

15. Anderson PA, Kadri A, Hare KJ, Binkley N. Preoperative bone health assessment and optimization in spine surgery. *Neurosurg Focus*. 2020;49(2):E2. doi:10.3171/2020.5.FOCUS20255. DOI 
16. Bioletto F, Berton AM, Barale M et al. Skeletal fragility in pituitary disease: how can we predict fracture risk?. *Pituitary*. 2024. doi:10.1007/s11102-024-01447-3. DOI 

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Grygoriy Griban

Zhytomyr Ivan Franko State University
40 Velyka Berdychivska St, 10008 Zhytomyr, Ukraine
e-mail: gribang@ukr.net

ORCID AND CONTRIBUTIONSHIP

Grygoriy Griban: 0000-0002-9049-1485 
Olha S. Zablotska: 0000-0002-0850-5754  
Inna O. Asauliuk: 0000-0001-8119-2726 
Dmytro G. Oleniev: 0000-0001-9685-725X 
Svitlana M. Dmytrenko: 0000-0001-5934-4893 
Oleh L. Morin: 0000-0001-5756-8359 
Nataliia O. Terentieva: 0000-0002-3238-1608 

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 03.11.2024

ACCEPTED: 09.06.2025



Training methods for correction of behavioral rigidity in medical students during lifestyle changes

Olha L. Korobanova¹, Neonila I. Korylchuk², Oleh Burlieiev³, Iryna B. Romash⁴, Kateryna V. Dzivak⁴, Mariya V. Blyzniuk⁴, Ihor S. Tymkiv⁴

¹PRIVATE HIGHER EDUCATIONAL ESTABLISHMENT «EUROPEAN UNIVERSITY», KYIV, UKRAINE

²I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

³INSTITUTE OF ARTS AND SCIENCES, BUCHA, UKRAINE

⁴IVANO-FRANKIVSK NATIONAL MEDICAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

ABSTRACT

Aim: To empirically investigate the possibilities of training methods for behavioral rigidity correction during lifestyle changes due to internal displacement of medical students.

Materials and Methods: Three stages of the research were realized. The current state of mental health, resilience, coping styles and behavioral rigidity of medical students was established at the stating stage, using Positive Mental Health Scale, Connor-Davidson resilience scale, Coping inventory for stressful situations and Self-assessment of mental states: Rigidity scale that were reapplied at the control stage. The formative stage was aimed at objectification, assessment and correction of rigid behavior, as well as improvement of adaptive capabilities of internally displaced medical students by training methods. The training developed by the authors was implemented at this stage. The control stage allowed to confirm the effectiveness of the proposed training program in the contexts of mental health, coping strategies, resilience and behavioral rigidity.

Results: The implementation of training methods was effective in overcoming the complex of symptoms associated with post-traumatic stress connected with lifestyle changes due to internal displacement, leading to lack of resilience and psychological protection in the form of behavioral rigidity and maladaptive coping styles of medical students.

Conclusions: Behavioral rigidity of future doctors during lifestyle changes under the pressure of internal displacement turned out to be a relevant empirically identified problem affecting their quality of life, mental health and psychological well-being in the new conditions. As such, this training technology is useful in psychoprophylactic correctional work and psychosocial support for vulnerable groups of young adults, which include internally displaced medical students, and can be applied in psychoeducational work with them.

KEY WORDS: medical students, lifestyle, mental health, coping skills, psychological resilience

Wiad Lek. 2025;78(9):1821-1830. doi: 10.36740/WLek/212520 DOI

INTRODUCTION

Being a student brings many challenges and complexities for young adults. They have to cope with a busy study schedule, meet academic requirements, solve personal financial difficulties, maintain necessary living conditions, and take care of their health and relationships with their peers. The Russo-Ukrainian war did not cancel the usual student problems, instead providing a large number of additional stressors into the daily lives of students.

The impact of war-related stressful experiences on students has been experimentally confirmed [1-7]. At the same time, maintaining psychological well-being, positive relationships, and satisfaction with lifestyle is a necessary background for students to learn productively. Students' physical and psychological well-being has

been recognized as an important component of achieving academic success [8], while the loss of well-being can affect it [1, 9]. Indeed, against the background of stress, depression, anxiety and some symptoms of post-traumatic stress disorder, medical students during the war showed a decrease in academic performance [1, 2]. The limitations of the learning process also relate to the quality of education due to the disruption of teaching during alarms and shelling and increased workload of teachers [10].

The traumatic impact of war affects the mentality and mental health of students [2, 3, 11], manifested in neurotic disorders, psychopathological symptoms of depression and anxiety, indicators of acute stress [12], depressive and anxiety experiences, manifestation of some symptoms of PTSD [3 – 5]. The presence of

such manifestations has been noted both in students studying near the frontline and in distant from military operations areas.

The forced displacement of Ukrainian students caused by the Russo-Ukrainian war turned out to be a strong trigger for changes in their lifestyle. The disruption of the habitual way of life among displaced students is one of the serious psychological traumas experienced by them [13]. Usually, lifestyle change is associated with loss of home, property, fear for one's life, communication problems [12], which can also entail serious psychological traumas. Changes in habits as a consequence of lifestyle changes also have a negative impact on mental health [14]. Internal displacement affects lifestyle, quality of life, and therefore subjective wellbeing [15] and entails experiencing the stress of a change of residence and the need to adapt one's lifestyle to the new environment [13].

Behavioral rigidity may occur as a response to stress. Changes in lifestyle and quality of life are associated with trauma and impaired mental health [7]. Behavioral rigidity usually acts as the link most sensitive to psychogenic factors, in particular to situations that require an abrupt change in life pattern, adaptation to the new or abandonment of the familiar. It is noted that behavioral rigidity or inflexibility can be a consequence of post-traumatic stress [16] or can act as protection against trauma [17].

Rigidity can also be seen as resistance to change and preference for habitual patterns and strategies of behavior, even when they are ineffective or inappropriate. While psychological flexibility is defined as the ability to stay in touch with the current moment and change one's behavior according to the situation, the essence of behavioral rigidity is inflexibility that prevents adaptation to new conditions [18, 19]. Behavioral rigidity can manifest itself as an individual's difficulty in adapting their behavior to meet the changing conditions and requirements of the situation. It is an aspect of maladaptive behavioral strategies that determine the way of life, and can significantly affect the mental health of students, limiting their adaptability to new or stressful situations.

Thus, behavioral rigidity of internally displaced students is a complex of symptoms which can be attributed to post-traumatic stress, lifestyle changes due to internal displacement, leading to lack of resilience and psychological protection in the form of rigidity and maladaptive coping. We will consider behavioral to be one of consequences of experiencing an internal crisis of lifestyle change in displaced students.

Internally displaced students find themselves in a situation of acute crisis in which established earlier

stable rules of life are violated. In crisis, life situations disturb the image of people's reality and change their picture of the world. Forced relocation and adaptation to new conditions leads to the crisis of lifestyle change, the crisis of adaptation of displaced people, the consequence of which is a decline in the standard of living of displaced Ukrainians [7].

At the same time, the need for internally displaced students to undergo a stage of social adaptation and integrate into the community in a new place actualizes issues of subjective well-being and life satisfaction [20]. The processes accompanying internal relocation experience mental health, and the coping strategies that displaced students adhere to influence their resilience [21]. We emphasize that for medical students, the factors listed above act in a complex way; stress, displacement, loss, and academic burden are amplified by the challenges of war. The impact of war trauma and related stressors persists when moving out of danger zones, while the challenges of moving, changing residence, and settling into a new place can intensify other negative experiences [12].

A study by Wang et al., 2024, found that the use of adaptive coping was associated with higher quality of life among Ukrainians [7], which may indicate the need for interventions to prevent young adults from practicing maladaptive strategies. So, all this has a great impact on the training of qualified physicians. Medical students emphasized the significant impact of war on learning, mental health and psychological well-being, they characterized their training as a challenge [9]. Accordingly, displaced medical students need psychological help and it can be realized in training. Specialists note the lack of psychosocial support in Ukraine [22], an important element of which is the organization of group meetings and trainings that promote mental health awareness, psychological resilience, social integration, and improve the quality of life of participants [12, 23, 24] that would cope with disruptive coping strategies [7].

Of importance for the topic under discussion is the theoretical notion by Lunov et al. (2023) about the phenomenon of interpersonal behavior as a predictor of the triad, which includes interpersonal communication, adaptive potential and psychological health of young people [11]. This means that problems and deficiencies in interpersonal behavior, for example, behavioral rigidity, will affect not only the quality of interpersonal communication, but also the adaptive capacity and mental health of young adults. Developing this thought, we approach the possibility through social-psychological training, revealing in the objective form of interpersonal communication problems and

shortcomings leading to the appearance of rigidity, to strengthen the capabilities of social-psychological adaptation, and improve the mental health of medical university students. Training in adaptive behavioral strategies and coping will improve the quality of life of medical students.

AIM

To empirically investigate the possibilities of training methods to correct behavioral rigidity in medical students during lifestyle changes.

MATERIALS AND METHODS

The sample of subjects consisted of 168 medical students of I. Horbachevsky Ternopil National Medical University, who were internally displaced, among them 84 students of the 4th year and 84 students of the 6th year at the age of 20 to 24 years, among them 33.3% of guys and 66.7% of girls.

Three stages of the research were realized – the stating, formative and control stages. The stating stage aimed to establish the initial state of behavioral characteristics of the study participants, to identify the tendency, presence, level and peculiarities of behavioral rigidity, to further monitoring the dynamics of changes and the effectiveness of the implemented interventions. The formative stage was the key stage aimed at improving students' adaptive capabilities in response to changes in their lives, as well as identifying, assessing and correcting rigid behavior. The control stage allowed to compare initial and final indicators of the behavioral rigidity symptom complex in order to establish the dynamics of changes and evaluate the effectiveness of interventions.

PROGRAM DESCRIPTION

Developed training was aimed at making participants aware of behavioral choices and teaching them to choose adaptive and situation-relevant strategies. A correctional training program was designed for 6 weeks and 6 key weekly activities (with 1.5 hour sessions), which combined individual and group work and were aimed at developing the ability to model situations and behavioral flexibility to adapt to new conditions. Each activity contained information messages and their discussion, role-playing games, brainstorming, group discussions, relaxation exercises. Twelve groups were organized with students of the 4th and 6th courses, in which 12 to 15 students participated. A selection of special psychoeducational influences and

psychocorrectional techniques was made, taking into account the traumatic experience of the majority of resettlement participants, which required a particularly sensitive approach to them in the training. At this stage, interventions for the formation of adaptive behavioral strategies were carried out. The program is given in an abbreviated form (See Appendix).

The program provided for further independent application by the participants of the learned techniques, as well as compliance with the basic principles promoting mental health, social-psychological adjustment and flexibility in crisis situations.

In order to control the psychological results of the implemented interventions, psychodiagnostic studies were conducted at the stating and control stages. The following methods were chosen for diagnostics: Positive Mental Health Scale (PMH-scale) (Lukat J., Margraf J., R. Lutz R. et al.) [25], Connor-Davidson resilience scale-10 (CD-RISK-10) [26], Coping inventory for stressful situations (CISS) (Endler N.S., Parker J.D.A.) [27], Self-assessment of mental states: Rigidity scale (Eysenck H.) [28].

RESULTS

The stating stage revealed increased rigidity and reduced adaptability of medical students who changed the location of residence and education to the safer Ternopil region during the war.

At the control stage, after conducting psychological training interventions aimed at reducing behavioral rigidity among displaced medical students, a repeated psychodiagnostics using the same methods was conducted. As a result of applied training interventions, positive dynamics of mental health in medical students was noted (Table 1).

Analysis of the results of the CD-RISC-10 showed positive dynamics after psychoeducational interventions in training (Table 2). Comparison of initial and final indicators shows significant positive changes in the resilience category of students after psychoeducational interventions.

The study conducted using the CISS shows significant changes in the behavioral patterns of students when coping with stress towards the use of active styles (Table 3).

The study using the rigidity scale indicates an increased ability to search for alternative ways to solve problems (Table 4).

In general, the results confirm the effectiveness of the corrective training program to reduce students' behavioral rigidity, which will contribute to their better adaptation to the changing conditions of life and learning during the war.

Table 1. PMH scale results of medical students: before and after training

PMH scale	Before		After	
High	32	19,1%	124	73,8%
Average	122	72,6%	44	26,2%
Low	14	8,3%	-	-

Source: compiled by the authors of this study

Table 2. Medical students' resilience: before and after training

Resilience category (N/%)	Before		After	
High resilience	37	22,0%	46	27,4%
Moderate resilience	110	65,5%	122	72,6%
Low resilience	21	12,5%	0	0

Source: compiled by the authors of this study

Table 3. Coping styles of medical students: before and after training

Coping styles (N/%)	1		2		3		4		5	
	Before	After	Before	After	Before	After	Before	After	Before	After
Task-oriented coping	18/ 10,7	0/ 0	56/ 33,3	26/ 15,5	64/ 38,1	94/ 56,0	20/ 11,9	30/ 17,9	10/ 6,0	18/ 10,7
Emotion-oriented coping	38/ 22,6	18/ 10,7	20/ 11,9	15/ 8,9	36/ 21,4	46/ 27,4	5/ 33,3	66/ 39,3	18/ 10,7	23/ 13,7
Avoidance	16/ 9,5	21/ 12,5	30/ 17,9	50/ 29,8	50/ 29,8	60/ 35,7	52/ 31,0	32/ 19,1	20/ 11,9	5/ 3,0
Avoidant-distracted coping	-	-	-	-	98/ 58,3	42/ 25,0	70/ 41,7	93/ 55,4	0/ 0	33/ 19,6
Avoidant-social coping	24/ 14,3	0/ 0	36/ 21,4	10/ 6,0	108/ 64,3	121/ 72,0	0/ 0	22/ 13,1	0/ 0	15/ 8,9

Source: compiled by the authors of this study

Table 4. Models of medical students' rigid behavior: before and after training

Responses to the rigidity scale (N/%)	2		1		0	
	Before	After	Before	After	Before	After
I change my habits with difficulty	58/34,5	36/21,43	68/40,48	80/47,62	42/25,00	52/30,95
I distract my attention to something else with	32/19,1	0/0	48/28,57	32/19,05	88/52,38	136/80,95
I treat with caution to anything new	52/31,0	12/7,14	98/34,52	108/64,29	18/10,71	48/28,57
It's difficult to persuade me	64/38,1	14/8,3	62/36,9	82/48,8	42/25,0	72/42,9
I often have thoughts in my mind which I should have got rid of	75/44,6	60/35,7	25/14,9	35/20,8	68/40,5	73/43,5
It's difficult for me to make friends	25/14,9	5/3,0	32/19,1	42/25,0	111/66,1	121/72,02
I get upset of even the smallest changes in a program	28/16,7	4/2,4	42/5,0	46/27,4	98/58,3	118/70,2
I often behave stubborn	8/4,8	0/0	25/14,9	10/6,0	135/80,4	158/94,1
I risk rarely	35/20,8	32/19,1	52/31,0	55/32,7	81/48,2	81/48,2
I sudden because of the changes to my routine	42/25,0	10/6,0	54/32,1	70/41,7	72/42,9	88/52,4

Source: compiled by the authors of this study

DISCUSSION

The study of different contexts of the situation of internal displacement is still relevant, as the number of internally displaced people in Ukraine continues to increase. Ukrainian medical students who are experiencing adaptation due to lifestyle changes influenced

by military events need psychological support and correction programs. This is all the more important as student status is one of the risks for internally displaced persons [4]. We hope that this article will contribute to filling the deficit of psychoeducational and psychosocial trainings on working with affected students [23, 24].

Ukrainian folk wisdom says that each generation has its own war and its own crisis. Frozen rigid reactions characterize the consequences of students' experience of crisis circumstances due to the influence of war, while adaptation to a different way of life requires a change in behavior patterns [29]. Improving quality of life can be associated with interventions that promote mental health and adaptive coping [7, 22] against the background of changing the dynamic stereotype, habits and living conditions of displaced medical students.

Experiencing psychological distress due to decreased quality of life by medical students may lead to reduction in their manifestation of personality traits that are important for successful medical practice in the future (such as empathy, humanity, compassion, patience, and others) [1]. Therefore, training interventions aimed at psychological support and psychocorrection are important, which will reduce the burden of mental health pressure, lead to a decrease in stress, anxiety levels, depression [30] and improve the quality of life of Ukrainian students.

Medical university education is oriented towards high professional standards and requires students to consistently put a lot of effort towards acquiring both medical knowledge and practical skills. Behavioral rigidity is a serious obstacle for medical students, especially when they face dramatic changes in learning, and its elimination will help them to better focus on their studies and complex tasks [30].

The importance of the considered aspect of the scientific problem lies in the need to find ways to help internal military migrants in Ukraine. Taking into account behavioral rigidity among their possible psychological problems allows to expand the field of study of internal

migration. Consideration of behavioral rigidity, which arises as a protective response to increased emotional and intellectual strain when changing the way of life during the war, should probably be continued in further research.

CONCLUSIONS

The Russo-Ukrainian war has brought a large number of traumatic events to Ukrainians, resulting in reduced quality of life and significant psychological harm in general. Displaced medical students are under significant pressure of circumstances that have changed their lifestyle. The crisis situation of internal displacement triggers a defensive reaction in most of them in the form of behavioral rigidity. The applied training interventions reduced the behavioral rigidity of medical students, which facilitated their adaptation to the changed living conditions and lifestyle, and enhanced their ability to model their behavior.

Considering apparent lack of psychosocial and correctional programs for support of displaced students in Ukraine, development of such training methods is important as a representation of practical psychocorrectional work that has been shown to be effective. This study contributes to validated methods of psychological support for young adults in extreme conditions and is important as a successful case study. Psychological work with rigid reactions and correction of behavioral rigidity is one of the promising areas of work with students in traumatic conditions.

Further research could focus on identifying optimal techniques, approaches and interventions to correcting behavioral rigidity with lifestyle changes for different groups of internally displaced people.

REFERENCES

1. Kokun O, Bezverkhyi O. Ukrainian Students' Personal Resources and Resistance to War Stress: A Cross-Sectional Survey. *J of Loss and Trauma*. 2024;29(8):976-993. doi:10.1080/15325024.2024.2325084. DOI [10.1080/15325024.2024.2325084](#)
2. Korda M, Shulhai A, Shevchuk O et al. Psychological well-being and academic performance of Ukrainian medical students under the burden of war: a cross-sectional study. *Front. Public Health*. 2025;12:1457026. doi:10.3389/fpubh.2024.1457026. DOI [10.3389/fpubh.2024.1457026](#)
3. Kurapov A, Danyliuk I, Loboda A et al. Six months into the war: a first-wave study of stress, anxiety, and depression among in Ukraine. *Front Psych*. 2023;14:1190465. doi:10.3389/fpsy.2023.1190465. DOI [10.3389/fpsy.2023.1190465](#)
4. Kurapov A, Kalaitzaki A, Keller V et al. The mental health impact of the ongoing Russian-Ukrainian war 6 months after the Russian invasion of Ukraine. *Front. Psych*. 2023;14:1134780. doi:10.3389/fpsy.2023.1134780. DOI [10.3389/fpsy.2023.1134780](#)
5. Kurapov A, Pavlenko V, Drozdov A et al. Toward an understanding of the Russian-Ukrainian war impact on university students and personnel. *J of Loss and Trauma*. 2022;28(2):1-8. doi: 10.1080/15325024.2022.2084838. DOI [10.1080/15325024.2022.2084838](#)
6. Stadnik AV, Melnyk YuB, Mykhaylyshyn UB et al. Peculiarities of the psychological well-being and social adaptation of young students and cadets in wartime conditions. *International Journal of Science Annals*. 2023;6(1):22-30. doi:10.26697/ijsa.2023.1.7. DOI [10.26697/ijsa.2023.1.7](#)
7. Wang S, Barrett E, Hicks MHR et al. Associations between mental health symptoms, trauma, quality of life and coping in adults living in Ukraine: A cross-sectional study a year after the 2022 Russian invasion. *Psychiatry Research*. 2024;339:116056. doi:10.1016/j.psychres.2024.116056. DOI [10.1016/j.psychres.2024.116056](#)

8. Srichawla BS, Khazeei Tabari MA, Găman MA et al. War on Ukraine: impact on Ukrainian medical students. *Int J Med Stud*. 2022;10:15–7. doi: 10.5195/ijms.2022.1468. [DOI](#)
9. Kuchyn I, Bielka K, Lymar L et al. Academic performance, perceptions, and motivations of medical PhD students in Ukraine during wartime: a mixed methods study. *BMC Med educ*. 2024;24(1):1421. doi: 10.1186/s12909-024-06400-3. [DOI](#)
10. Mayer A, Yaremko O, Shchudrova T et al. Medical education in times of war: a mixed-methods needs analysis at Ukrainian medical schools. *BMC Med Educ*. 2023;23:804. doi: 10.1186/s12909-023-04768-2. [DOI](#)
11. Lunov V, Litvinenko O, Maltsev O et al. The impact of Russian military aggression on the psychological health of Ukrainian youth. *American Behavioral Scientist*. 2022;67(3):426–448. doi: 10.1177/ 00027642231214083. [DOI](#)
12. Mykhaylyshyn UB, Stadnik AV, Melnyk YuB et al. Psychological Stress among University Students in Wartime: A Longitudinal Study. *Int j sci ann*. 2024;7(1):27–40. doi:10.26697/ijsa. [DOI](#)
13. Ryan D, Dooley B, Benson C. Theoretical Perspectives on Post-Migration Adaptation and Psychological Well-being among Refugees: Towards a Resource-Base Model. *Journal of Refugee Studies*. 2008;21(1):1–18. doi: 10.1093/jrs/fem047. [DOI](#)
14. Barchielli B, Cricenti C, Gallè F et al. Climate Changes, Natural Resources Depletion, COVID-19 Pandemic, and Russian-Ukrainian War: What Is the Impact on Habits Change and Mental Health? *Int J Environ Res Public Health*. 2022;19(19):11929. doi: 10.3390/ijerph191911929. [DOI](#)
15. Perelly-Harris B, Zavisca J, Levchuk N et al. Internal displacement and subjective well-being: the case of Ukraine. *Economic and Social Research Council. ESRC Centre for Population Change*. 2022, p.29.
16. Giommi F, Bauer PR, Berkovich-Ohana A et al. The (In)flexible self: Psychopathology, mindfulness, and neuroscience. *Int J Clin Health Psychol*. 2023;23(4):100381. doi: 10.1016/j.ijchp.2023.100381. [DOI](#)
17. Schmelzer GL. *Journey through Trauma. A Trial Guide to the 5-Phase Cycle of Healing Repeated Trauma*. New York. Avery. Penguin Random House. 2018, p.336.
18. Schultz PW, Searleman A. Rigidity of thought and behavior: 100 years of research. *Genet Soc Gen Psychol Monogr*. 2002;128(2):165–207.
19. Steinmetz JP, Loarer E, Houssemand C. Rigidity of Attitudes and Behaviors: A Study on the Validity of the Concept. *Individual Differences Research*. 2011;9(2):84–106.
20. Roshchik I, Bilan Y, Krol V et al. Social Integration of Internally Displaced Persons in Ukraine: Problems and Challenges for Governing Local Communities. *Problems and Perspectives in Management*. 2024;22(1):728–740. doi: 10.21511/ppm.22(1).2024.57. [DOI](#)
21. Rizzi D, Ciffo G, Landoni M et al. Psychological and environmental factors influencing resilience among Ukrainian refugees and internally displaced persons: a systematic review of coping strategies and risk and protective factors. *Front Psychol*. 2023;14:1266125. doi:10.3389/fpsyg.2023.1266125. [DOI](#)
22. Buchcik J, Kovach V, Adedeji A. Mental health outcomes and quality of life of Ukrainian refugees in Germany. *Health Qual Life Outcomes*. 2023;21(1):23. doi:10.1186/s12955-023-02101-5. [DOI](#)
23. Vus VI, Shkoliar MV, Proskuriakov S et al. 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 Mercur Lek*. 2024;52(3):373–379. doi:10.36740/Merkur202403116. [DOI](#)
24. Vus V, Shkoliar M. Leveraging Communities of Practice to Sustain Mental Health and Psychosocial Support in Crisis Contexts. *MHGJ*. 2025;8(1):48–59. doi: 10.56508/mhgj.v8i1.274. [DOI](#)
25. Lukat J, Margraf J, Lutz R et al. Psychometric properties of the Positive Mental Health Scale (PMH-scale). *BMC Psychology*. 2016;4(8):1–14. doi:10.1186/s40359-016-0111-x. [DOI](#)
26. Connor KM, Davidson JR. Development of a new resilience scale: The Connor-Davidson resilience scale (CD-RISC). *Depression Anxiety*. 2003;18(2):76–82.
27. Endler NS, Parker JDA. *Coping inventory for stressful situations (CISS): Manual (2nd ed.)*. Toronto: MultiHealth Systems. 1999. doi: 10.1037/t02138-000. [DOI](#)
28. Eysenck HJ, Wilson GD. *Know your own personality*. Harmondsworth, Eng. Baltimore etc: Penguin Books. 1976, 206 p.
29. Korobanova O, Schulzhenko N. Psychology of home and Ukrainian migrants' adaptation abroad. *SSSPJ*. 2022;28(2). doi:10.33120/ssspj.vi50(53).604. [DOI](#)
30. da Silva CCG, Bolognani CV, Amorim FF et al. Effectiveness of training programs based on mindfulness in reducing psychological distress and promoting well-being in medical students: a systematic review and meta-analysis. *Syst Rev*. 2023;12(1):79. doi:10.1186/s13643-023-02244-y. [DOI](#)

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Olha L. Korobanova

European University

16V Academician Vernadsky blvd, 03115 Kyiv Ukraine

e-mail: olha.korobanova@e-u.edu.ua

ORCID AND CONTRIBUTIONSHIP

Olha L. Korobanova: 0000-0003-3539-871X **A C D E F**

Neonila I. Korylchuk: 0000-0002-1055-9292 **A B C F**

Oleh Burliev: 0000-0002-6450-8618 **E F**

Iryna B. Romash: 0000-0002-9749-778 **E F**

Kateryna V. Dzivak 0000-0002-3481-9482 **E F**

Mariya Blyzniuk 0000-0002-0612-785X **E F**

Ihor S. Tymkiv 0000-0001-5229-2760 **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: 18.04.2025

ACCEPTED: 28.08.2025



APPENDIX 1

Introductory Session. Awareness of Rigidity and its Impact

Aim: To introduce students to the concepts of behavioral rigidity, its role in stressful situations and to teach them to be aware of their own reactions to change.

Objectives: to understand what behavioral rigidity is and how it can hinder adaptation; to analyze how rigid attitudes influence behavior and reactions in new conditions; to teach students to identify rigid patterns in their own behavior and analyze their influence.

Methods: information messages, group discussion, brainstorming, analysis of case studies, written reflection.

1. Introductory part (10-15 min.). Greeting and familiarization with the topic. The psychologist begins the session by explaining the importance of the topic of behavioral rigidity, referring to the works of psychologists A. Beck (1995) on cognitive rigidity and L. Festinger (1957) on cognitive dissonance. It is emphasized that rigidity can be a barrier to adaptation, especially in medicine where active change, due to the demands of the times, is the norm. Questions for students: Have you ever had a time when you could not accept change even when you understood the need for it? How do you respond to new teaching methods? What is your reaction to changes in specialization requirements? How do you react to the fact that it is possible that you may be mobilized as a health professional?

2. Main part (40-45 min.). Review and analysis of rigidity questionnaires (10 min.). Definition of behavioral rigidity (according to A. Beck and A. Adler) and its impact on training and professional activity of a doctor. Discussion of rigidity in student life (15 min.). 1, 1.5 hours

The psychologist invites students to give examples of rigidity in their own learning experiences (e.g., inability to accept new teaching methods, resistance to change in teaching, difficulty in changing teachers). The discussion takes place in a brainstorming format. Exercise "Analyzing Rigid Situations" (15-20 min.). Students in small groups discuss real situations when it was difficult for them to adapt to changes (e.g., switching to distance learning, first going to a hospital for an internship). Each group analyzes their reactions: emotional (anxiety, fear, anger), behavioral (resistance, avoidance), cognitive (negative attitudes, beliefs).

3. Final part (20-30 min.). Written reflection "What situations cause me the most rigidity?" (10-15 min.). Students analyze in writing their own trigger situations where they felt rigidity and try to find ways to improve adaptation. Group discussion of reflections (10-15 min.). Several students volunteer to share their findings. The psychologist summarizes the importance of self-observation and awareness of one's own rigidity reactions.

Homework. Students should write down three more situations where they noticed their own rigidity and suggest possible ways to overcome it.

Expected Outcomes. Students will be aware of what behavioral rigidity is and how it affects their adaptation. They will identify their own behavioral patterns and be better able to recognize their reactions to changes, develop skills of self-reflection and critical thinking about their own behavior.

APPENDIX 1 cont.

Development of awareness and emotional self-control

Aim: To teach students to recognize and manage emotions that cause rigidity in order to increase adaptability in stressful situations.

Objectives: to develop skills of awareness of their own emotional reactions in response to stress; to develop the ability to control emotional impulses and maintain emotional flexibility; to learn to use conscious self-regulation techniques to reduce the influence of negative emotions; to develop skills of reflection and analysis of their own emotional state.

Methods: information messages, group discussion, role playing games, analysis of case studies, relaxation exercises, written reflection.

1. Introductory part (10-15 min). Introduction to the topic of the concept: explanation of the importance of awareness and emotional self-control in overcoming behavioral rigidity. Discussion of the influence of emotions on decision making and behavior. What emotions are important that prevent us from being flexible? How does stress affect our ability to adapt to change?

2. Theoretical block (15 min). The mechanism of emotions: how the brain reacts to a stressful situation. The link between emotions and behavioral rigidity: how fear, anxiety, and anger can contribute to fixed patterns of behavior. The role of mindfulness in emotion management: the concept of "emotional pause" (momentary awareness of an emotional response before responding).

3. Practical part (40 min). Exercise 1: Conscious breathing (10 min). Teaching the technique of deep breathing to stabilize the emotional state. Execution of the exercise "4-7-8" (inhale for 4 seconds, support for 7 seconds, exhale for 8 seconds). Discussion of sensations after the exercise. Exercise 2: "Emotional Diary" (15 min). Students write down a situation during the day that caused strong emotions (positive or negative). Record their thoughts, feelings and reactions. Analyze how much control they had over their reaction and what could have been changed. Exercise 3: "Step Back" - developing emotional flexibility (15 min). Participants support cases with quick stressful situations. Their task is to analyze the stress, change emotions, and offer options for a conscious response. Discussion of how attention can be modified for more adaptive focusing behavior.

4. Group discussion and reflection (20 min). Sharing experiences on the "difficulty" of the difficulty. Psychologist gives feedback and recommendations. Discussion of practical strategies for maintaining emotional flexibility in daily life.

Homework. Continue to keep the Emotional Diary for 3 more days. Do the "4-7-8" exercise every morning and before bed. Identify one stressor for next week and try to do the "Step Back" method.

Expected Results. Improved skills in consciously recognizing one's own emotions. Developing the ability to manage emotions without impulsive reactions. Developing greater emotional flexibility and adaptability to change.

Session 2

1, 1.5 hours

Development of flexible thinking and the possibility of alternative approaches

Aim: to develop the ability to think flexibly, to change stereotypical attitudes and to form skills of alternative approach to problem solving.

Objectives: to teach students to rethink the situation and consider alternative solutions; to develop skills to overcome thinking rigidity through the development of open thinking; to expand the ability to see the problem from different perspectives; to develop critical thinking and argumentation skills.

Methods: information messages, group discussion, role playing games, analysis of case studies, brainstorming, and written reflection. Exercise "Alternative Solutions": students consider real or apparent situations and formulate the best options for their solution. Exercise "Changing Perspective": each participant chooses a problem and analyzes it from different perspectives. A group discussion is held on the importance of critical thinking and the ability to rethink.

1. Introductory part (10 min). Familiarization with the topic of the concept: what flexibility of thinking is and why it is important. Discussion: How do stereotypes influence our thinking? Have you ever had to change your point of view under the influence of new facts?

2. Theoretical block (15 min). What is cognitive rigidity and how does it manifest itself? Principles of flexible thinking: Ability for perspective changes. Alternative approaches to problem solving. Openness to new information. The link between thinking and decision making: how fixed attitudes can limit possibilities.

3. Practical part (45 min.). Exercise 1: "Alternative solutions" (20 min). Students work in groups and are given a task (e.g., conflict with a teacher, group dilemma with learning, conflict with a patient). Task: Formulate possible solutions to these situations. Presentation of solutions and group discussion. Analysis of non-obvious but effective options. Exercise 2: "Changing Perspective" (15 min). Each participant chooses his/her own problem or receives a task with a problem from the psychologist. Task: analyze the problem from different perspectives (e.g., teacher's perspective, patient's perspective, neutral observer, skeptic, etc.). Discussion in pairs or groups: did their perception of the problem change after the analysis? Exercise 3: "Improving Critical Thinking" (10 min). The psychologist offers participants statements (e.g., "all young people are addicted to social networks", "people do not change", "all students are stupid", "all doctors are mediocre"). The task is to find counterarguments and build an alternative point of view. Collective discussion: how to learn not to take information as absolute truth, but to analyze it?

4. Group discussion and reflection (20 min.). Sharing experience in expanding one's own point of view. Discussion of barriers that prevent opinions from being flexible. Psychological feedback and recommendations for further development of critical and flexible thinking.

Homework. During the week, try to evaluate any complex situation from three different perspectives. Analyze whether the perception of this situation has changed after alternative consideration. Keep a "Changing Perspective" diary - record a system in which participants consciously practice alternative thinking.

Expected Outcomes. Improved thinking flexibility skills. Changing the influence of stereotypes on decision making. Increased ability to analyze situation from different perspectives. Formation of more open and critical thinking. Choice of alternative behavior in non-standard situations.

Session 3

1, 1.5 hours

APPENDIX 1 cont.

Behavioral Flexibility Skills and Adaptation to New Conditions

Aim: to develop skills of adaptation to change and teach students to act flexibly in non-standard situations, reducing the fear of uncertainty.

Objectives: to practice adaptive behavior in the face of change; to develop skills of openness to new circumstances and conditions; to learn to make quick decisions and adjust their behavior in unpredictable situations; to understand their own emotional reactions to change and be able to regulate them.

Methods: information messages, group discussion, role playing games, analysis of case studies, written reflection.

1. Introductory part (10 min.). Familiarization with the topic of the lesson: why adaptation is a key skill in the modern world. Discussion: Do you find it easy to adapt to new conditions? What factors are most likely to cause difficulties when a situation changes? How do you usually react to sudden changes of plans?

2. Theoretical block (15 min). What is behavioral flexibility and why is it important? How the brain reacts to change: the mechanism of resistance to the new and ways to overcome it. Basic adaptation strategies: Readiness for variability of decisions. Developing a positive attitude towards change. Use of flexible planning. Assessing one's own level of tolerance to uncertainty.

3. Practical part (45 min). Exercise 1: Role-playing "Unexpected scenarios" (20 min). Students are given individual or group situations in which they have to change their plans and adapt. For example: a sudden change of schedule, the need to act in unfamiliar conditions, a new group for a task. Participants have to quickly find a solution and present it to the group. Discussion: what emotions arose, what difficulties were experienced, what helped to adapt faster? Exercise 2: "My place in the change" (15 min). Participants recall a recent change in their lives that caused discomfort. Task: describe their first reaction and try to change it to a more adaptive one. Group work: discuss alternative approaches to adaptation. Exercise 3: "Alternative Behavior" (10 min). The psychologist offers participants situations in which they have to choose one of several behavioral options. Analysis of each option: what can be the consequences? Which option is the most flexible? Collective discussion: how to learn to quickly find the best solution?

4. Group discussion and reflection (20 min). What was the most difficult part of working with adaptation? What skills helped to cope with the change faster? How can behavioral flexibility be developed in everyday life? Psychological feedback and tips for working with adaptation.

Homework. During the week, try to consciously respond to any changes (even small ones) with openness. Analyze your emotions and ways of adaptation in a diary. Perform the "Alternative Solution" exercise: write down the situation that needed adaptation and propose 3 different behavioral options.

Expected results. Improved ability to adapt to change. Reduction of fear of instability and uncertainty. Development of decision-making speed in new conditions. Formation of a positive attitude towards change and the ability to act effectively in unpredictable situations.

Session 4

1, 1.5 hours

Developing positive reappraisal and working with cognitive attitudes

Aim: to teach medical students to positively reevaluate difficult situations and see them as opportunities for development, as well as to reduce rigidity of thinking by changing restrictive cognitive attitudes.

Objectives: to develop skills to positively reappraise difficult life situations; to learn to reframe negative experiences, reducing their impact on behavioral rigidity; to identify and change restrictive cognitive attitudes to more flexible ones; to develop skills to see opportunities in changing and uncertain situations.

Methods: information messages, group discussion, brainstorming, analysis of case studies, written reflection.

1. Introduction (10 min) Introduction to the topic of the lesson: what are cognitive attitudes and how they influence our behavior and perception of reality. Discussion: Do you have beliefs that limit your behavior? How often do you see opportunities in difficult situations?

2. Theoretical block (15 min). What we understand under term "cognitive attitude"? Automatic beliefs that determine reactions to events. Examples of rigid attitudes ("I don't know how to do this", "Change is always bad"). Positive reappraisal as a tool for mental flexibility: How does the cognitive reappraisal mechanism work? Examples of people who used crisis as an opportunity for development. Cognitive restructuring: Learning to transform negative attitudes into more adaptive ones.

3. Practical part (45 min). Exercise 1: "Positive Reassessment" (20 min). Participants recall a stressful or difficult situation that had a negative impact on them. Task: Describe what emotions this situation aroused. Try to find at least three positive aspects or opportunities for development. Discuss whether attitudes have changed after this reassessment. Group discussion of the results. Exercise 2: "Cognitive restructuring" (15 min). Each participant writes down their most common limiting thought (e.g., "I can never do it," "I always fail"). The group then works together to help find evidence that this attitude is not universal (e.g., when the participant has successfully overcome challenges). Task: to formulate a new, more flexible attitude that allows them to see more possibilities. Discussion: how might the new attitude change behavior? Exercise 3: "Reframing Change" (10 min). The psychologist provides participants with an example of a certain stressful situations (e.g., changing groups, moving, failing an exam). Task: instead of a negative view of the situation, find potential positive opportunities in it. Group discussion: how does the perception of the problem change with this approach?

4. Group discussion and reflection (20 min.). What was the most difficult part of trying to change the attitude? Were you able to find benefits in negative situations? How can the skills of positive reassessment be applied in real life? Psychological feedback and tips for practicing cognitive flexibility.

Homework. During the week, consciously analyze difficult or unpleasant situations and look for at least one positive possibility in them. Write down at least three limiting attitudes and develop alternative, more flexible attitudes for them. Keep a "Positive Reassessment Diary" and write down situations in which you managed to change your attitude to the problem.

Expected Outcomes. Improved ability to rethink negative experiences. Formation of more flexible thinking and reduction of the influence of limiting beliefs. Increased emotional resilience and ability to see possibilities in change. Learning cognitive restructuring skills for further independent use.

Session 5

1, 1.5 hours

APPENDIX 1 cont.

Summarizing the results and forming strategies for further behavioral flexibility		
Aim: to summarize the results of the program, to assess students' progress in developing behavioral flexibility and to develop a personal action plan for further self-development.		
Objectives: to assess changes in the level of behavioral rigidity during the program period; to form individual strategies for developing behavioral flexibility; to identify areas requiring further improvement; to strengthen self-reflection and adaptive thinking skills.		
Methods: group discussion, analysis of case studies, written reflection.		
Session 6	1. Introductory part (10 min). Discussion of the goals of the meeting: what we will summarize today, why it is important to evaluate progress and develop strategies for further development. Discussion: How do you evaluate your changes during the program period? Were there situations when you consciously applied new skills?	1, 1,5 hours
	2 Evaluating progress (20 min) Exercise 1: "Flexibility Wheel". Participants receive a template of the "wheel of flexibility" divided into segments (adaptation to change, emotional flexibility, openness to alternative points of view, readiness to new conditions, etc.). Task: to assess your level in each segment before the program (retrospectively) and now (after the program). Comparison of results and reflection: which areas have improved and which still need work? Rigidity self-assessment. Participants complete a short questionnaire with reflexive questions: What skills have I developed during this time? How has my behavior changed in stressful situations? In what situations do I still struggle with flexibility?	
	3. Development of an individual strategy (30 min.). Exercise 2: "My development plan". Each participant makes a personal action plan for maintaining and developing flexibility: What skills do I want to strengthen? How will I practice behavioral flexibility in my daily life? What methods or exercises will help me maintain progress? How will I track my progress? Working in pairs: participants present their plans and get feedback and suggestions from others.	
	4. Group discussion and reflection (20 min). Sharing experiences: what was most valuable in the program? Discussion of difficulties: what challenges remain? Final recommendations: How to maintain and improve behavioral flexibility in the future? How to act in case of a return to rigid behaviors?	
	5. Program wrap-up (10 min). Review of key topics covered in the course. Recommendations for further support. Self-assessment of the level of rigidity by questionnaire or reflection. Individual counseling for those who wish to work more deeply on specific aspects. Possibility of continuing group meetings to maintain adaptability skills. Expected results. Awareness of one's own progress and changes in the level of behavioral rigidity. Clearly defined personal strategies for developing flexibility. Readiness to apply the acquired skills in real life. Increased confidence in the ability to adapt to change.	
		Total 9 hours

SNP rs2981579 in the FGFR2 gene as a risk factor for class II malocclusion in the Ukrainian population

Svitlana Doroshenko¹, Oleksandr Opekha¹, Vladimir Shkarupa², Liliya Gumenyuk²

¹PRIVATE HIGHER EDUCATIONAL ESTABLISHMENT «KYIV MEDICAL UNIVERSITY», KYIV, UKRAINE

²NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

Aim: The aim of the study was to analyze the association of SNPrs2981579 FGFR2 gene as a risk factor for skeletal class II malocclusion in a Ukrainian population.

Materials and Methods: Genotyping of 103 patients from different regions of Ukraine diagnosed with of class II malocclusion was performed. The control group included 106 residents of Kyiv City without orthodontic pathologies and chronic diseases. The association of the T rs2981579 allele of the FGFR2 gene with the risk of developing of class II malocclusion was investigated (OR = 1.58, $p = 0.02$).

Results: The risk class II malocclusion in the control group did not depend on the allelic status of SNP rs2981579; the additive inheritance pattern showed that for heterozygotes (C/T) OR was 1.54, $p = 0.01$, for homozygotes for the variant allele (T/T) OR was 1.53, $p = 0.01$.

Conclusions: The SNP rs2981579 (C>T) of FGFR2 gene locus is a factor of increased susceptibility to the development of class II malocclusion in the Ukrainian population.

KEY WORDS: FGFR2 gene, class II malocclusion, Ukrainian population

Wiad Lek. 2025;78(9):1831-1836. doi: 10.36740/WLek/208829 DOI

INTRODUCTION

The Angle's class II accounts for more than a third of all malocclusions in the world, and is more common in Caucasians than in other races [1]. The phenotype of skeletal abnormalities of this type of occlusion is not homogeneous and is usually characterized by retrusion of the lower jaw (mandibular retrognathism), protrusion of the upper jaw (maxillary prognathism) or a combination of both. It can manifest as an isolated malocclusion or as part of a number of syndromes [1-3].

The etiology of skeletal class II malocclusion appears to have multifactorial nature; it has been shown that the influence of environmental, genetic, developmental factors and their combination play a significant role in the development of skeletal anomalies of this type. The discovery of a significant hereditary component in the formation of the skeletal class II malocclusion has naturally led to a growing interest in uncovering the genetic mechanisms that contribute to the development of these anomalies. Studies of twins have shown that class II is inherited as a variable autosomal dominant trait or as a polygenic expression of critical morphological features [4]. Molecular studies have identified specific genes [5-8] and signaling pathways involved in jaw

growth and the development of dental occlusion that may contribute to the formation of pathological forms of malocclusion [8,9].

FGFR2 affects the proliferation, differentiation, and apoptosis of osteoblasts, participating in bone growth [9]. FGFR2 is a highly conserved tyrosine kinase receptor that is involved in a number of signal transduction pathways that are crucial for osteogenic differentiation [9-11]. Autosomal dominant mutations in *FGFR2* are associated with the development of a number of skeletal diseases, including Behar-Stevens syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome, Cruson syndrome, and Apert syndrome, which can be accompanied by malocclusion [5,12]. In orthodontics, cases of malformations caused by FGFR2 mutations are accompanied by maxillary hypoplasia, relative mandibular prognathism, and related problems of pathological occlusion formation [13]. Mutations of this gene have been shown to be important in the development of non-syndromic craniosynostosis accompanied by the malocclusions [14].

FGFR2 is known to be involved in 19 of the 20 major skeletal signaling pathways associated with class III malocclusion. At the same time, it was also found that FGFR2 is also associated with class II skeletal maloc-

clusion and is present in 17 of the 20 major signaling pathways associated with class II malocclusion [8]. The few genetic studies have detected associations of a number of SNP *FGFR2* gene with the risk of development of malocclusion, most of which are located in the 2nd intron of the gene [6,8,9,15,16]. Studies on the significance of SNP *rs2981579 FGFR2* for the formation of class II malocclusion have not yet been conducted.

AIM

The aim of the study was to analyze the association of SNP *rs2981579 FGFR2* gene as a risk factor for class II malocclusion in a Ukrainian population.

MATERIALS AND METHODS

The genotyping of 103 patients (59 female and 44 male participants) with class II malocclusion from different regions of Ukraine, who were seeking orthodontic treatment at the Department of Prosthodontics and Orthodontics of the Kyiv Medical University, was carried out. The diagnosis of skeletal class II malocclusion was made based on of cephalometric examination with analysis of lateral cephalometric images by the method of A.M. Schwarz.

The following parameters were taken into account when making the diagnosis class II malocclusion: true length of the lower jaw (inclusion criterion – less than the required norm (N-Se+3 mm); true length of the upper jaw (inclusion criterion – meets the required norm: 2/3 of the true length of the lower jaw, or it may be more than the desired (Sol) value); ÆF angles (inclusion criterion – more than 85°), and ÆMM (inclusion criterion – more than 90°).

The control group consisted of 106 residents with an orthognathic occlusion without dental anomalies and chronic diseases (59 female and 47 male participants). All participants (or their parents in case of children younger than 18) gave written inform consent. The study was conducted in accordance with the requirements of the Medical Ethics Commission, developed in accordance with the provisions of the Council of Europe Convention for the Protection of Human Dignity with regard to Biomedicine (1997) and the World Medical Association's Helsinki Declaration (2008).

Genomic DNA was extracted from buccal epithelial samples using the Scientific GeneJET Genomic DNA Purification Kit (Thermo Scientific, USA) according to the manufacturer's instructions. Genotyping was performed by PCR-RFLP (polymerase chain reaction, restriction fragment length polymorphism analysis). For amplification of the *FGFR2* gene region (rs

2981579, C>T), specific primers were used: forward (5'- GTGACTCCCTTCATCGTG-3') and reverse (5'- GGCTCCTGGTCTATTTCTC-3'). Amplification was performed on a GeneAmp PCR System 2400 thermal cycler (Perkin Elmer, Singapore). Amplification mode: initial denaturation – 94°C, 5 min; 35 cycles: denaturation – 94°C, 30 sec, hybridization – 55°C, 30 sec, elongation – 72°C, 30 sec; final elongation – 72°C, 10 min. After amplification, the PCR product was exposed to 10 U of PstI restriction enzyme (CTGCA↓G) for 16 hours at 37°C. The lengths of restriction fragments were visualized by electrophoresis using 2% agarose gel. The TT genotype corresponded to the presence of a fragment of 437 bp, CC – 350 and 87 bp, and CT – 437, 350 and 87 bp.

The distribution of genotype frequencies was checked for compliance with Hardy-Weinberg equilibrium (χ^2 test). The allelic, recessive, dominant, and additive inheritance models were evaluated using the logistic regression method. The degree of association was determined by calculating the odds ratio (OR) and its confidence interval (CI).

RESULTS

The frequency of the *rs2981579* genotypes of the *FGFR2* gene in the control group was: CC – 30.2%, CT – 54.7% TT – 15.1%; frequency of the minor allele (T) – 0.43. In the experimental group with a class II malocclusion: CC – 13.6%, CT – 65.0% TT – 21.4%; frequency of the minor allele (T) – 0.54. The frequency of subjects carrying homozygous of the major C allele in the control group was 2.22 times higher than in the experimental group of patients with a class II malocclusion ($p < 0.05$). The 1.42-fold increase in the frequency of homozygous carriers of the minor T allele in the experimental group of patients with class II malocclusion compared to the control group was nominal and did not have a sufficient level of statistical significance ($p = 0.24$). The distribution of genotypes in the control group did not differ from the population equilibrium ($p = 0.4$), however, in the group of patients with a class II malocclusion, the distribution of genotypes differed statistically significantly ($p = 0.02$) from the Hardy-Weinberg equilibrium. Deviations from the principle of population equilibrium can be caused by various reasons: randomness due to insufficient sample size; genotyping errors; heterogeneity of the sample – it may consist of representatives of different populations with different allele frequencies; heterogeneity of the sample may also be due to selective advantages of carrying certain genotypes in different forms of pathology. Considering the fact that the distribution of genotypes in the control

Table 1. Association of the SNP rs2981579 allele of the FGFR2 gene with the risk of developing class II malocclusion

Inheritance model	Experimental group, n = 103	Control group, n = 106	OR (odds ratio)		p
Allelic	allele frequency		value	95 % CI	
C	0.461	0.575	0.63	0.43 – 0.93	0.02
T	0.539	0.425	1.58	1.08 – 2.33	
Additive	genotype frequency		value	95 % CI	
C/C	0.136	0.302	0.36	0.18 – 0.73	0.01
C/T	0.650	0.547	1.54	0.88 – 2.69	
T/T	0.214	0.151	1.53	0.75 – 3.11	
Dominant	genotype frequency		value	95 % CI	
C/C vs	0.136	0.302	0.36	0.18 – 0.73	0.004
C/T+T/T	0.864	0.698	2.75	1.37 – 5.53	
Recessive	genotype frequency		value	95 % CI	
C/C + C/T vs	0.786	0.849	0.65	0.32 – 1.33	0.24
T/T	0.214	0.151	1.53	0.75 – 3.11	

Source: compiled by the authors of this study

group corresponds to the Hardy-Weinberg law, and the number of individuals genotyped is comparable to the number of genotyped patients with a class II malocclusion (106 and 103, respectively), the most likely reason for the discrepancy in distribution may be the heterogeneity of the sample of patients with class II malocclusion. So that it is necessary to take these features into account when interpreting the results.

The results of the analysis of the association of SNP *rs2981579* of *FGFR2* gene with the risk of class II malocclusion in different inheritance patterns are presented in Table 1.

Table 1 shows that the frequency of the variant allele among patients with a class II malocclusion is statistically significantly higher than in the control group (0.54 and 0.43, respectively, $p = 0.02$). Variant allele T (SNP *rs2981579*) increases the risk of developing a class II malocclusion by 1.58 times (OR = 1.58, $p = 0.02$). The additive inheritance model revealed statistically significant differences in the distribution of genotypes between the experimental group of patients with class II malocclusion and the control group ($p = 0.01$). At the same time, the risk of developing class II malocclusion was not additive and did not depend on the allelic status of the minor allele T. Both heterozygous (CT) and homozygous (TT) carriers of the minor allele showed an increased risk of developing this pathology – the odds ratio was 1.54 and 1.53 ($p = 0.01$), respectively. The dominant model of inheritance also revealed statistically significant differences in the distribution of SNP

rs2981579 genotypes of the *FGFR2* gene between the control and experimental groups. In particular, in the group of carriers of the C/T + T/T genotypes, the risk of developing a class II malocclusion is 2.75 times higher than in homozygous carriers (CC) of the major allele ($p = 0.004$). Homozygous carriage of the major allele of SNP *rs2981579* has a protective effect on the development of this orthodontic pathology, OR = 0.36 ($p = 0.004$). In the recessive inheritance model, there were no statistically significant differences in the distribution of the SNP *rs2981579* genotypes of the *FGFR2* gene between the study groups. This is due to the fact that both heterozygous and homozygous carriers of the variant allele of T SNP *rs2981579* have an equally increased risk of developing a class II malocclusion (additive model).

DISCUSSION

rs2981579 is localized in the second intron of the *FGFR2* gene and is a proxy for *rs1219648*, which is part of a haplotype of 8 closely linked SNPs, which, in turn, is a risk factor for breast cancer development by increasing *FGFR2* gene transcription [17]. It should be noted that the currently known SNPs of *FGFR2* gene associated with skeletal abnormalities are also localized in the 2-nd intron and are closely linked. At the same time, more SNPs of *FGFR2* genes were detected in skeletal class III malocclusion than in skeletal class II malocclusion. In particular, *rs2981578* (OR, 1.708; $P = 0.007$) and *rs10736303* (OR, 1.717; P

= 0.007) were associated only with class III skeletal anomalies, but not with class II malocclusion [9]. In the same study, it was shown that *rs2162540* (OR, 1.717; *P* = 0.003) is associated only with the risk of developing a class II malocclusion. Thus, different polymorphisms of *FGFR2* gene may have different effects on the development of sagittal occlusion.

It was found that the SNP of *FGFR2* in the 2nd intron, associated with a predisposition to abnormal bite patterns, are binding sites for RUNX2 and SMAD4, which are the main regulators of osteoblast differentiation and proliferation. [9, 18, 19]. Binding of RUNX2 and SMAD4 promotes *FGFR2* gene expression. RUNX2 directly regulates *FGFR2* gene, increasing the proliferation of osteoblast precursors, and SMAD4 is involved in signaling pathways (*BMP* and *TGF-β*) that play a fundamental role in the development of the embryonic skeleton and postnatal bone homeostasis [9, 20, 21]. The study by Jiang Q. et al. [9], which revealed the association of the SNPs *rs2981578* and *rs10736303* of the *FGFR2* gene only with class III abnormalities, but not with class II abnormalities, showed that minor alleles of these SNPs reduced the binding affinity and enhancing effect of RUNX2 and SMAD4 and decreased the expression level of *FGFR2* gene.

Craniofacial syndromes caused by *FGFR2* gene mutations often include multiple premature fusions of cranial suture; however, the mechanisms of their effect on skeletal class III malocclusion remain unclear. One possible mechanism may be the early closure of the midline of the upper jaw and other facial sutures between the upper jaw and zygomatic bone, the edge of the eye socket, and the nasal bones [22]. The mandible is craniofacial bone that does not have a suture connection, can be affected by changes in *FGFR2* gene expression and grow to normal size, resulting in class III skeletal malocclusion. Jiang Q. et al. [9] believe that, thus, the loss of binding of pro-osteogenic transcription factors may correlate with hypoplasia of the maxilla, but not with mandibular prognathism. One of the possible explanations for the association of *rs2981579* with the risk of class II malocclusion found in our study could be that minor alleles of *rs2981579*, on the contrary, cause an increase in *FGFR2* gene expression [17]. The mechanism of their effect will be the opposite of the one described by

Meyer K. B. et al. [17], which, accordingly, could lead to the development of class II skeletal anomalies.

It should be noted that in the above-mentioned study by Jiang Q. et al. [9], no regulatory effects similar to *rs2981578* and *rs10736303* were found in the SNP *rs2162540*, which showed an association with the risk of developing class II skeletal anomalies. However, we suggest, the effect of the SNP *rs2981579* of the *FGFR2* gene is more complex and may cause the development disorder of a normal sagittal relationship between maxilla and mandible in general at early stages, and further dental malocclusions in the mesial or distal planes may involve additional factors and various types of their interactions. This assumption is due to the fact that previous studies have also found an association of *rs2981579* with the risk of developing a skeletal class III malocclusion in a Ukrainian population [16]. The situation is complicated by the fact that mutations in SNPs of *FGFR2* can directly affect the growth of both the upper and lower jaw, since *FGFR2* gene is expressed not only in the sutures but also in significant amounts in the periphery of the membranous bones. Indirect confirmation of the assumptions about the complex nature of the impact of the *FGFR2* gene on the formation of sagittal plane malocclusions may be confirmed by studies that show that different SNPs of a number of the same genes and their interactions may be involved in the etiology of sagittal and vertical malocclusions [23].

CONCLUSIONS

We investigated the association between the T *rs2981579* allele of the *FGFR2* gene and the risk of developing a class II malocclusion (OR = 1.58, *p* = 0.02). The risk of developing a skeletal class II malocclusion in the study group did not depend on the allelic status of SNP *rs2981579*; the additive inheritance model showed that for heterozygotes (C/T) OR was 1.54, *p* = 0.01, for homozygotes for the variant allele (T/T) OR was 1.53, *p* = 0.01. The SNP *rs2981579* (C>T) of *FGFR2* gene locus is a factor of increased susceptibility to the development of skeletal class II malocclusion in a Ukrainian population. However, the mechanisms that determine the effect of minor alleles of *rs2981579* on the formation of skeletal class II malocclusion require further research.

REFERENCES

1. Alhammadi MS, Halboub E, Fayed MS et al. Global distribution of malocclusion traits: A systematic review. *Dental Press J Orthod.* 2018;2340-e1. doi:10.1590/2177-6709.23.6.40.e1-10.onl. DOI
2. Nielsen IL. Transverse Malocclusions: Etiology, Development, Diagnosis and Treatment. *Taiwanese Journal of Orthodontics.* 2023;35(1). doi:10.38209/2708-2636.1328. DOI

3. Nielsen IL. Etiology, development, diagnosis and considerations in treatment of the Class II, Division 2 malocclusion: what the clinician should know about this malocclusion (part I). *Taiwanese Journal of Orthodontics*. 2021;33(1):1. doi:10.38209/2708-2636.1097. [DOI](#)
4. Santana LG, Flores-Mir C, Iglesias-Linares A et al. Influence of heritability on occlusal traits: a systematic review of studies in twins. *Progress in Orthodontics*. 2020;21:1-11. doi:10.1186/s40510-020-00330-8. [DOI](#)
5. Neela PK, Atteeri A, Mamillapalli PK et al. Genetics of dentofacial and orthodontic abnormalities. *Glob Med Gen*. 2020;7(04): 095-100. doi: 10.1055/s-0040-1722303. [DOI](#)
6. da Fontoura CG, Miller SF, Wehby GL et al. Candidate gene analyses of skeletal variation in malocclusion. *J Dent Res*. 2015;94 (7): 913-920. doi:10.1177/0022034515581643. [DOI](#)
7. Lone IM, Zohud O, Midlej K et al. Skeletal class II malocclusion: from clinical treatment strategies to the roadmap in identifying the genetic bases of development in humans with the support of the collaborative cross mouse population. *J Clin Med*. 2023;12(15):5148. doi:10.3390/jcm12155148. [DOI](#)
8. Gershater E, Li C, Ha P et al. Genes and pathways associated with skeletal sagittal malocclusions: a systematic review. *Int J Molecul Scien*. 2021;22(23):13037. doi:10.3390/ijms222313037. [DOI](#)
9. Jiang Q, Mei L, Zou Y et al. Genetic polymorphisms in FGFR2 underlie skeletal malocclusion. *J Dent Res*. 2019;98(12):1340-1347. doi:10.1177/0022034519872951. [DOI](#)
10. Lee KK, Peskett E, Quinn CM et al. Overexpression of Fgfr2c causes craniofacial bone hypoplasia and ameliorates craniosynostosis in the Crouzon mouse. *Dis Mod & Mechanisms*. 2018;11(11)6dmm035311. doi: 10.1242/dmm.035311. [DOI](#)
11. Miraoui H, Oudina K, Petite H et al. Fibroblast growth factor receptor 2 promotes osteogenic differentiation in mesenchymal cells via ERK1/2 and protein kinase C signaling. *Journal of biological chemistry*. 2009;284(8):4897-4904. doi:10.1074/jbc.M805432200. [DOI](#)
12. Muenke M, Schell U. Fibroblast-growth-factor receptor mutations in human skeletal disorders. *Trends Genet*. 1995;11(8):308-313. doi: 10.1016/s0168-9525(00)89088-5. [DOI](#)
13. Cakan DG, Ulkur F, Taner T. The genetic basis of facial skeletal characteristics and its relation with orthodontics. *Eur J Dent*. 2012;6(3):340-345. doi:10.1055/s-0039-1698971. [DOI](#)
14. Boyadjiev SA. Genetic analysis of non-syndromic craniosynostosis. *Orthod. Craniofac. Res*. 2007;10(3):129-137. doi: 10.1111/j.1601-6343.2007.00393.x. [DOI](#)
15. George AM, Felicita AS, Tania SM, Priyadharsini JV. Systematic review on the genetic factors associated with skeletal Class II malocclusion. *Indian Journal of Dental Research*. 2021;32(3):399-406. doi: 10.4103/ijdr.IJDR_59_20. [DOI](#)
16. Storozhenko KV, Shkarupa VM. Association of FGFR2 (rs2981579) gene polymorphism with the risk of mesial occlusion. *Cytol Genet*. 2017;51:361- 364. doi:10.3103/S0095452717050103. [DOI](#)
17. Meyer KB, Maia AT, O'Reilly M et al. Allele-specific up-regulation of FGFR2 increases susceptibility to breast cancer. *PLoS biology*. 2008;6(5):e108. doi: 10.1371/journal.pbio.0060108. [DOI](#)
18. Buo AM, Tomlinson RE, Eidelman ER et al. Connexin 43 and Runx2 interact to affect cortical bone geometry, skeletal development, and osteoblast and osteoclast function. *J Bone Miner Res*. 2017;32(8):1727-1738. doi: 10.1002/jbmr.3152. [DOI](#)
19. Karner CM, Lee SY, Long F. Bmp induces osteoblast differentiation through both Smad4 and mTorc1 signaling. *Mol Cell Biol*. 2017;37(4):e00253-16. doi: org/10.1128/MCB.00253-16. [DOI](#)
20. Kawane T, Qin X, Jiang Q et al. Runx2 is required for the proliferation of osteoblast progenitors and induces proliferation by regulating Fgfr2 and Fgfr3. *Sci Rep*. 2018;8(1):13551. doi: 10.1038/s41598-018-31853-0. [DOI](#)
21. Wu M, Chen G, Li YP. TGF-beta and BMP signaling in osteoblast, skeletal development, and bone formation, homeostasis and disease. *Bone Res*. 2016;4:16009. doi: 10.1038/boneres.2016.9. [DOI](#)
22. Azoury SC, Reddy S, Shukla V, Deng CX. Fibroblast growth factor receptor 2 (FGFR2) mutation related syndromic craniosynostosis. *Int J Biol Sci*. 2017;13(12):1479-1488. doi: 10.7150/ijbs.22373. [DOI](#)
23. Küchler EC, Reis CLB, Carelli J et al. Potential interactions among single nucleotide polymorphisms in bone-and cartilage-related genes in skeletal malocclusions. *Orthodontics & craniofacial research*. 2021;24(2): 277-287. doi: 10.1111/ocr.12433. [DOI](#)

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Oleksandr Opekha

Kyiv Medical University

2 Borispilska St., 02099 Kyiv, Ukraine

e-mail: opekha.alex@gmail.com

ORCID AND CONTRIBUTIONSHIP

Svitlana Doroshenko: 0009-0006-2984-2078 **A** **B** **C** **E** **F**
Oleksandr Opekha: 0009-0002-6167-0975 **A** **B** **C** **E** **F**
Vladimir Shkarupa: 0000-0001-8890-2794 **C** **D** **E** **F**
Liliya Gumenyuk: 0000-0001-6279-6647 **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: 17.10.2024
ACCEPTED: 31.07.2025



Prevalence of risk factors for the occurrence of orthodontic pathology among children in the city of Poltava: regional features

Natalia A. Lyakhova, Iryna A. Holovanova, Ivan Yu. Popovich, Inna V. Bielikova, Alevtyna M. Bilous, Oksana I. Krasnova, Valerii V. Loburets

POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

Aim: The aim of our research was to investigate the regional features of the prevalence of risk factors for the occurrence of orthodontic pathology among the children's population of Poltava.

Materials and Methods: sociological, forecasting, bibliseomatic, analytical, medical-statistical. Materials: results of examination by a pediatric dentist of schoolchildren of different age groups (406 children), results of a questionnaire of parents of examined schoolchildren of different age groups (406 respondents).

Results: In our study, using the method of simple logistic regression, regional features of the prevalence of risk factors associated with the occurrence of orthodontic pathology were identified: the chances of detecting orthodontic pathology increase with the use of a pacifier, somatic morbidity in the first year of life (dysbacteriosis, rickets), the presence of caries in the child (complicated caries), the removal of permanent teeth due to caries, concomitant diseases (otorhinolaryngological pathology) in the child, the presence of heredity (orthodontic pathology in the family), and occupational hazards during the mother's pregnancy.

Conclusions: The identified risk factors for orthodontic pathology are mostly modifiable, that is, they are amenable to correction. Therefore, it is extremely necessary for pediatricians, family doctors and pediatric dentists to carry out both preventive measures to prevent the negative impact of these factors, and explanatory work with parents of children, who must be aware of the importance and necessity of prevention.

KEY WORDS: children, orthodontic pathology, risk factors, prevalence, regional characteristics

Wiad Lek. 2025;78(9):1837-1842. doi: 10.36740/WLek/212523 DOI

INTRODUCTION

The modern increase in the pace of life, urbanization, decreased quality of nutrition, increased stress, and deterioration of the environment affect the morbidity of the population, especially the health of the child population [1-6]. The health of children and adolescents, including dental health, is one of the most sensitive indicators that reflect the socio-economic situation in Ukraine, the state of the environment, and is an indicator of the well-being of society as a whole. The high level of dental morbidity in the pediatric population has remained one of the current medical problems for many years; in different age groups, the incidence of caries, periodontal diseases, and disorders of tooth development and formation has been steadily increasing, which has a negative impact on the health of the child [7].

Analysis of epidemiological data [1, 3, 8-11] on the prevalence of dental diseases in Ukraine showed a negative trend in the growth of dental pathology: 67.8–77.4% of children aged 12 had carious lesions of per-

manent teeth, with CFE = 4.3–5.6 teeth; in 15-year-old children, the prevalence of caries was 75.2–88.1% with CFE = 4.3–5.2 teeth. The prevalence rates of dentofacial anomalies (DFA) were also very high: 58.9–70.2% of 12-year-old children and 23.6–33.7% of 15–17-year-old children required urgent orthodontic treatment [9, 12-14]. Morphological disorders in the dentofacial region in children were most often combined with functional speech disorders (15.6–17.2%), swallowing disorders (24.5–25.4%), nasal breathing disorders (36.7–37.3%), and chewing disorders.

Modern science explains these trends by the action of very stable and practically unchanging pathogenetic factors: dangerous environmental conditions, changes in the composition of baby food products and deficiency of macro- and microelements, chronic somatic diseases, heredity, reduction changes in the chewing apparatus, etc. [15-20]. The result of this influence is a change in the natural position of the teeth, which is registered as a dentofacial anomalies (DFA).

Over the past decades, the frequency of detection of bite anomalies has increased, and the need for therapeutic and preventive measures is 36.9% in case of variable bite, and more than 40% in case of permanent bite, and constantly increases with age [21-24]. Taking into account all of the above, the study of both the prevalence and the degree of influence of various risk factors on the occurrence of orthodontic pathology is relevant.

AIM

The aim of our research was to investigate the regional features of the prevalence of risk factors for the occurrence of orthodontic pathology among the children’s population of Poltava.

MATERIALS AND METHODS

Research methods: sociological, forecasting, bibliosemantic, analytical, medical-statistical. Materials: results of examination by a pediatric dentist of schoolchildren of different age groups (406 children), results of a questionnaire of parents of examined schoolchildren of different age groups (406 respondents), a questionnaire created by the authors and containing 45 questions related to the presence/absence of risk factors for orthodontic pathology in children (socio-economic, behavioral, medical, biological, environmental, organizational), the level of awareness of parents regarding factors affecting children’s health, and satisfaction with medical care.

RESULTS

The age of the children we examined was as follows (by age groups): 6-12 years old – 237 (58.37%), 12-15 years old – 120 (29.56%), 15-18 – 49 (12.07%) (Fig. 1). So, the changed bite was in 58.37% of children, permanent – in 41.63%. Orthodontic pathology of various types was detected during the examination in the period of the changed bite – in 48.6% of children, in the period of the permanent bite – in 52.4% of children. Thus, every second child has one or another pathology of the dentofacial area.

During the study, we identified the prevalence of risk factors for orthodontic pathology affecting children in the antenatal and postnatal periods (Table 1).

The goal of the next stage of our study was to analyze the associations between the detection of orthodontic pathology and the effect of risk factors that have already been studied by researchers, namely: social status, place of residence, financial security, and age of the child over 15 years old. In our study, among social and medical-demographic factors, only social status was found to be a

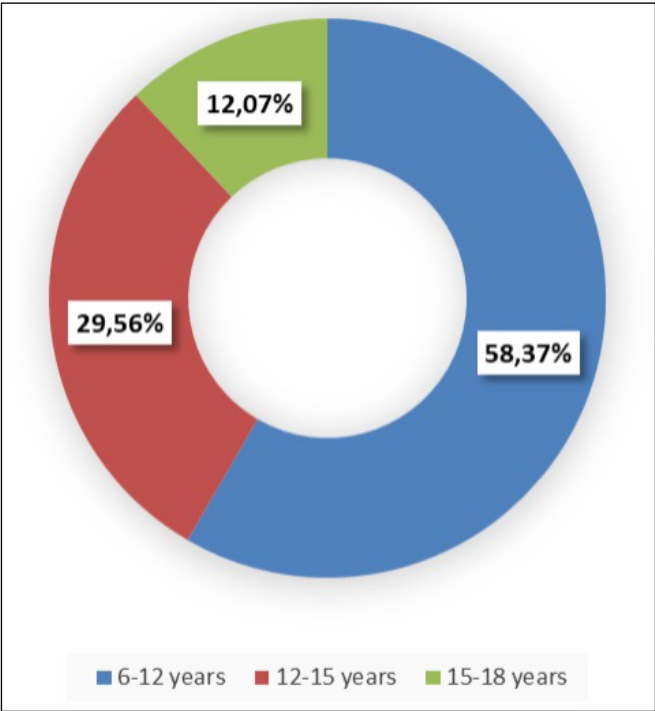


Fig. 1. Distribution of examined children by age groups
Picture taken by the authors

significant relationship in simple logistic regression analysis: if parents are blue-collar workers, the chance of detecting orthodontic pathology increases by 1.4 times (OR 1,4 [95% CI 1,034-2,097]) (Table 2).

The use of a pacifier, as shown by many researchers and also indicated in breastfeeding recommendations, leads to a violation of the bite of teeth to the same extent as poor nutrition of the mother [13, 15-17]. We have classified these two factors as behavioral because they track a person’s choice to act in one way or another. In addition, we asked questions about tobacco and alcohol use, and poor maternal nutrition during pregnancy, but none of the respondents indicated that they led an unhealthy lifestyle during this time. Significant associations were found between the use of a pacifier, the chances of detecting orthodontic pathology increase by 1.8 times (OR 1,80 [95% CI 1,08-3,02]) (Table 3).

Incidence in the first years of life could affect the normalization of ontogenesis and calcium metabolism and subsequently cause malocclusion. Complications during childbirth – especially with breech presentation, the actions of the obstetrician-gynecologist at the time of delivery of the fetal head, the application of obstetric forceps, which can affect the child’s growth zones and also contribute to the occurrence of this nosology. Removed primary and permanent teeth, trauma may indicate odontogenic diseases, which can subsequently cause orthodontic pathology [13, 15-17]. Significant reliable associations of the occurrence of orthodontic pathology with somatic morbidity at 1 year of life (OR 1,79 [95% CI 1,08-2,98]), caries (OR 2,04 [95% CI 1,35-

Table 1. Prevalence of risk factors identified in different periods of child development (according to parent survey data)

The influence of risk factors in the antenatal period of child development (abs., %)	The influence of risk factors in the postnatal period of child development (abs., %)
Mother's diet during pregnancy is unsatisfactory – 12 (2,9%)	Diseases of a child in the first year of life – (dysbacteriosis) – 74 (18,2%);
Acquired diseases during pregnancy – 18 (4,4%);	Artificial feeding – 166 (40,9%);
Stressful situations during pregnancy – 50 (12,3%)	Use of a pacifier – 122 (30,0%)
Occupational hazards during pregnancy – 11 (2,7%);	Bad habits of the child: finger sucking, tongue sucking – 52 (12,8%);
Consumption of alcohol and tobacco during pregnancy – 4 (1,0%);	Concomitant diseases – 46 (11,3%);
Adverse factors during pregnancy (gynecological diseases) – 9 (2,2%);	
Non-compliance by the mother with the work and rest regime during pregnancy – 5 (1,2%);	The child's diet in infancy (timely introduction of complementary foods, variety and rationality of the child's diet) is unsatisfactory – 3 (0,7%)
Pregnancy complications – 52 (12,8%);	
Complications during childbirth – 83 (20,4%);	

Source: compiled by the authors of this study

Table 2. Associations between social and medical-demographic risk factors of parents and the detection of orthodontic pathology in children ($p < 0,05$)

Social and medical-demographic risk factors	Examined children, n=406		Odds ratio (95% CI)	p
	orthodontic pathology detected, n=161 abs. (%)	orthodontic pathology no detected, n=245 abs. (%)		
Social status: working profession of parents, n=191	84 (44,0)	107 (56,0)	1,41 (1,03-2,09)	0,050

Source: compiled by the authors of this study

Table 3. Associations between maternal behavioral risk factors and the detection of orthodontic pathology in children ($p < 0,05$)

Maternal behavioral risk factors	Examined children, n=406		Odds ratio (95% CI)	p
	orthodontic pathology detected, n=161 abs. (%)	orthodontic pathology no detected, n=245 abs. (%)		
Use of pacifier, n= 320	136 (42,5)	184 (57,5)	1,80 (1,08-3,02)	0,015

Source: compiled by the authors of this study

Table 4. Determined associations between medical factors and the detection of orthodontic pathology in children ($p < 0,05$)

Medical factors	Examined children, n=406		Odds ratio (95% CI)	p
	orthodontic pathology detected, n=161 abs. (%)	orthodontic pathology no detected, n=245 abs. (%)		
Somatic disease in the first years of life, n=74	38 (51,4)	36 (48,6)	1,79 (1,08-2,98)	0,017
Diagnosed dental caries, n=225	106 (47,1)	119 (52,9)	2,04 (1,35-3,08)	0,001
Removal of permanent teeth due to caries, n=60	31 (51,7)	29 (48,3)	1,75 (1,01-3,04)	0,032
Concomitant diseases in the child (otorhinolaryngological pathology), n=46	34 (73,9)	12 (26,1)	5,18 (2,59-6,35)	0,001
Orthodontic pathology in the family, n=70	55 (78,6)	15 (21,4)	3,93 (2,06-7,49)	0,001

Source: compiled by the authors of this study

3,08)), removal of permanent teeth due to caries (OR 1,75 [95% CI (1,01-3,04)]), concomitant diseases in the child (OR 5,18 [95% CI (2,59-6,35)]) and orthodontic pathology in the

family (OR 3,93 [95% CI (2,06-7,49)]) were found. All these factors increase the chances of orthodontic pathology in a child (Table 4).

Table 5. Determined associations between sanitary and hygienic factors of parents and children and the detection of orthodontic pathology ($p<0,05$)

Sanitary and hygienic factors of parents and children	Examined children, n=406		Odds ratio (95% CI)	p
	orthodontic pathology detected, n=161 abs. (%)	orthodontic pathology no detected, n=245 abs. (%)		
Bad condition of the oral cavity, n=48	26 (54,2)	22 (45,8)	1,95 (1,06-3,58)	0,022
Low sanitary and hygienic awareness of parents, n=24	2 (8,3)	22 (91,7)	0,13 (0,03-0,55)	0,001
The child visited the dentist only for treatment, n=240	78 (32,5)	162 (67,5)	0,48 (0,32-0,72)	0,000
The child did not visit the orthodontist for preventive purposes, n=144	43 (29,9)	101 (70,1)	0,52 (0,34-0,80)	0,002

Source: compiled by the authors of this study

Table 6. Determined associations between adverse factors during pregnancy and the detection of orthodontic pathology ($p<0,05$)

Adverse factors during pregnancy	Examined children, n=406		Odds ratio (95% CI)	p
	orthodontic pathology detected, n=161 abs. (%)	orthodontic pathology no detected, n=245 abs. (%)		
Occupational hazards, n=11	9 (81,8)	2 (18,2)	7,19 (1,53-33,74)	0,005

Source: compiled by the authors of this study

The next step was to investigate sanitary and hygienic factors that would indicate the preventive awareness of patients and their parents. It was found that the presence of poor oral health increases the chances of detecting orthodontic pathology (OR 1,95 [95% CI (1,06-3,58)]. At the same time, the chances of detecting this nosology decrease with: low sanitary and hygienic awareness of parents (OR 0,19 [95% CI (0,03-0,55)], not having the child visit an orthodontist for preventive purposes (OR 0,52 [95% CI (0,34-0,80)]. Obviously, if a child does not visit an orthodontist, it is more difficult to detect pathology in them. The low level of sanitary and hygienic education of parents may be the reason that parents are not motivated to bring their child to an orthodontist for earlier detection of pathology (Table 5).

Among the organizational factors, we indicated the presence of an orthodontist in the settlement. We did not find any significant associations between organizational factors and detected orthodontic pathology.

Among the adverse factors experienced by the mother during pregnancy, only one significant relationship was found between occupational hazards (heavy physical labor and radiation from a computer) and the occurrence of orthodontic pathology, which increase the chances of detecting orthodontic pathology (OR 7,19 [95% CI (1,53-33,74)]), which, according to researchers, may also affect ontogenesis [13, 15-17] (Table 6).

DISCUSSION

According to the literature, numerous factors have been identified that can lead to the occurrence of orthodontic

pathology and operate both in the antenatal and postnatal periods [15]: pregnancy complications; previous illnesses, occupational hazards and stressful situations during pregnancy; alcohol and tobacco use during pregnancy; failure of the mother to observe the work and rest regime, poor nutrition during pregnancy; complications during childbirth; increased morbidity of the child in the first years of life; artificial feeding; use of a pacifier; harmful habits of the child himself: sucking his finger, tongue; concomitant diseases of the child. Scientists around the world are devoting a lot of attention to this issue, studying both the prevalence of the pathology among children and risk factors. There is 1799 adolescents aged 11-15 years old from 18 middle schools in 6 districts of Shanghai were recruited to investigate oral health status and related risk factors using cluster random sampling method in 2021 and the prevalence of malocclusion in adolescents in Shanghai was 83.5% [25]. A study of 503 Japanese children aged 3-6 years [26] showed that 62.0% of preschool children in the present study exhibited malocclusion, and 27.8% exhibited incompetent lip seal. Nail biting was the most frequent oral habit with a prevalence of 18.9%. Nasal obstruction was recorded in 30.4% of children. The results of binary logistic regression showed that incompetent lip seal was significantly related to malocclusion, and that nail biting was significantly negatively related.

Sadoun C. at all [27] found that the chances of diagnosing a malocclusion were higher for children with bottle nutrition when compared to breast-fed children. Breastfeeding provides protection against malocclusions. In the same manner, persistent NNSH habits appeared to be associated with in-

creased chances of having malocclusions. The longer the child was breastfed, the shorter the duration of the pacifier habit and the lower the risk of developing moderate/severe malocclusions. The duration of the habits has a positive influence on the appearance of occlusion defects. A study conducted in France examined social characteristics (collected during pregnancy), neonatal characteristics (collected at birth), duration of breast-feeding (collected prospectively), sucking habits at 3 years, and open lips (as an indicator of mouth breathing), and two logistic regressions were performed. It has been found that preterm birth appears to be a risk factor specific for posterior crossbite (OR: 3.13; 95% CI: 1.13-8.68), whereas small for gestational age seems to be associated with a lower risk of posterior crossbite (OR: 0.32; 95% CI: 0.12-0.87). Ongoing pacifier or thumb sucking at 3 years is a risk factor for both posterior crossbite and anterior open bite.

In our study, using the method of simple logistic regression, regional features of the prevalence of risk factors associated with the occurrence of orthodontic pathology were

identified: the chances of detecting orthodontic pathology increase with the use of a pacifier, somatic morbidity in the first year of life (dysbacteriosis, rickets), the presence of caries in the child (complicated caries), the removal of permanent teeth due to caries, concomitant diseases (otorhinolaryngological pathology) in the child, the presence of heredity (orthodontic pathology in the family), and occupational hazards during the mother's pregnancy.

CONCLUSIONS

The identified risk factors for orthodontic pathology are mostly modifiable, that is, they are amenable to correction. Therefore, it is extremely necessary for pediatricians, family doctors and pediatric dentists to carry out both preventive measures to prevent the negative impact of these factors, and explanatory work with parents of children, who must be aware of the importance and necessity of prevention.

REFERENCES

1. Bezvushko EV, Lahoda LS. Stan tverdykh tkanyn zubiv u ditei mista Lutska [The condition of hard dental tissues in children of the city of Lutsk]. Aktualni problemy suchasnoi medytsyny: Visnyk ukrainskoi medychnoi stomatolohichnoi akademii. 2017;2(58):232-235. (Ukrainian)
2. Dienha OV, Osadcha AO. Poshyrenist y intensyvnist kariiesu zubiv i zakhvoriuvan parodontu u ditei 13-15 rokiv, shcho zaimaiutsia sportom vyshchikh dosiahnen [Prevalence and intensity of dental caries and periodontal diseases in children aged 13-15 years who are involved in high-level sports]. Visnyk stomatolohii. 2022;121(4):68-73. (Ukrainian)
3. Lebedyk SV, Konovalenko SO. Analiz stomatolohichnoho zdorovia shkolariv mista Ternopolia [Analysis of dental health of schoolchildren of the city of Ternopil]. Medsestrynstvo. 2021;2:43-45. (Ukrainian)
4. Peres MA, Macpherson LMD, Weyant RJ et al. Oral diseases: a global public health challenge. Lancet. 2019;394(10194):249-60. doi:10.1016/S0140-6736(19)31146-8. DOI
5. Winkelmann J, Listl S, van Ginneken E et al. Universal health coverage cannot be universal without oral health. Lancet Public Health. 2023;8(1):e8-10. doi:10.1016/S2468-2667(22)00315-2. DOI
6. Okunseri C, Zheng C, Zhang Y et al. Acculturation and Children's dental service utilization in the United States. Community Dent Oral Epidemiol. 2023;51(3):380-387. doi: 10.1111/cdoe.12860. DOI
7. Zhou X, Zhang Y, Wang Y et al. Prevalence of Malocclusion in 3- to 5-Year-Old Children in Shanghai, China. Int J Environ Res Public Health. 2017;14(3):328. doi: 10.3390/ijerph14030328. DOI
8. Lahoda LS, Musii-Sementsiv KhH. Urazhennia zubiv kariiesom u ditei, yaki prozhyvaiut na terytoriakh iz riznym ekolohichnym zabrudnenniam [Dental caries in children living in areas with various environmental pollution]. Klinichna stomatolohiia. 2017;4:66-72. (Ukrainian)
9. Chukhrai NL, Smoliar NI, Mirchuk BM, Lesitskyi MYu. Dynamika struktury zuboshchelepnykh anomalii u ditei shkilnoho viku [Dynamics of the structure of dentofacial anomalies in school-age children]. Via Stomatologiae. 2024;1(3):44-53. (Ukrainian)
10. Melnyk VS, Horzov LF, Duhanchyk Yal. Strukturnyi analiz stomatolohichnoi zakhvoriuvanosti ditei shkilnoho viku m. Uzhhoroda [Structural analysis of dental morbidity in school-age children of Uzhgorod]. Intermedical journal. 2017;2(10):52-56. (Ukrainian)
11. Sujlana A, Baweja D, Kaur A, Kaur PP. Barriers of dental care utilization for children living in military and civilian areas. J Indian Soc Pedod Prev Dent. 2016;34(2):115-9. doi: 10.4103/0970-4388.180410. DOI
12. Lombardo G, Vena F, Negri P et al. Worldwide prevalence of malocclusion in the different stages of dentition: A systematic review and meta-analysis. Eur J Paediatr Dent. 2020;21(2):115-122. doi: 10.23804/ejpd.2020.21.02.05. DOI
13. De Ridder L, Aleksieva A, Willems G et al. Prevalence of Orthodontic Malocclusions in Healthy Children and Adolescents: A Systematic Review. Int J Environ Res Public Health. 2022;19(12):7446. doi: 10.3390/ijerph19127446. DOI
14. Londono J, Ghasemi S, Moghaddasi N et al. Prevalence of malocclusion in Turkish children and adolescents: A systematic review and meta-analysis. Clin Exp Dent Res. 2023;9(4):689-700. doi: 10.1002/cre2.771. DOI
15. Lyakhova NA. Analysis of risk factors of orthodontic pathology: literature review. Wiad Lek. 2018;71(5):1084-1088.

16. Chukhrai NL, Mashkarynets OO, Lysak TYu et al. Stomatolohichniy status ditei na tli somatichnoi patolohii (ohliad literatury) [Dental status of children against the background of somatic pathology (literature review)]. *Via Stomatologiae*. 2024;1(2):5-15.
17. Festa P, Mansi N, Varricchio AM et al. Association between upper airway obstruction and malocclusion in mouth-breathing children. *Acta Otorhinolaryngol Ital*. 2021;41(5):436-442. doi: 10.14639/0392-100X-N1225. [DOI](#)
18. Bardellini E, Amadori F, Garo ML et al. Is there any correlation between otitis media and dental malocclusion in children? A systematic review. *Eur Arch Paediatr Dent*. 2023;24(4):441-449. doi: 10.1007/s40368-023-00807-0. [DOI](#)
19. Borrie FR, Bearn DR, Innes NP, Iheozor-Ejiofor Z. Interventions for the cessation of non-nutritive sucking habits in children. *Cochrane Database Syst Rev*. 2015;2015(3):CD008694. doi: 10.1002/14651858.CD008694.pub2. [DOI](#)
20. Todor BI, Scrobota I, Todor L et al. Environmental Factors Associated with Malocclusion in Children Population from Mining Areas, Western Romania. *Int J Environ Res Public Health*. 2019;16(18):3383. doi: 10.3390/ijerph16183383. [DOI](#)
21. Holovanova IA, Lyakhova NA, Sheshukova OV et al. Studying the skills attitudes on factors affecting dental health of children. *Wiad Lek*. 2018;71(3):640-647.
22. Lyakhova NA, Filatova VL, Sheshukova OV et al. Studying and analyze the factors that affect compliance dentist recommendations from parents of child patients. *Wiad Lek*. 2020;73(8):1730-1734. doi: 10.36740/WLek202008127. [DOI](#)
23. Moraes RB, Menegazzo GR, Knorst JK, Ardenghi TM. Availability of public dental care service and dental caries increment in children: a cohort study. *J Public Health Dent*. 2021;81(1):57-64. doi: 10.1111/jphd.12401. [DOI](#)
24. de Souza FA, Carneiro DPA, Meneghim MC, Vedovello SAS. Parental perception of malocclusion, its severity and aesthetic concerns in children with mixed dentition: A cross-sectional study. *Int Orthod*. 2022;20(2):100637. doi: 10.1016/j.ortho.2022.100637. [DOI](#)
25. Yin J, Zhang H, Zeng X et al Prevalence and influencing factors of malocclusion in adolescents in Shanghai, China. *BMC Oral Health*. 2023;23(1):590. doi: 10.1186/s12903-023-03187-5. [DOI](#)
26. Otsugu M, Sasaki Y, Mikasa Y et al. Incompetent lip seal and nail biting as risk factors for malocclusion in Japanese preschool children aged 3-6 years. *BMC Pediatr*. 2023;23(1):532. doi: 10.1186/s12887-023-04366-7. [DOI](#)
27. Sadoun C, Templier L, Alloul L et al. Effects of non-nutritive sucking habits on malocclusions: a systematic review. *J Clin Pediatr Dent*. 2024;48(2):4-18. doi: 10.22514/jocpd.2024.029. [DOI](#)

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Nataliia Liakhova

Poltava State Medical University

24 Shevchenko St., 36000 Poltava, Ukraine

e-mail: NataNew2017@ukr.net

ORCID AND CONTRIBUTIONSHIP

Natalia A. Lyakhova: 0000-0003-0503-9935 [A](#) [E](#) [F](#)

Iryna A, Holovanova: 0000-0002-8114-8319 [A](#) [F](#)

Ivan Yu. Popovich: 0000-0003-1720-095X [B](#) [C](#) [D](#)

Inna V. Bielikova: 0000-0002-0104-3083 [B](#) [C](#) [D](#)

Alevtyna M. Bilous: 0000-0002-7165-0516 [B](#) [C](#) [D](#)

Oksana I. Krasnova: 0000-0001-9819-1818 [C](#) [D](#)

Valerii V. Loburets: 0000-0001-8538-9649 [B](#) [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: 28.04.2025

ACCEPTED: 29.08.2025



Coherent connections of brain biopotentials in military personnel during recovery from mine-blast closed craniocerebral injuries

Liudmyla P. Zabrodina, Volodymyr O. Korshnyak, Yuliia V. Bovt, Nataliya M. Pryvalova, Viktor V. Sukhorukov

THE STATE INSTITUTION "P.V. VOLOSHIN INSTITUTE OF NEUROLOGY, PSYCHIATRY AND NARCOLOGY OF THE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE", KHARKIV, UKRAINE

ABSTRACT

Aim: To investigate interhemispheric and intrahemispheric coherence of brain biopotentials in military personnel during the recovery period following mine-blast closed craniocerebral injuries (MBCCI), as well as to assess the cumulative effect of repeated injuries on coherence patterns.

Materials and Methods: The study included 28 military personnel with single (14 patients) and multiple (14 patients) MBCCIs, along with 11 healthy controls without neurotrauma. Background electroencephalograms recorded prior to treatment initiation were subjected to coherence analysis.

Results: Demonstrated a significant reduction in both inter- and intrahemispheric coherence in military personnel with single, and particularly multiple, MBCCIs, indicating impaired integrative brain functioning. In both groups of injured military personnel, the most pronounced reductions in interhemispheric coherence relative to healthy controls were observed within the delta, theta, alpha, and low-beta frequency bands, predominantly in the frontal and parietal regions. Multiple MBCCIs were associated with generalized interhemispheric dysfunction across all frequency bands, involving the central, occipital, and temporal regions, as well as an imbalance of intrahemispheric coherence—manifested as suppressed activity in the left hemisphere and compensatory hyperactivation in the right. These alterations in coherence parameters correlated with clinical manifestations of neurological, emotional, and cognitive impairments, reflecting varying degrees of functional reserve depletion in military personnel with single and multiple MBCCIs.

Conclusions: The findings may serve as a basis for the development of pathogenetically grounded, individualized neurorehabilitation programs.

KEY WORDS: mine-blast closed craniocerebral injuries; interhemispheric coherence; intrahemispheric coherence; neurophysiological criteria

Wiad Lek. 2025;78(9):1843-1848. doi: 10.36740/WLek/212519 DOI

INTRODUCTION

Mine-blast closed craniocerebral injuries (MBCCI) are a complex type of combat neurotrauma that leads to long-term cognitive, sensorimotor, and emotional disorders [1]. One of the important areas of such disorders research is the study of inter-hemispheric and intra-hemispheric coherence of electroencephalographic (EEG) signals as potential biomarkers of neuroplasticity and brain recovery in affected military personnel. Clinical studies have shown a significant decrease in EEG-phase coherence in individuals with MBCCI. In particular, diffusion tensor imaging and a highly-sensitive method of weighted phase coherence revealed a decrease in inter-hemispheric phase in the frontal lobes of the brain, which correlated with the white matter damage [2]. Synchronization disorders in the 25–40 Hz range associated with a decrease in fractional anisotropy in the lower cerebellar lobe were

confirmed, indicating microstructural damage of the white matter. Improved phase synchronization analysis revealed a correlation between reduced coherence at high frequencies and microstructural changes in the brain [3].

Functional probing using magnetic-resonance tomography (MRT) at the state of rest revealed a decrease in connectivity in both diffuse mode network (DMN) and visual networks. It was found that veterans with mild MBCCI had significantly reduced DMN connectivity, as well as the participation coefficient in the frontal lobes of the brain. In addition, a decrease in functional connectivity between the structures of the visual system (LGN, V1, LO, FG) and the frontal cortex of the brain correlated with the degree of cognitive impairment [4, 5].

According to the functional MRT data, recurrent MBCCI causes hyper-connectivity between the thalamus and

the cerebral cortex. A study using functional MRT at the state of rest revealed increased functional connectivity between the thalamic nuclei and the passive mode network of the brain in the acute period – approximately 6 ± 3 days after injury. It has been shown that repeated injuries lead to a progressive increase in thalamocortical connectivity, the degree of which increases depending on the number of injuries sustained [6].

Experimental animal models also confirm the cumulative nature of mine-blast injuries. In particular, subclinical seizures, disorders of the blood-brain barrier integrity, and increased expression of pro-inflammatory markers such as TDP-43 and Piezo2 have been detected after repeated explosive brain injuries [7]. Proteomic analysis of the hippocampus in rats revealed significant changes in the protein profile, indicating profound molecular transformations in brain tissues. In addition, high-density EEG-recording showed that the long-term effects of repeated mine-blast injuries include increased power in the alpha and beta ranges [8]. A link has also been established between post-traumatic amnesia, loss of consciousness, cognitive difficulties and changes in the EEG-spectrum. Additional studies that took into account the presence of post-traumatic stress disorder (PTSD) showed that although post-traumatic stress disorder (PTSD) and MBCCI cause spectral changes in the EEG, their topography differs: in MBCCI, it is the prefrontal and right-temporal areas, while in PTSD, it is the right temporo-parietal area [9].

According to the results obtained by using various neuroimaging methods, it has been determined that even so-called 'mild' MBCCI has the potential to cause profound structural, functional, and molecular changes in the brain. Of particular significance is the fact that repeated injuries have a cumulative negative effect, in particular by exacerbating disorders of neuronal network coherence [10, 11]. This, in turn, highlights the importance of systematic analysis of inter- and intra-hemispheric coherence as an effective diagnostic and monitoring tool in the rehabilitation of military personnel who have suffered MBCCI.

AIM

The aim of this study is to analyze inter-hemispheric and intra-hemispheric coherent connections of brain biopotentials in military personnel during recovery from MBCCI, as well as to study the cumulative effect of repeated MBCCI on the nature of coherent changes.

MATERIALS AND METHODS

Twenty-eight military personnel who suffered mild to moderate mine-blast trauma (MBT) (concussion

and brain contusion, acoustic trauma) during combat operations due to the full-scale war in Ukraine in 2022-2024 were examined. The period since the last MBT confirmed by primary medical documentation ranged from 3 to 12 months. All patients were men with an average age of (33.9 ± 1.8) years.

The first group (14 men) included patients who had only one MBCCI, and the second group (14 men) included patients who had more than one c in the last two years, with an average of 2-3 injuries.

All examined patients who had undergone MBCCI had numerous complaints of neurological, vegetative and somatic nature. The most common were headache, photophobia, sensitivity to sounds, nausea, double vision, blurred vision, hearing loss, tinnitus, dizziness, unsteadiness when walking, speech disorders, pain in the spine, limited movement in the limbs, muscle pain, cramps, paresthesia, weakness, tremor, limb movement disorders, general asthenia, local or generalized hyperhidrosis, tachycardia, and arterial hypertension. Cognitive disorders were noted, in particular, decreased memory, attention, difficulty concentrating, as well as emotional disorders – increased anxiety, irritability, sleep disorders.

Clinical-and-neurological examination revealed a predominance of liquor-hypertensive, vestibule-cochlear, and vestibule-ataxic syndromes. In a number of cases, disorders of functioning of the cranial nerves, mainly the auditory nerves, as well as oculomotor disorders were recorded. Symptoms of peripheral nervous system damage were detected, with a predominance of manifestations of cerebrastronic syndrome, combined with signs of vegetative dysfunction and general brain disorders. The course of the post-traumatic recovery period in patients was significantly complicated by the presence of mine-blast injuries of internal organs, soft tissues and bones, most often of a multiple or combined nature. Analysis of clinical data showed that the severity of neurological symptoms was significantly greater in patients in the second group.

The control group included patients (11 persons) who did not have MBCCI. The average age of the control group patients was (31.8 ± 2.3) years.

All categories of examinees underwent EEG recording using a "Neuron-Spectrum-4/P" computerized electroencephalograph with 20 standard monopolar leads according to the <10-20> system. For coherent analysis, four artefact-free epochs (5.12 s each) of the background EEG recording were selected, followed by calculation of interhemispheric and intra-hemispheric coherence indices of bio-potentials for five frequency ranges, corresponding to delta – (0.5 – 3.9 Hz), theta – (4.0 – 7.9 Hz), alpha – (8.0-12.9 Hz), low-frequency beta

(LF) – (13.0 – 19.9 Hz) and high-frequency beta (HF) – (20.0 – 35.0 Hz) rhythms. Interhemispheric coherence analysis was performed in 8 pairs of leads (Fp1-Fp2; F3-F4; F7-F8; T3-T4; T5-T6; C3-C4; P3-P4; O1-O2), and intra-hemispheric coherence in 12 pairs of leads (Fp1-F3; F3-C3; C3-P3; P3-O1; Fp2-F4; F4-C4; C4-P4; P4-O2; F7-T3; T3-T5; F8-T4; T4-T6).

Statistical data processing was performed using Excel and SPSS software, the mean values (M) and standard error of the mean (m) were calculated, and the significance of differences between indicators was determined using the nonparametric Wilcoxon-Mann-Whitney criterion at a significance level of $p \leq 0.05$.

RESULTS

A comparison of inter-hemispheric coherent connections in patients in the first group and in healthy subjects was performed. The data are presented in Table 1.

Table 1 shows that patients in the first group, compared to the control group, had a statistically significant ($p \leq 0.05$) decrease in inter-hemispheric coherent connections, mainly in pairs of frontal lobes (Fp1-Fp2; F7-F8) and parietal (P3-P4) leads in the delta-, theta-, alpha-, and beta- low-frequency ranges. In the delta-range, a weakening of inter-hemispheric coherent connections was also observed in pairs of central (C3-C4) and temporal (T3-T4) leads. Similarly, a comparison of inter-hemispheric coherent connections was performed in patients of the second group and in the control group. The data are presented in Table 2.

As can be seen from Table 2, patients in the second group, unlike healthy subjects, showed significantly lower inter-hemispheric coherence in frontal pairs (Fp1-Fp2; F3-F4), central (C3-C4) and parietal (P3-P4) leads in all studied frequency ranges of brain bio-potentials. In patients of the second group, a significant decrease in inter-hemispheric coherence was also determined in pairs of lower frontal (F7-F8) and central (C3-C4) leads in the delta-, theta-, alpha-, and beta- low-frequency ranges. Low inter-hemispheric coherence indices in patients of the second group were also noted in pairs of temporal (T3-T4; T5-T6) leads in the delta-, theta-, and beta- low frequency ranges (Table 2).

We also conducted a comparative analysis of inter-hemispheric coherence indicators in patients from the first and second groups. Significant differences were found only in the delta- and beta- frequency ranges. In the delta- range, there were mixed changes, namely, in pairs of frontal (F3-F4) leads, inter-hemispheric coherence indices in patients in the first group were significantly ($p=0.03$) lower than in patients in the second group (0.32 ± 0.09 and 0.38 ± 0.04 , respectively), while in

the pairs of central (C3-C4) leads, they are significantly ($p=0.03$) higher (0.55 ± 0.06 and 0.34 ± 0.03 , respectively). In the beta- low frequency range in pairs of occipital (O1-O2) and temporal (T5-T6) leads, inter-hemispheric coherence indices are significantly lower in patients in the second group. To confirm this, we present data in pairs of occipital (O1-O2) leads in patients of the first group, where inter-hemispheric coherence indices of beta- frequency range bio-potentials corresponded to a value of 0.39 ± 0.06 , and in the second group – 0.24 ± 0.03 ; and in pairs of temporal (T5-T6) leads, these indicators in the first group were 0.24 ± 0.03 and in the second group – 0.13 ± 0.01 , which has a high reliable ($p=0.01$) discrepancy.

Thus, analysis of interhemispheric coherence indicators revealed a general tendency toward a decrease in functional interaction between hemispheres in patients in both groups – both with single and multiple MBCCI – compared to the control group. The most pronounced decreases in coherence were observed in the delta-, theta-, alpha-, and beta- frequency ranges, with predominant localization in the frontal and parietal regions of the cerebral cortex. In patients with multiple MBCCI, a significantly greater number of significant differences were recorded, in particular low coherence indices also extended to the central, occipital and temporal regions, covering the theta-, beta- LF and beta- HF ranges, indicating a more generalized dysfunction of interhemispheric connections. A comparative analysis of patients with single and multiple MBCCI demonstrated that it is precisely in multiple injuries that a significant decrease in coherence in the beta- HF range is observed, mainly in pairs of occipital and temporal leads. These changes correlate with clinical manifestations – more pronounced neurological symptoms, emotional instability and cognitive disorders, which is probably due to a wider damage to the brain network structures responsible for the integration of sensory information, regulation of attention, memory and emotional reactivity.

Changes in intra-hemispheric coherence of brain bio-potentials were analyzed in all observation groups. In patients of the first group, who had only one MBCCI in their medical history, compared with the control group, a significant ($p=0.05$) decrease in intra-hemispheric coherence indices was determined only in the delta- frequency range in the pair of frontal (Fp1-F3) leads of the left hemisphere of the brain (0.43 ± 0.08 and 0.67 ± 0.03 , respectively). In patients in the second group with multiple MBCCI, there were significantly more significant differences from the control group. The data are presented in Table 3.

Table 1. Significant differences in inter-hemispheric coherence indices in patients of the first group and in the control group.

Frequency range	EEG pairs	Inter-hemispheric coherence indices		Intergroup differences P≤0,05
		Patients of Group 1	Control group	
Delta-range	FP1-FP2	0,37 ± 0,09	0,68 ± 0,06	0,01
	C3-C4	0,55 ± 0,06	0,61 ± 0,04	0,04
	P3-P4	0,45 ± 0,02	0,53 ± 0,04	0,04
	F7-F8	0,37 ± 0,06	0,49 ± 0,04	0,03
	T3-T4	0,30 ± 0,06	0,52 ± 0,03	0,05
Theta-range	P3-P4	0,53 ± 0,07	0,60 ± 0,03	0,05
Alpha-range	FP1-FP2	0,44 ± 0,06	0,72 ± 0,03	0,01
	F7-F8	0,36 ± 0,03	0,52 ± 0,03	0,01
Beta-low frequency range	P3-P4	0,35 ± 0,04	0,52 ± 0,03	0,01
	F7-F8	0,24 ± 0,04	0,35 ± 0,02	0,03

Source: compiled by the authors of this study

Table 2. Significant differences in inter-hemispheric coherence indices in patients of the second group and in the control group

Frequency range	EEG pairs	Inter-hemispheric coherence indices		Intergroup differences P≤0,05
		Patients of Group 2	Control group	
Delta-range	FP1-FP2	0,43 ± 0,07	0,68 ± 0,06	0,02
	F3-F4	0,38 ± 0,04	0,62 ± 0,05	0,00
	C3-C4	0,34 ± 0,03	0,61 ± 0,04	0,00
	P3-P4	0,35 ± 0,03	0,53 ± 0,04	0,01
	O1-O2	0,30 ± 0,03	0,47 ± 0,03	0,00
	F7-F8	0,23 ± 0,04	0,49 ± 0,04	0,00
	T3-T4	0,27 ± 0,05	0,52 ± 0,03	0,00
	T5-T6	0,20 ± 0,04	0,39 ± 0,03	0,01
Theta- range	FP1-FP2	0,42 ± 0,07	0,66 ± 0,06	0,01
	F3-F4	0,47 ± 0,05	0,68 ± 0,05	0,02
	C3-C4	0,45 ± 0,05	0,68 ± 0,04	0,01
	P3-P4	0,44 ± 0,05	0,60 ± 0,03	0,03
	O1-O2	0,38 ± 0,04	0,48 ± 0,03	0,05
	T3-T4	0,28 ± 0,05	0,42 ± 0,04	0,02
Alpha- range	FP1-FP2	0,44 ± 0,06	0,72 ± 0,03	0,00
	F3-F4	0,49 ± 0,05	0,70 ± 0,02	0,00
	C3-C4	0,49 ± 0,05	0,66 ± 0,03	0,01
	P3-P4	0,51 ± 0,04	0,64 ± 0,03	0,04
	F7-F8	0,36 ± 0,03	0,52 ± 0,03	0,01
Beta- low frequency range	FP1-FP2	0,24 ± 0,07	0,55 ± 0,04	0,01
	F3-F4	0,27 ± 0,07	0,57 ± 0,03	0,01
	C3-C4	0,25 ± 0,06	0,54 ± 0,03	0,01
	P3-P4	0,24 ± 0,05	0,52 ± 0,03	0,00
	O1-O2	0,24 ± 0,03	0,43 ± 0,03	0,00
	F7-F8	0,21 ± 0,05	0,35 ± 0,02	0,04
	T5-T6	0,13 ± 0,01	0,22 ± 0,02	0,00
Beta- high frequency range	FP1-FP2	0,20 ± 0,05	0,33 ± 0,03	0,03
	F3-F4	0,17 ± 0,03	0,31 ± 0,03	0,01
	C3-C4	0,18 ± 0,03	0,32 ± 0,03	0,01
	P3-P4	0,19 ± 0,03	0,29 ± 0,03	0,02

Source: compiled by the authors of this study

Table 3. Significant differences in intra-hemispheric coherence indices in patients in the second group and in the control group

Frequency range	EEG pairs	Intra-hemispheric coherence indices		Intergroup differences P≤0,05
		Patients of Group 2	Control group	
Delta-range	Fp1-F3	0,54 ± 0,04	0,67 ± 0,03	0,02
	Fp2-F4	0,52 ± 0,04	0,65 ± 0,03	0,03
	T3-T5	0,47 ± 0,06	0,73 ± 0,04	0,01
Theta- range	T3-T5	0,53 ± 0,06	0,69 ± 0,06	0,04
Beta- low frequency range	C4-P4	0,87 ± 0,04	0,78 ± 0,02	0,02
Beta- high frequency range	C4-P4	0,85 ± 0,05	0,77 ± 0,01	0,03

Source: compiled by the authors of this study

The data presented in Table 3 show that patients in the second group have a significant decrease in intra-cerebral coherence in pairs of frontal (Fp1-F3; Fp2-F4) of the left and right hemispheres of the brain in the delta-activity range and in pairs of temporal (T3-T5) leads of the left hemisphere of the brain in the delta- and theta- frequency ranges. In the beta- low and beta- high frequency ranges, a significant increase in intra-hemispheric coherence indices was recorded in pairs of central-parietal (C4-P4) leads of the right hemisphere of the brain. When comparing intra-hemispheric coherence indices in both groups of patients, no significant differences were recorded.

DISCUSSION

Analysis of intra-hemispheric coherence showed higher stability of functional connections in patients with single MBCCI, indicating partial preservation of integrative activity of local neural networks within each hemisphere. In patients with multiple MBCCI, on the contrary, multidirectional changes in intra-hemispheric coherence were recorded: a decrease in its indicators in the delta- and theta- ranges in the frontal and temporal regions of mainly the left hemisphere of the brain, as well as an increase in coherence in the beta- range in the central-parietal areas of the right hemisphere. This pattern of changes may indicate a disorder of regulatory mechanisms within the hemispheres, as well as an imbalance between excitatory and inhibitory neural networks – a probable consequence of the cumulative effect of repeated traumatic injuries [7]. Decreased coherence in the left hemisphere frontal-temporal areas correlates with cognitive-emotional resource depletion, executive function and attention disorders, while increased coherence in the right-hemispheric central-parietal areas may reflect compensatory pro-

cesses aimed at preserving adaptive capabilities in the context of chronic psycho-emotional stress characteristic of combat conditions [9]. This combination of neurophysiological changes is associated with clinical manifestations of autonomic nervous system dysfunction, increased emotional tension, and symptoms of asthenia, indicating depletion of the brain's functional reserves and a decrease in the effectiveness of its regulatory mechanisms.

CONCLUSIONS

1. Military personnel with single and especially multiple MBCCI showed a significant decrease in inter-hemispheric and intra-hemispheric coherence, indicating a disorder in the integrative activity of the brain.
2. In both groups of military personnel, the most pronounced changes in interhemispheric coherence compared to healthy individuals were recorded in the delta-, theta-, alpha- and beta- frequency ranges, mainly in the frontal and parietal areas of the brain.
3. In cases of multiple traumatic brain injury, generalized dysfunction of interhemispheric interaction was detected in all studied frequency ranges, involving the central, occipital, and temporal areas, as well as an imbalance in intra-hemispheric coherence: with suppression of activity in the left hemisphere and compensatory hyperactivity in the right.
4. The obtained changes in coherence indicators correlate with clinical manifestations of neurological, emotional and cognitive disorders, reflecting varying degrees of depletion of functional reserves in the brains of military personnel with single and multiple MBCCI, and may form the basis for the development of pathogenetically sound, individualized neuro-rehabilitation programs.

REFERENCES

1. Bryden DW, Tilghman JJ, Hinds SR 2nd. Blast-Related Traumatic Brain Injury: Current Concepts and Research Considerations. *J Exp Neurosci*. 2019;13:1179069519872213. doi: 10.1177/1179069519872213. [DOI](#)
2. Sponheim SR, McGuire KA, Kang SS et al. Evidence of disrupted functional connectivity in the brain after combat-related blast injury. *NeuroImage*. 2011;54(1):S21–S29. doi: 10.1016/j.neuroimage.2010.09.007. [DOI](#)
3. Aviyente S, Bernat EM, Sponheim SR. Phase synchrony analysis of electrophysiological signals using complex wavelets. *Clin Neurophysiol*. 2015;126(5):1031–1042. doi: 10.1016/j.clinph.2014.07.012. [DOI](#)
4. Robinson ME, Lindemer E, Fonda JR et al. Close-range blast exposure is associated with altered functional connectivity in veterans independent of concussion symptoms at time of exposure. *Brain Connectivity*. 2015;5(9):419–427. doi: 10.1089/brain.2015.0342. [DOI](#)
5. Han K, Mac Donald CL, Johnson AM et al. Disrupted modular organization of resting-state cortical functional connectivity in U.S. military personnel following concussive ‘mild’ blast-related traumatic brain injury. *NeuroImage*. 2014;84:76–96. doi: 10.1016/j.neuroimage.2013.08.017. [DOI](#)
6. Sours C, Zhuo J, Roys S et al. Disruption of the thalamic resting-state network following traumatic brain injury. *Front Neurol*. 2015;6:60. doi: 10.3389/fneur.2015.00060. [DOI](#)
7. Rubovitch V, Ten-Bosch M, Zohar O et al. A mouse model of repeated mild traumatic brain injury: Functional and pathological outcomes. *Front Neurosci*. 2019;13:266. doi: 10.3389/fnins.2019.00266. [DOI](#)
8. Franke LD, Garnett M, Hiraad AA et al. Repetitive mild traumatic brain injury alters EEG spectral power and is associated with cognitive dysfunction in military personnel. *Front Neurol*. 2023;14:1049557. doi: 10.3389/fneur.2023.1049557. [DOI](#)
9. Franke LM, Perera RA, Sponheim SR. Longterm resting EEG correlates of repetitive mild traumatic brain injury and loss of consciousness: alterations in alpha–beta power. *Front in Neurol*. 2023;14:1241481. doi: 10.3389/fneur.2023.1241481. [DOI](#)
10. Eierud C, Craddock RC, Fletcher S et al. Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *NeuroImage: Clinical*. 2014;4:283–294. doi:10.1016/j.nicl.2013.12.009. [DOI](#)
11. Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. *Mol Cell Neurosci*. 2015;66(B):75–80. doi: 10.1016/j.mcn.2015.03.001. [DOI](#)

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Liudmyla P. Zabrodina

P. V. Voloshin Institute of Neurology,
Psychiatry and Narcology of the National Academy of
Medical Sciences of Ukraine
46 Academician Pavlova St., 61000 Kharkiv, Ukraine
e-mail: inpn_zabrodina@ukr.net

ORCID AND CONTRIBUTIONSHIP

Liudmyla P. Zabrodina: 0000-0001-8756-3479 [A](#) [B](#) [E](#) [F](#)

Volodymyr O. Korshnyak: 0000-0002-3041-3944 [A](#) [B](#) [C](#) [F](#)

Yuliia V. Bovt: 0000-0002-0693-2242 [C](#) [D](#)

Nataliya M. Pryvalova: 0009-0001-3251-5071 [C](#) [E](#)

Viktor V. Sukhorukov: 0000-0001-8970-8475 [B](#) [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: 16.04.2025

ACCEPTED: 29.08.2025



Potential use of bacteriophages for the oral microbiota modulation in periodontal diseases within the context of maxillofacial pathology

Tetiana Timokhina¹, Marina V. Kryvtsova², Mykola Y. Spivak³, Nina S. Proshchenko¹, Alla V. Kharina⁴, Oleksandra Bondarenko⁵

¹BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

²UZHGOROD NATIONAL UNIVERSITY, UZHGOROD, UKRAINE

³NATIONAL ACADEMY OF SCIENCES OF UKRAINE, KYIV, UKRAINE

⁴BIOLOGY AND MEDICINE INSTITUTE SCIENCE EDUCATIONAL CENTER OF TARAS SHEVCHENKO NATIONAL UNIVERSITY, KYIV, UKRAINE

⁵NEOPROBIOCARE UKRAINE LTD., KYIV, UKRAINE

ABSTRACT

Aim: To study the susceptibility of isolates obtained from the oral cavities of individuals with inflammatory periodontal diseases and maxillofacial pathology to bacteriophages.

Materials and Methods: Biological specimens were obtained from the Dental Medical Center and University Clinic of O.O. Bogomolets National Medical University and the National Specialized Children's Hospital OKHMATDYT. Biomaterial was collected from the wound surface using a sterile FLmedical transport system (Italy). Clinical isolates used in the studies included *Escherichia coli*, *Klebsiella spp.*, *Pseudomonas spp.*, and *Staphylococcus aureus*. We assessed the susceptibility of microorganisms to bacteriophages by administering 0.01 ml of bacteriophage culture to a bacterial culture. A suspension (inoculum) was prepared from a 24-hour culture of microorganisms in sterile saline and then Mueller Hinton agar was inoculated with it. The results were recorded 24 hours post-incubation in a thermostat at 37°C.

The study used bacteriophages from the bacterial test cultures *Klebsiella pneumoniae* DSM30104, *Staphylococcus aureus* DSM 799, *Escherichia coli* DSM 1103, and *Pseudomonas aeruginosa* DSM 50071, provided by NeoProBioCare Ukraine Ltd.

Results: The susceptibility rates of isolates to phages were 40% for *Klebsiella spp.*, 73.3% for *S. aureus*, 50.0% for *E. coli*, and 20.0% for *Pseudomonas spp.* Prior research confirms the effectiveness of bacteriophages in oral diseases. This method may be beneficial in controlling opportunistic microorganisms and maintaining the oral microbiota balance.

Conclusions: The application of bacteriophages for inflammatory oral diseases appears promising and warrants further research. Clinical trials and additional scientific investigations are necessary to confirm its safety and effectiveness.

KEY WORDS: antimicrobial action, alternative antimicrobial agents, periodontitis, maxillofacial diseases

Wiad Lek. 2025;78(9):1849-1856. doi: 10.36740/WLek/210022 DOI

INTRODUCTION

The idea of using viruses for treating human infectious diseases emerged nearly concurrently with the discovery of phages in 1915. However, the application of phages in medicine was suspended after the introduction of antibiotics [1]. Bacteriophages (phages) are viruses that invade bacterial cells and interfere with their metabolism. During the lytic cycle, they induce bacterial lysis. The principal advantages of phage therapy encompass higher strain specificity with minimal effects on the commensal microbiome, the capacity to multiply at the infection site while simultaneously disappearing alongside the target pathogen, the absence of apparent

toxicity, relatively simple to isolate and use in genetic engineering, and co-evolving with their bacterial hosts to eliminate drug-resistant strains [2].

Currently, bacteriophage therapy is a promising method for treating infectious dental conditions [1]. Due to the escalating clinical issue of antibiotic resistance, phage therapy for infectious diseases has once more attracted the interest of specialists. Bacteriophages have been suggested as natural antimicrobial agents to combat antibiotic-resistant bacteria associated with human infections [2].

The oral phage population comprises over 2000 species that infect bacteria from the Actinobacteria

(>300 phages), Bacteroidetes (>300 phages), Firmicutes (>1000 phages), Fusobacteria (>200 phages), and Proteobacteria (>700 phages). Bacteriophage activity inhibits relapses of infectious diseases and the chronicity of inflammatory processes. Bacteriophages in oral cells primarily stimulate anti-inflammatory mediators, including IL-6 and IL1RN, to modulate innate and adaptive immunity, thereby indirectly influencing cell signaling and physiological processes [3]. The application of phage therapy in dentistry remains an entirely unsolved issue [4, 5]. Regrettably, the rapidly advancing bacteriophage therapy presents new challenges for clinical implementation, including phage resistance. At the same time, phage resistance develops approximately tenfold more slowly than antibiotic resistance [6]. A viable strategy to reduce antibiotic dosage and prevent antibiotic resistance during treatment includes the combination of phages with antibiotics. Antibiotics and bacteriophages can not only deal with phage resistance but also reduce antibiotic resistance. The function of engineered phages in reducing bacterial pathogenicity is under investigation. Research indicates that alternating the administration of the antibiotic and phage yields superior outcomes compared to simultaneous administration [7].

Traditional approaches to periodontal disease management, including dental biofilm control, enhanced oral hygiene, adjunctive gingivitis therapy, mechanical plaque removal, and the application of topical and/or systemic antimicrobials, are recognized as insufficiently effective [8]. Considering the widespread occurrence of antimicrobial-resistant bacteria in the oral cavity, the prevailing viewpoint supports various forms of phage therapy as a supplementary approach to standard periodontal treatment to reduce systemic adverse effects. Bacteriophages that selectively infect bacterial cells are now acknowledged as a novel therapeutic approach for eradicating plaque biofilms in periodontal diseases [9].

Bacteriophage therapy represents an innovative and promising strategy for combating multidrug-resistant bacteria that cause serious dental diseases. Furthermore, investigations into phage therapy for endodontic and periapical infections are underway. The findings indicate that, in contrast to traditional antibiotics, phage therapy may necessitate reduced or more restricted doses, demonstrating effectiveness comparable to or better than standard therapies. The majority of phages isolated to date exhibit considerable specificity for dental pathogens. This benefit reduces the harmful risk to the natural oral microbiota while eliminating the adverse effects associated with chemical antibiotics. Phage therapy presents new opportunities in dentistry,

both therapeutically and scientifically, similar to its impact in various medical fields.

AIM

To study the susceptibility of isolates obtained from the oral cavities of individuals with inflammatory periodontal diseases and maxillofacial pathology to bacteriophages.

MATERIALS AND METHODS

Biological specimens were obtained from the Dental Medical Center and University Clinic of O.O. Bogomolets National Medical University and the National Specialized Children's Hospital OKHMATDYT. Biomaterial was collected from the wound surface using a sterile FLmedical transport system (Italy). The study on antimicrobial activity was conducted in the microbiological laboratory of the Department of Genetics, Plant Physiology, and Microbiology at Uzhhorod National University. Clinical isolates used in the studies included *Escherichia coli*, *Klebsiella* spp., *Pseudomonas* spp., and *Staphylococcus aureus*. We assessed the susceptibility of microorganisms to bacteriophages by administering 0.01 ml of bacteriophage culture to a bacterial culture. A suspension (inoculum) was prepared from a 24-hour culture of microorganisms in sterile saline and then Mueller Hinton agar was inoculated with it. The results were recorded 24 hours post-incubation in a thermostat at 37°C.

The study used bacteriophages from the bacterial test cultures *Klebsiella pneumoniae* DSM30104, *Staphylococcus aureus* DSM 799, *Escherichia coli* DSM 1103, and *Pseudomonas aeruginosa* DSM 50071, provided by NeoProBioCare Ukraine Ltd.

RESULTS

The investigation into the susceptibility of bacterial cultures obtained from patients revealed that *Staphylococcus aureus* exhibited the highest percentage of susceptible isolates (Table 1, Fig. 1). Out of the 30 strains, 22 isolates had susceptibility to the examined bacteriophage, representing 73.3%.

Bacteria of the genus *Klebsiella* spp. demonstrated the lowest susceptibility to bacteriophage. Susceptibility studies of clinical isolates of *Klebsiella pneumoniae* indicated a phage susceptibility rate of 40% (Table 1, Fig. 2). Simultaneously, 20.0% inhibited the growth of the tested clinical cultures (Fig. 2).

Among the *Escherichia coli* isolates studied, 50.0% showed susceptibility to bacteriophages (Table 1, Fig. 3).

Table 1. Susceptibility of clinical isolates from complicated wounds to bacteriophages

Microorganism	Number of strains tested, abs.	Number of susceptible isolates, abs.	Percentage of susceptible isolates, %
<i>Klebsiella spp.</i>	25	10	40.0%
<i>Staphylococcus aureus</i>	30	22	73.3%
<i>Escherichia coli</i>	28	14	50.0 %
<i>Pseudomonas spp.</i>	15	3	20.0 %

Source: compiled by the authors of this study

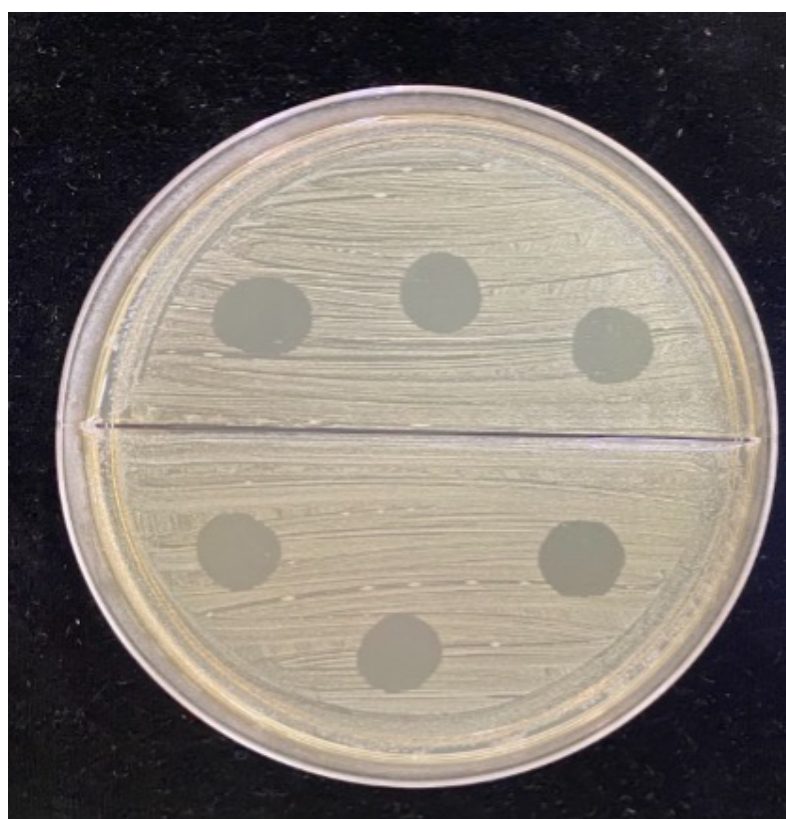


Fig. 1. Susceptibility of a clinical isolate of *Staphylococcus aureus* to a specific bacteriophage
Picture taken by the authors

Research on the susceptibility of clinical isolates of *Pseudomonas aeruginosa* indicated a phage susceptibility rate of 63.3% (Table 1, Fi1. 4).

The majority of isolates from the bacterial species *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* exhibited polyantibiotic resistance. In these circumstances, the application of bacteriophage may be the sole alternative for sanitizing the oral cavity and diminishing the prevalence of antibiotic-resistant microorganisms.

The results regarding the susceptibility of clinical isolates to bacteriophages (Fig. 4) suggest that, if the pathogen is specifically susceptible, bacteriophages may serve as an alternative to antibiotic therapy or significantly enhance the effectiveness of antibiotic treatment.

The examined isolates are composed of opportunistic bacteria, noted for their significant antibiotic resistance (Table 2). It was demonstrated that 25.9% of *Klebsiella spp.*, 20.0% of *Staphylococcus aureus*, 39.3% of *Esch-*

erichia coli, and 40.0% of *Pseudomonas spp.* showed concurrent resistance to three antibiotics. The identified patterns demonstrate the enduring presence of antibiotic-resistant bacteria in the oral cavity, which are challenging to manage and may contribute to complications.

It is noteworthy that some antibiotic-resistant isolates exhibited susceptibility to bacteriophages. Consequently, no discernible patterns in the susceptibility or resistance to bacteriophages were identified among polyantibiotic-resistant isolates.

The identified patterns of strain-specific susceptibility of opportunistic bacterial isolates to antibiotics suggest that the examined bacteriophages may serve as alternatives to antimicrobial therapy or adjuncts to antibiotic treatment.

The data analysis allowed us to determine the susceptibility of isolates from the oral cavities of patients with periodontal diseases and maxillofacial pathology to

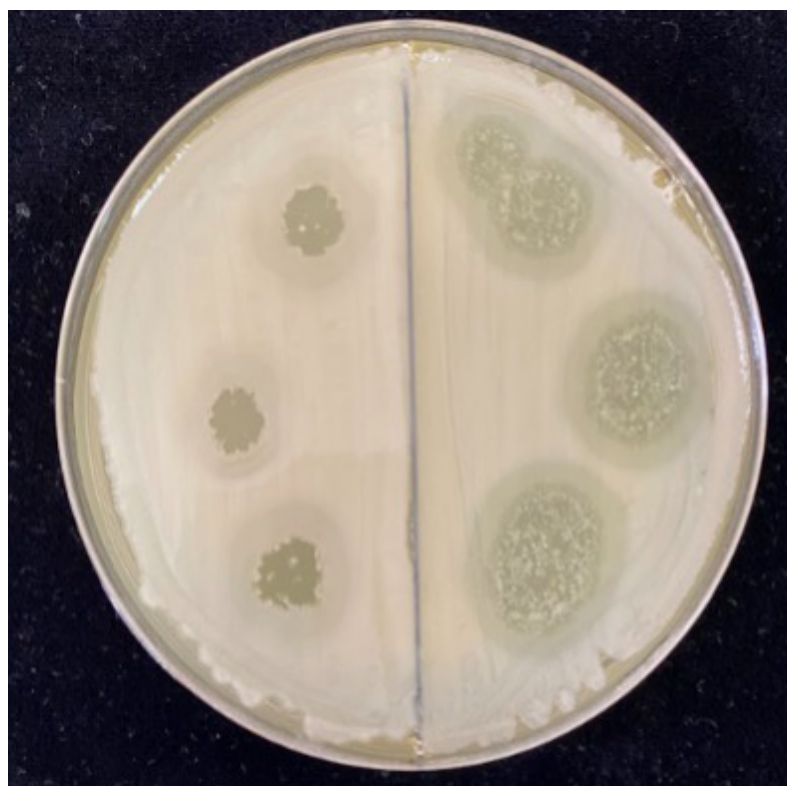


Fig. 2. Susceptibility of a clinical isolate of *Klebsiella pneumoniae* to a specific bacteriophage
Picture taken by the authors

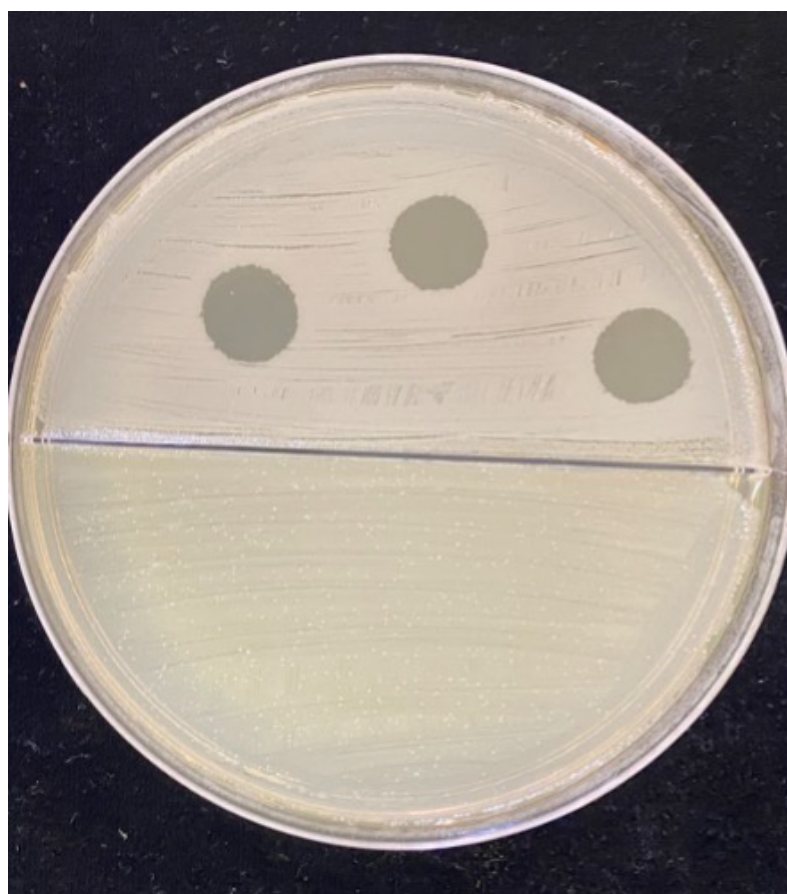


Fig. 3. Susceptibility of a clinical isolate of *Escherichia coli* to a specific bacteriophage
Picture taken by the authors

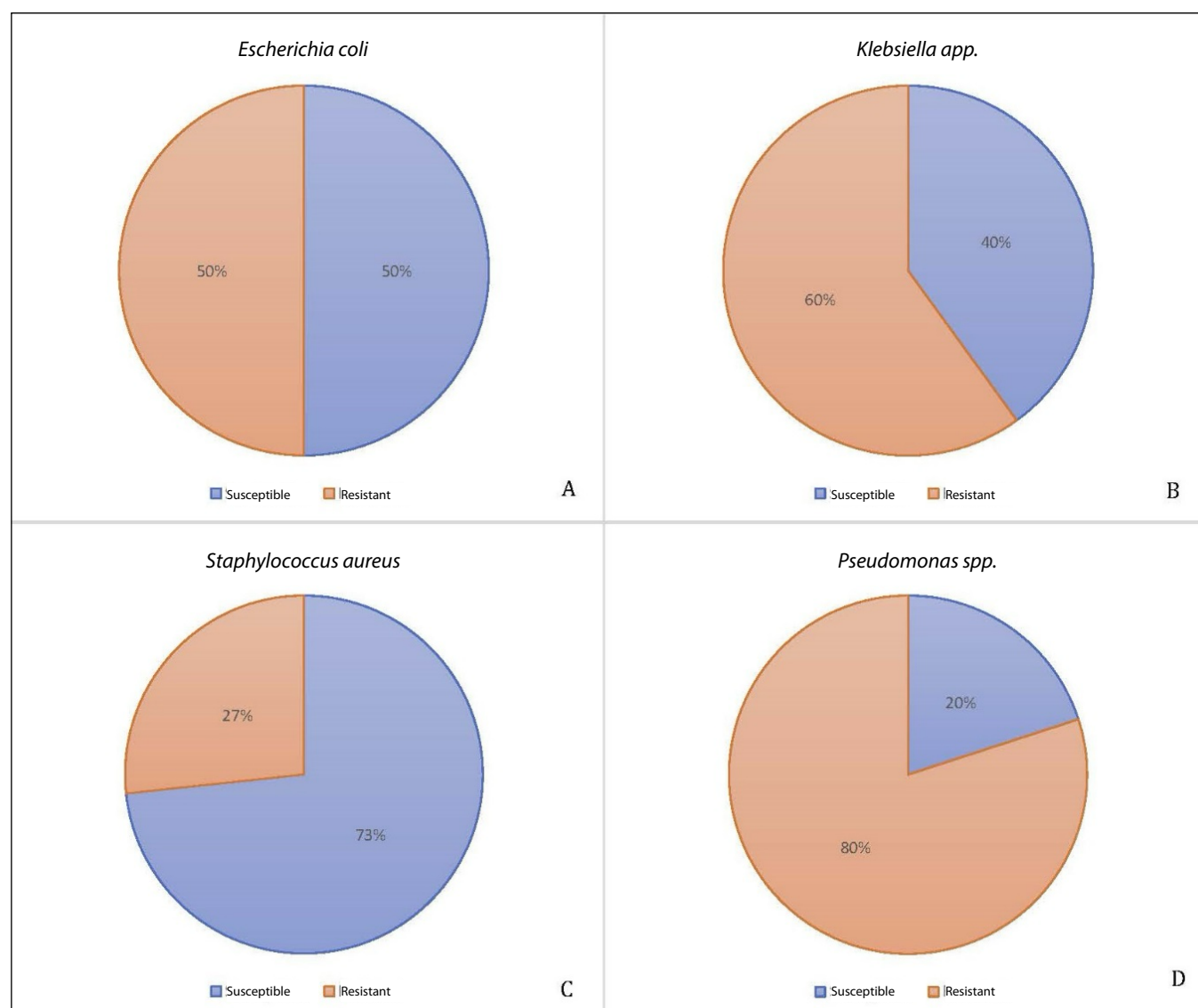
bacteriophages. Their susceptibility to phages was strain-specific, necessitating the assessment of susceptibility to the phage suspension before initiating treatment.

Prior research confirms the effectiveness of using bacteriophages in the treatment of oral diseases. This approach is effective in combating pathogenic microorganisms and in maintaining the balance of oral microbiota.

Table 2. Susceptibility of clinical isolates from complicated wounds to bacteriophages

Microorganisms	Number of strains tested, abs.	Number of isolates resistant to class III antibiotics, abs.	Percentage of isolates resistant to class III antibiotics, %
<i>Klebsiella spp.</i>	25	7	25.9%
<i>Staphylococcus aureus</i>	30	6	20.0%
<i>Escherichia coli</i>	28	11	39.3 %
<i>Pseudomonas spp.</i>	15	6	40.0 %

Source: compiled by the authors of this study

**Fig. 4.** Percentage of bacteriophage-susceptible and -resistant clinical isolates from the oral cavity

Picture taken by the authors

DISCUSSION

The literature review suggests individual studies regarding the use of bacteriophages in oral diseases of microbial etiology.

Biofilms are found in almost all infectious diseases that threaten oral health, such as caries, periodontitis, gingivitis, endodontic infections, and peri-implantitis.

Steier et al. (2019) examined the structure of bacteriophages and their action on bacteria within biofilms, emphasizing the potential use of bacteriophages in dentistry [10].

Caries-associated problems are challenging to treat with standard methods due to the development of a biofilm of cariogenic bacteria, which protects them

and reduces the effectiveness of common antibacterial agents [11]. It is essential to create therapeutic techniques specific to cariogenic bacteria with a low risk of resistance [12]. Bacteriophage therapy is a promising alternative method. Thus, phage SMHBZ8, specifically targeting *S. mutans*, has been identified as a potential method for preventing and treating dental caries [13]. H. Ben-Zaken et al. (2021) conducted an experimental investigation on human saliva samples. They discovered that SMHBZ8 is a lytic phage capable of infiltrating, regulating, and suppressing the growth of *S. mutans* biofilm [14].

Enterococcus faecalis (*E. faecalis*) is known for its notable resistance to numerous antimicrobial agents. [15, 16]. J. Wong et al. (2021) reported that in root canal infections, *E. faecalis* was detected in every canal, and its presence in the biofilm induces inflammation of the pulp tissue, finally resulting in pulp necrosis and the spread of inflammation/infection to the peri-root tissues [17]. In clinical settings, isolated phages have demonstrated remarkable effectiveness when combined with alkaline disinfectants frequently used to deal with endodontic infections [15].

M. El-Telbany et al. (2021) demonstrated a phage-mediated reduction in *E. faecalis* biofilms in ex vivo dental models. The lytic activity of phage vB_ZEFP against *E. faecalis* biofilms confirmed its capability to inhibit the growth of *E. faecalis* in vitro and to prevent *E. faecalis* root canal infections [18].

The presence of many bacterial types inside the biofilm structure imposes constraints on the strategies employed to combat them [19]. Historically, it has been contended that while bacteriophages may function as effective antibacterial agents, the heterogeneity of the oral microbiota raises concerns over their effectiveness in treating periodontal diseases [20]. At the same time, in the context of the persistence of opportunistic microorganisms within the oral microbiota and dysbacteriosis, characterized by the dominance of microbial associations from the facultative component of the microbiome, the application of bacteriophages is a justified alternative to antibiotics and antiseptics. Kabwe et al. (2019) identified and studied FNU1, a lytic phage that targets *F. nucleatum*, which forms the basis of a polymicrobial biofilm in periodontitis. The introduction of FNU1 into a biofilm containing *F. nucleatum* led to a 70% decrease in the biomass of this bacterium [21]. A. Abdulkareem et al. (2021) highlighted that the use of bacteriophages in periodontal therapy remains restricted to in vitro investigations. Nonetheless, using bacteriophages to combat periodontal pathogens in

periodontal diseases seems promising and can effectively deal with the increasing resistance of bacteria to currently available medicines. At the same time, clinical trials to either confirm or refute this concept in periodontal therapy have been practically nonexistent. However, it has been established that, in contrast to broad-spectrum antibiotics, bacteriophages can destroy periodontal biofilms without disrupting the local oral ecology [22].

A restriction of phage therapy is that only a limited fraction of phages is suitable for medicinal purposes. Only 50% of phages isolated from the environment can be used in medicine [23]. Phage resistance has been recorded in human phage treatment, presenting a potential challenge for the practical use of phage therapy [24]. Various encapsulated carriers, such as fibers, hydrogels, and particles, have been used in phage delivery systems, demonstrating the advantage of maintaining their stability. These systems can function alongside other dental materials to treat or prevent infectious diseases, including periodontitis. Therefore, given that periodontitis is a chronic disease caused by several bacteria, G. Pinto et al. (2016) suggested a phage cocktail as an alternative to standard treatment techniques and outlined the steps for producing phage-based products. The authors emphasize that active bacteriophage combinations in cocktail therapy are crucial for preventing the rapid emergence of phage resistance [25].

CONCLUSIONS

1. The research revealed that the susceptibility of isolates to phages was 40% for *Klebsiella spp.*, 73.3% for *S. aureus*, 50.0% for *E. coli*, and 20.0% for *Pseudomonas spp.* This suggests the potential use of phage therapy in protocols for managing periodontal diseases alongside concurrent maxillofacial pathologies. Strain-specific susceptibility to bacteriophages was determined among isolates resistant to class III antibiotics.
2. The specific susceptibility of strains to bacteriophages necessitates the assessment of the isolate's susceptibility to bacteriophage before initiating treatment for inflammatory oral diseases, including periodontal diseases and maxillofacial pathologies.
3. The application of bacteriophages for inflammatory oral diseases appears promising and warrants further research. Clinical trials and additional scientific investigations are necessary to confirm its safety and effectiveness.

REFERENCES

1. Shlezinger M, Khalifa L, Houri-Haddad Y et al. A New horizon in the antibacterial treatment of oral pathogens. *Curr Top Med Chem.* 2017;17(10):1199-211. doi: 10.2174/1568026616666160930145649. DOI 
2. Rehman S, Ali Z, Khan M et al. The dawn of phage therapy. *Rev Med Virol.* 2019;29(4):e2041. doi: 10.1002/rmv.2041. DOI 
3. Szafranski SP, Slots J, Stiesch M. The human oral phageome. *Periodontol 2000.* 2021;86(1):79-96. doi: 10.1111/prd.12363. DOI 
4. Guo X, Wang X, Shi J et al. A review and new perspective on oral bacteriophages: manifestations in the ecology of oral diseases. *J Oral Microbiol.* 2024;16(1):2344272. doi: 10.1080/20002297.2024.2344272. DOI 
5. Baker JL, Mark Welch JL, Kauffman KM et al. The oral microbiome: diversity, biogeography and human health. *Nat Rev Microbiol.* 2024;22(2):89-104. doi: 10.1038/s41579-023-00963-6. DOI 
6. Figueiredo CM, Malvezzi Karwowski MS, Da Silva Ramos RCP et al. Bacteriophages as tools for biofilm biocontrol in different fields. *Biofouling.* 2021;37(6):689-709. doi: 10.1080/08927014.2021.1955866. DOI 
7. Li X, He Y, Wang Z et al. A combination therapy of phages and antibiotics: two is better than one. *Int J Biol Sci.* 2021;17(13):3573-82. doi: 10.7150/ijbs.60551. DOI 
8. Sanz M, Herrera D, Kebschull M et al. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. *J Clin Periodontol.* 2020;47(22):4-60. doi: 10.1111/jcpe.13290. DOI 
9. Shanmugasundaram S, Nayak N, Puzhankara L et al. Bacteriophages: the dawn of a new era in periodontal microbiology? *Crit Rev Microbiol.* 2024;50(2):212-23. doi: 10.1080/1040841X.2023.2182667. DOI 
10. Steier L, De Oliveira SD, De Figueiredo JAP. Bacteriophages in dentistry-state of the art and perspectives. *Dent J (Basel).* 2019;7(1):6. doi: 10.3390/dj7010006. DOI 
11. Rugg-Gunn A. Dental caries: strategies to control this preventable disease. *Acta Med Acad.* 2013;42(2):117-30. doi: 10.5644/ama2006-124.80. DOI 
12. Yon MJY, Gao SS, Chen KJ et al. Medical model in caries management. *Dent J (Basel).* 2019;7(2):37. doi: 10.3390/dj7020037. DOI 
13. Wolfvoviz-Zilberman A, Kraitman R, Hazan R et al. Phage targeting *Streptococcus mutans* in vitro and in vivo as a caries-preventive modality. *Antibiotics (Basel).* 2021;10(8):1015. doi: 10.3390/antibiotics10081015. DOI 
14. Ben-Zaken H, Kraitman R, Copenhagen-Glazer S et al. Isolation and characterization of *Streptococcus mutans* phage as a possible treatment agent for caries. *Viruses.* 2021;13(5):825. doi: 10.3390/v13050825. DOI 
15. Ramadan A, Abdel-Monem MO, El-DougDoug NK et al. Fully characterized effective bacteriophages specific against antibiotic-resistant *Enterococcus faecalis*, the Causative Agent of Dental Abscess. *Medicina (Kaunas).* 2024;60(3):501. doi: 10.3390/medicina60030501. DOI 
16. García-Solache M, Rice LB. The *Enterococcus*: a model of adaptability to its environment. *Clin Microbiol Rev.* 2019;32(2):e00058-18. doi: 10.1128/CMR.00058-18. DOI 
17. Wong J, Manoil D, Näsman P et al. Microbiological aspects of root canal infections and disinfection strategies: an update review on the current knowledge and challenges. *Front Oral Health.* 2021;2:672887. doi: 10.3389/froh.2021.672887. DOI 
18. El-Telbany M, El-Didamony G, Askora A et al. Bacteriophages to control multi-drug resistant *enterococcus faecalis* infection of dental root canals. *Microorganisms.* 2021;9(3):517. doi: 10.3390/microorganisms9030517. DOI 
19. Dahlen G, Basic A, Bylund J. Importance of virulence factors for the persistence of oral bacteria in the inflamed gingival crevice and in the pathogenesis of periodontal disease. *J Clin Med.* 2019;8(9):1339. doi: 10.3390/jcm8091339. DOI 
20. Hitch G, Pratten J, Taylor PW. Isolation of bacteriophages from the oral cavity. *Lett Appl Microbiol.* 2004;39(2):215-9. doi: 10.1111/j.1472-765X.2004.01565.x. DOI 
21. Kabwe M, Brown TL, Dashper S et al. Genomic, morphological and functional characterisation of novel bacteriophage FNU1 capable of disrupting *Fusobacterium nucleatum* biofilms. *Sci Rep.* 2019;9(1):9107. doi: 10.1038/s41598-019-45549-6. DOI 
22. Abdulkareem A, Abdulbaqi H, Gul S et al. Classic vs. novel antibacterial approaches for eradicating dental biofilm as adjunct to periodontal debridement: An evidence-based overview. *Antibiotics (Basel).* 2021;11(1):9. doi: 10.3390/antibiotics11010009. DOI 
23. Lin J, Du F, Long M, Li P. Limitations of Phage Therapy and Corresponding Optimization Strategies: A Review. *Molecules.* 2022;27(6):1857. doi: 10.3390/molecules27061857. DOI 
24. Pires DP, Costa AR, Pinto G et al. Current challenges and future opportunities of phage therapy. *FEMS Microbiol Rev.* 2020;44(6):684-700. doi: 10.1093/femsre/fuaa017. DOI 
25. Pinto G, Silva MD, Peddey M et al. The role of bacteriophages in periodontal health and disease. *Future Microbiol.* 2016;11:1359-69. doi: 10.2217/fmb-2016-0081. DOI 

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Tetiana Timokhina

Bogomolets National Medical University

13 T. Shevchenko Blvd., 01601 Kyiv, Ukraine

e-mail: tanyatimokhina@gmail.com

ORCID AND CONTRIBUTIONSHIP

Tetiana Timokhina: 0000-0002-0220-0220 **A** **B** **C** **D** **F**

Marina V. Kryvtsova: 0000-0001-8454-2509 **A** **E** **F**

Mykola Y. Spivak: 0000-0002-4394-7275 **E** **F**

Nina S. Proshchenko: 0000-0001-7317-6590 **C**

Alla V. Kharina: 0000-0002-0722-6374 **E**

Oleksandra Bondarenko: 0009-0003-6594-2621 **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: 07.02.2025

ACCEPTED: 28.08.2025



Impact of lifestyle modification interventions on metabolic syndrome and obesity in adults

Svitlana V. Kucher¹, Ulyana O. Mudra¹, Vitalii V. Tkachuk², Mariia M. Ruda¹, Tetiana Yu. Chernets¹, Iryna M. Nikitina³, Volodymyr H. Dzhyvak¹

¹I. YA. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

²ODESA NATIONAL MEDICAL UNIVERSITY, ODESA, UKRAINE

³SUMY STATE UNIVERSITY, SUMY, UKRAINE

ABSTRACT

Aim: The aim of this review article is to provide a comprehensive analysis of the impact of lifestyle interventions – dietary modifications, physical activity, and behavioral strategies – on the management of metabolic syndrome and obesity in adults.

Materials and Methods: This review is based on an analysis of recent studies, systematic reviews, and meta-analyses that investigate the relationship between lifestyle modifications and improvements in MetS and obesity. Sources include peer-reviewed research articles, clinical trials, and public health data on dietary interventions, physical activity, and behavioral strategies. The effectiveness of interventions was assessed through key metabolic parameters such as weight loss, waist circumference reduction, insulin sensitivity, lipid profiles, and cardiovascular health markers.

Conclusions: Lifestyle interventions play a crucial role in managing MetS and obesity by addressing the underlying metabolic dysfunctions and reducing the risk of related diseases, including cardiovascular disease and type 2 diabetes. However, long-term adherence remains a significant challenge. Emerging approaches, such as technology-assisted self-monitoring and group-based programs, offer promising strategies to enhance engagement and effectiveness. Future efforts should focus on scalable, inclusive, and sustainable interventions to reduce the global burden of MetS and obesity.

KEY WORDS: Metabolic syndrome, obesity, lifestyle interventions, Mediterranean diet, time-restricted eating, physical activity

Wiad Lek. 2025;78(9):1857-1865. doi: 10.36740/WLek/212515 DOI

INTRODUCTION

Metabolic syndrome (MetS) and obesity have emerged as escalating global health concerns, contributing significantly to the growing burden of non-communicable diseases (NCDs) such as cardiovascular diseases (CVDs) and type 2 diabetes mellitus (T2DM) [1]. MetS is characterized by a constellation of interrelated conditions, including abdominal obesity, hypertension, dyslipidemia, and insulin resistance, which synergistically amplify the risk of heart disease, stroke, and diabetes [2]. This multifaceted syndrome serves as both a warning sign and a critical target for early intervention to mitigate the progression of NCDs [3]. Obesity is defined as an excessive accumulation of adipose tissue in the body, usually measured by body mass index (BMI). A BMI of ≥ 30 kg/m² is a generally accepted criterion for the diagnosis of obesity. It is a condition that results primarily from an imbalance between energy intake and energy expenditure,

although genetic, endocrine and socioeconomic factors also play an important role [4]. Obesity itself is a risk factor for a number of diseases, including cardiovascular disease, type 2 diabetes, osteoarthritis and certain types of cancer. MetS is characterized by a constellation of interrelated conditions, including abdominal obesity, hypertension, dyslipidemia, and insulin resistance, which synergistically amplify the risk of heart disease, stroke, and diabetes. This multifaceted syndrome serves as both a warning sign and a critical target for early intervention to mitigate the progression of NCDs. The global prevalence of metabolic syndrome has witnessed a sharp increase over the past two decades, now affecting approximately one-quarter of the world's population [5]. This alarming statistic underscores the urgent need for coordinated public health strategies to address the underlying causes and modifiable risk factors. Similarly, obesity, a major driver of MetS – has reached epidemic proportions, with rising

trends observed across all regions, age groups, and socioeconomic strata [6]. For example, data from England illustrate the pervasive nature of this issue. Recent studies reveal that eight out of ten men aged 55 to 64 are classified as overweight or obese, with body mass index (BMI) measurements exceeding healthy thresholds [7]. This demographic trend reflects broader patterns of sedentary lifestyles, increased caloric intake, and the widespread availability of ultra-processed foods, all of which contribute to the global surge in obesity rates.

The financial burden associated with MetS and obesity is both substantial and far-reaching, reflecting their widespread prevalence and the complexity of managing related health conditions. In the United States, the economic impact of obesity alone has reached staggering proportions, with obesity-related medical costs estimated at \$173 billion annually as of 2019 [8]. The economic ramifications of MetS and obesity are similarly profound in Europe, with significant healthcare expenditures attributed to these conditions. In Germany, the healthcare costs associated with MetS in patients with hypertension were estimated at €24.4 billion, reflecting the high prevalence of hypertension as a key component of MetS. In Spain, the economic burden of MetS-related healthcare was calculated at €1.9 billion, highlighting the strain on the national healthcare system. Italy reported healthcare costs of €4.9 billion attributable to MetS, with projections suggesting continued growth in expenditures due to the rising prevalence of obesity and related metabolic disorders [9].

Individuals with metabolic syndrome and obesity are at markedly elevated risks of developing numerous serious and potentially life-threatening health conditions [10,11]. These risks are particularly pronounced in individuals with an «apple-shaped» body, where fat is predominantly stored in the abdominal region. This pattern of fat distribution, known as central or visceral obesity, is strongly associated with metabolic disturbances and systemic inflammation, which underlie the development of various diseases. Research shows that people with apple-shaped bodies – those with a wider midsection and less defined waist – face a higher risk of serious health problems compared to their pear-shaped counterparts, who tend to carry excess weight in the hips, buttocks and thighs. Findings from systematic review and meta-analysis Ahmad Jayedi et al. (2020) support the assertion that individuals with an “apple shape” (central obesity) have a higher risk of all-cause mortality compared to those with a “pear shape.” [12].

Given the rising prevalence and substantial economic and health burdens of MetS and obesity, there is an urgent need for effective strategies to mitigate these

conditions [13]. Lifestyle interventions, including dietary modifications, physical activity, and behavioral changes, are critical components in the prevention and management of MetS and obesity.

Dietary interventions play a key role in the fight against metabolic syndrome and obesity, with certain dietary patterns showing significant health benefits. Among these, the Mediterranean diet has been widely studied and consistently associated with positive outcomes, including weight loss, reduced body fat, and reduced risk of non-communicable diseases such as type 2 diabetes and cardiovascular disease. The Mediterranean diet is characterized by a high intake of fruits, vegetables, whole grains, legumes, nuts, and olive oil; moderate consumption of fish and poultry; and limited intake of red meat and processed foods. Its unique composition provides a balance of monounsaturated fats, fiber, antioxidants, and anti-inflammatory nutrients [14]. Research highlights the effectiveness of the Mediterranean diet in managing obesity and metabolic disorders [15]. For example, the PREDIMED trial demonstrated that individuals adhering to the Mediterranean diet supplemented with extra virgin olive oil or nuts experienced a significant reduction in the risk of major cardiovascular events. The mechanisms of action include the diet's ability to improve insulin sensitivity and reduce systemic inflammation. Olive oil and nuts provide monounsaturated fats, which lower LDL cholesterol and increase HDL cholesterol. Dietary fiber from fruits and whole grains promotes satiety and supports gut health, which can contribute to weight loss and the prevention of insulin resistance. Additionally, Sandra Martín-Peláez et al. (2020) found that the Mediterranean diet significantly reduces the risk of type 2 diabetes in individuals at high risk [16]. The long-term sustainability of the Mediterranean diet makes it particularly effective for lifestyle interventions targeting MetS and obesity. Its palatability and cultural adaptability increase adherence rates, which are critical for achieving meaningful health improvements.

Regular physical activity offers numerous health benefits and is a crucial tool in combating obesity and its associated comorbidities, including cardiovascular diseases. Engaging in consistent exercise not only prevents the onset and progression of cardiovascular disease but also serves as an effective therapeutic strategy to enhance outcomes for patients already diagnosed with such conditions. The American College of Cardiology and the American Heart Association recommend that adults engage in at least 150 minutes per week of moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity to achieve and maintain weight loss and improve

cardiovascular health [17]. Moreover, studies have demonstrated that regular physical exercise can lower blood pressure, improve lipid profiles, and enhance insulin sensitivity, thereby reducing the risk of developing type 2 diabetes and other metabolic disorders. For instance, a systematic review published in the *British Journal of Sports Medicine* found that higher levels of cardiorespiratory fitness are associated with a lower risk of all-cause mortality, regardless of body weight [18]. Incorporating physical activity into daily routines, such as walking, cycling, or resistance training, can significantly contribute to weight management and overall health. Health organizations emphasize the importance of combining cardiovascular exercises with resistance training to improve heart and lung health, reduce the risk of chronic diseases, and enhance longevity.

Comprehensive lifestyle interventions that integrate diet, exercise, and behavioral modifications have demonstrated significant improvements in metabolic parameters among individuals with metabolic syndrome (MetS). A systematic review and meta-analysis published in *Reviews in Endocrine and Metabolic Disorders* evaluated the efficacy of education-based lifestyle intervention programs incorporating unsupervised exercise. The study found that such interventions led to reductions in waist circumference and improvements in quality of life among adults with MetS. Specifically, the meta-analysis Casey L. Peiris et al. (2021) revealed that lifestyle intervention programs with unsupervised exercise reduced waist circumference by an average of 2.82 cm and improved physical activity levels when compared to usual care. Additionally, there was evidence suggesting enhancements in quality of life metrics, indicating the holistic benefits of these interventions [19].

Despite the documented benefits, several challenges persist in implementing lifestyle interventions such as maintaining long-term adherence to lifestyle changes remains a significant hurdle. Factors influencing adherence include individual motivation, socioeconomic status, and cultural influences.

Emerging trends in lifestyle interventions for MetS and obesity focus on enhancing effectiveness and feasibility through alternative approaches such as integration of technology, including mobile applications and wearable devices, is being explored to support behavior change and monitor progress. A study in *Diagnostics* examined the utility of digital health-based lifestyle interventions using healthcare devices for the prevention and management of MetS. The findings suggest that these tools can effectively aid in self-care by promoting lifestyle changes and sustained health improvements [20].

AIM

The aim of this review article is to provide a comprehensive analysis of the impact of lifestyle interventions – dietary modifications, physical activity, and behavioral strategies – on the management of metabolic syndrome and obesity in adults.

MATERIALS AND METHODS

A systematic review and literature analysis were conducted using leading scientific databases, including PubMed, Scopus, and Google Scholar, to provide a deeper understanding of the current state of research on metabolic syndrome (MetS) and obesity in adults and to identify the most evidence-based scientific data. Preference was given to systematic reviews, clinical trials, and analytical articles published in English in peer-reviewed journals. Inclusion criteria encompassed studies investigating the causes or consequences of MetS and obesity, scientific works addressing medical, metabolic, and socioeconomic factors and outcomes, research involving adult populations (aged 18 years and older), and publications from peer-reviewed sources. Studies were excluded if they focused solely on pediatric populations, did not address MetS or obesity, or were published in non-peer-reviewed outlets. The search was performed using the following keywords and their combinations: «metabolic syndrome,» «obesity,» «lifestyle interventions,» «Mediterranean diet,» «time-restricted eating,» «physical activity and metabolic health,» «insulin resistance,» «visceral obesity,» «cardiovascular disease risk,» and «economic burden of obesity.» Data were systematically collected, evaluated, and synthesized to assess the prevalence, pathophysiological mechanisms, health impacts, economic consequences, and efficacy of lifestyle interventions (dietary modifications, physical activity, and behavioral strategies) in managing MetS and obesity, ensuring a comprehensive analysis supported by high-quality evidence.

REVIEW AND DISCUSSION

Metabolic syndrome and obesity are closely intertwined, sharing several pathophysiological mechanisms that contribute to their mutual development and associated health risks. Obesity, particularly visceral adiposity, plays a pivotal role in the development of insulin resistance – a key feature of MetS. Excess adipose tissue increases the release of free fatty acids and pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), which impair insulin signaling pathways. This impairment

disrupts glucose homeostasis, leading to hyperglycemia and significantly increasing the risk of type 2 diabetes. Studies Herbert Tilg & Alexander R. Moschen (2008) and Federica Zatterale et al. (2020) have highlighted these mechanisms and their central role in MetS pathophysiology [21,22]. Adipose tissue in obese individuals often exhibits a state of chronic, low-grade inflammation. This is characterized by increased secretion of pro-inflammatory cytokines like TNF- α and IL-6, as well as activation of macrophages within the adipose tissue [23]. These inflammatory mediators exacerbate insulin resistance, promote endothelial dysfunction, and contribute to atherosclerotic plaque formation, thereby increasing the risk of cardiovascular complications associated with MetS [24]. Obesity is closely linked to dyslipidemia, characterized by elevated triglycerides, increased levels of small dense LDL particles, and reduced HDL cholesterol. These lipid abnormalities are hallmark components of MetS and significantly heighten the risk of cardiovascular diseases. Additionally, obesity-related mechanisms, including insulin resistance and inflammation, contribute to the development of hypertension. This is mediated through pathways such as increased sympathetic nervous system activity, activation of the renin – angiotensin – aldosterone system (RAAS), and altered vascular function. Collectively, dyslipidemia and hypertension amplify cardiovascular risk in individuals with obesity and MetS [25,26].

Mediterranean diet (MD), emphasizing fruits, vegetables, whole grains, and healthy fats, has been extensively studied for its beneficial effects on metabolic health. A systematic review and meta-analysis Papadaki, A. et al. (2020) examined the MD's impact on MetS incidence and components. The study concluded that adherence to the MD significantly reduced the risk of developing MetS and improved related risk factors, including waist circumference and lipid profiles [27]. Further supporting these findings, a systematic review Katherine Esposito et al. (2013) in analyzed data from various studies and confirmed that the MD is associated with a lower prevalence of MetS. The review highlighted that the MD's emphasis on monounsaturated fats, fiber, and antioxidants contributes to its protective effects against MetS components [28].

Time-restricted eating (TRE), a form of intermittent fasting, has shown promising benefits in weight loss and metabolic health, making it a compelling intervention for managing metabolic syndrome and obesity. TRE involves limiting food intake to a specific time window, often 8-10 hours, while fasting for the remainder of the day [29]. This approach aligns eating patterns with the body's circadian rhythms, optimizing metabolic processes. Mechanisms of action include improved in-

sulin sensitivity, reduced abdominal fat, and enhanced circadian rhythm regulation. TRE promotes extended fasting periods that lower insulin levels, encouraging fat utilization for energy. This is particularly effective in reducing visceral fat, which is strongly associated with MetS and cardiovascular diseases. Additionally, TRE helps stabilize glucose levels and improves insulin signaling, addressing key aspects of metabolic dysfunction. Kelsey Gabel et al. (2018) evaluated the effects of an 8-hour time-restricted feeding (TRF) regimen (eating only between 10:00 AM and 6:00 PM) over 12 weeks in 23 obese adults [30]. Compared to a historical control group, the TRF group experienced modest weight loss (-2.6% body weight), reduced calorie intake (-341 kcal/day), and decreased systolic blood pressure (-7 mm Hg). The findings suggest that TRF may aid weight loss and improve blood pressure without the need for calorie counting.

Humaira Jamshed et al. (2022) randomized clinical trial compared early time-restricted eating (eTRE; an 8-hour eating window from 7:00 AM to 3:00 PM) to eating over a period of 12 or more hours (control) for weight loss and fat loss in 90 adults with obesity. At 14 weeks, eTRE led to greater weight loss (-6.3 kg vs. -4.0 kg) but did not significantly enhance fat loss overall, though secondary analysis showed benefits in completers. eTRE also reduced diastolic blood pressure and improved mood (reduced fatigue and depression, increased vigor). No significant differences were observed in most fasting cardiometabolic markers. The study highlights eTRE's potential for weight loss and hypertension management, suggesting larger trials are needed to evaluate effects on fat loss and metabolic health [31]. In addition to weight loss and metabolic benefits, TRE has been associated with improved cardiovascular health, including lower blood pressure and triglyceride levels, as well as reduced inflammation markers such as CRP and IL-6. TRE also supports gut health by promoting microbial diversity and enhancing digestion during active hours, while better alignment with circadian rhythms improves sleep quality. TRE is a flexible and sustainable intervention, popular schedules, such as 16:8, 14:10, and 12:12, can be tailored to individual preferences, making it accessible to a broad population.

Engaging in regular physical activity, encompassing both aerobic and resistance exercises, plays a crucial role in enhancing insulin sensitivity and facilitating weight management. Aerobic exercises, such as cycling, have been shown to significantly improve metabolic health. For instance, a study conducted by the University of Aberdeen found that sedentary middle-aged men who participated in regular cycling for one hour a day, five days a week, experienced notable improvements

in metabolic health and an average weight loss of 2.6 kg over eight weeks. Research by Stephen R. Baird and John A. Hawley (2017) confirms that physical activity (PA) and exercise improve insulin sensitivity (IS) and glycaemic control in a variety of populations, including healthy individuals, people with metabolic syndrome (MS), prediabetes or type 2 diabetes (T2D). Moderate aerobic exercise (≥ 30 minutes, 3-5 days per week) and high-intensity interval training (HIIT) are both effective, with HIIT potentially offering similar or greater benefits with less time commitment. Resistance training (REX) also improves SI, especially when combined with aerobic exercise. The benefits of exercise on SI often occur independently of weight loss and are associated with molecular changes, such as increased GLUT4 and improved skeletal muscle capillarity [32]. This systematic review and meta-analysis Anna K. Jansson et al. (2022) examined the effects of resistance training (RT) on glycosylated hemoglobin (HbA1c) in adults with type 2 diabetes mellitus (T2DM) across 20 randomized controlled trials (n=1172) [33]. RT significantly reduced HbA1c levels compared to control groups (weighted mean difference = -0.39% , $p < 0.001$), demonstrating its effectiveness in glycemic control. Improvements in muscular strength were associated with greater reductions in HbA1c, highlighting the importance of strength gains in RT programs. No significant differences were found between RT and aerobic training in reducing HbA1c, suggesting both are effective. Intervention duration (8-52 weeks) did not significantly influence HbA1c reduction, indicating similar benefits from shorter and longer programs. Supervised RT programs had better adherence and outcomes, but variability in RT protocols (frequency, intensity, type of exercises) underscores the need for standardized approaches. In conclusion, RT is an effective strategy to reduce HbA1c in T2DM, particularly when it results in strength improvements. Fiona C Bull et al. (2020) in their article 'World Health Organisation 2020 guidelines on physical activity and sedentary behaviour' emphasise the importance of regular aerobic physical activity and physical activity aimed at strengthening muscles, as well as reducing sedentary behaviour. All physical activity is beneficial, and this applies to people of all ages and abilities. Their recommendation is that all adults should do 150-300 minutes of moderate-intensity physical activity or 75-150 minutes of vigorous-intensity physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity per week [34].

Maintaining the benefits of lifestyle interventions for metabolic syndrome (MetS) and obesity necessitates ongoing effort and strategic approaches, regular follow-ups and support systems are crucial for sustaining

lifestyle changes. Group-based programs have been shown to be effective in providing social support and accountability, which are essential for long-term adherence. The article by Muhammad Daniel Azlan Mahadzir et al. (2021) focused on group interventions aimed at lifestyle change as a strategy for the prevention and management of metabolic syndrome [35]. The study performed a scoping review of existing interventions to assess their effectiveness and provide a strategic framework for future research in this area. It analyses three main intervention designs: randomised controlled trials, pre- and post-test interventions, and quasi-experiments. The interventions were predominantly multicomponent, focused on nutrition, physical activity and behaviour change, and involved multidisciplinary teams of health professionals and peer educators. Most significant improvements were seen in waist circumference, followed by blood pressure. Research highlights the role of social support and group interaction in increasing motivation, sharing experiences and achieving sustainable lifestyle changes. It concludes that group interventions can be a practical and cost-effective approach to reducing MetS-related risks and calls for more systematic evaluations to better understand the long-term impact of such programmes.

This article Maria Letizia Petroni et al. (2023) explores the long-term impact of lifestyle interventions on diabetes incidence among individuals with non-alcoholic fatty liver disease (NAFLD) [36]. It compares two approaches: a traditional group-based intervention (GBI) and a web-based intervention (WBI). Both methods aimed to promote weight loss and healthier lifestyles, focusing on their effectiveness in preventing diabetes over a five-year period. NAFLD, a prevalent condition linked to obesity and type 2 diabetes, often progresses to severe liver diseases and associated comorbidities. Given the challenges of maintaining adherence to traditional in-person programs, the study investigates whether WBI could serve as a viable alternative to GBI, providing more flexibility while maintaining comparable outcomes. The research followed 546 individuals with NAFLD, excluding those with diabetes at enrollment, and tracked their progress through regular clinical assessments. The results showed that both interventions achieved similar reductions in average body weight and improvements in lifestyle behaviors. The incidence of diabetes during the follow-up was influenced primarily by baseline prediabetes and the degree of weight loss, rather than the type of intervention. Weight loss emerged as a key factor in reducing diabetes risk, demonstrating the effectiveness of lifestyle modification regardless of the delivery method. The study highlights the potential of web-based inter-

ventions to expand access to behavioral treatment for NAFLD and reduce healthcare costs. While both GBI and WBI showed promise, differences in participant demographics, attrition rates, and follow-up duration were noted, suggesting that these approaches may cater to distinct populations. The findings emphasize the importance of weight management and tailored strategies to improve long-term health outcomes in individuals.

Integrating healthy habits into daily life enhances well-being and increases the likelihood of sustaining these behaviors long-term. Establishing achievable objectives is crucial for maintaining motivation and ensuring progress. Utilizing the SMART criteria – Specific, Measurable, Achievable, Relevant, and Time-bound – can aid in formulating effective goals. For instance, instead of aiming to “exercise more,” commit to “walking for 30 minutes, three times a week”.

Self-monitoring is a cornerstone strategy for managing obesity and achieving sustainable weight loss. By tracking dietary intake, physical activity, and weight, patients can gain insights into their behaviors and make informed adjustments. Regular self-monitoring not only enhances accountability but also helps identify patterns that contribute to unhealthy habits, making it a valuable tool in obesity management. Keeping a food diary is one of the most effective ways to monitor caloric intake and food choices. Patients can log meals, portion sizes, and emotional triggers that influence eating behaviors. Studies show that consistent journaling is associated with greater weight loss outcomes. Mobile apps, such as MyFitnessPal or Loselt, provide user-friendly platforms for tracking food intake, activity levels, and weight. Many apps offer features like barcode scanning, nutrient breakdowns, and personalized goals, making them practical tools for daily use. A study Michele L. Patel et al. (2019) demonstrated that individuals using a mobile app for self-monitoring lost significantly more weight compared to those using traditional methods [37].

The intertwined epidemics of metabolic syndrome and obesity continue to challenge global health systems, revealing a complex interplay of biology, behavior, and environment that defies simple solutions [38]. While lifestyle interventions have emerged as a cornerstone of management, their broader implications invite a deeper exploration of how these conditions reflect – and are shaped by – evolving societal dynamics [39]. This discussion ventures beyond established evidence to consider untapped opportunities, emerging paradigms, and the transformative potential of integrating interdisciplinary approaches to address these pervasive health threats. One intriguing dimension is the role of the gut-brain axis in modulating the

progression of MetS and obesity. Recent advances in neuroscience suggest that the bidirectional communication between the gastrointestinal tract and the central nervous system influences not only appetite regulation but also systemic inflammation and stress responses – key contributors to metabolic dysfunction [40]. Fermented foods, rich in probiotics, and prebiotic fibers are gaining attention for their potential to recalibrate gut microbiota, reducing the inflammatory cascade that exacerbates visceral fat accumulation [41,42]. Unlike traditional dietary interventions, which focus on macronutrient balance, this approach targets microbial ecology as a leverage point, offering a novel avenue for intervention that could complement existing strategies. The psychological benefits – such as reduced stress and improved mood – may further enhance adherence, addressing a critical gap in long-term behavior change. Another underexplored frontier is the impact of sleep architecture on metabolic health [43]. Emerging research indicates that disrupted circadian rhythms, driven by irregular sleep patterns or excessive exposure to artificial light, amplify insulin resistance and fat storage, independent of diet or activity levels. In a world increasingly dominated by 24/7 connectivity and shift work, restoring sleep hygiene could emerge as a low-cost, high-impact intervention [44,45]. Techniques such as chronotherapy – aligning eating and activity with natural light cycles – might amplify the benefits of dietary and exercise regimens, creating a holistic framework that synchronizes metabolic processes with environmental cues [46]. This perspective shifts the focus from isolated behaviors to the orchestration of daily rhythms, potentially redefining how we approach prevention and management. The advent of wearable technology and ambient intelligence offers a radical rethinking of how lifestyle interventions are delivered and monitored [47].

Beyond tracking steps or calories, next-generation devices could measure real-time biomarkers – such as glucose fluctuations, cortisol levels, or even inflammatory markers – providing immediate feedback to users and clinicians. Imagine a smart home system that adjusts lighting to optimize sleep, prompts movement during sedentary periods, or suggests meals based on metabolic needs detected through skin sensors. Such innovations could transform passive interventions into dynamic, adaptive systems, empowering individuals to respond proactively to their body's signals. However, this technological leap raises ethical questions about data privacy and the risk of over-reliance on automation, potentially undermining intrinsic motivation. Social connectivity, often overlooked in metabolic health discussions, may hold untapped potential for

amplifying intervention success. The rise of virtual communities – fueled by social media and gaming platforms – offers a new paradigm for fostering accountability and motivation. Gamified health challenges, where participants compete or collaborate to meet fitness or dietary goals, could harness the power of peer influence in ways that traditional group programs cannot. This approach aligns with the growing trend of «social prescribing,» where healthcare providers connect patients to community resources to combat isolation, a known risk factor for obesity-related behaviors. By reframing health as a collective endeavor rather than an individual burden, such strategies could reshape cultural attitudes toward lifestyle change, particularly in younger demographics increasingly detached from conventional healthcare systems.

The environmental context of MetS and obesity also warrants a bold reimagination. Climate change, with its cascading effects on food security and physical activity patterns, introduces a new layer of complexity. Rising temperatures and extreme weather may discourage outdoor exercise, while disruptions to agricultural systems could limit access to nutrient-dense foods, pushing reliance on shelf-stable, processed alternatives. Conversely, the push for sustainability – through plant-based diets or reduced meat consumption – aligns serendipitously with metabolic health goals, offering a dual benefit for individuals and the planet. Public health campaigns could capitalize on this synergy,

framing lifestyle interventions as both a personal and ecological imperative, potentially galvanizing broader societal support.

CONCLUSIONS

Lifestyle interventions play a pivotal role in managing metabolic syndrome and obesity, addressing the root causes of these conditions and reducing the risk of related complications, including cardiovascular disease and type 2 diabetes. Dietary changes, such as the Mediterranean diet, combined with regular physical activity and behavioral support, have consistently shown significant improvements in metabolic health and weight management. However, adherence remains a major challenge, influenced by socioeconomic factors, cultural norms, and individual motivation. Emerging strategies, such as the use of digital tools, personalized approaches, and community-based programs, show promise in overcoming these barriers and enhancing the effectiveness of lifestyle modifications. To reduce the global burden of MetS and obesity, future efforts must prioritize the development of sustainable, scalable, and inclusive interventions that integrate into daily life and address health disparities. Through collaboration between healthcare providers, researchers, and policymakers, it is possible to create effective solutions for these pressing health challenges.

REFERENCES

1. Chowdhury K, Sinha S, Ahmad R et al. Type 2 Diabetes Mellitus and Cardiometabolic Prospects: A Rapid Narrative Review. *Cureus*. 2024;16(7):e65808. doi: 10.7759/cureus.65808. DOI
2. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis*. 2017;11(8):215-225. doi: 10.1177/1753944717711379. DOI
3. Budreviciute A, Damiani S, Sabir DK et al. Management and Prevention Strategies for Non-communicable Diseases (NCDs) and Their Risk Factors. *Front Public Health*. 2020;8:574111. doi: 10.3389/fpubh.2020.574111. DOI
4. Schwartz MW, Seeley RJ, Zeltser LM et al. Obesity Pathogenesis: An Endocrine Society Scientific Statement. *Endocr Rev*. 2017;38(4):267-296. doi: 10.1210/er.2017-00111. DOI
5. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep*. 2018;20(2):12. doi: 10.1007/s11906-018-0812-z. DOI
6. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep*. 2018;20(2):12. doi: 10.1007/s11906-018-0812-z. DOI
7. Nuttall FQ. Body Mass Index: Obesity, BMI, and Health: A Critical Review. *Nutr Today*. 2015;50(3):117-128. doi: 10.1097/NT.0000000000000092. DOI
8. Cawley J, Biener A, Meyerhoefer C et al. Direct medical costs of obesity in the United States and the most populous states. *J Manag Care Spec Pharm*. 2021;27(3):354-366. doi: 10.18553/jmcp.2021.20410. DOI
9. Scholze J, Alegria E, Ferri C et al. Epidemiological and economic burden of metabolic syndrome and its consequences in patients with hypertension in Germany, Spain and Italy; a prevalence-based model. *BMC Public Health*. 2010;10:529. doi: 10.1186/1471-2458-10-529. DOI
10. Pi-Sunyer X. The medical risks of obesity. *Postgrad Med*. 2009;121(6):21-33. doi: 10.3810/pgm.2009.11.2074. DOI
11. Fruh SM. Obesity: Risk factors, complications, and strategies for sustainable long-term weight management. *J Am Assoc Nurse Pract*. 2017;29(S1):S3-S14. doi: 10.1002/2327-6924.12510. DOI

12. Jayedi A, Soltani S, Zargar MS et al. Central fatness and risk of all cause mortality: systematic review and dose-response meta-analysis of 72 prospective cohort studies. *BMJ*. 2020;370:m3324. doi: 10.1136/bmj.m3324. DOI
13. Chong KS, Chang YH, Yang CT et al. Longitudinal economic burden of incident complications among metabolic syndrome populations. *Cardiovasc Diabetol*. 2024;23(1):246. doi: 10.1186/s12933-024-02335-7. DOI
14. Estruch R, Ros E, Salas-Salvadó J et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med*. 2018;378(25):e34. doi: 10.1056/NEJMoa1800389. DOI
15. Muscogiuri G, Verde L, Sulu C et al. Mediterranean Diet and Obesity-related Disorders: What is the Evidence? *Curr Obes Rep*. 2022;11(4):287-304. doi: 10.1007/s13679-022-00481-1. DOI
16. Martín-Peláez S, Fito M, Castaner O. Mediterranean Diet Effects on Type 2 Diabetes Prevention, Disease Progression, and Related Mechanisms. A Review. *Nutrients*. 2020;12(8):2236. doi: 10.3390/nu12082236. DOI
17. Arnett DK, Blumenthal RS, Albert MA et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e563-e595. doi: 10.1161/CIR.0000000000000677. DOI
18. Weeldreyer NR, De Guzman JC, Paterson C et al. Cardiorespiratory fitness, body mass index and mortality: a systematic review and meta-analysis. *Br J Sports Med*. 2025;59(5):339-346. doi: 10.1136/bjsports-2024-108748. DOI
19. Peiris CL, van Namen M, O'Donoghue G. Education-based, lifestyle intervention programs with unsupervised exercise improve outcomes in adults with metabolic syndrome. A systematic review and meta-analysis. *Rev Endocr Metab Disord*. 2021;22(4):877-890. doi: 10.1007/s11154-021-09644-2. DOI
20. Lee JH, Lee KH, Kim HJ et al. Effective Prevention and Management Tools for Metabolic Syndrome Based on Digital Health-Based Lifestyle Interventions Using Healthcare Devices. *Diagnostics (Basel)*. 2022;12(7):1730. doi: 10.3390/diagnostics12071730. DOI
21. Tilg H, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. *Mol Med*. 2008;14(3-4):222-31. doi: 10.2119/2007-00119.Tilg. DOI
22. Zatterale F, Longo M, Naderi J et al. Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Front Physiol*. 2020;10:1607. doi: 10.3389/fphys.2019.01607. DOI
23. Kim JA, Choi KM. Newly Discovered Adipokines: Pathophysiological Link Between Obesity and Cardiometabolic Disorders. *Front Physiol*. 2020;11:568800. doi: 10.3389/fphys.2020.568800. DOI
24. McArdle MA, Finucane OM, Connaughton RM et al. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. *Front Endocrinol (Lausanne)*. 2013;4:52. doi: 10.3389/fendo.2013.00052. DOI
25. Shariq OA, McKenzie TJ. Obesity-related hypertension: a review of pathophysiology, management, and the role of metabolic surgery. *Gland Surg*. 2020;9(1):80-93. doi: 10.21037/gs.2019.12.03. DOI
26. Islam MS, Wei P, Suzaudulla M et al. The interplay of factors in metabolic syndrome: understanding its roots and complexity. *Mol Med*. 2024;30(1):279. doi: 10.1186/s10020-024-01019-y. DOI
27. Papadaki A, Nolen-Doerr E, Mantzoros CS. The Effect of the Mediterranean Diet on Metabolic Health: A Systematic Review and Meta-Analysis of Controlled Trials in Adults. *Nutrients*. 2020;12(11):3342. doi: 10.3390/nu12113342. DOI
28. Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Mediterranean diet and metabolic syndrome: an updated systematic review. *Rev Endocr Metab Disord*. 2013;14(3):255-63. doi: 10.1007/s11154-013-9253-9. DOI
29. Kim J, Song Y. Early Time-Restricted Eating Reduces Weight and Improves Glycemic Response in Young Adults: A Pre-Post Single-Arm Intervention Study. *Obes Facts*. 2023;16(1):69-81. doi: 10.1159/000527838. DOI
30. Gabel K, Hoddy KK, Haggerty N et al. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. *Nutr Healthy Aging*. 2018;4(4):345-353. doi: 10.3233/NHA-170036. DOI
31. Jamshed H, Steger FL, Bryan DR et al. Effectiveness of Early Time-Restricted Eating for Weight Loss, Fat Loss, and Cardiometabolic Health in Adults With Obesity: A Randomized Clinical Trial. *JAMA Intern Med*. 2022;182(9):953-962. doi: 10.1001/jamainternmed.2022.3050. DOI
32. Bird SR, Hawley JA. Update on the effects of physical activity on insulin sensitivity in humans. *BMJ Open Sport Exerc Med*. 2017;2(1):e000143. doi: 10.1136/bmjsem-2016-000143. DOI
33. Jansson AK, Chan LX, Lubans DR et al. Effect of resistance training on HbA1c in adults with type 2 diabetes mellitus and the moderating effect of changes in muscular strength: a systematic review and meta-analysis. *BMJ Open Diabetes Res Care*. 2022;10(2):e002595. doi: 10.1136/bmjdr-2021-002595. DOI
34. Bull FC, Al-Ansari SS, Biddle S et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54(24):1451-1462. doi: 10.1136/bjsports-2020-102955. DOI
35. Mahadzir MDA, Quek KF, Ramadas A. Group-Based Lifestyle Intervention Strategies for Metabolic Syndrome: A Scoping Review and Strategic Framework for Future Research. *Medicina (Kaunas)*. 2021;57(11):1169. doi: 10.3390/medicina57111169. DOI
36. Petroni ML, Brodosi L, Armandi A et al. Lifestyle Intervention in NAFLD: Long-Term Diabetes Incidence in Subjects Treated by Web- and Group-Based Programs. *Nutrients*. 2023;15(3):792. doi: 10.3390/nu15030792. DOI

37. Patel ML, Hopkins CM, Brooks TL, Bennett GG. Comparing Self-Monitoring Strategies for Weight Loss in a Smartphone App: Randomized Controlled Trial. *JMIR Mhealth Uhealth*. 2019;7(2):e12209. doi: 10.2196/12209. DOI 
38. Clemente-Suárez VJ, Martín-Rodríguez A, Redondo-Flórez L et al. New Insights and Potential Therapeutic Interventions in Metabolic Diseases. *Int J Mol Sci*. 2023;24(13):10672. doi: 10.3390/ijms241310672. DOI 
39. Kirkbride JB, Anglin DM, Colman I et al. The social determinants of mental health and disorder: evidence, prevention and recommendations. *World Psychiatry*. 2024;23(1):58-90. doi: 10.1002/wps.21160. DOI 
40. Prodan A, Dzhyvak V. Bariatric surgery impact upon oxidative stress markers. *East Ukr Med J*. 2023;11(4):453-60. doi:10.21272/eumj.2023;11(4):453-460. DOI 
41. Leeuwendaal NK, Stanton C, O'Toole PW, Beresford TP. Fermented Foods, Health and the Gut Microbiome. *Nutrients*. 2022;14(7):1527. doi: 10.3390/nu14071527. DOI 
42. Valentino V, Magliulo R, Farsi D et al. Fermented foods, their microbiome and its potential in boosting human health. *Microb Biotechnol*. 2024;17(2):e14428. doi: 10.1111/1751-7915.14428. DOI 
43. Dejenie TA, G/Medhin MT, Admasu FT et al. Impact of objectively-measured sleep duration on cardiometabolic health: A systematic review of recent evidence. *Front Endocrinol (Lausanne)*. 2022;13:1064969. doi: 10.3389/fendo.2022.1064969. DOI 
44. Meléndez-Fernández OH, Liu JA, Nelson RJ. Circadian Rhythms Disrupted by Light at Night and Mistimed Food Intake Alter Hormonal Rhythms and Metabolism. *Int J Mol Sci*. 2023;24(4):3392. doi: 10.3390/ijms24043392. DOI 
45. Duez H, Staels B. Circadian Disruption and the Risk of Developing Obesity. *Curr Obes Rep*. 2025;14(1):20. doi: 10.1007/s13679-025-00610-6. DOI 
46. Franzago M, Alessandrelli E, Notarangelo S et al. Chrono-Nutrition: Circadian Rhythm and Personalized Nutrition. *Int J Mol Sci*. 2023;24(3):2571. doi: 10.3390/ijms24032571. DOI 
47. Dzhyvak VH, Klishch IM, Khlibovska OI, Levenets SS. Potentials and impact of platelet-rich plasma (PRP) on the regenerative properties of muscle tissue. *Biopolymers Cell*. 2024;40(1):3-13. doi:10.7124/bc.000AA9. DOI 

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Volodymyr H. Dzhyvak

Ivan Horbachevsky Ternopil National Medical University
1 Voli Square, 46001 Ternopil, Ukraine
e-mail: djyvak@tdmu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Svitlana V. Kucher: 0000-0003-1026-9567    

Ulyana O. Mudra: 0000-0001-8160-4962  

Vitalii V. Tkachuk: 0000-0002-8323-5467 

Mariia M. Ruda: 0000-0002-5407-3315  

Tetiana Yu. Chernets: 0000-0001-7575-8391 

Iryna M. Nikitina: 0000-0001-6595-2502  

Volodymyr H. Dzhyvak: 0000-0002-4885-7586   

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 16.05.2025

ACCEPTED: 29.08.2025



Pseudoexfoliation syndrome: modern concepts of morphological and clinical manifestations, classification and treatment

Volodymyr O. Melnyk^{1,2}, Borys I. Palamar¹

¹BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

²LLC «VISIOBUD CLINIC», KYIV, UKRAINE

ABSTRACT

Aim: To develop an updated and refined classification of pseudoexfoliation syndrome (PEX) in the context of its complication by pseudoexfoliation glaucoma (PEXG), taking into account the current understanding of the morphological and clinical criteria of PEX and its treatment methods.

Materials and Methods: The study analyzed and systematized the scientific publications regarding the modern understanding of PEX and PEXG from PubMed and Scopus databases. The publications analyzed mainly for the period 2015–2024 concerned existing classifications of PEX, as well as descriptions of PEX and PEXG symptoms, and surgical methods of their treatment. Analytical and bibliographic methods were employed.

Conclusions: A comprehensive approach is required for the clear identification of PEX signs and early diagnosis of PEXG. Involvement of all tissues of the anterior segment leads to a range of intraocular complications that are significant for the treatment strategy. PEX is not designated as a separate nosological entity in the International Classification of Diseases; however, several classifications of PEX exist, none of which are used in practice. We propose an original classification of PEX that takes into account morphological and clinical changes of the anterior segment of the eye (the pattern of pseudoexfoliative material distribution, pupil diameter, degree of iridodonesis and phacodonesis, presence of lens or intraocular lens dislocation) and simultaneously implies the appropriate surgical intervention.

Careful monitoring of PEX symptoms is necessary to prevent complications and to ensure timely initiation of appropriate medical and surgical glaucoma treatment, taking into account the risk of operative complications. The developed, modern, improved classification of PEX can be used in the training and clinical practice of ophthalmologists.

KEY WORDS: ophthalmology, pseudoexfoliation syndrome, glaucoma, classification, treatment

Wiad Lek. 2025;78(9):1866–1873. doi: 10.36740/WLek/212521 DOI

INTRODUCTION

Pseudoexfoliation is a complex, progressive, systemic age-related disorder. The early stage of extracellular fibrillar material deposition on ocular and extraocular tissues is referred to as pseudoexfoliation syndrome (PEX). The severe advanced stage of this syndrome is known as pseudoexfoliation glaucoma (PEXG), which manifests with elevated intraocular pressure (IOP) and optic nerve damage [1]. As early as 1987 it was recognized that PEX is common and possibly responsible for a larger proportion of glaucoma cases than previously thought [2]. It is estimated that PEX may occur in 10–20% of the global population over 60 years old (approximately 70 million people). The prevalence of PEX is increasing worldwide, and many patients with this condition may remain undiagnosed [3].

The pseudoexfoliative material (PEXM) that forms in PEX mostly accumulates on various structures of the anterior segment of the eye. The nature of this material is predominantly fibrillar, consisting of fibers made up of microfibrils coated with amorphous material. The composition of these fibrils is diverse, including components of the basement membrane as well as enzymes involved in extracellular matrix maintenance [4]. Accumulation of PEXM contributes to early diffuse decompensation of the corneal endothelium, and the severity of PEX is significantly associated with a reduction in corneal endothelial cell density [5]. Through the accumulation of PEXM, local inflammation of the ocular surface increases, leading to stenosis of the lacrimal puncta [6].

Interest in PEX is also driven by the fact that it is a systemic condition and a risk factor for other diseases.

PEX is statistically significantly associated with a history of angina pectoris, hypertension, or a combined history of angina, acute myocardial infarction, or stroke. Signs of PEX detected with a slit-lamp can identify individuals with increased vascular risk, highlighting vascular associations with PEX in the context of the widespread elastosis affecting many tissues, including the walls of blood vessels [7].

Thus, the main complication of PEX is undoubtedly open-angle glaucoma, although angle-closure glaucoma can also occur due to pupillary or ciliary block [8]. The prevalence of PEX increases markedly with age. Individuals with PEX tend to have thinner and flatter corneas; however, no differences have been found in cataract characteristics or age-related macular degeneration compared to those without PEX [9].

The various manifestations of PEX need to be investigated and systematized, as knowledge of them can help improve the classification of PEX and thus pave the way for better-targeted treatment of both PEX and PEXG.

AIM

To develop an updated and refined classification of PEX in the context of its complication by PEXG, taking into account current understanding of the morphological and clinical criteria of PEX and its treatment methods.

MATERIALS AND METHODS

The study analyzed and systematized global and domestic scientific literary sources and electronic resources regarding the modern understanding of PEX and PEXG from the scientometric databases PubMed and Scopus. The search for publications was carried out using keywords and their logical combinations: ophthalmology, PEXG, PEX classification, symptoms and treatment of PEX. A total of 35 sources were analyzed, mainly from the period 2015-2024 (only 7 of them were published earlier). The inclusion criteria were the presence of existing PEX classifications in the publications, as well as a description of the symptoms of PEX and PEXG, surgical methods of their treatment. Analytical and bibliographic methods were employed.

REVIEW AND DISCUSSION

Clinical and histopathological manifestations of PEX involve damage to the lens, the zonular apparatus, the ciliary body, the iris, the trabecular meshwork, and the cornea [10]. PEX is not limited to the anterior segment of the eye. Information exists about histopathological characteristics of PEX in various structures – fibrillar and

eosinophilic deposits on the anterior lens capsule, as well as on the eyelid and conjunctiva – indicating systemic distribution of PEXM. Understanding the systemic consequences of PEX for ocular and extraocular tissues may lead to more comprehensive treatment strategies for patients with this condition [11].

PEX has been associated with ocular surface diseases, specifically chronic eyelid redness caused by the long-term use of multiple glaucoma medications (with or without preservatives), due to the more aggressive disease course and late-stage glaucoma [12].

Purely clinical evaluation is insufficient for the clear identification of PEX and PEXG signs. The level of IOP and the degree of trabecular dysfunction correlate significantly with the amount of pigmentation and PEXM in the anterior segment of the eye [13]. Indices of peripheral blood related to systemic immune inflammation – including the systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), and aggregate index of systemic inflammation (AISII) – were elevated in patients with PEX compared to healthy control individuals. Therefore, these indices could serve as simple, practical, and cost-effective tools for assessing the degree of systemic inflammation in PEX patients, potentially guiding treatment [14].

The presence of PEX is associated with an increased risk of nuclear cataract [15]. The prevalence of PEX was significantly higher in older patients with mature cataract. The mean IOP was significantly higher in eyes with PEX than in those without it [16]. However, other data indicate that only a small percentage of eyes with PEX had elevated IOP, and even fewer had glaucomatous optic neuropathy. Thus, no correlation was found between elevated IOP and the stage of PEX. Additionally, in eyes with early-stage PEX, good pupillary dilation was observed [17].

Damage to all tissues of the anterior segment of the eye leads to a spectrum of intraocular complications that are significant for the treatment strategy. Intraocular complications occurring during or after ocular surgery in the context of PEX include phacodonesis, lens dislocation, and an increased frequency of vitreous loss during extracapsular cataract extraction. Other possible complications include pseudo-uveitis, anterior chamber hypoxia, hemorrhage in the iris stroma, dispersion of pigment epithelial melanin, and poor or asymmetric pupillary dilation. Due to the involvement of all cellular layers of the iris, posterior synechiae may form [8].

PEX is not designated as a separate nosological entity and thus is not included in the International Classification of Diseases (ICD-10 or ICD-11), unlike PEXG, which is classified as a form of secondary glaucoma. Several classifications of PEX have been proposed, but

Table 1. Classification of PEX

PEX Stage	Biomicroscopic Criteria	Pupil Diameter	Iridodonesis / Phacodonesis	Lens or IOL Dislocation	Preferred Surgical Appro
1	PEXM on the pupillary margin and anterior lens surface during mydriasis	≥8 mm	Absent	Absent	Standard phacoemulsification with IOL implantation
2a	PEXM on pupillary margin and anterior lens surface during mydriasis, also in the anterior chamber angle, on the iris and corneal endothelium	5-8 mm	Mild, not requiring fixation devices	Absent	Phacoemulsification at physiological IOP, no nucleus rotation, low vacuum, IOL implanted without fixation device
2b	PEXM on pupillary margin and anterior lens surface during mydriasis, also in the anterior chamber angle, on the iris and corneal endothelium	5-8 mm	Clinically and intraoperatively pronounced; require fixation devices (e.g., capsular tension ring)	Absent	Phacoemulsification at physiological IOP, no nucleus rotation, low vacuum, IOL implantation with fixation device (e.g., capsular tension ring)
3	PEXM on pupillary margin and anterior lens surface during mydriasis, also in the anterior chamber angle, on the iris and corneal endothelium	<5 mm	Clinically and intraoperatively pronounced; require fixation devices (e.g., capsular tension ring)	Absent	Phacoemulsification at physiological IOP, no nucleus rotation, low vacuum, IOL implantation with fixation device (e.g., capsular tension ring)
4	PEXM on pupillary margin and anterior lens surface during mydriasis, also in the anterior chamber angle, on the iris and corneal endothelium	<5 mm	Clinically and intraoperatively pronounced	Partial or complete dislocation of the lens or IOL	Phacoemulsification at physiological IOP, no nucleus rotation, low vacuum, IOL implantation with scleral or iris fixation

Source: compiled by the authors of this study

they are not used in clinical practice. PEX is considered a systemic disease, in which PEXM can deposit in the skin, heart, lungs, liver, kidneys, and other organs. Both unilateral and bilateral manifestations are possible. Myocardial infarction, cerebrovascular events, and systemic hypertension have also been associated with PEX. However, PEX was first described based on characteristic findings of white-gray flakes on the anterior lens capsule [18].

One review article on PEX presented a classification based on light biomicroscopy data, distinguishing four stages of qualitative changes [19]: from initial manifestations of PEX as punctate deposits on anterior segment structures at Stage I to disturbances of the spatial relationships of anterior segment structures at Stage IV. Another classification divides PEX into three grades based on the pattern of PEXM distribution: mild (partial involvement of the pupil margin), moderate (entire pupil margin), and severe (entire pupil margin and the surface of the iris) [5].

A different classification concerns phenotypic variants of PEX: the *pigmented* form (thin radial pigmented lines on the lens surface, often not involving the pupil), the *classic* form (a “dandruff-like” appearance of deposits on the lens capsule, pupillary margin, or iris), and the *combined* form, which combines features of both pre-

vious types and is characteristic of a more advanced stage of PEX. In a study of eyes with PEX of different phenotypes, glaucoma with significant IOP changes, with or without optic disc damage, was observed in 32% of eyes with the pigmentary form, 39% with the classic form, and 50% with the combined form of PEX. Different phenotypic variants of PEX were associated with a 30% risk of developing ocular hypertension and a 50% risk of developing glaucoma [20].

The treatment approach for patients with PEX, particularly the choice of surgical intervention, depends on the severity of degenerative changes in the iris, capsule, and zonular apparatus of the lens. Therefore, we propose an original classification of PEX (Table 1) that takes into account the morphological and clinical changes in the anterior segment of the eye (the pattern of PEXM distribution, pupil diameter, degree of iridodonesis and phacodonesis, and the presence of lens or intraocular lens [IOL] dislocation) and simultaneously prescribes the corresponding surgical intervention. This classification is the result of an analysis of 67 ophthalmic surgeries performed from December 2024 through April 2025 on patients with various stages of PEX: 22 eyes with stage 1, 20 with stage 2a, 13 with stage 2b, 11 with stage 3, and 1 eye with stage 4 of PEX [21].

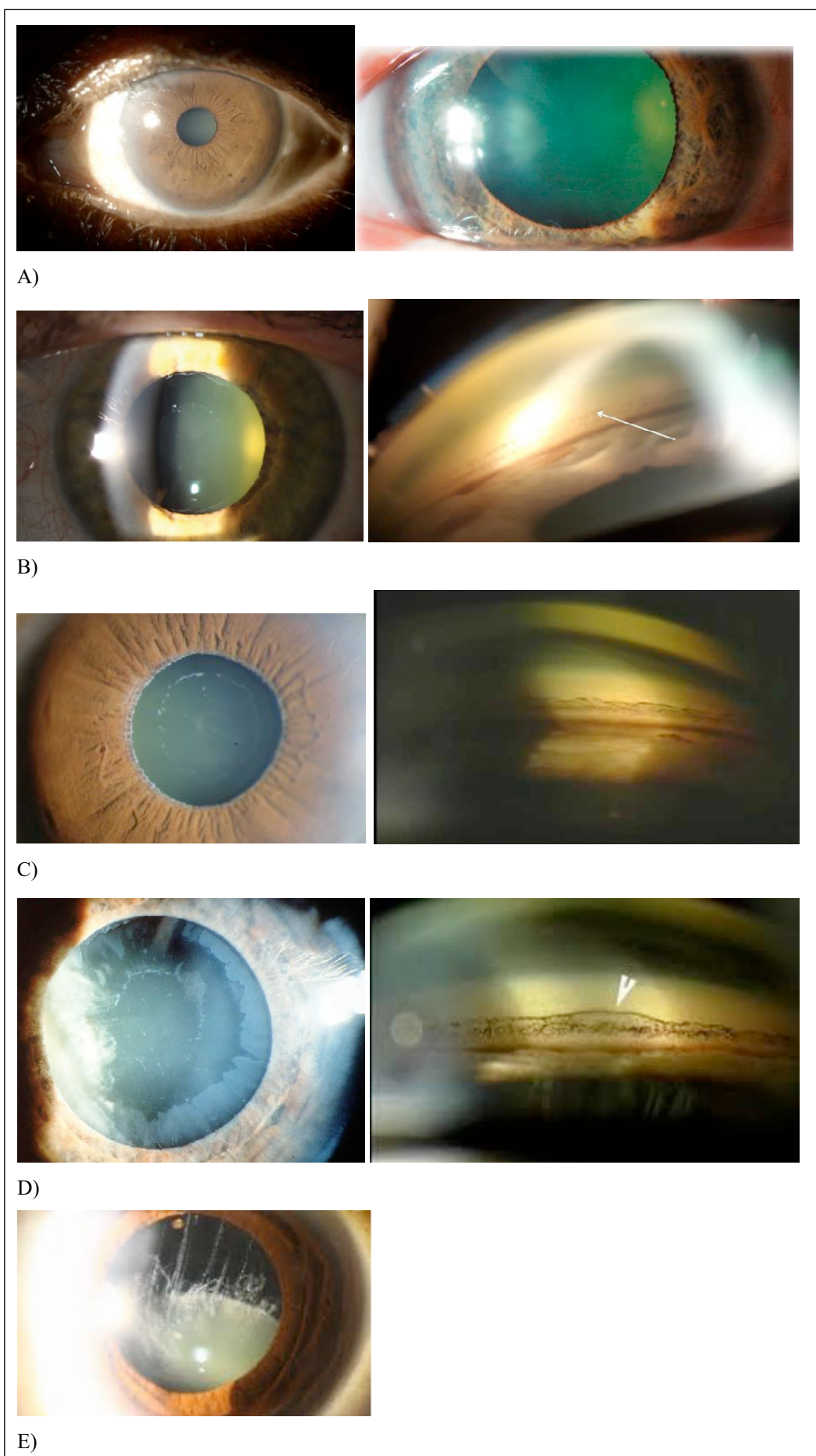


Fig. 1. The photos of eyes with different stages of PEX: A) PEX 1; B) PEX 2a; C) PEX 2b; D) PEX 3; E) PEX 4
Source: compiled by the authors based on [21]

The photos of eyes with different stages of PEX, taken using a slit lamp, are presented in Fig. 1.[21].

Thanks to the proposed classification, it is possible to predict the extent of the necessary surgical intervention. All classification criteria (maximum pupil width, extent of pseudoexfoliation spread, presence or absence of phacodonesis, and presence of lens dislocation in stage 4) are identified during the preoperative diagnostic stage. The scope and complexity of surgical treatment, as well as the need for additional IOL fixation devices, depend on the stage of PEX as defined in this classification. By determining the PEX stage according to this system, one can anticipate the volume, complexity, duration, and risk of potential postoperative complications. This creates a basis for determining the required level of surgical expertise, estimating the cost of the procedure, calculating the number of necessary consumables, and planning the involvement of additional resources (such as hospitalization or an anaesthesiologist). Moreover, this classification provides information to the patient (as well as to insurance companies, administrative or legal bodies, etc.) about the causes of complications and adverse outcomes.

An advantage of this classification is the ability to scientifically systematize results in clinical studies. Patients with different stages of PEX are expected to have differing risks of developing glaucoma. The availability of a clear and easily implementable patient grading system enables broad multicenter studies, in which all investigators can follow a unified principle of patient stratification, thereby contributing to the understanding and prevention of glaucoma onset and progression.

Patients with PEX and PEXG require continuous monitoring and individualized treatment, taking into account the specifics of their medical history. In one population-based study of PEX patients, 16% required treatment following evaluation [10]. The use of topical medications in PEX patients usually leads to poor long-term outcomes, but various surgical methods have been proposed for treating PEX, such as argon laser or selective laser trabeculoplasty. When examining patients with PEX and/or PEXG, all relevant factors must be considered to determine the most appropriate treatment strategy. Patients should also be informed about the increased risk of potential complications [22]. Phacoemulsification for cataract removal results in significant IOP reduction and visual improvement, making it a more effective option for treating PEXG [23], particularly in cases with preoperative IOP below 20 mmHg [24].

PEXG is characterized by larger IOP fluctuations and is more resistant to topical therapy than primary

open-angle glaucoma. Therefore, first-line prostaglandin monotherapy is important for better control of elevated IOP and the tendency toward progressive glaucomatous vision loss. Timely selective laser trabeculoplasty and/or various micro-invasive glaucoma surgery (MIGS) procedures are also indicated for PEXG when other treatment methods prove ineffective. In particular, combined cataract surgery with translimbal trabeculotomy under gonioscopic guidance is highly effective in reducing IOP in PEXG (possibly by washing out PEXM from the anterior chamber and trabecular meshwork) [25]. Managing patients with concomitant PEXG and cataract is a complex task due to its worse prognosis compared to other types of glaucoma and the increased risk associated with surgical intervention for cataract [26].

Compared to primary open-angle glaucoma, PEXG demonstrates more pronounced optic nerve damage and a weaker response to medical therapy. The effects of argon laser therapy and filtering surgery are similar for these two types of glaucoma, but primary laser trabeculoplasty has been shown to yield better results in PEXG than in primary open-angle glaucoma [27].

Laser trabeculoplasty and medical treatment of PEXG are equally effective, but both lose effectiveness over several years. It is also necessary to monitor the IOP in the contralateral eye, given the potential development of glaucoma in it. A significantly high risk of complications (capsular rupture, vitreous loss, lens nucleus dislocation, and IOL dislocation) has been reported following cataract surgery in eyes with PEX. The use of modern phacoemulsification techniques and devices for capsular support substantially reduces these risks [28].

Due to zonular damage associated with pseudoexfoliation, cataract surgery on eyes with PEX carries an increased risk of surgical complications [29]. Phacodonesis and lens subluxation may occur, as well as late dislocation of an in-the-bag IOL even years after an uncomplicated cataract surgery [30]. The frequency of cataract surgery complications did not differ statistically between patients with bilateral PEX and those with clinically unilateral PEX [31]. Intraoperative difficulties occurred in 27,4% of operated eyes with PEX, with the most common problems being poor pupillary dilation and zonular dehiscence [32].

PEXG is a more progressive disease than primary open-angle glaucoma, with higher IOP levels and greater diurnal fluctuation. Cases of PEXG usually require more aggressive antiglaucoma treatment, so glaucoma surgery is often performed in these patients [33]. Certain complications occurred more frequently in

the PEXG group compared to the primary open-angle glaucoma group. For example, postoperative best-corrected visual acuity of $\geq 20/40$ was achieved in 20% of PEXG eyes versus 40% of primary glaucoma eyes; nonetheless, both groups experienced improvements in vision-related quality of life [34].

It is worth noting the need to study MIGS methods. It has been reported that most surveyed ophthalmology residents in the United States intend to treat glaucoma surgically in their future practice, but training in such procedures is not mandatory in ophthalmology residency programs [35].

CONCLUSIONS

PEX is a complex and prevalent ocular pathology that is difficult to diagnose and treat; it can lead to glaucoma and, ultimately, to blindness. Thorough monitoring of

patients with PEX is essential for continuous control of IOP and other PEX symptoms, as well as for the timely initiation of appropriate medical and surgical glaucoma treatments while taking into account the risk of surgical complications.

A review of global experience regarding PEX manifestations, complications, and treatment methods has led to the development of a modern, refined classification of PEX that can be used in the education and clinical practice of ophthalmologists. In particular, the new classification provides the ability to predict the volume and complexity of the necessary surgical intervention, determine the required level of surgeon expertise, estimate the cost of the procedure, and assess the risks of potential postoperative complications. Additionally, this classification opens up the possibility of systematic categorization of patients in clinical research.

REFERENCES

1. Kapuganti RS, Alone DP. Current understanding of genetics and epigenetics in pseudoexfoliation syndrome and glaucoma. *Mol Aspects Med.* 2023;94:101214. doi: 10.1016/j.mam.2023.101214. DOI
2. Prince AM, Streeten BW, Ritch R et al. Preclinical Diagnosis of Pseudoexfoliation Syndrome. *Arch Ophthalmol.* 1987;105(8):1076–1082. doi: 10.1001/archophth.1987.01060080078032. DOI
3. Yüksel N, Yılmaz Tuğcan B. Pseudoexfoliation Glaucoma: Clinical Presentation and Therapeutic Options. *Turk J Ophthalmol.* 2023;53(4):247–256. doi: 10.4274/tjo.galenos.2023.76300. DOI
4. Elhawy E, Kamthan G, Dong CQ, Danias J. Pseudoexfoliation syndrome, a systemic disorder with ocular manifestations. *Hum Genomics.* 2012;6(1):22. doi: 10.1186/1479-7364-6-22. DOI
5. Aoki T, Kitazawa K, Inatomi T et al. Risk Factors for Corneal Endothelial Cell Loss in Patients with Pseudoexfoliation Syndrome. *Sci Rep.* 2020;10(1):7260. doi: 10.1038/s41598-020-64126-w. DOI
6. Eroglu FC, Sekeroglu MA, Ceran TH et al. Evaluation of lacrimal drainage system in Pseudoexfoliation syndrome. *Eye (Lond).* 2022;36(11):2094–2098. doi: 10.1038/s41433-021-01799-1. DOI
7. Mitchell P, Wang JJ, Smith W. Association of pseudoexfoliation syndrome with increased vascular risk. *Am J Ophthalmol.* 1997;124(5):685–687. doi: 10.1016/s0002-9394(14)70908-0. DOI
8. Naumann GO, Schlötzer-Schrehardt U, Küchle M. Pseudoexfoliation syndrome for the comprehensive ophthalmologist. Intraocular and systemic manifestations. *Ophthalmology.* 1998;105(6):951–968. doi: 10.1016/S0161-6420(98)96020-1. DOI
9. Rumelaitiene U, Speckauskas M, Tamosiunas A et al. Exploring association between pseudoexfoliation syndrome and ocular aging. *Int Ophthalmol.* 2023;43(3):847–857. doi: 10.1007/s10792-022-02486-0. DOI
10. Jeng SM, Karger RA, Hodge DO et al. The risk of glaucoma in pseudoexfoliation syndrome. *J Glaucoma.* 2007;16(1):117–121. doi: 10.1097/01.jgg.0000243470.13343.8b. DOI
11. Stejar LD, Istrate-Ofiteru AM, Tofolean IT et al. Histopathological Analysis of Pseudoexfoliation Material in Ocular Surgeries: Clinical Implications. *Diagnostics (Basel).* 2024;14(19):2187. doi: 10.3390/diagnostics14192187. DOI
12. Dermenoudi M, Matsou A, Keskin C, Anastasopoulos E. Ocular Surface Disease Signs and Symptoms in Patients with Pseudoexfoliative Glaucoma: A Case-Control Study. *Vision (Basel).* 2022;6(1):11. doi: 10.3390/vision6010011. DOI
13. Iwanejko M, Turno-Kręcicka A, Tomczyk-Socha M et al. Evaluation of the anterior chamber angle in pseudoexfoliation syndrome. *Adv Clin Exp Med.* 2017;26(5):795–801. doi: 10.17219/acem/64023. DOI
14. Özer Ö, Güçlü ES. Evaluation of pseudoexfoliation syndrome patients with systemic immune indexes. *BMC Ophthalmol.* 2024;24(1):494. doi: 10.1186/s12886-024-03767-1. DOI
15. Kanthan GL, Mitchell P, Burlutsky G et al. Pseudoexfoliation syndrome and the long-term incidence of cataract and cataract surgery: the blue mountains eye study. *Am J Ophthalmol.* 2013;155(1):83–88.e1. doi: 10.1016/j.ajo.2012.07.002. DOI
16. Kalaycı M. Pseudoexfoliation Syndrome Prevalence in Somali Patients with Senile Cataract. *İstanbul Med J.* 2020;21(5):380–383. doi: 10.4274/imj.galenos.2020.12269. DOI

17. Philip SS, John SS, Simha AR et al. Ocular clinical profile of patients with pseudoexfoliation syndrome in a tertiary eye care center in South India. *Middle East Afr J Ophthalmol*. 2012;19(2):231-236. doi: 10.4103/0974-9233.95259. DOI
18. Bora RR, Prasad R, Mathurkar S et al. Cardiovascular Manifestations of Pseudoexfoliation Syndrome: A Narrative Review. *Cureus*. 2024;16(1):e51492. doi: 10.7759/cureus.51492. DOI
19. Kozariychuk N, Sykorytska T. Psevdoeksfoliatyvnyi syndrom – suchasni aspekty (ohliad literatury). [Pseudoexfoliation syndrome – contemporary aspects]. *Klinichna ta eksperymental'na patolohiya*. 2017;16(1):168-172. doi: 10.24061/1727-4338.XVI.1.59.2017.38. (Ukrainian) DOI
20. Rao A, Padhy D, Sahay P et al. Clinical spectrum of pseudoexfoliation syndrome-An electronic records audit. *PLoS One*. 2017;12(10):e0185373. doi: 10.1371/journal.pone.0185373. DOI
21. Palamar BI, Melnyk VO. Certificate of Copyright Registration (Ukraine) # 136593. *Tvir naukovo-praktychnoho kharakteru «Klasyfikatsiia Psevdoeksfoliatyvnoho syndromu»*. [Scientific and Practical Work «Classification of Pseudoexfoliative Syndrome»]. Ukrainian National Office for Intellectual Property and Innovations (UANIPIO). *Ofitsiyni elektronnyi biuleten «Avtorske Pravo i Sumizhni Prava»*. 2025;90:455. (Ukrainian)
22. Plateroti P, Plateroti AM, Abdolrahimzadeh S, Scuderi G. Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma: A Review of the Literature with Updates on Surgical Management. *J Ophthalmol*. 2015;2015:370371. doi: 10.1155/2015/370371. DOI
23. Azaripour E, Khakpour Y, Soltani-Moghadam R et al. Outcomes of Phaco-viscocanalostomy in Primary Open Angle Glaucoma versus Pseudoexfoliation Glaucoma. *J Ophthalmic Vis Res*. 2021;16(4):566-573. doi: 10.18502/jovr.v16i4.9746. DOI
24. Carolan JA, Liu L, Alexeeff SE et al. Intraocular Pressure Reduction after Phacoemulsification: A Matched Cohort Study. *Ophthalmol Glaucoma*. 2021;4(3):277-285. doi: 10.1016/j.ogla.2020.10.002. DOI
25. Hynes A. Contemporary pseudo-exfoliation glaucoma management and treatment options. *Can J Optom*. 2024;86(2):7-34. doi: 10.15353/cjo.v86i2.5585. DOI
26. Kang E, Park JH, Yoo C et al. Comparison of intraocular pressure fluctuation and glaucoma progression rate between phakic and pseudophakic eyes in pseudoexfoliation glaucoma. *Sci Rep*. 2024;14:6. doi: 10.1038/s41598-023-49099-w. DOI
27. Drolsum L, Ringvold A, Nicolaissen B. Cataract and glaucoma surgery in pseudoexfoliation syndrome: a review. *Acta Ophthalmol Scand*. 2007;85(8):810-821. doi: 10.1111/j.1600-0420.2007.00903.x. DOI
28. Fontana L, Coassin M, Iovieno A et al. Cataract surgery in patients with pseudoex-foliation syndrome: current updates. *Clin Ophthalmol*. 2017;11:1377-1383. doi: 10.2147/OPTH.S142870. DOI
29. Konstas AGP, Holló G, Teus MA, Ritch R. Exfoliation Syndrome and Glaucoma. In: Samples J, Schacknow P, eds. *Clinical Glaucoma Care*. New York (NY): Springer; 2014, p. 345-359. doi: 10.1007/978-1-4614-4172-4_17. DOI
30. European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition. *Br J Ophthalmol*. 2021;105(1):1-169. doi: 10.1136/bjophthalmol-2021-egsguidelines. DOI
31. Jammal H, Abu Ameera M, Al Qudah N et al. Characteristics of Patients with Pseudoexfoliation Syndrome at a Tertiary Eye Care Center in Jordan: A Retrospective Chart Review. *Ophthalmol Ther*. 2021;10(1):51-61. doi: 10.1007/s40123-020-00319-w. DOI
32. Joshi RS, Singanwad SV. Frequency and surgical difficulties associated with pseudoexfoliation syndrome among Indian rural population scheduled for cataract surgery: Hospital-based data. *Indian J Ophthalmol*. 2019;67(2):221-226. doi: 10.4103/ijo.IJO_931_18. DOI
33. Tekin K, Inanc M, Elgin U. Monitoring and management of the patient with pseudoexfoliation syndrome: current perspectives. *Clin Ophthalmol*. 2019;13:453-464. doi: 10.2147/OPTH.S181444. DOI
34. Turalba A, Cakiner-Egilmez T, Payal AR et al. Outcomes after cataract surgery in eyes with pseudoexfoliation: Results from the Veterans Affairs Ophthalmic Surgery Outcomes Data Project. *Can J Ophthalmol*. 2017;52(1):61-68. doi: 10.1016/j.jcjo.2016.07.019. DOI
35. Halenda KM, Lee TJ, Sharma A et al. Survey of Microinvasive Glaucoma Surgery and Other Glaucoma Surgical Experience among United States Ophthalmology Residency Programs. *J Acad Ophthalmol* (2017). 2021;13(2):e108-e113. doi: 10.1055/s-0040-1721072. DOI

The research was conducted as part of the scientific project «Scientific Rationale for Improving Organizational Principles of the Healthcare System Under Modern Transformational Changes» (state registration number 0123U101432, registration date 03.03.2023).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Volodymyr O. Melnyk

Bogomolets National Medical University

13 Taras Shevchenko Ave., 01601 Kyiv, Ukraine

e-mail: volo_mel@ukr.net

ORCID AND CONTRIBUTIONSHIP

Volodymyr O. Melnyk: 0009-0001-4177-4702 **A** **B** **D**

Borys I. Palamar: 0000-0003-2510-0713 **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: 10.05.2025

ACCEPTED: 29.08.2025



The path to the first heart transplant and current transplantology in Poland

Maciej Słomian¹, Katarzyna Grudnik¹, Małgorzata Grudnik¹, Julia Smyczek¹, Mateusz Jagielski², Karol Płaszewski³, Karolina Lau⁴, Janusz Kasperczyk⁴

¹STUDENT SCIENTIFIC CIRCLE AT THE CHAIR AND DEPARTMENT OF MEDICINE AND ENVIRONMENTAL EPIDEMIOLOGY, FACULTY OF MEDICAL SCIENCES IN ZABRZE, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, ZABRZE, POLAND

²INTERN DOCTOR, INDEPENDENT PUBLIC HEALTH CARE FACILITY, SIEDLCE, POLAND

³INTERN DOCTOR, ZAGLEBIOW, CLINICAL HOSPITAL, CZELADZ, POLAND

⁴CHAIR AND DEPARTMENT OF MEDICINE AND ENVIRONMENTAL EPIDEMIOLOGY, FACULTY OF MEDICAL SCIENCES IN ZABRZE, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, ZABRZE, POLAND

ABSTRACT

For centuries, knowledge about the heart, one of the most important organs in the human body, was limited to assumptions and theories. These ideas often served as a basis for understanding the functioning of the circulatory system, but they lacked scientific confirmation. It was not until the 17th century that scientists began to conduct more detailed, although often risky, experiments that shed light on the functioning of the heart. These experiments marked the beginning of reliable insights into the functioning of the circulatory system. As medical knowledge developed, the focus shifted to the treatment of circulatory system diseases. Initially, treatment consisted of minor procedures, but advances in science and technology paved the way for groundbreaking achievements. A historic milestone occurred on December 7, 1967, when the world's first successful heart transplant was performed. This achievement revolutionized medicine, giving new hope to patients with serious heart diseases. Today, a heart transplant is often considered a treatment of last resort, saving lives when other treatments have failed and significantly reducing mortality from cardiovascular disease (Circulatory System Disease). Despite advances in medical science, cardiovascular disease remains a global health challenge, affecting about 40% of the world's population. In Poland alone, about 12 million people suffer from conditions such as hypertension, myocardial infarction, stroke or atherosclerosis. These diseases have become a major public health problem, underlining the importance of prevention, early detection and advanced treatment options to combat their prevalence and impact.

KEY WORDS: heart transplant, transplantology, circulatory system, transplantation, transplant procedure

Wiad Lek. 2025;78(9):1874-1885. doi: 10.36740/WLek/209684 DOI

INTRODUCTION

Over the last few years, with the dynamic development of medicine, the definition of human death has also changed- there has been a departure from the concept of human death as a whole. It has been assumed that the determinant of human death- as a whole- is brain death. In most Western countries, brain death is considered the definitive moment of a person's death. The introduction of this definition facilitated the development of transplantation. Legal systems are based on medical criteria confirmed by medical specialists.

These societies are more pragmatic in their approach to brain death, although there are still religious or philosophical groups (e.g. traditional Catholics or conservative Jewish groups) that question this concept. In Japan and South Korea, brain death is more controversial. Culturally and religiously (influenced by Buddhism

and Confucianism), life is seen as a whole, and as long as the heart is beating, some people do not consider the person dead.

In Japan, for years, restrictive regulations regarding transplantation were in force, and society had limited confidence in the definition of brain death. An additional controversy is "presumed consent". In Poland and France, there is a system of presumed consent. In these countries, the lack of formal objection means that a person can become an organ donor after brain death. The mechanism works on the principle of efficiency- more organs available for transplantation, shorter waiting lists. This is the Act of 1 July 2005 on the collection, storage and transplantation of cells, tissues and organs- the so-called "Transplantation Act". Art. 5 of the Act reads: "The collection of cells, tissues or organs from a deceased person may be carried out if they did not express an objection during their lifetime."

In the USA, Japan, and Germany, on the other hand, there is a system of expressed consent. Only people who have clearly declared their willingness to be donors can donate their organs after death. Main regulation: Law on the Donation, Removal, and Transfer of Organs and Tissues-“Transplantation Act-TPG”, of November 5, 1997, effective December 1, 1997. “Anyone who makes a declaration regarding organ and tissue donation may consent to organ and tissue removal in accordance with Section 3, object to it, or delegate the decision to a named person of their trust”.

It requires broad public education and encouraging people to register as donors. The effectiveness is lower, which leads to longer queues of people waiting for a transplant. Complex problems, disputes and dilemmas around the term of brain death and presumed consent to the removal of organs from a deceased donor have become the subject of numerous acts of international law. In 1978, the Committee of Ministers of the Council of Europe issued a resolution to unify the legislation of member states on the removal and transplantation of organs and tissues from living and deceased donors [1, 2].

The Catholic Church has also taken a position on transplants, thus supporting the treatment of patients with end-stage organ failure. Pope John Paul II and bishops have repeatedly expressed this in their teaching and in collegial speeches, emphasizing that “the body of the deceased deserves respect, and the removal of an organ after death does not violate its dignity or any rights of a human person” [3]. In 2000, John Paul II, at a meeting with participants of the 18th International Transplantology Congress in Rome, said: “Transplantation is a great step forward in the service of science to mankind and currently many people owe their lives to a transplanted organ” [3].

AIM

The aim of the paper is to present the path to the first heart transplant in Poland. The paper, by explaining the basic terminology in the field of transplantology, will go through a historical outline, including several important dates that have a great significance for the further course of the performed operations. Then we will focus on the first transplant attempt in Poland and the subsequent procedures performed. We will focus on the statistics related to transplants in Poland in the last 10 years and explain the process of qualifying the patient and donor for the heart transplant procedure.

MATERIAL AND METHODS

This publication is based on studies published in PubMed and Google Scholar. A thorough literature

search was conducted, covering publications from the years 1985-2024 to provide a comprehensive and up-to-date review of relevant findings. The search strategy included the use of specific keywords “first transplantation in Poland”, “history of transplantology” and “transplant qualification process”. The initial search yielded approximately 30 articles. After a detailed review, 18 articles related to the topic of the article were selected. The selection process gave priority and a primary theme to articles that provided direct information on the history and present of transplantology in Poland and worldwide.

The remaining 12 articles were excluded due to irrelevance or lack of focus on important aspects in the history of transplantology and current patient qualification processes in Poland. The selection of 18 key articles forms the basis of this review, ensuring that the conclusions drawn are both justified and consistent with current scientific knowledge.

REVIEW

HISTORICAL OUTLINE

The term transplantation– organ transplantation, means the transplantation of an organ in whole or in part, tissue or cells from one body to another (or within one body). The name comes from the Latin *transplantare* – “to graft”, *plantare* – “to plant” [4]. Cells (bone marrow, pancreas, brain or epidermis), parts of organs (heart valves, skin flaps, blood vessels) or entire organs can be transplanted: most often kidneys, heart, liver and pancreas. This has become possible thanks to the progress of immunology and new immunosuppressive drugs that prevent rejection of the transplanted organ [5]. Modern transplantology is considered a relatively young field of medicine, because its intensive development occurred in the first years of the 20th century. It is widely considered to be the greatest achievement of modern medicine. However, unsuccessful attempts at organ transplantation, as reported in records and various legends, date back to the Middle Ages. Man has long wanted to replace lost or diseased organs with healthy ones. The first mentions of a successful transplant date back to the 13th century. A legend from the life of Saints Cosmas and Damian (4th century) about the transplantation of a leg to a sick person has survived to this day. This successful procedure has been recorded in numerous paintings kept in the Louvre in Paris [6]. Initially, the source of transplanted tissues and organs were animals. These are so-called xenogenic transplants. Only with the gaining of experience and the conducting of numerous studies in the field of

genetics and immunology did transplants of tissues and organs taken from humans begin to be performed more frequently [7]. The first tissue transplanted to a human was sheep blood, which took place in the years 1635–1704 thanks to the work of J.B. Denis and P.E. Emmeretz. However, due to numerous fatal complications, this procedure was banned. The breakthrough came in 1901, when K. Landsteiner discovered blood groups A, B and O, and a year later A. von Castello and A. Sturli added group AB, which significantly contributed to the development of transplantology [7]. In 1902, Ullmann in Vienna performed the first autotransplantation of a kidney in a dog, and in 1905 Alexis Carrel repeated the experiment, although the transplanted kidneys did not function. Both surgeons, however, developed a technique for suturing vessels, including the so-called Carrel suture, which earned him the Nobel Prize in 1912 [8]. Another important discovery was the identification of the Rh factor by K. Landsteiner and A.S. Winer in 1940, which enabled the widespread use of blood transfusions. The Polish scientist L. Hirsfeld also distinguished himself in the study of serological conflicts [7]. During World War II, it was noticed that many seriously injured patients died of acute renal failure, which focused attention on the development of transplants. The first human kidney transplant was performed in 1933 by the Russian surgeon J. J. Voronoi. In the years 1947–1952, attempts were continued in Canada and France, although without major success [9]. The first successful kidney transplant between twins was performed by Murray and Merrill in Boston in 1954. Progress in this field required overcoming problems related to complications after transplants. An important step was the discovery of immunological causes of transplant rejection, which was studied by, among others, Medawar and Dausset, who in 1958 described the histocompatibility antigen HLA [8]. In 1980, Benacerraf, Dausset and Snell demonstrated genetic dependencies in protein structures on the cell surface [7]. The second half of the 20th century brought successes thanks to the development of immunosuppression methods, i.e. treatment that inhibits the body's immune reactions. Initially, body irradiation was used, but the breakthrough came with the introduction of drugs such as 6-mercaptopurine (6-MP) and cyclosporine, as well as the use of antilymphocyte serums and globulins [7]. In ophthalmology, corneal transplantation has been used since 1906, initially developed by E. K. Zirm and improved by Moner in the 1940s. In reconstructive surgery, skin and artificial skin grafts are used, and since 1957, urology has used the small intestine for bladder plastic surgery. In 1963, J.D. Hardy performed a successful lung transplant, in 1966 W. Kelly and R. Lillehei transplanted a pancreas, and in

1967 C. Barnard performed the first heart transplant.

THE FIRST HEART TRANSPLANT IN THE WORLD

Christiaan Barnard was born on November 8, 1922 in Beaufort West, a small town in South Africa. The heart surgeon was 5 years old when his brother, who was 2 years younger, died of tetralogy of Fallot, which is a rare congenital heart defect. It was the death of his brother and the thought [...] "what would it feel like to have another person's heart beating in my chest" that caused his fascination with the circulatory system and especially the heart. He trained by conducting heart transplants on dogs. Together with his team (including his second younger brother Dr. Marius Barnard), on December 7, 1967, he attempted the first heart transplant at the Groote Schuur Hospital in Cape Town. The patient was 53-year-old Louis Washkansky. The patient suffered from heart failure and had also suffered 3 heart attacks during his life. The heart to be transplanted belonged to a victim of a road accident-25-year-old Denise Darvall. Before the procedure, Dr. Barnard assured the man's family that the chance of success was very high and amounted to 80% [10]. The heart transplant operation on the grocery store owner lasted 5 hours and was attended by 30 people. After the procedure, the patient woke up and was in very good condition- he talked to doctors, gave interviews, posed for photos. However, he died after 18 days, from causes that were not directly related to the procedure. The cause of death was pneumonia, which developed after the administration of anti-rejection drugs and at the same time weakened the body's resistance to various infections. After his death, Christiaan Barnard was criticized by most ethicists for misleading the family and the patient himself regarding the very high percentage points of the chance for a successful procedure and prognosis. Barnard later justified his decision with a vivid metaphor: "If a lion chases you onto the bank of a river infested with crocodiles...". This analogy, while emotionally compelling, has been critiqued in bioethics for oversimplifying patient consent and minimizing the uncertainty of experimental procedures. Public reactions to Barnard's operation ranged from severe criticism to enthusiastic admiration, reflecting the ethical and societal tensions of the time [11, 12].

THE FIRST HEART TRANSPLANT IN EUROPE

On April 27, 1968, in Paris, a team of cardiac surgeons led by Professor Christian Emile Albert Cabroli undertook a heart transplant. The patient was a 66-year-old man

suffering from advanced heart failure, which threatened his life. His health condition was so serious that a heart transplant was the only chance for survival. Due to the lack of effective pharmacological treatments, the operation was classified as experimental. The donor heart was a patient who had died as a result of a brain injury. In 1968, the criteria for declaring brain death were not yet well established, which was one of the controversial aspects of the operation. The donor heart was taken shortly after the death was announced to ensure its best condition. The procedure was considered successful despite the patient's death after 51 hours due to the fact that the heart was accepted by the recipient and began to beat in the patient's body. The patient's immune system attacked the new heart, a common problem at the time, when the effectiveness of immunosuppressive drugs was limited. Cabrol was a very well-known person in France. In addition to the field of cardiac surgery and transplantology, which he dealt with mainly, he was also a local government official, politician, and MEP of the 4th term. The history of Christian Cabrol places him in the first row of great scientists who achieved great achievements in the field of transplantology, because this event became the first milestone in European cardiac surgery [12].

THE FIRST ATTEMPT AT A HEART TRANSPLANT IN POLAND

In December 1968, a patient with an advanced heart defect was admitted to the hospital. Professor Jan Moll, together with professors Antoni Dziatkowiak and Kazimierz Rybiński, undertook the first attempt at a heart transplant in Poland on January 4, 1969. Jan Moll led the team operating on the recipient, while Kazimierz Rybiński led the team at the donor's table. The donor was a 27-year-old boy with irreversible brain damage. When the doctors decided to disconnect the equipment and pronounced brain death, they asked the deceased's mother about saving the heart for transplantation into another organism. During the operation, it turned out that the organ recipient could not be disconnected from extracorporeal circulation due to the fact that the heart had swollen and distended, which resulted in the loss of contractile strength. Despite further attempts to stimulate and support the heart, the patient could not be saved. He died on the operating table. The first unsuccessful transplant attempt resulted in the deceased's family filing a crime report with the prosecutor's office. Although the case was dismissed, Prof. Moll did not attempt any more transplants. Rybiński changed his specialization to endocrinology and became the founder of Polish endocrine surgery [13].

At that time, Poland lacked modern heart-lung machines, which were already standard in countries such as the US and France. The equipment used was outdated, which made it difficult to control circulatory and oxygenation parameters during surgery. At that time, Poland did not have access to modern immunosuppressive drugs, such as azathioprine or corticosteroids, which were already used in Western countries. This significantly increased the risk of transplant rejection. In Poland, there were no clear regulations governing the issue of organ harvesting for transplantation, including the definition of brain death.

The death of the donor was determined mainly on the basis of cardiac arrest, which caused delays in organ harvesting and reduced their chances for successful transplantation.

The lack of legal regulations led to ethical controversies—both in the medical community and in society. Heart transplantation was an innovative procedure that aroused mixed reactions in Poland, especially among more conservative circles. Some religious and social groups considered heart transplantation to be unnatural or inconsistent with the teachings of the Church. The first transplant attempt was a milestone in the world of cardiac surgery. The experience from this operation allowed for the gradual construction of modern transplantology in Poland, and in the following decades the country became one of the leaders in this field in Central and Eastern Europe [11, 13].

PATIENT FROM KRZEPICE FOR TRANSPLANT

Professor Marian Zembala, found out that the father of a friend from his hometown was staying in the Cardiology Clinic. According to Professor Marian Zembala, the patient was breathing with great difficulty and could barely speak. During the conversation with the patient, he mentioned that his heart would not withstand such an operation and suggested a heart transplant in cooperation with Professor Religa. He reassured him and explained that people with a new heart can continue to live. He told him about a case in France, about a man who had had a new heart for eighteen years. The patient from Krzepice agreed without a second thought because he knew he did not have much time left to live, while Zbigniew Religa did not make such a decision right away. He saw that he was not an ideal patient for a transplant. The patient was exhausted by a long-term severe heart disease. A conversation with the patient, a discussion with Professor Pasyk and members of the team decided that having a donor for a transplant with the ORh (+) group, they would try to take a risk. The patient was transferred in October to

the Provincial Cardiology Center (WOK), in Zabrze. The doctors were skeptical about making the attempt, because the patient was receiving a continuous infusion of dopamine and any attempt to disconnect it resulted in shortness of breath. His heart contracted only as a result of the administration of stimulants. The plan to undertake the transplant was still in the doctors' heads and the confirmation was the fact that the National Duty Physician reported the need for a heart donor. On Monday, November 4, 1985, the patient looked weaker and weaker, but the ward was revived, as it turned out that a donor for a new heart had been found. Around 2 a.m. after reaching the WOK, Zbigniew Religa informed the patient that the heart was on its way to Zabrze [11].

ORGAN DONOR

The organ donor turned out to be 29-year-old Włodzimierz Z, who had been in the Wolski Hospital in Warsaw for neurosurgery since November 1 with a damaged skull and brain. The donor was found on a bench in a park in the capital of Poland. He was bleeding badly, he had probably been hit with a non-sharp object. Despite immediate surgery, doctors were unable to cope with the injuries that were too severe. The drop in body temperature, the lack of eyeball response to stimuli and the lack of independent breathing caused them to disconnect the artificial respiration apparatus on November 4 and issue a death certificate. Doctors contacted Religa, knowing about his idea. The proposal to save another person's life using the organs of a deceased person was met with no objections from the potential donor's family. Tissue compatibility tests were performed by taking samples from the inguinal lymph nodes and blood. The results had to wait until late at night that same day. The results were communicated to the WOK by phone, and after midnight Doctor Grzegorz Gallert (anaesthesiologist) and Cichoń, together with the donor, got into the transport ambulance. The people travelling in the ambulance were constantly supplementing the donor's body with the necessary drugs to maintain the organs' ability to be transplanted. The results were correct and the organ was suitable for transplantation. In this way, the heart reached Zabrze and the recipient was ready to receive the organ, which started the procedure for the donor and the recipient [10, 11].

AFTER THE OPERATION

The patient woke up at around 2 p.m. Doctors recommended that the patient stay in bed and do breathing exercises. On November 7, the patient's condition

deteriorated significantly. He was urinating less and less and blood was still flowing from the drains, which doctors concluded that he had problems with clotting. At around 4 p.m., his chest was reopened, and there were a lot of clots in it. Doctors tried to transfuse blood, but kidney failure, a ruptured stomach ulcer, and the aforementioned lack of clotting caused the patient's death. The patient died on November 11, 1985 at 8:02 a.m. An autopsy was performed, which found no traces of the transplant rejection process. The cause of death was most likely multiple organ failure resulting from postoperative complications. At that time, immunosuppressive drugs, which prevent rejection of transplanted organs, were not yet available in Poland in sufficient quantities, which made it difficult to control the heart rejection process [12]. The first heart transplant performed in the Zabrze clinic, despite its dramatic course, did not discourage the team of cardiac surgeons led by Professor Zbigniew Religa from continuing such operations. A week later, on November 12, 1985, the second transplant was performed. The patient was a 25-year-old man suffering from stage IV heart failure according to the NYHA classification, caused by post-inflammatory cardiomyopathy. The patient's condition was constantly deteriorating, and conservative treatment proved ineffective. The ejection fraction of his left ventricle was 35%, and the pulmonary pressure reached 45 mmHg. The donor was a 30-year-old man in a state of brain death after a skull injury. Initially, there were no complications after the surgery, and biopsies did not show any rejection of the transplant. However, after several weeks, the patient struggled with infections, including fungal pneumonia and generalized sepsis, which led to his death 39 days after the procedure. The transplanted heart functioned properly, which indicates the success of the transplant— if not for the complications related to the necessary immunosuppression, the patient would have had a chance for a long-term improvement in health [10]. The third heart transplant in the Zabrze clinic took place on April 25, 1986. The patient was a 34-year-old man with advanced heart failure, which was a consequence of previous heart attacks and bypass surgeries. His ejection fraction was only 10%, and pulmonary pressure— 75 mmHg. The donor was a 35-year-old man who had been diagnosed with brain death after a skull injury. The surgery was initially without complications, but from the second day onwards, progressive right ventricular failure appeared, associated with persistent pulmonary hypertension. Despite intensive therapy, the patient died on the seventh day after the transplant. This case confirmed that persistent pulmonary hypertension is a key contraindication to heart transplantation. The next, fourth

transplantation took place on May 11, 1986 and was successful. The recipient was a 35-year-old patient with a history of two heart attacks and increasing dyspnea and circulatory failure of NYHA class IV. The donor was a 35-year-old woman who died of acute respiratory failure. The operation was successful and the patient regained full circulatory capacity [12, 13]. After four weeks he left the clinic in good condition and his health remained at a satisfactory level for many years. It was the first fully successful heart transplant performed in Poland, proof of the determination and skills of Polish cardiac surgeons.

At that time, the availability of modern immunosuppressive drugs in Poland was limited. The introduction of cyclosporine in the early 1980s revolutionized transplantology, but its use in Poland was difficult due to high costs and limited access. These drugs were crucial for preventing rejection of transplanted hearts, but they had numerous side effects, such as kidney damage, increased risk of infection and cancer. In the 1980s, methods of monitoring rejection were less advanced than they are today. Endomyocardial biopsies were difficult to perform, and immunological tests were less precise. Thanks to state support and the involvement of Professor Religa's team, cyclosporine was introduced into postoperative therapy. Intensive cooperation with foreign centers helped to obtain modern drugs and knowledge about their use [11, 12].

THE ROLE OF TACROLIMUS IN MODERN IMMUNOSUPPRESSIVE REGIMENS: A COMPARATIVE CLINICAL PERSPECTIVE

Immunosuppressive therapy remains the cornerstone of successful solid organ transplantation, aiming to prevent graft rejection while minimizing adverse effects and maintaining long-term patient and graft survival. Among the various classes of immunosuppressants, calcineurin inhibitors (CNIs) – primarily cyclosporine and tacrolimus – have been the mainstay of maintenance immunosuppression since the late 20th century. Over the past two decades, extensive clinical research, randomized controlled trials, and systematic reviews have focused on comparing the efficacy and safety of these two agents in different transplant settings, including heart, kidney, and liver transplantation.

Tacrolimus, first approved for clinical use in the 1990s, is generally considered more potent than cyclosporine and has been associated with improved outcomes in various transplant populations. A systematic review and meta-analysis by Webster et al. (2005), which included 30 randomized controlled trials involving kidney transplant recipients, demonstrated that tacrolimus signifi-

cantly reduced the risk of acute rejection compared to cyclosporine (RR = 0.56, 95% CI: 0.43–0.73) without increasing overall mortality [1]. Similar findings were observed in heart transplant recipients. A meta-analysis conducted by Penninga et al. (2010) evaluated seven randomized trials with 885 patients and concluded that tacrolimus was associated with a lower incidence of severe acute rejection at both 6 and 12 months (RR ~0.61–0.69), while also showing a trend toward reduced treatment discontinuation [2]. Although tacrolimus was linked to a higher incidence of new-onset diabetes after transplantation (NODAT), its superior efficacy in reducing immunological complications often made it the preferred first-line agent.

In Poland, observational cohort studies have corroborated these global trends. A multicenter study conducted on 734 kidney transplant recipients across several Polish centers revealed that tacrolimus-based regimens were associated with significantly fewer episodes of biopsy-proven acute rejection and tended toward improved one- and five-year graft survival compared to cyclosporine-based therapy. These benefits were especially notable in patients with high immunologic risk or delayed graft function, highlighting the drug's applicability in challenging clinical scenarios.

In liver transplantation, tacrolimus has similarly outperformed cyclosporine in several domains. According to a Cochrane review by Haddad et al. (2006), tacrolimus improved patient and graft survival at one year and resulted in better control of blood pressure and lipid profiles. However, this came at the cost of higher incidence of metabolic side effects, particularly post-transplant diabetes mellitus. Despite this, due to its ability to more effectively suppress T-cell mediated rejection, tacrolimus became the preferred CNI in many liver transplant protocols worldwide, especially in the early post-transplant period [14].

An important aspect of this therapeutic comparison lies in long-term follow-up. While short-term benefits of tacrolimus are well documented, long-term exposure to calcineurin inhibitors, regardless of type, is associated with nephrotoxicity, neurotoxicity, hypertension, and metabolic syndrome. Thus, many transplant centers are moving toward minimization strategies, such as lowering tacrolimus trough levels, introducing adjunctive agents (e.g., mTOR inhibitors or mycophenolate mofetil), or switching to CNI-free regimens in select patients. Yet, most comparative studies still suggest that tacrolimus offers a more favorable risk-benefit profile, particularly when metabolic side effects are carefully monitored and managed [15].

In conclusion, both tacrolimus and cyclosporine remain foundational drugs in transplant immunology,

but the evidence from large- scale meta- analyses and clinical trials consistently favors tacrolimus in terms of reducing acute rejection, improving graft survival, and achieving superior overall outcomes across organ types. Nonetheless, patient- specific factors, comorbidities, and risk of metabolic complications must guide therapeutic decisions. Ongoing research is also exploring pharmacogenetic predictors of CNl response, aiming to tailor immunosuppression more precisely and safely in the future.

ORGAN PROCUREMENT PROCEDURE AND ORGANIZATION

In Poland, there is Act No. 169 item 1411 of 2005, which allows for the removal of organs from a deceased person only if they did not express their objection to such a procedure during their lifetime. People who do not want their organs to be used after death are required to file their objection in the Central Register of Objections. For those who have not registered such an objection, the organ harvested from the deceased can be used for transplantation. However, this process involves many procedures to ensure that the organ goes to the most suitable recipient. A key aspect that determines the success of the transplant is the precise matching of donors and recipients, which involves a number of detailed medical and immunological tests.

The first step in this process is the compatibility of blood groups between the donor and the recipient, which is the basis for the initial selection. Then it is necessary to look for the greatest possible genetic compatibility between the donor and the recipient in terms of histocompatibility antigens (MHC – Major Histocompatibility Complex). The complex MHC plays a key role in recognizing histocompatibility antigens, especially HLA (Human Leukocyte Antigens) class I and II proteins, which are present in all human cells [16, 17]. Obtaining organs for transplantation is the most important problem in transplantology. Advances in medicine and the development of modern transplantology have caused an imbalance between the number of people waiting for transplants and the number of organs obtained. The problem is growing not only in Poland, but also all over the world. This is related to the paradox occurring in transplant medicine – a living organ is needed for organ transplantation. It can be obtained from a deceased donor, then we talk about *ex mortus* transplants, but for it to be successful, it depends to a large extent on the quality of the organ obtained. In addition to many factors (e.g. donor age, health condition, course of brain death, conditions of organ storage), the quality of the organ obtained is also influenced by organizational

activities in the process of organ collection. Organs can also be obtained from a living donor – then these are *ex vivo* transplants. The procedure for obtaining organs is then slightly different and less complicated [18].

In the initial period, organs from donors were collected in designated hospitals that ran transplant centers. This involved sending corpses to these centers, which often caused conflicts with the families of the deceased. In the 1990s, attempts were made to improve the system of collecting organs for transplantation. In 1996, the Organizational and Coordination Center for Transplantation *Poltransplant* was established. It is a budget unit subordinate to the Ministry of Health and Social Welfare, established under the Transplantation Act of 1996. The *Poltransplant* office is located in the Infant Jesus Hospital in Warsaw [18]. The process of collecting organs for transplantation requires extensive knowledge, responsibility, planning, and efficient flow of information at many levels. It is also difficult because in this process (especially when it concerns *ex mortus* transplants) one should not skip the conversation with the family, providing them with sufficient information, care and support [19].

Transplant coordinators play an important role in this process. A transplant coordinator is a person responsible for the organization, supervision and coordination of the entire process of organ procurement. Usually, this is a specialist with medical education, e.g. a doctor or nurse, who deals with a wide range of activities, from the identification and qualification of donors, through the organization of the procurement process, to the care of transplant recipients. Coordinators also deal with documentation and education, organizing workshops and information campaigns. In order to effectively perform their duties, coordinators must have knowledge in the field of clinical transplantology, immunology, intensive care, but also in clinical psychology, law, and organization and management. In countries with a well-developed network of transplant coordinators, such as Spain, the Netherlands or the United States, the number of donors who are identified and qualified for transplants is much higher, and the system functions more efficiently. In Poland, however, there is a shortage of coordinators, and their tasks are usually limited to transplantation centers or regional coordinators. Finding the right specialists in hospitals where potential donors are identified is difficult, and the system still requires improvement. A special role is played by local coordinators, who work in hospitals where it is possible to identify potential deceased donors, and therefore where organs can be collected for transplantation. In Poland, the transplant system has undergone significant changes in recent years. According to data from the

Supreme Audit Office (NIK) from the first half of 2021, there were 388 hospitals in the country with the potential for organ donation, of which 255 facilities (66%) employed a total of 314 transplant coordinators [20].

The process of organ collection begins with the identification of the donor and reporting to the regional coordinator. In order to streamline the activities, a so-called 6-step strategy was developed (Table 1). After the collection of organs, the team involved in donor identification receives written and oral information from the coordinator about the results of the transplanted organs. The donor's family also receives information and support, but the recipient remains anonymous. Even if the diagnosis of brain death is clear, families often experience emotional resistance to this decision, especially in the case of young people who have suffered serious injuries or accidents. In such situations, a key role is played by anaesthesiologists who ensure appropriate communication with the family, providing support and explaining difficult issues related to the diagnosis and the possibility of organ collection. Poltransplant organizes training for anaesthesiologists, which aims to prepare them to conduct difficult conversations with the families of the deceased. In Poland, the family of the deceased formally has no right to object to organ donation, because the principle of presumed consent applies. The decision to donate organs depends solely on whether the deceased person objected during life in the manner provided for by law. If no objection was raised, it is assumed that the deceased agreed to be a donor. Despite the legal basis of organ donation based on "presumed consent", each interaction with the family should be full of respect, sensitivity and care. Failure in this respect can lead to social resistance to transplantation, which is why proper communication and emotional support are so important and should accompany the entire process [18, 21].

NUMBERS IN POLAND AND THE WORLD – HEART TRANSPLANTATION

From 1985 to 2023, 3,272 heart transplants were performed in Poland. Out of 38,288 total transplants, this is 8.55%. The table shows the last 10 years of the annual summary by the Polish Society of Transplantology. According to the WHO global reports, in 2021 (this is a report from December 2022), hearts were transplanted 8,409 times, which was 5.82% of all 144,302 transplants in the world. Although the result is reduced by 0.42% of all transplants compared to the previous year, 308 more transplants were performed than in 2020. Bar chart showing the distribution of heart transplants performed on individual continents in 2020.

In the years 2013–2023, the number of heart transplants in Poland showed a clear upward trend, which is reflected in the data presented in the table. In 2013, only 87 heart transplants were performed, which constituted 5.40% of all organ transplants in the country. In the following years, this number systematically increased, reaching a maximum in 2021– 200 transplants, which constituted as much as 14.99% of all transplants, which may be the effect of increased activity after the period of pandemic restrictions in 2020. In 2023, 182 heart transplants were performed, which – despite a decrease compared to 2021 – still indicates a persistently high level of transplant activity [22].

The increase in the number of heart transplants can be associated with advances in diagnostics, patient qualification, the development of organ perfusion technology, as well as improvements in the organization of donation. It is interesting, however, that despite the growing number of transplants performed, the total number of transplants (of all organs) did not show a stable increase- for example, in 2014 and 2015, 1,619 and 1,508 transplants were performed, respectively, while in 2021 there were only 1,334. This means that the share of heart transplants in the total number of transplants in Poland increased not only due to the increase in the number of these operations, but also as a result of a decrease in the transplantation of other organs in some years. Such a phenomenon may indicate the need for further analysis of human resources and infrastructure in the transplant system. The years 2017 and 2018 are also particularly important, as there was a decrease in the number of heart transplants (97 and 145, respectively), which may suggest local organizational problems, a temporary limitation in the availability of donors, or the effects of legislative changes. In total, however, the data for the years 2013–2023 reflect a clear trend in the development of Polish heart transplantology, with the simultaneous need to continue supporting it through systemic and social activities, such as educating the public about organ donation, developing donation programs after cardiac arrest (DCD) or expanding donor qualification criteria (Table 2) [23–25].

The second graph illustrates the number of heart transplants in individual WHO regions and confirms the significant disproportion in access to transplantology between world regions. The Americas region (mainly the USA and Canada) leads with 4,419 transplants per year, while the European region – second in terms of the number of transplants – performs 2,513 operations per year. The Western Pacific region is next in line (949 transplants), and much lower values are observed in Southeast Asia (122), the Mediterranean region (98), while the African region does not record any heart transplants (Fig. 1).

Table.1. 6 Step Strategy

STEP I Identification of potential organ donors among the deceased (ICU patients – with symptoms of brain death)
STEP II Fulfillment of legal and clinical requirements necessary for organ collection (data from medical history, previous laboratory tests, bacteriological, viral, fungal, tumor tests, certifying brain death)
STEP III Assessment of organ use, fulfillment of legal and social requirements: organ collection in accordance with Polish legislation, proper conduct of conversation with family, relatives.
STEP IV Appropriate care for the potential donor (limitation of the negative impact of systemic disorders related to brain death on the biological quality of organs)
STEP V Correct collection of organs for transplantation (protection against ischemia and ensuring proper transport)
STEP VI Selection of the appropriate recipient based on established criteria

Source: [14]

Table 2. The last 10 years of the annual summary by the Polish Society of Transplantology

Year	Heart transplants	Total	Percent of heart transplants to all transplants [%]
2023	182	1898	9,59
2022	173	1495	11,57
2021	200	1334	14,99
2020	145	1236	11,73
2019	142	1541	9,21
2018	145	1447	10,02
2017	97	1608	6,03
2016	101	1545	6,54
2015	99	1508	6,56
2014	76	1619	4,69
2013	87	1610	5,40

Source: [20]

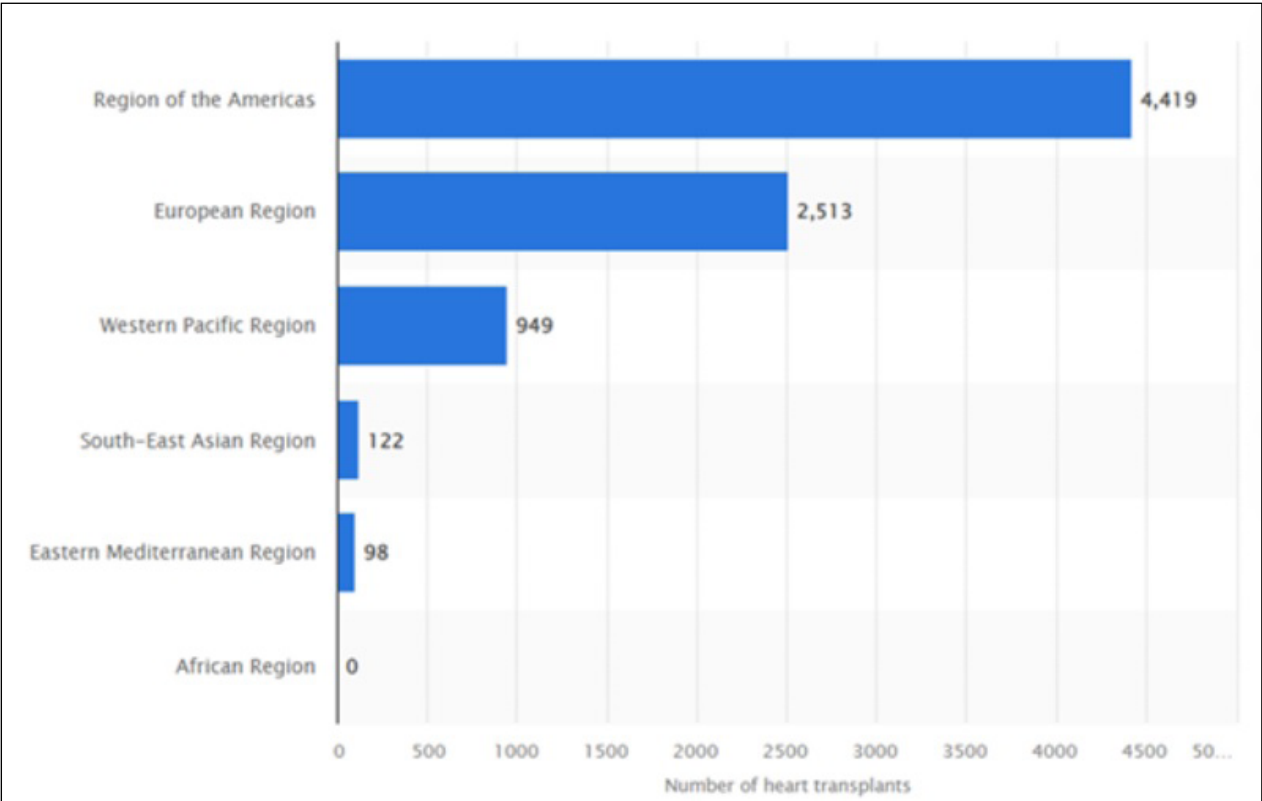


Fig. 1. Bar chart showing the distribution of heart transplants performed on each continent in 2020

Source: [21]

These data indicate inequalities resulting from the level of development of healthcare systems, infrastructure, availability of qualified personnel and cultural and legislative conditions in the field of organ donation [26].

In the context of heart transplantation, Poland still remains below the European average, but the gradual increase in the number of transplants indicates a positive direction of change. Despite systemic difficulties and organizational challenges, the years 2020–2023 have shown that the transplant system in Poland is resistant to crises such as the COVID-19 pandemic. The data indicate the need for further development of programs to increase the number of donors and intensification of educational activities in society.

CONCLUSIONS

Modern transplantology in Poland and around the world is developing dynamically, although with visible regional differences. In Poland, the activity coordinated by *Poltransplant* focuses on increasing the number of deceased donors and improving the organization of transplants, but the system still struggles with social barriers, a shortage of specialized personnel and limited infrastructure. These difficulties became particularly visible during the COVID-19 pandemic, when transplant activity was drastically reduced, despite the implementation of new safety procedures. At the same time, Spain is the world leader, achieving the highest donation rate (over 52 deceased donors per million inhabitants), thanks to an effective coordination system, modern technologies and wide social acceptance.

Globally, there is an increase in the number of transplants, the development of specialized teams for organ procurement and the increasing role of international organizations such as WHO, which develop strategies to ensure ethical and equitable access to transplantation. Common challenges include the development of donor registries, improving social education and the use of technologies such as ECMO and *ex vivo* perfusion.

The development of transplantology in Poland has resulted in the establishment of many specialist centres. However, the problem remains the low availability of organ donors for transplantation. The development of clinical transplantology will be possible thanks to the activity and actions promoting reliable knowledge about organ donation and transplantation. Social awareness plays a significant role- the knowledge that in order to save someone's life, an organ is needed. The hope for a better understanding of the relationship between transplantation and saving human life encourages us to get involved in the process of creating a culture of life in the modern world, where there are many ambiguities and negative stereotypes surrounding transplantology.

According to data from the Central Statistical Office, in 2019, deaths due to CVD amounted to 39% of all deaths. A year later, 72,095 citizens of the Republic of Poland died of CVD. Which, compared to the result of 181,984 of all deaths, gave 39.6% of the causes of all deaths in 2020. In 2021, the number of deaths due to diseases related to vessels and, of course, the heart increased by over 150% compared to the previous year and amounted to 180,662. 270,662 people died then, which constitutes 66.74% of all deaths in 2021. The conclusion from this is very simple- more and more people are dying from circulatory system diseases, so the event that was started in the world by Christiaan Barnard, continued by other colleagues, cardiac surgeons, including Professor Zbigniew Religa and Prof. Marian Zembala, and is continued by their sons, Professors Michał Zembala and Grzegorz Religa, was, is and will be a great step in saving human life. The future of transplant medicine depends to a decisive extent not only on the willingness and knowledge of doctors, existing legal solutions, but also on the level of social acceptance, the spread of attitudes ready to come to the aid of another person. Any opposition, even well-motivated from a moral and ethical point of view, is ineffective against therapy, effective, but above all the only possibility of saving life.

REFERENCES

1. Nielubowicz J, Tak to się zaczęło [That's how it started]. *Wiedza i Życie*, 1996;1:10-15. (Polish)
2. Skarek A, Pośmiertne oddanie organów – kwestie prawne i etyczne w protokole II do EKB w sprawie transplantacji organów i tkanek pochodzenia ludzkiego [Posthumous organ donation – legal and ethical issues in Protocol II to the European Cancer Council on the Transplantation of Organs and Tissues of Human Origin]. *Kardiolog Torakochirurg Pol*. 2008;5(3):339-344. (Polish)
3. Jankowska I, Wybrane zagadnienia etyczne dotyczące przeszczepiania narządów od żyjącego spokrewnionego dawcy [Selected ethical issues regarding organ transplantation from a living related donor]. *Stand Med Pediatr*. 2009;5:829-832. (Polish)
4. Skowrońska-Petrozolin B, Transplantologia wczoraj i dziś [Transplantology yesterday and today]. *Nowa encyklopedia powszechna PWN*. PWN, Warszawa, 1998, p. 45. (Polish)
5. Fibak J, Chirurgia – repetytorium [Surgery – revision]. *Wydawnictwo Lekarskie PZWL*, Warszawa, 2004. (Polish)
6. Muszala A, Encyklopedia bioetyki, Wydawnictwo Polwen, Radom, 2009. (Polish)

7. Szczepaniak L, Transplantacja – próba syntezy etycznej [Transplants – an attempt at ethical evaluation]. *Bioetyczny Zeszyt Pediatr* 2005;2(2):63-87. (Polish)
8. Coronavirus: COVID-19 Information for Transplant Professionals, www.bts.org.uk [Access:27.08.2012].
9. Rowiński W, Wałaszewski J, Pączek LR. *Transplantologia kliniczna* [Clinical transplantology]. Wydawnictwo Czelej, Warszawa, 2004. (Polish)
10. Sterkowicz S. Historia medycyny. Historia pierwszych transplantacji serca w Polsce [History of medicine. The history of the first heart transplants in Poland]. *Kardiochir Torakochir Pol* 2009, 6.3, 313-316. (Polish)
11. Osuchowski P. Gra o życie [Game of life]. PZWL, Warszawa, 1988. (Polish)
12. Sterkowicz S. Czterdzieści lat później, Transplantacja serca – wczoraj, dziś, jutro [Forty Years Later: Heart Transplantation – Yesterday, Today and Tomorrow]. *Kardiochirurg Torakochirurg Pol*. 2007, 4(4), 423-427. (Polish)
13. 56. Rocznicą pierwszej próby przeszczepu serca w Polsce, https://polskieradio24.pl/artykul/2240796%2C56-rocznica-pierwszej-proby-przeszczepu-serca-w-polsce-posluchaj-wspomnien-lekarza-ktory-przeprowadzil-operacje?utm_source=chatgpt.com [Access: 4.01.2025]. (Polish)
14. Penninga L, Penninga EI, Möller CH, Iversen M, Steinbrüchel DA, Gluud C. Tacrolimus versus cyclosporine as primary immunosuppression for heart transplant recipients. *Cochrane Database Syst Rev*, 2013 May 31, 5, CD008817. doi: 10.1002/14651858.CD008817.pub2. DOI
15. Szumilas K, Wilk A, Wiśniewski P, Gimpel A, Dziedzicko V, Kipp M, Pawlik A. Current status regarding immunosuppressive treatment in patients after renal transplantation, *Int J Mol Sci* 2023 Jun 18;24(12):10301. doi: 10.3390/ijms241210301. DOI
16. Kucharska E, Necek R. Transplantacja w trosce o zdrowie i życie bliźniego. [Transplantation for the sake of the health and life of another person]. *Przegl Lek*. 2011;68(12):1208-1214, PMID: 22519283. (Polish)
17. Lisiecki T, Płocka-Molińska M, Kędziora-Kornatowska K. Postawy społeczeństwa wobec przeszczepiania narządów od dawców żywych i martwych [Attitudes of selected social groups towards their informed consent to harvesting organs for transplantations]. *Pol Med Rodz*. 2004;6(1):298-301. (Polish)
18. Mąkosa P, Olszyńska A, Petryszyn K, Kozłowska H, Tomszys E, Stoltmann A, Małyszko J. Organ procurement in Poland: legal and medical aspects, *Transplant Proc*. 2020 Sep;52(7):2015-2025. doi: 10.1016/j.transproceed.2020.01.120. DOI
19. Foryś Z, Dębska G, Królczyk C. Transplantologia wczoraj i dziś. [Transplantology yesterday and today]. In: Dobrowolska B, Foryś Z, Jaśkiewicz J (eds). *Pielęgniarstwo na rzecz milenijnych celów rozwoju* [Nursing for the Millennium Development Goals]. Krakowska Akademia im. Andrzeja Frycza Modrzewskiego, Kraków, 2014, pp. 33-46. (Polish)
20. Rutkowski B. Wytyczne dotyczące zasad zgłaszania, kwalifikacji i przygotowania zmarłych dawców do pobrania narządów – przewodnik praktyczny [Guidelines on the principles of reporting, qualifying and preparing deceased donors for organ donation – a practical guide]. *Via Medica*, Gdańsk, 2009. (Polish)
21. Kruszyński Z. Wykłady z anestezjologii i intensywnej terapii. Przygotowanie dawcy narządu [Lectures on anesthesiology and intensive care. Organ donor preparation]. Wydawnictwo Lekarskie PZWL, Warszawa, 2009. (Polish)
22. Statystyka przeszczepiania narządów od zmarłych dawców w latach 1985-2023 [Statistics of organ transplantation from deceased donors, 1985-2023]. <https://www.poltransplant.org.pl/biuletyny.html> [Access: 3.05.2025]. (Polish)
23. Yancy C, Jessup M, Bozkurt B, Butler J, et al. ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017 Aug 8;136(6):e137-e161. doi: 10.1161/CIR.0000000000000509. DOI
24. Vieira J, Cherikh S, Lindblad K, Stehlik J, Mehra R. Cocaine use in organ donors and long-term outcome after heart transplantation: an International Society for Heart and Lung Transplantation registry analysis. *J Heart Lung Transplant*. 2020 Dec;39(12):1341-1350. doi: 10.1016/j.healun.2020.08.018. DOI
25. Stehlik J, Edwards B, Kucheryavaya Y, Aurora P, Christie D, Kirk R, Hertz I. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report – 2010. *J Heart Lung Transplant*. 2010 Oct;29(10):1089-103. doi: 10.1016/j.healun.2010.08.007.
26. Estimated number of organ transplantations worldwide in 2020, <https://www.statista.com/statistics/398645/global-estimation-of-organ-transplantations/> [Access: 1.07.2025].

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Katarzyna Grudnik

Faculty of Medical Sciences in Zabrze,
Medical University of Silesia in Katowice,
Student Scientific Society at the Chair and Department
of Environmental Medicine and Epidemiology,
Zabrze, Poland
e-mail: katarzyna.grudnik15@gmail.com

ORCID AND CONTRIBUTIONSHIP

Maciej Słomian: 0009-0008-9060-2860 **A** **B** **D**
Katarzyna Grudnik: 0009-0006-1583-0041 **A** **B** **D**
Małgorzata Grudnik: 0009-0000-4959-8830 **A** **B** **D**
Julia Smyczek: 0009-0002-8882-7776 **A** **B** **D**
Mateusz Jagielski: 0009-0004-2482-7253 **A** **B** **D**
Karol Płaszewski: 0009-0004-3432-9792 **A** **B** **D**
Karolina Lau: 0000-0002-8654-0301 **E** **F**
Janusz Kasperczyk: 0000-0002-6945-1200 **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: 18.04.2025

ACCEPTED: 16.08.2025



Research of Ukrainian scientists on the development of national medical education systems: A meta-analysis

Borys P. Savchuk¹, Olga Y. Snitovska², Halyna M. Tsaryk², Oleg Ya. Dovgij¹, Ivanna R. Humenna³, Larysa Ya. Fedoniuk³, Halyna V. Bilavych¹

¹VASYL STEFANYK PRECARPATHIAN NATIONAL UNIVERSITY, IVANO-FRANKIVSK, UKRAINE

²DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

³I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

ABSTRACT

Aim: To carry out a holistic structured reconstruction of the Ukrainian scientific discourse of the 1990s and the first quarter of the XXI century on the development of medical education in foreign countries on the basis of the developed meta-analysis programme.

Materials and Methods: the developed meta-analysis programme integrates the general meta-analysis methodology and methods of monographic and relevant analysis, discourse analysis, content analysis, historiographic, paradigmatic, and phenomenological analysis. These tools have been used to analyse three samples of scientific papers on the development of national medical education systems that appeared in Ukraine in the 1990s and the first quarter of the twenty-first century: the general population (the total number of papers is about 1450); a sample population (380), and a representative sample (70). 20 bibliographic indexes were processed to determine the general population (GP – total number) of scientific papers published in 1991–2024. A search was conducted via the Google engine using a combination of three groups of keywords that denoted: a) the type of publication (monograph, dissertation, article); b) the subject of the study (development of medical education abroad; training of doctors/nurses abroad, etc.); c) a list of countries and regions.

Conclusions: the results of the study showed that the historiography of the problem mentioned above has a pronounced interdisciplinary, multi-level, speciality-oriented character. The analysis of the dynamics of scientific knowledge accumulation has shown that the researchers have moved away from studying foreign experience of vocational training of healthcare professionals through the prism of its use in Ukraine under the influence of European integration processes and have begun to study national medical education systems as a separate subject. The focus of scientists' attention was revealed to be drawn to the study of trends in the development of national medical education systems, related to decentralisation of management, strengthening of university autonomy, requirements for the selection of applicants, etc.

KEY WORDS: medical education, meta-analysis, foreign countries, training of medical professionals

Wiad Lek. 2025;78(9):1886–1892. doi: 10.36740/WLek/212532 DOI

INTRODUCTION

In the 1990s and the first quarter of the XXI century, Ukraine has been consistently implementing the course of European integration and joining the world educational and scientific space. This led to an increase in the attention of scientists to the study of foreign experience in medical education. As a result, a significant amount of scientific literature on this issue has been accumulated. The meta-analysis methodology is an effective tool for its holistic structured study. We consider the implementation of such a research project to be of interest to scientists and doctors from different countries for scientific self-reflection and comparison of different national receptions of medical education in foreign countries.

AIM

To carry out a holistic structured reconstruction of the Ukrainian scientific discourse of the 1990s and the first quarter of the XXI century on the development of medical education in foreign countries on the basis of the developed meta-analysis programme.

MATERIALS AND METHODS

Meta-analysis was first used in experimental medicine. Over time, this effective methodology has been adapted in the social sciences for the analysis of large amounts of scientific literature [1–7]. Based on this scientific experience and considering the subject of our study, we have developed our own meta-analysis

programme. It involves solving the following tasks in a systematic way: 1) development of criteria for inclusion/exclusion of original research into the scope of meta-analysis; 2) search and selection of studies according to the defined criteria; 3) determining and evaluating various parameters (content, methodology, quality, etc.) of the studies included in the meta-analysis; 4) assessment of their statistical heterogeneity.

More than 20 bibliographic indexes were processed to determine the general population (GP – total number) of scientific papers published in 1991-2024. A search was conducted via the Google engine using a combination of three groups of keywords that denoted: a) the type of publication (monograph, dissertation, article); b) the subject of the study (development of medical education abroad; training of doctors/nurses abroad, etc.); c) a list of countries and regions.

The resulting GP consisted of more than 1450 selection units (publications). According to the fixed effects model (after M. Borenstein [5], R. Rosenthal, M. DiMatteo [6]), a sample population (SP) consisting of about 380 selection units was formed for the secondary analysis. The selection was based on formal and content criteria (title; author; time and place of publication; type, rank, form of presentation). Priorities were given to theses and monographs, as well as original scientific articles.

Along with the method of meta-analysis, the examination of the SP was carried out using effective methods of monographic and relevant analysis as well as the main body of knowledge [1]; discourse analysis and content analysis [7]; methods of historiographic [8], paradigmatic [9], and phenomenological [10] analysis. The examination of the studies of the SP was carried out according to formal quantitative and qualitative criteria: structural and content characteristics (common, special); year of publication; author's personality; source base; methodological level; territorial vector; novelty of content, etc. Based on the results, the third sample was formed – the representative sample (RS), which consisted of 70 studies. Given that the RS fundamentally reflects the main features of the GP and the SP, it was used as the basis for the subject meta-analysis.

REVIEW AND DISCUSSION

The meta-analytical study of the research conducted by Ukrainian scientists on the development of medical education abroad is based on six main parameters: 1) diversity; 2) stages of scientific knowledge accumulation; 3) territorial spectrum; 4) methodology; 5) subject matter; 6) originality.

The GP is taken as the basis for determining the first parameter, as it gives a general idea of the

share of different types of studies on the problem under discussion. The results of formal quantitative calculations revealed that out of the 1450 units selected, scientific articles accounted for about 43%; materials (abstracts) of scientific conferences – 34%; dissertations – 4%; monographs – 2%; bibliographic indexes and other types of literature – 17%. However, it is dissertations and monographs, which, along with a number of scientific articles, formed the basis of the RS, that reflect the qualitative indicators of the growth of new knowledge on the problem under study. It should be noted that our analysis concerns only subject-specific studies and does not take into account numerous studies that address its individual aspects.

The second parameter is the pivotal one, since it outlines the changes in other components of the meta-analytical study. In general terms, the dynamics of the increase in scientific knowledge on the problem under consideration is reflected in three somewhat conditional periods: 1) post-Soviet (1991-2000), when Ukrainian scientists began to study foreign experience in medical education impartially, getting rid of old ideologies; 2) pro-European one (2001-2009/2010), when research priorities shifted to the context of Ukraine's accession to the Bologna Process; 3) country studies (since 2011/2012), when there was a conceptual reorientation of studies towards the exploration of national medical education systems of individual countries.

In this context, the third parameter was changing: the territorial range of research was gradually expanding, but remained rather narrow in general. According to formal, a priori approximate, but informative calculations, about 30% of scientific papers were related to the development of medical education in the USA; 37% – in the UK, Poland, Germany, Austria, Canada; 33% – in other European countries and, to a lesser extent, in the Asian region (China, India, Japan).

The modification of the fourth parameter – methodology – is determined by a number of key features and components: interdisciplinarity; category and conceptual apparatus; scientific and analytical tools; the nature of scientific discourse, etc. The systematic analysis showed that most of the research on the issue under consideration was developed at the intersection of medicine and pedagogical comparative studies, which examines foreign education systems. In particular, theses were mainly prepared by certified medical professionals under the supervision of pedagogical scientists and defended in the specialties of general pedagogy and history of pedagogy, as well as theory and methods of vocational education. Many articles were written by experts in the fields of economics, public administration, philosophy of

education, etc. This was reflected in the research methodology, as the authors a priori used analytical methods developed in their fields of expertise.

The terminology became a weak point of many studies, since the researchers mainly used the definitions accepted in Ukrainian science, which are not always consistent with the categorical apparatus used in the national medical education systems of the countries under study. It was also found that Ukrainian authors neglected the scientific and analytical tools developed by foreign scientists to study the professional training of future doctors and nurses in higher education institutions. The descriptive style of presenting research results and the neglect of synergy methods led to a linear descriptive coverage of the functioning of foreign medical education systems as such that develop only in an upward direction, constantly progress, do not experience qualitative and quantitative fluctuations, stagnation and crisis phenomena.

A positive trend towards understanding the functioning of foreign medical education systems from the perspective of pluralism has been observed in the works of the last decade. Acknowledging that it is difficult to achieve "generally accepted knowledge" within a certain scientific paradigm or a specific research problem, scientists have begun to critically evaluate the theory and practice of vocational training of healthcare professionals in foreign countries from the perspective of alternative and controversial views and then compare it with the corresponding domestic models.

The most difficult fifth parameter of the meta-analysis requires the clarification of the general thematic and content range of studies and their internal structure. Important insights into these priorities are provided by the analysis of the SP by titles and keywords of publications carried out using the method of relevant analysis (according to O. Adamenko [1]). The obtained results are classified into concepts-lexemes, which are divided into groups according to the frequency of use (by the formula 40-30>29-20>19-10>9-1). These groups denote the following:

I. Subject area (sphere), direction, content of the research: 'medical education', 'higher medical education', 'pharmaceutical education', 'training of future doctors/nurses' (40-30); 'university education' (29-20); 'continuing/postgraduate medical education', 'advanced training' (19-10).

II. Direction, trend, structure of the training process: 'development', 'reform' (40-30); 'Bologna Process', 'integration', 'European integration', 'globalisation' (29-20); 'trend', "transformation", 'system' (19-10).

III. Aims and results: 'quality of medical education/training' (40-30); 'professional culture', 'competence',

'professional competence' (29-20); "readiness"; 'professional communication', 'professional ethics' (19-10).

IV. Organisation of the educational process: 'training', "credit-module system" (40-30); "methods", 'methodology', "theory and practice", "model" (29-20).

V. Object of study: 'future doctors/nurses/pharmacists', 'medical students' (29-20); 'masters', 'bachelors' [by specialities] (19-10); 'teachers' (9-1).

Based on the aforementioned territorial vectors, three priority thematic and content blocks of studies on the development of medical education abroad have been identified. The first, dominant one – Euro-Atlantic – reflects the study of the problem in the global and regional-European context. The strengthening of this trend at the beginning of the XXI century is evidenced by the information-analytical and educational materials prepared by teams of scientists [11-13], which reveal the impact of globalisation and European integration on the processes of standardisation and quality improvement of medical education (unity of approaches to licensing and accreditation; recognition of diplomas and certificates; international cooperation), etc.

The second block is represented by a large group of studies in which foreign experience in the development of medical education is revealed in terms of Ukraine's integration into the Bologna process and its implementation in the national system of training future as well as certified doctors, pharmacists, nurses, etc. (Y. Voronenko, S. Hordiyshuk, N. Leonchenko, V. Kazakov, M. Pervak, O. Panasenko, V. Buriak, A. Kaplaushenko, O. Sichkoriz, O. Talalaenko, etc.). A number of works highlight the experience of European integration of individual educational institutions, for example, the Bogomolets National Medical University [12] and others.

The third historiographical block outlines the country studies and thematic diversity of research, so it is considered in the context of the sixth parameter of the meta-analysis, which is related to the originality of individual studies. On the one hand, they reflect the general national reception of the development of medical education abroad, and, on the other hand, they show the personal contribution of researchers to the study of this problem. Given the limited scope of the article, we synthesise this legacy from the perspective of phenomenology, highlighting the productive narratives that are characteristic of each work.

T. Khvalyaboga's doctoral thesis (2020) presents a comprehensive analysis of the history of professional training of doctors at US universities in two stages: pre-reform (early XVII century – 1910), which indicates its formation in the conditions of functioning of unaccredited private schools, and post-reform (1910

– early XXI century).), when the system of academic medical education was formed due to the introduction of accreditation, expansion of the list of professional disciplines, increasing role of scientific research, etc. It is the models of its functioning developed by the researcher that look interesting: structural (covering bachelor's, MD and DO degree programmes that are implemented in hospitals and consulting schools) and functional (denoting the undergraduate and postgraduate stages of professional training of doctors) [14]. Such a reception holistically reflects the essence of the phenomenon under study and creates the foundation for its comparison with the models of medical education in other countries.

We can compare the above-mentioned paper with M. Shumylo's dissertation (2023) on the functioning of the system of higher medical education in the USA in the XX-XXI centuries. Having traced its genesis since 1620, the author analysed the factors behind its development (social conditions, level of education, multiculturalism, decentralisation of education management, financial and technological support) and characterised current trends of modernisation in the form of strengthening state control over the quality of education as well as diversification of medical training specialities, etc. These two papers provide an example of how differently the content is revealed in studies that are similar in subject matter [15].

The studies on the development of higher medical education in the UK are also worth comparing. K. Magrlamova's doctoral thesis outlines the concept of its functioning, which is manifested in the following aspects: implementing strategies for professional training of international medical organisations; integrity of medical education as an open system that is subject to influence on the part of social factors and includes target, theoretical and methodological, organisational, content, technological and performance components; and the graduated system, which is implemented through the alternate obtaining of bachelor's, master's and doctoral degrees. This paper is favourably distinguished by showing the peculiarities of medical education in different regions of the country (England, Ireland, Wales, Scotland), clarifying the impact of Brexit on its development and showing this process in the dynamics of five stages. The presented classification of British medical education institutions divides them by the nature of their functioning ('old', 'new', 'open') and by the organisational structure (federated, collegiate, unitary), etc. [16].

A comprehensive understanding of the system of professional training of family doctors in the UK medical schools is provided by the work of I. Palamarenko, who showed its genesis, organisational principles, structural

components and characteristics of its functioning stages: admission; enrolment; professional training process; postgraduate education; advanced training. It is highlighted that the balance of its development ensures the alignment of public needs for medical services and personal interests of future doctors, which are determined at the stage of pre-professional training [17].

Along with the works mentioned above, which claim to provide a comprehensive understanding of national medical education systems, we note studies that reveal individual areas and components of their functioning. Thus, having carried out a comparative analysis of the formation of the communicative culture of medical students in the UK and the USA, Y. Hrebenyk-Kozachenko revealed the common and special features of their organisational and pedagogical foundations [18]. Also, from the perspective of Ukrainian didactics, N. Symonenko showed the organisation of independent work of students in medical colleges and universities in the United States [19].

The 'overseas' vector of research is expanded by the work of Yu. Lavrysh on the training of nurses in Canadian universities. She gives an example of the approach described above, when the model of medical education of a particular country is revealed through the prism of general standards and characteristics inherent in all national systems of professional education. From this perspective, the author has shown the peculiarities of the tiered training of nurses in Canada (bachelor's, master's, doctoral degrees in nursing): differentiation by specialties and curricula; focus on psychological, pedagogical and technological training; continuity of professional development through the activities of professional associations, etc. [20].

The 'European' vector of the research on medical education is widely represented by studies on its development in German-speaking countries and Poland. As an example, N. Kuchumova's comparative analysis of the national models of pre-professional, professional, and postgraduate medical education in Switzerland, Germany, and Austria is worth mentioning. According to the author, the general trends of European policy contributed to the unification of their standards and the transition to the principles of student centred and patient orientation approaches [21]. By contrast, H. Klishch's thesis proves that along with European standards, the development of medical education in Austria was determined by the national reforms that defined its 41 standards and priorities for modernising the clinical base, attracting the best researchers and medical practitioners to teach, and preparing students to conduct preventive and educational work with citizens [22].

Among the studies that reflect the development of Ukrainian medical polonistics, the monograph by L. Hryshchuk and V. Horodetsky (2006), who conducted a systematic analysis of the history of medical education in Poland with an emphasis on trends and experience of its modernisation during the 80s and 90s of the XX century, should be noted [23]. Also, the thesis of K. Khomenko (2017) on the formation of professional competence of future doctors in Polish universities in 1990-2015 is worth noting. The author showed this process through the prism of three stages: creation of the structure and transformation of medical universities activity on the basis of European democracy (1990-2005); content and procedural transformation of medical education (2005-2011); its modernisation through the transition to European standards (2011-2015) [24].

The increase in knowledge of medical polonistics is reflected in numerous scientific articles that reveal the peculiarities of the formation of the Polish model of European medical education (N. Dzhavadova, T. Kovalchuk, B. Pereviznyk) as well as the experience and innovative methods of organising the educational process in higher medical education institutions in Poland (A. Bedeniuk, T. Bodnar, A. Dorofeev, T. Myahkova, V. Khorostovska, etc.).

The dissertation defended in Ukraine by a Polish researcher P.-B. Uliash on the impact of relations between Poland and Ukraine on the development of higher medical education and science in these countries in the XIII – early XX centuries deserves special mention. Unlike Ukrainian studies that focus on contemporary processes, the author showed the stages and factors of the creation of medical institutions, their borrowing of European experience, the spread of Polish influence from the western parts of Ukraine to the eastern ones, etc. in a retrospective of seven centuries [25]. This study confirms that over the centuries, medical education in Ukraine has been developing in line with the European educational space, so under current conditions it is not 'entering' [for the first time], but rather 'returning' to it.

The concept of the continuity of medical education is a central theme in the studies of the development of medical education abroad. In the current historiographical situation, the monograph "The System of Continuous Medical Education" (1994) is still relevant, in which, based on extensive factual material, the authors gave a detailed description and compared the peculiarities of its development in Europe, Central and South America, and India [26]. In the absence of other significant works on this issue, we note the dissertation of N. Belousova (2021), which described the professional training of medical representatives of pharmaceutical companies in Germany as an original

model of continuing education development. In this context, the organisational, legal, and didactic support for pharmacists' advanced training is analysed and the experience of solving this problem across the EU countries is compared [27].

At the beginning of the XXI century, the study of nursing education gained momentum in Ukraine. An important role in this is played by the scientific and practical journal 'Nursing' published by Ternopil National Medical University. Its first issue in 2006 alone contained two dozen articles on European standards and the American experience of its development. Among the comprehensive studies on this issue, K. Picon's thesis (2021) on the training of nursing specialists in the US tiered education system is worth mentioning. Having shown a century-long retrospective of its formation and the complexity of the modern organisational structure, the author described the specifics of nursing training at different levels of higher education (junior specialist, bachelor's, master's, doctoral degrees in nursing) and presented a comprehensive model for comparing nursing training systems in the USA and other countries [28].

Given that Ukraine is in a state of war and the prospects for post-war development, the study of foreign experience in the organisation of military medical education is of particular importance. The need for a profound understanding of this problem is evidenced by the works of I. Honcharenko, B. Klishevych, and V. Furdyk on its development in developed countries, in particular, in NATO.

CONCLUSIONS

The developed meta-analysis programme made it possible to identify and cover with a systematic structured analysis a significant array of various works of Ukrainian researchers on the development of medical education abroad accumulated in the 90s of XX – the first quarter of XXI century. The findings of the study revealed that the historiography of the problem mentioned above has a pronounced interdisciplinary, multi-level, profile-oriented character. The analysis of the dynamics of scientific knowledge accumulation has shown that under the influence of European integration processes, scholars have moved away from studying foreign experience of medical education development through the prism of its use in Ukraine and have begun to study its national systems as a separate subject. Despite the increase in the total number of studies, their country studies vector remains rather narrow, focusing on the United States and a number of European countries. Researchers have made significant progress in studying the main trends in the development of

national medical education systems, related to the decentralisation of its management, strengthening of university autonomy and requirements for professional selection of applicants, etc. We believe that the

presented Ukrainian perspective on the development of medical education abroad can become the basis for its comparison with the corresponding research of scientists from other countries.

REFERENCES

1. Adamenko OV *Ukrainska pedahohichna nauka v druhii polovyni XX st.* [Ukrainian pedagogical science in the second half of the 20th century]. Luhansk: Alma-mater. 2005, p.708. (Ukrainian)
2. Conley CS, Durlak JA, Kirsch AC. A Meta-analysis of universal mental health prevention programs for higher education students. *Prev Sci.* 2015;16(4):487-507. doi: 10.1007/s11121-015-0543-1. DOI
3. Corcoran J. Meta-Analyses. *The Handbook of Social Work Research Methods* / ed. by B. Thyer. London; Washington: SAGE. 2010, pp.299–312.
4. Field AP. Is the meta-analysis of correlation coefficients accurate when population correlations vary? *Psychol Methods.* 2005;10;4:444–467. doi: 10.1037/1082-989X.10.4.444. DOI
5. Borenstein M., Hedges L., Higgins J., Rothstein H. *Introduction to Meta-Analysis.* John Wiley & Sons, Ltd. 2009, p.413.
6. Rosenthal R, DiMatteo MR. Meta-analysis: Recent developments in quantitative methods for literature reviews. *Ann Rev Psychol.* 2001;52:59–82. doi: 10.1146/annurev.psych.52.1.59. DOI
7. White MD, Marsh E. Content Analysis: A Flexible Methodology. *Library Trends.* 2006;55(1):22-45. doi: 10.1353/lib.2006.0053. DOI
8. Kalakura YaS. *Metodolohiia istoriohrafichnoho doslidzhennia* [Methodology of historiographical research]. Kyiv: «Kyiv University». 2016, p.319 (Ukrainian)
9. Romanenko MI. *Profesiina pidhotovka simeinykh likariv u vyshchykh medychnykh shkolakh Velykoi Brytanii* [Social and paradigmatic-cognitive determinants of the development of modern education]. Dissertation Doctor of Philosophy: Dnipropetrovsk. 2003, p.433. (Ukrainian)
10. Alhazmi AA, Kaufmann A. Phenomenological Qualitative Methods Applied to the Analysis of Cross-Cultural Experience in Novel Educational Social Contexts. *Front Psychol.* 2022;13:785134. doi:10.3389/fpsyg.2022.785134. DOI
11. Polyachenko Yu.V. et al. *Medychna osvita v sviti ta Ukraini* [Medical education in the world and in Ukraine]. Kyiv: Book Plus. 2005, p.384. (Ukrainian)
12. Moskalenko VF et al. *Realizatsiia pryntsyviv Bolonskoi deklaratsii v NMU imeni O. O. Bohomoltsia.* [Implementation of the principles of the Bologna Declaration at the O. O. Bogomolets National Medical University]. *Medychna osvita.* 2005;2:24-26. (Ukrainian)
13. Moskalenko VF et al. *Vyshcha medychna osvita i Bolonskyi protses* [Higher medical education and the Bologna process]. Kyiv: Ministry of Health of Ukraine. 2005, p.298. (Ukrainian)
14. Khvaliboga TI. *Teoretyko-orhanizatsiini zasady profesiinoi pidhotovky maibutnikh likariv v universytetakh SShA* [Theoretical and organizational principles of professional training of future doctors in US universities]. Dissertation Doctor of Pedagogical Sciences. Drohobych. 2020, p.557. (Ukrainian)
15. Shumylo MYu. *Rozvytok vyshchoi medychnoi osvity v SShA (XX–XXI st.)* [Development of higher medical education in the USA (XX–XXI centuries)]. Dissertation Doctor of Philosophy. Lviv. 2023, p.292. (Ukrainian)
16. Magrlamova KG *Teoretychni ta praktychni zasady profesiinoi pidhotovky maibutnikh likariv u vyshchykh medychnykh navchalnykh zakladakh Velykoi Brytanii* [Theoretical and practical principles of professional training of future doctors in higher medical educational institutions of Great Britain]. Dissertation Candidate of Pedagogical Sciences Uman. 2018, p. 659. (Ukrainian)
17. Palamarenko IO. *Profesiina pidhotovka simeinykh likariv u vyshchykh medychnykh shkolakh Velykoi Brytanii.* [Professional training of family doctors in higher medical schools of Great Britain]. Dissertation Candidate of Pedagogical Sciences: 13.00.04. Kyiv. 2012, p.227. (Ukrainian)
18. Hrebenyk-Kozachenko YuS. *Orhanizatsiino-pedahohichni osnovy formuvannia komunikatyvnoi kultury studentiv medychnykh koledzhiv Velykoi Brytanii ta SShA* [Organizational and pedagogical foundations of the formation of communicative culture of students in medical colleges of Great Britain and the USA]. Dissertation Candidate of Pedagogical Sciences. Sumy. 2016, p.254. (Ukrainian)
19. Symonenko NO. *Orhanizatsiia samostiinoi roboty studentiv u vyshchykh medychnykh navchalnykh zakladakh SShA* [Organization of independent work of students in higher medical educational institutions of the USA]. Dissertation Candidate of Pedagogical Sciences. Sumy. 2018, p.338. (Ukrainian)
20. Lavrysh YuE. *Profesiina pidhotovka medychnykh sester v universytetakh Kanady.* [Professional training of nurses at Canadian universities: dissertation of the candidate of pedagogical sciences]. Kyiv. 2009, p.256. (Ukrainian)
21. Kuchumova NV, Kuchumova NV. *Rozvytok systemy vyshchoi medychnoi osvity v nimetskomovnykh krainakh (druha polovyna XX – pochatok XXI st.)*. [Development of the system of higher medical education in German-speaking countries (second half of the 20th – beginning of the 21st century)]. Dissertation Candidate of Pedagogical Sciences. Drohobych. 2012, p. 225. (Ukrainian)

22. Klisch GI. Profesiina pidhotovka likariv v avstriiskyykh universytetakh [Professional training of doctors in Austrian universities]. Dissertation Candidate of Pedagogical Sciences. Ternopil. 2013, p.349. (Ukrainian)
23. Hryshchuk LA, Horodetsky VE. Medychna osvita v Polshchi [Medical education in Poland]. Ternopil: Ternopil State Medical University. 2006, p.124. (Ukrainian)
24. Khomenko KV. Formuvannya profesiinoi kompetentnosti maibutnikh likariv u VNZ Polshchi (1990–2015 rr.) [Formation of professional competence of future doctors in Polish universities (1990–2015)]. Dissertation Candidate of Pedagogical Sciences. Kyiv. 2017, p.237. (Ukrainian)
25. Uliyash P-BA. Vplyv polsko-ukrainskykh zviazkiv na rozvytok vyshchoi medychnoi osvity ta nauky v Polshchi ta Ukraini do pochatku XX stolittia [The influence of Polish-Ukrainian ties on the development of higher medical education and science in Poland and Ukraine until the beginning of the 20th century]. Dissertation Candidate of Pedagogical Sciences. Kyiv. 2008, p.237. (Ukrainian)
26. Kazakov VM et al. Systema bezperervnoi medychnoi osvity [System of continuous medical education]. Donetsk. 1994, p.175. (Ukrainian)
27. Belousova NA. Profesiina pidhotovka medychnykh predstavnykh farmatsevychnykh kompanii FRN. [Professional training of medical representatives of pharmaceutical companies in the Federal Republic of Germany]. Dissertation Candidate of Pedagogical Sciences. Kyiv. 2021, p.249. (Ukrainian)
28. Picon KS. Profesiina pidhotovka maibutnikh spetsialistiv medsestrynstva v konteksti pisladyplomnoi osvity u vyshchykh navchalnykh zakladakh SSHA. [Professional training of future nursing specialists in the context of graduate education in higher educational institutions of the USA]. Rivne. 2021, p. 266. (Ukrainian)

The work was carried out according to the research work of I. Horbachevsky Ternopil National Medical University "Foreign language communication in the training system of a modern doctor" (state registration number 0125U000112).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Larysa Ya. Fedoniuk

I. Horbachevsky Ternopil National Medical University

1 Maidan Voli, 46001 Ternopil, Ukraine

e-mail: fedoniuklj@tdmu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Borys P. Savchuk: 0000-0003-2256-0845 **A** **B** **D** **E** **F**

Olga Y. Snitovska: 0000-0002-3086-9503 **D** **E** **F**

Halyna M. Tsaryk: 0000-0003-0994-2910 **D** **E**

Oleg Ya. Dovgij: 0000-0002-9718-3442 **D** **E**

Ivanna R. Humenna: 0000-0002-2830-7878 **D** **E** **F**

Larysa Ya. Fedoniuk: 0000-0003-4910-6888 **D** **E** **F**

Halyna V. Bilavych: 0000-0002-1555-0932 **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: 14.04.2025

ACCEPTED: 27.08.2025



Modern biomaterials for direct pulp capping: A literature review

Kinga Kosiń¹, Wojciech Liszka², Alicja Polak³, Maria Malina⁴, Jakub Kiwior³

¹PRIVATE DENTAL PRACTICE- KINGA KOSIŃ, CRACOW, POLAND

²PRIVATE DENTAL PRACTICE- WOJCIECH LISZKA, CRACOW, POLAND

³FACULTY OF MEDICINE, MEDICAL UNIVERSITY OF SILESIA, KATOWICE, POLAND

⁴FACULTY OF MEDICINE, JAGIELLONIAN UNIVERSITY MEDICAL COLLEGE, CRACOW, POLAND

ABSTRACT

The development of biomaterials for direct pulp capping has significantly transformed modern vital pulp therapy. For decades, calcium hydroxide was considered the gold standard, but its limitations – such as lack of sealing ability and tendency for resorption – have prompted the search for improved solutions. The introduction of calcium silicate cements and new-generation bioceramics has led to better biological and clinical outcomes. This review aims to discuss the latest advances in biomaterials used for direct pulp capping and to compare their properties, efficacy, and limitations. Literature published between 2018 and 2024, including systematic reviews, meta-analyses, and clinical studies, was analyzed. The results show that bioceramics and contemporary calcium silicate cements exhibit high bioactivity, enable the formation of a dentin bridge, and present a favorable safety profile. Appropriate material selection, meticulous clinical technique, and effective control of infection and moisture are essential for clinical success. The review also highlights certain limitations, such as the higher cost of new materials, technical requirements, and the lack of long-term clinical data. In conclusion, bioceramics currently represent the best choice for direct pulp capping, and further research should focus on optimizing clinical protocols and evaluating long-term outcomes to ensure predictable, minimally invasive dental care.

KEY WORDS: bioceramics, calcium silicate cements, dental pulp therapy, dental biomaterials, pulp regeneration

Wiad Lek. 2025;78(9):1893-1898. doi: 10.36740/WLek/209474 DOI

INTRODUCTION

Recent years have seen significant advances in vital pulp therapy, especially direct pulp capping (DPC) and partial pulpotomy, which are now considered the gold standard for managing exposed or nearly exposed pulps in both permanent and primary teeth. The introduction of novel bioactive materials – including hydraulic calcium silicate cements (e.g., Biodentine XP, NeoPUTTY, Well-Root PT, and TheraCal LC) – has improved the prognosis of these procedures and shifted the focus from traditional calcium hydroxide to materials with superior sealing ability, bioactivity, and clinical longevity [1, 2].

Contemporary protocols emphasize the preservation of pulp vitality, which not only maintains the tooth's natural function and proprioception but also allows clinicians to avoid or delay the need for conventional endodontic treatment in appropriately selected cases [1, 3].

Systematic reviews and meta-analyses from 2018–2024 confirm that, with modern protocols and case

selection, vital pulp therapy achieves high rates of pulp vitality preservation and radiographic success – even in cases of carious or mechanical pulp exposure [1,3].

For many years, calcium hydroxide was the standard capping material, later replaced by mineral trioxide aggregate (MTA), which became the gold standard for vital pulp therapy. However, contemporary bioactive materials such as hydraulic calcium silicate cements have demonstrated improved clinical and biological performance, prompting a shift in clinical protocols and material selection in recent years [2, 3].

AIM

The aim of this literature review is to summarize the latest evidence (2018–2024) regarding clinical protocols, indications, material selection, treatment outcomes, and future directions in direct pulp capping and partial pulpotomy, with special attention to the effectiveness of new-generation bioceramic and light-cured materials.

MATERIALS AND METHODS

For this literature review, publications from 2018 to 2024 (including systematic reviews, meta-analyses, and clinical studies) were analyzed to gather relevant evidence on direct pulp capping and partial pulpotomy. The analysis focused on high-quality clinical studies and reviews to ensure comprehensive coverage of current advances in biomaterials and vital pulp therapy technique

REVIEW

PATHOPHYSIOLOGY AND BIOLOGICAL PRINCIPLES

The clinical success of direct pulp capping and partial pulpotomy relies on understanding the biological response of the dental pulp to injury and biomaterial application. When the pulp is exposed by caries or trauma, the inflammatory response and healing capacity depend on the extent of bacterial contamination, the duration of exposure, and the biological compatibility of the capping material [1, 2].

Modern research confirms that the pulp retains the ability to regenerate if bacterial contamination is limited and a biologically compatible material is placed [2, 3]. Bioactive calcium silicate materials (e.g., Biodentine XP, NeoPUTTY) initiate a sequence of events at the pulp-dentin interface:

- Calcium ion release: The high calcium ion release and alkaline pH stimulate the differentiation of pulp stem cells into odontoblast-like cells [2, 4].
- Reparative dentin formation: These cells lay down a matrix of reparative (tertiary) dentin, leading to the formation of a mineralized dentin bridge at the exposure site [4,5].
- Natural seal: The dentin bridge acts as a natural barrier, protecting the pulp from further injury and sealing it from bacterial ingress [4, 7].

Calcium silicate cements also exhibit antimicrobial properties and excellent sealing, which minimize pulpal inflammation and support a favorable healing environment [4, 7]. Histological studies and recent clinical trials demonstrate that new-generation cements induce the formation of a continuous, mineralized dentin bridge of good quality, superior to that formed by older materials such as calcium hydroxide [4, 5, 7]. Light-cured resin-modified materials (e.g., TheraCal LC) are easy to apply and set rapidly, but ongoing clinical trials are still assessing their long-term ability to induce complete, homogeneous dentin bridge formation and to support true pulp healing [6]. An evidence-based choice of capping material is thus critical for achieving predictable biological repair and long-term tooth survival [1, 8] .

MATERIAL SELECTION AND COMPARATIVE EFFECTIVENESS

Recent advances in biomaterials have transformed the landscape of direct pulp capping and partial pulpotomy. Historically, calcium hydroxide was the material of choice for decades due to its ease of use and initial biocompatibility. However, its limitations – including poor sealing, high solubility, and formation of porous, incomplete dentin bridges – led to a search for better alternatives. For many years, mineral trioxide aggregate (MTA) emerged as the gold standard for vital pulp therapy, thanks to its excellent biocompatibility, sealing ability, and consistent formation of continuous dentin bridges. However, MTA's handling properties (e.g., long setting time, potential discoloration) motivated the development of new-generation hydraulic calcium silicate cements [1, 2].

Current options include:

• **Biodentine XP, NeoPUTTY, Well-Root PT:** These materials offer improved handling, faster setting, and enhanced bioactivity compared to traditional MTA. Multiple systematic reviews and meta-analyses published between 2021 and 2024 confirm that modern calcium silicate cements result in similar or higher clinical and radiographic success rates compared to MTA, while minimizing drawbacks such as discoloration and handling difficulty [2,3,4] .

• **Light-cured resin-modified materials (e.g., TheraCal LC):** These materials offer easy application and rapid setting but show variable long-term performance in terms of dentin bridge quality and pulpal healing. Ongoing trials are further evaluating their clinical effectiveness in comparison to bioceramic cements [5, 6].

A 2023 systematic review and network meta-analysis found that new-generation hydraulic calcium silicate cements (Biodentine, NeoPUTTY, Well-Root PT) were associated with equal or superior outcomes for pulp vitality, dentin bridge formation, and periapical health compared to both MTA and resin-modified materials [2,3,4] . Material selection should therefore prioritize modern calcium silicate cements in most cases, with resin-modified or light-cured materials reserved for select indications or as adjuncts [1-4]. The comparative characteristics of these materials are summarized in Table 1.

CLINICAL PROTOCOL

Successful vital pulp therapy depends on strict adherence to contemporary protocols, established for both direct pulp capping (DPC) and partial pulpotomy in permanent and primary teeth. Recent systematic reviews and meta-analyses (2018–2024) support the following evidence-based steps for optimal clinical outcome [1-3]:

Table 1. Comparative characteristics of pulp capping materials (2018–2024)

Material	Advantages	Limitations / Drawbacks	Key References
Biodentine XP	Fast setting, high biocompatibility, strong sealing, bioactivity, promotes homogeneous dentin bridge	Handling sensitive to moisture, higher cost	[2,3,4]
NeoPUTTY	Putty consistency (easy to apply), rapid setting, bioactive, stable color	Limited long-term data, higher price	[2,3,4]
Well-Root PT	Excellent sealing, biocompatible, good handling, minimal discoloration	Newer product – less long-term evidence	[2,3,4]
MTA	Gold standard for years, excellent pulp healing, robust dentin bridge	Prolonged setting time, handling difficulties, possible discoloration	[1,2]
TheraCal LC	Light-cured (rapid set), easy to handle, useful for small exposures	Resin content may cause cytotoxicity, less mineralization, lower long-term pulp vitality	[5,6]
Calcium Hydroxide	Historic standard, widely available, low cost	Poor sealing, dissolution over time, incomplete dentin bridge, low long-term success	[1,2,3]

Direct Pulp Capping (DPC) protocol

- 1. Diagnosis and Case Selection:** Confirm that pulp exposure is small, recent, and without signs of irreversible pulpitis; best results are achieved in exposures due to trauma or shallow caries, especially in young or asymptomatic teeth [1, 4].
- 2. Isolation:** Achieve strict rubber dam isolation to prevent contamination [2, 4].
- 3. Hemostasis:** Control bleeding with a sterile saline or 2.5–3% sodium hypochlorite-soaked cotton pellet for up to 5 minutes; persistent bleeding indicates a poor prognosis and may require pulpotomy or endodontic treatment [2, 5].
- 4. Disinfection (optional):** A brief rinse with sodium hypochlorite may be recommended for antimicrobial effect, followed by a saline rinse [2,5].
- 5. Application of Capping Material:** Place a 1–2 mm layer of hydraulic calcium silicate cement (e.g., Biodentine XP, NeoPUTTY, Well-Root PT) directly over the exposure site; ensure material adaptation and absence of voids [7]. If a light-cured material (e.g., TheraCal LC) is used, follow the manufacturer's guidelines for incremental layering and curing [6].
- 6. Permanent Restoration:** After the capping material has set, place a protective base or liner if indicated, and restore the tooth with a well-sealed adhesive restoration. Achieving an immediate and adequate coronal seal is critical to prevent microleakage [2,3,4].
- 7. Follow-Up:** Perform clinical and radiographic evaluations at approximately 6, 12, and 24 months to confirm continued pulp vitality and normal periapical status. Long-term monitoring is important to ensure success [1, 3, 9].

Partial pulpotomy protocol

• **Indication:** Partial pulpotomy is indicated if hemostasis cannot be achieved with direct capping (e.g., persistent bleeding at the exposure site) or in deeper carious exposures where a larger volume of inflamed pulp needs removal [10].

• **Pulp removal:** Using a sterile, water-cooled diamond bur, remove about 2–3 mm of the exposed superficial pulp tissue to excise inflamed pulp until healthy, bleeding pulp remains [10].

• **Capping and restoration:** Achieve hemostasis as described above, then apply a bioceramic capping cement over the remaining pulp stump, and restore the tooth immediately with a well-sealed restoration [5, 7, 9].

• **Outcomes:** Partial pulpotomy is especially effective in young permanent teeth. Recent studies report >90% success rates at 1–3 years of follow-up for partial pulpotomies in appropriate cases, demonstrating excellent potential for long-term pulp vitality preservation [7].

Key points

• **Material choice matters:** Modern calcium silicate cements provide the highest long-term success rates and are preferred for most direct pulp capping cases [2–4].

• **Technique sensitivity:** These procedures are technique-sensitive, requiring careful case selection, strict moisture control (rubber dam use), and precise adherence to the protocol for each material [2, 4, 7].

• **Age and pulp status:** The best outcomes occur in teeth with young, vital, and minimally inflamed pulps; older teeth or those with significant pulp inflammation have lower success rates for vital pulp therapy [1, 9, 10].

Indications and contraindications

Recent evidence (2018–2024) supports the use of vital pulp therapy (direct capping or partial pulpotomy) in the following clinical situations:

Indications:

- Mechanical or shallow carious pulp exposures in asymptomatic, vital permanent teeth without clinical or radiographic signs of irreversible pulpitis [1,3,4].
- Recently erupted or young permanent teeth (children/adolescents) with open apices, due to their high regenerative potential; vital pulp therapy can also be considered in mature teeth with careful case selection [2,5].
- Cases where bleeding at the exposure site is easily controlled within approximately 5 minutes, indicating a healthy or only reversibly inflamed pulp status [2,7].
- Teeth where preserving pulp vitality is desirable to maintain normal root development (in immature teeth), proprioception, and to avoid or delay more invasive endodontic treatment [1,2,3].

Contraindications:

Vital pulp therapy is not recommended when any of the following are present:

- Signs or symptoms of irreversible pulpitis, such as spontaneous pain (especially nighttime pain) or prolonged sensitivity to hot/cold, or presence of swelling indicating pulpal degeneration [3, 5].
- Radiographic evidence of periapical pathology (e.g., periapical radiolucency, root resorption, or furcation involvement in multi-rooted teeth) suggesting loss of pulp vitality or chronic infection [3, 7].
- Uncontrolled bleeding at the exposure site (hemorrhage cannot be stopped within ~5 minutes), which is indicative of advanced pulpal inflammation or partial necrosis [2, 7].
- Extensive tooth structure loss from caries or trauma that would prevent achieving an adequate seal or proper restoration (high risk of microleakage or restoration failure) [3,7].
- Teeth with a poor overall prognosis due to periodontal disease or non-restorable crown/fracture, where maintaining the pulp is futile [4,7].

Clinical pearls:

- **Case selection is critical:** Accurate assessment of pulp status (to confirm that the pulp is vital and only reversibly inflamed) and the ability to achieve complete hemostasis are essential for success in vital pulp therapy [2,8].
- **Partial pulpotomy preference:** In situations where hemostasis cannot be quickly achieved with direct capping, or when the pulp exposure is large with suspicion of deeper pulp inflammation, a partial pulpotomy is often the preferred approach over a simple direct cap [7,9].

Limitations and complications

Despite the high success rates of modern vital pulp therapy, several important limitations and possible complications should be considered.

• **Technique and case-sensitive outcomes:** The success of direct pulp capping or pulpotomy is highly dependent on proper case selection, accurate diagnosis of the pulp's condition, and strict adherence to the clinical protocol (including excellent isolation and asepsis). Errors or deviations in any of these steps can significantly increase the risk of failure [1, 2].

• **Material-related limitations:** Hydraulic calcium silicate cements (bioceramics) are technique-sensitive and can be relatively costly or difficult to handle in some clinical scenarios [3, 4]. Light-cured resin-modified materials have limited long-term clinical data, and their resin components may reduce bioactivity and increase cytotoxic effects on pulp tissue [2]. Additionally, MTA, while effective, can cause tooth discoloration and has a prolonged setting time which may be impractical in certain cases [4].

• **Inappropriate case factors:** Vital pulp therapy is unlikely to succeed in teeth that actually have irreversible pulpitis, in cases where pulpal bleeding cannot be controlled, or when a durable coronal seal cannot be achieved (for example, due to extensive decay or insufficient tooth structure) [2, 3, 7]. Such cases are better managed with more advanced endodontic treatment.

• **Restorative failures:** Even after initial successful pulp capping, failure of the coronal restoration (e.g., microleakage, secondary caries, or restoration fracture) can lead to bacterial re-contamination and late-onset pulp necrosis [7].

Complications

• **Pulp necrosis or chronic inflammation:** In some instances, the capped pulp may undergo necrosis or remain chronically inflamed, especially if bacteria were not fully eliminated or if the pulp's initial inflammatory status was underestimated [3,7]. This outcome would necessitate root canal therapy despite the initial vital pulp therapy attempt.

• **Tooth discoloration:** Some pulp capping materials, particularly certain MTA formulations, can cause discoloration of the crown dentin over time. While newer bioceramics aim to minimize this issue, discoloration remains a potential cosmetic complication, notably for anterior teeth [4].

Future directions

Most studies to date report outcomes only up to 1–3 years of follow-up, highlighting the need for longer-term data (≥5 years) to fully assess the durability of new biomaterials and techniques [2, 4, 5, 8]. Addi-

tionally, further research is needed to optimize clinical protocols, evaluate emerging biomaterials, and determine the effectiveness of vital pulp therapy in more challenging scenarios (e.g. older patients or teeth with significant comorbid conditions) [3, 4, 11].

• **Development of novel biomaterials:** Continued innovation is focused on next-generation pulp-capping materials, including advanced bioceramics, nanomaterials, bioactive additives, and injectable scaffolds. These are being investigated to improve the quality of dentin bridge formation, enhance pulpal healing, and provide superior antimicrobial properties [1, 2, 4, 11].

• **Combination therapies:** Researchers are exploring the combined use of hydraulic calcium silicate cements with other therapeutic modalities (such as remineralizing agents, growth factors, or even stem cell therapy) to further enhance pulp regeneration and improve long-term vitality of the tooth [12].

• **Digital diagnostics and artificial intelligence:** Modern imaging techniques and AI-driven diagnostic tools are under development to improve the accuracy of pulp status assessment and to aid in standardized case selection. Such technologies could help predict

which cases are ideal for vital pulp therapy and improve clinical decision-making [13].

• **Long-term randomized controlled trials:** There is a clear need for extended follow-up studies (>5 years) and multicenter randomized controlled trials to definitively determine the long-term success, durability, and optimal treatment protocols for new pulp capping materials and techniques as they continue to evolve [2, 4, 5].

CONCLUSIONS

Modern vital pulp therapy, based on current high-quality evidence, enables the preservation of pulp vitality and natural tooth structure in appropriately selected cases. The evolution from calcium hydroxide to bioceramic cements, and ongoing innovation in material science, has significantly improved the success and predictability of direct pulp capping and partial pulpotomy. Strict adherence to clinical protocol, careful case selection, and use of contemporary materials are essential for optimal outcomes. As new technologies and materials are validated, the role of vital pulp therapy in minimally invasive and regenerative dentistry is expected to expand further.

REFERENCES

- Elmsmari F, Ruiz XF, Miró Q, Feijoo-Pato N, Durán-Sindreu F, Olivieri JG. Outcome of partial pulpotomy in cariously exposed posterior permanent teeth: a systematic review and meta-analysis. *J Endod*. 2019;45(11):1296–1306.e3. doi: 10.1016/j.joen.2019.07.005. [DOI](#)
- Parirokh M, Torabinejad M, Dummer PMH. Mineral trioxide aggregate and other bioactive endodontic cements: an updated overview – Part I: vital pulp therapy. *Int Endod J*. 2018;51(2):177–205. doi: 10.1111/iej.12841. [DOI](#)
- Fasoulas A, Keratiosis G, Spineli L, Pandis N, De Bruyne MAA, De Moor RJG, Meire MA. Comparative efficacy of materials used in patients undergoing pulpotomy or direct pulp capping in carious teeth: A systematic review and meta-analysis. *Clin Exp Dent Res*. 2023;9(6):1129–1148. doi: 10.1002/cre2.767. [DOI](#)
- Cushley S, Duncan HF, Lappin MJ, Chua P, Elamin AD, Clarke M, El-Karim IA. Efficacy of direct pulp capping for management of cariously exposed pulps in permanent teeth: A systematic review and meta-analysis. *Int Endod J*. 2021;54(4):556–571. doi: 10.1111/iej.13449. [DOI](#)
- Iaculli F, Rodríguez-Lozano FJ, Briseño-Marroquín B, Wolf TG, Spagnuolo G, Rengo S. Vital pulp therapy of permanent teeth with reversible or irreversible pulpitis: An overview of the literature. *J Clin Med*. 2022;11(14):4016. doi: 10.3390/jcm11144016. [DOI](#)
- Novotná B, Holík P, Morozova Y, Rosa M, Galandáková A, Langová K. Evaluation of cytotoxicity of the dental materials TheraCal LC, TheraCal PT, ApaCal ART and Biodentine used in vital pulp therapy: an in vitro study. *Dent J*. 2024;12(8):249. doi: 10.3390/dj12080249. [DOI](#)
- Albaiti SS, Albishri RF, Alhowig MT, Tayyar WI, Alqurashi NF, Alghamdi FT. Partial pulpotomy as an applicable treatment option for cariously exposed permanent posterior teeth: a systematic review of randomized clinical trials. *Cureus*. 2022;14(7):e26573. doi: 10.7759/cureus.26573. [DOI](#)
- Tong HJ, Seremidi K, Stratigaki E, Kloukos D, Duggal M, Gizani S. Deep dentine caries management of immature permanent posterior teeth with vital pulp: A systematic review and meta-analysis. *J Dent*. 2022;124:104214. doi: 10.1016/j.jdent.2022.104214. [DOI](#)
- Zhang M, Xiong Y, Wang X, Wang Y, Cai Y, Xu J, Zhang C, Li J. Factors affecting the outcome of full pulpotomy in permanent posterior teeth diagnosed with reversible or irreversible pulpitis. *Sci Rep*. 2022;12:20280. doi: 10.1038/s41598-022-24815-0. [DOI](#)
- Duncan HF, Galler KM, Tomson PL, et al. European Society of Endodontology position statement: Management of deep caries and the exposed pulp. *Int Endod J*. 2019;52(7):923–934. doi: 10.1111/iej.13080. [DOI](#)
- Komora P, Vámos O, Gede N, et al. Comparison of bioactive material failure rates in vital pulp treatment of permanent matured teeth – a systematic review and network meta-analysis. *Sci Rep*. 2024;14:18421. doi: 10.1038/s41598-024-69367-7. [DOI](#)
- Kwak KH, Lee HW. Clinical Potential of Dental Pulp Stem Cells in Pulp Regeneration: Current Endodontic Progress and Future Perspectives. *Front Cell Dev Biol*. 2022 Apr 11;10:857066. doi: 10.3389/fcell.2022.857066. [DOI](#)

13. Altukroni A, Alsaeedi A, Gonzalez-Losada C, Lee JH, et al. Detection of the pathological exposure of pulp using an artificial intelligence tool: a multicentric study over periapical radiographs. *BMC Oral Health*. 2023;23:553. doi: 10.1186/s12903-023-03251-0. 

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Kinga Kosiń

Private Dental Practice – Kinga Kosiń

Kraków, Poland

e-mail: kinga17555@gmail.com

ORCID AND CONTRIBUTIONSHIP

Kinga Kosiń: 0009-0009-4569-3633  

Wojciech Liszka: 0009-0005-6511-8039 

Alicja Polak: 0009-0009-7324-4675 

Maria Malina: 0009-0001-7205-2788 

Jakub Kiwior: 0009-0000-0901-8117 

 – Work concept and design,  – Data collection and analysis,  – Responsibility for statistical analysis,  – Writing the article,  – Critical review,  – Final approval of the article

RECEIVED: 12.05.2025

ACCEPTED: 15.08.2025



Economic determinants in healthcare quality optimization in Ukrainian metropolises

Vladyslav Smiiianov¹, Olexsander Korniiichuk², Iryna Khomenko³, Anatolii Tsarenko³, Oleksandra Ivakhno³, Viktoriia Yasenok¹, Olha Smiiianova¹

¹SUMY STATE UNIVERSITY, SUMY, UKRAINE

²INSTITUTE OF DEMOGRAPHY AND QUALITY OF LIFE RESEARCH NAMED AFTER MYKHAILO PTUKHA, NAS OF UKRAINE, KYIV, UKRAINE

³SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

ABSTRACT

Aim: The objective of the study is to analyze the economic determinants that contribute to enhancing the quality of medical care in the context of metropolitan zoning.

Materials and Methods: The study draws on statistical data from the Center for Medical Statistics of the Ministry of Health of Ukraine, the State Statistics Service of Ukraine, and the Health Departments of the metropolitan cities of Dnipro and Kharkiv for the years 2010, 2013–2014, and 2018–2020. The research employed methods of statistical analysis and synthesis, logical analysis, generalization, and systems approaches.

Conclusions: An analysis was conducted of morbidity trends in the Dnipro metropolis during 2010, 2013–2014, and 2018–2020 with respect to socially significant diseases – hypertension, myocardial infarction, stroke, HIV/AIDS, as well as AIDS-related mortality, all of which pose risks of premature death (18 years and older). Consideration was also given to the human resources available in primary health care and prevailing demographic trends. A comparative analysis of the effectiveness of health care systems in the metropolises of Dnipro and Kharkiv was undertaken by assessing the number of emergency medical service calls per 100,000 average annual population. The study proposes approaches to assessing the influence of metropolitan health care infrastructure on medical institutions within the metropolitan region and substantiates the prospects for establishing a unified metropolitan health care system.

In the context of the ongoing war in Ukraine, there is an urgent need to create a competitive health care environment in metropolitan areas, prioritizing economic determinants of quality optimization. This will require the joint efforts of government, business, academia, and the media in developing modern competitiveness strategies for metropolitan development, supported by the adoption and implementation of legislation on the status and functions of metropolises. Such measures are expected to reduce irrational and unjustified financial expenditures in the health care sector.

KEY WORDS: Ukrainian metropolises, quality of medical care, economic determinants, city of Dnipro

Wiad Lek. 2025;78(9):1899–1908. doi: 10.36740/WLek/212533 DOI

INTRODUCTION

Ukraine needs a scientifically grounded approach to the development of modern organisational and financial strategies for establishing new metropolises (according to the criteria of France – 10–13) with strong competitive potential at the national, regional, and, eventually, global levels. This need primarily concerns the development of a competitive model of the health care system within metropolitan areas, one that ensures high-quality individualisation of primary care services [1], specialisation of medical services and the concentration of specialised healthcare in regional centres and metropolitan cities. The impact of metropolitan areas on public health is revealed through the assessment of the process of spatial growth and urban development as a system of human viability; the issues of socio-medical interventions to reduce prenatal mortality among people living

in disadvantaged socio-economic conditions [2], the peculiarities of the socio-economic status of the population and mental health conditions [3], the state of mental and physical health of metropolitan residents, taking into account their gender and areas of influence of metropolitan areas in the provision of specialised medical care [4], inequalities in access to medical care for urban and rural residents, including the lower likelihood of rural residents receiving influenza vaccinations or having a regular healthcare provider [5]. The use of attacks on the healthcare system as a weapon of war in Ukraine has been studied [6], as well as the survival characteristics of patients with rare diseases under wartime conditions [7], the health consequences for refugees from Ukraine due to the war with the Russia [8], the catastrophic medical consequences of the war in Ukraine [9], the effects of war on children's health given the existing

levels of child mortality, low rates of routine immunisation, and high prevalence of infectious diseases [10], and the health needs of refugees from Ukraine [11].

Ukrainian researchers define a metropolis as an urban agglomeration formed as a result of the territorial unification of a large city with surrounding settlements, or an agglomeration of the metropolitan area (two or more cities) [12, 13].

The idea behind the study is to justify the current development priorities of the healthcare system within the metropolitan areas, based on decentralisation reform and the establishment of modern models for delivering primary healthcare at the community level, and specialised care at the district, metropolitan, and regional (oblast) levels. In this context, the influence of the metropolitan healthcare system will be inversely proportional to the level of development and accessibility of medical services in communities and regions.

AIM

The aim of the study is to substantiate methodological approaches for determining the key priorities in the development of the medical space of metropolitan areas in Ukraine, and to examine the specific impact of specialised healthcare infrastructure located in metropolitan areas or regional medical centers on the healthcare sector. The study also analyses the features of the healthcare system in the metropolitan area of Dnipro and its development priorities in the context of Russia's full-scale war against Ukraine.

MATERIALS AND METHODS

The study draws on statistical data from the Center for Medical Statistics of the Ministry of Health of Ukraine, the State Statistics Service of Ukraine, and the Health Departments of the metropolitan cities of Dnipro and Kharkiv for the years 2010, 2013–2014, and 2018–2020. The research employed methods of statistical analysis and synthesis, logical analysis, generalization, and systems approaches.

REVIEW AND DISCUSSION

Taking into account the structuring of metropolitan influence zones, the authors define the healthcare system space of a subregion (several regions) as the healthcare system space of the area within a 300 km radius of influence from the agglomeration centre and the agglomeration healthcare system space with consideration of a 5 km zone beyond the city limits [12–14]. This corresponds to a 10 km zone from the center of the agglomeration (metropolis), including 5 km within the city and 5 km beyond its boundary. Thus, for example, the agglomeration boundary for Kharkiv is 5–15

km, and for Dnipro – 15–20 km. Thus, the metropolitan space of the healthcare system of the area is the healthcare infrastructure within the radius of influence of the agglomeration centre (300 km). It is assumed that the spatial influence of the metropolitan center in the healthcare sector is strongest within the first zone of influence (up to 5 km), and decreases with distance, being weakest in the third zone (up to 300 km).

According to the decentralisation reform, initiated in 2014, the city community is responsible for organising primary healthcare (metropolitan influence zone No. 1), the district – for specialised medical care (influence zone No. 2, with a radius of up to 60 km), the region – for specialised healthcare from the perspective of the metropolis and regional centres (influence zone No. 3, serving a population of no less than 1 million people).

According to the author's estimates, the strength of influence of the metropolitan infrastructure in the healthcare sector from 1991 to 2014, the beginning of real reforms, was determined using the following formula:

$$P_{if} = f \left(\frac{D_{smc}, D_{emc}, M_p, Q_r, F_{av}, Q_q}{D_{pmc}, D_{prmc}, D_{emmc}, E_{health}, D_{tlm}, Dis_{hc}} \right)$$

P_{if} – power of influence;

D_{smc} – development of specialised medical care in metropolises and regional centres;

D_{emc} – development of emergency medical care;

M_p – morbidity of the population;

Q_r – quality of roads;

F_{av} – financial accessibility;

Q_q – quality of communication;

D_{pmc} – development of preventive medical care;

D_{prmc} – development of primary medical care;

D_{emmc} – development of emergency medical care;

E_{health} – development of electronic healthcare;

D_{tlm} – development of telemedicine;

Dis_{hc} – distance to a healthcare facility.

After 2014, in addition to these indicators, it is also determined by the effectiveness of the National Health Service of Ukraine (NHSU) in each type of medical care according to the formula:

$$P_{if} = f \left(\frac{D_{smc}, D_{emc}, M_p, Q_r, F_{av}, Q_q}{D_{pmc}, D_{prmc}, D_{emmc}, E_{health}, D_{tlm}, Dis_{hc}, Q_{nszu}} \right)$$

Q_{nszu} is the quality of services provided by the NHSU in financing the healthcare facility network, based on the compliance of services with licensing requirements.

The creation of a unified healthcare space in metropolitan areas should be based on a shared information space within the healthcare system built on electronic

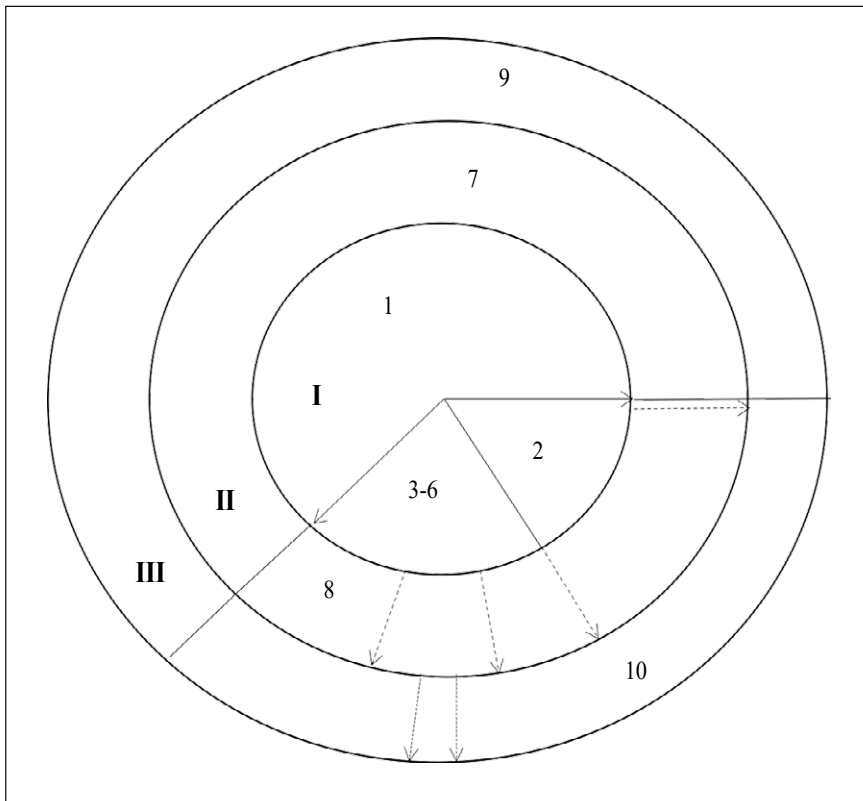


Fig. 1. Prospective medical space of the metropolis in the healthcare sector.

Directions and strength of metropolitan influence in the first zone

Directions and strength of influence of a metropolis in the second zone

Directions and strength of influence of a metropolis in the third zone

I-III - zones of metropolitan influence;

1 - primary healthcare facilities in the first zone of influence;

2 - specialised healthcare facilities in the first zone of influence;

3-6 - a unified integrated medical care space of supra-cluster institutions of the metropolis;

(3 - infrastructure of the Ministry of Healthcare facilities in the first zone of influence;

4 - infrastructure of the National Academy of Medical Sciences of Ukraine in the first zone of influence;

5 - infrastructure of institutions of ministries and departments in the first zone of attraction;

6 - infrastructure of specialised medical care of the metropolis in the first zone of attraction);

7 - primary healthcare facilities in the second zone of influence;

8 - specialised medical care facilities in the second zone of influence;

9 - primary healthcare facilities in the third zone of influence;

10 - specialised medical care facilities in the third zone of influence.

Picture taken by the authors

healthcare and telemedicine, including the implementation of electronic patient records. Access to these records should be granted not only to family doctors and specialists (with the patient's permission), but also to the patients themselves [15], [16].

At the same time, taking into account both external and internal threats related to attempts by the Russian Federation to impose a federal or confederal system on Ukraine, experts consider the top priority to be the completion of the formation of 30% of new territorial communities and the reorganisation of 20% of existing ones in accordance with scientifically grounded profiles of their development potential [17], [18].

Until 2014, the healthcare system of metropolitan areas was characterised by underdevelopment of primary healthcare across all three zones of influence, alongside the dominance of specialised medical care in the areas of specialised healthcare, metropolises and regional centres. Since the onset of reform, there has been an expansion of primary healthcare services in all three zones of influence.

The prospect of developing a metropolitan healthcare space is linked to the need to create a unified healthcare space by transferring all departmental healthcare institutions (those under ministries and other state agencies) under the authority of local or regional

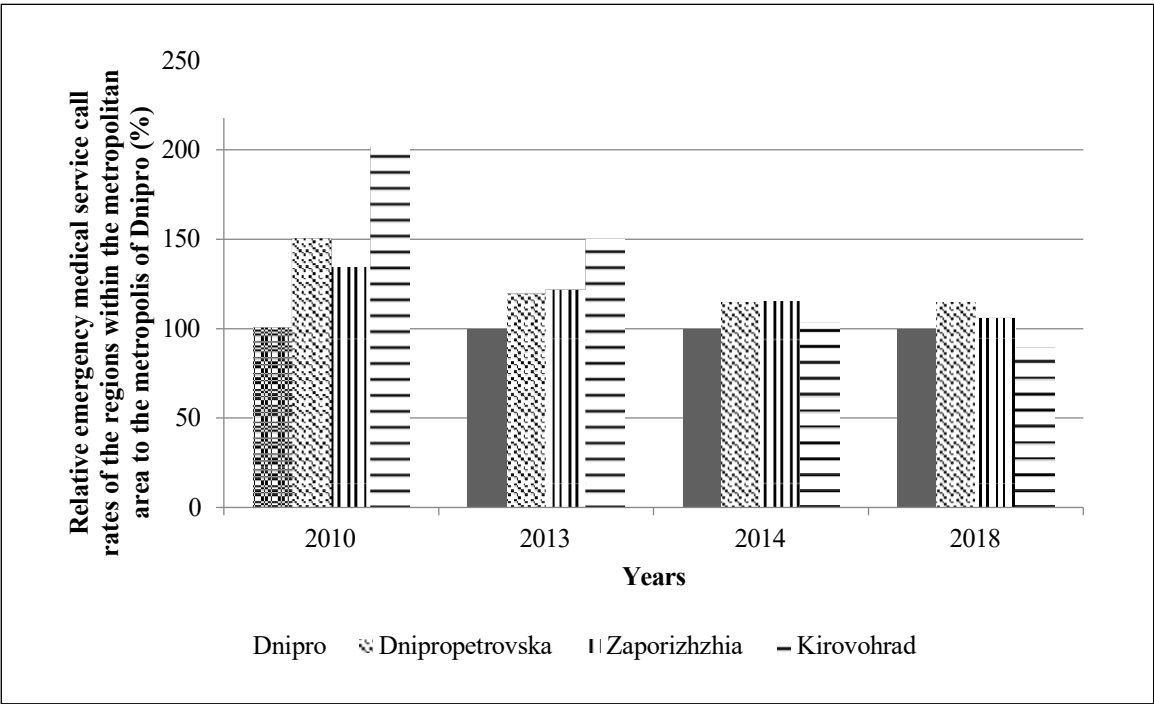


Fig. 2. Relative emergency medical service (EMS) call rates in the regions of the metropolitan area compared to the metropolis of Dnipro (%)
Note: Data for 2021–2022 are unavailable
Source: compiled by the authors based on [21]

governments. This process should take place after the completion of the decentralisation reform and on the territories liberated from the occupation after the end of hostilities (Fig. 1).

This process will likely be accompanied by the expansion of primary healthcare across all zones of influence and the concentration of specialised medical care resources in metropolises and regional centers through their consolidation at the regional level.

These processes will imply the integration of the metropolitan space for specialised medical care across metropolitan areas and regional centres (1-4), as well as a significant improvement in the quality of primary healthcare services within the metropolitan community (5) supported by autonomous financing..

In the second zone of metropolitan influence, a significant improvement in primary healthcare (7) is also likely, which, in turn, may lead to a reduced demand for specialised medical care services (8). This is expected to be accompanied by the continued influence of specialised medical care provided in metropolises and regional centers.

In the third zone of metropolitan influence, an increase in primary healthcare services (9) is also likely, along with the alignment of specialised medical care services with the actual needs of the population (10). This will make it possible to concentrate infrastructure, personnel, and information flows, and to scale up the provision of spe-

cialised medical services in metropolises and regional centers. As a result, it may also lead to reduced costs for the population for this type of medical care

The application of a functional approach to the assessment of metropolitan processes within settlement systems suggests that, prior to 2014, the concentration of specialised medical care in metropolises and regional centres within the zone of metropolitan influence played a system-forming role in the healthcare infrastructure. This infrastructure primarily included primary and specialised medical care. Patients' routes were not coordinated by primary care physicians and often began with spontaneous and chaotic visits to specialised medical personnel in metropolitan or regional healthcare facilities. This was largely due to the functional dominance of specialised medical care in metropolitan and regional centres, which spread concentrically from the point of service delivery, especially during the transition period of establishing modern primary health care based on family medicine principles.

Since 2014, the healthcare system in metropolitan areas has been able to build and strengthen the capacity of primary healthcare at the community level, specialised medical care at the district level, and specialised medical care in metropolises and regional centers. However, the pace of positive change lags behind societal needs due to the existing post-Soviet system of monopolised control over human, financial,

Table 1. Emergency medical service call rate per 100,000 average annual population in the metropolitan area of Dnipro city in Dnipro, Zaporizhzhia and Kirovohrad regions in 2010, 2013–2014, and 2018

2010		2013	
Bipolar metropolis (zones of influence 1–3)	Call rate per 100,000 average annual population	Bipolar metropolitan area (zones of influence 1–3)	Call rate per 100,000 average annual population
Dnipro	20934,9	Dnipro	21984,9
Dnipropetrovska	31365,6	Dnipropetrovska	26161,5
Zaporizhzhya	28070,4	Zaporizhzhya	26664,9
Kirovograd	42202,4	Kirovohradska	32901,1
2014		2018	
Bipolar metropolitan area (zones of influence 1–3)	Calls per 100,000 average annual population	Bipolar metropolitan area (zones of influence 1–3)	Call rate per 100,000 average annual population
Dnipro	22814,3	Dnipro	22070,7
Dnipropetrovska	26120,4	Dnipropetrovska	25239,5
Zaporizhzhya	26256,5	Zaporizhzhya	23258,2
Kirovohrad	23389,9	Kirovohradska	19615,3
2019		2020	
Bipolar metropolis (zones of influence 1–3)	Calls per 100,000 average annual population	Bipolar metropolitan area (zones of influence 1–3)	Call rate per 100,000 average annual population
Dnipro* city	7114,2	Dnipro* city	6892,5
Dnipropetrovska	24058,8	Dnipropetrovska	22272,0
Zaporizhzhya	21850,0	Zaporizhzhya	18497,5
Kirovohrad	22583,8	Kirovohradska	16014,4

Note: * Data for the city of Dnipro in 2019–2020 are inaccurate; data for 2021–2022 are unavailable.

Source: compiled by the authors based on [21]

Table 2. Emergency medical service calls per 100,000 average annual population in metropolitan areas of Kharkiv and Dnipro in 2010, 2013–2014, 2018–2020

2010		2013		2014	
Metropolitan areas	Call rate per 100,000 average annual population	Metropolitan areas	Call rate per 100,000 average annual population	Metropolitan areas	Call rate per 100,000 average annual population
Dnipro	20934,9	Dnipro	21984,9	Dnipro	22814,3
Kharkiv	19982	Kharkiv	24214	Kharkiv	17294
2018		2019		2020	
Dnipro	22070,7	Dnipro* city	7114,2	Dnipro*	6892,5
Kharkiv	17715	Kharkiv	21341,7	Kharkiv	20101,3

Note: * data for the city of Dnipro are inaccurate for 2019–2020 - incorrect; data for 2021–2022 – are unavailable

Source: compiled by the authors based on [21]

and informational resources by the chiefs of medical institutions. This is partly attributable to the focus of the Ministry of Health of Ukraine and local authorities (until May 2019) on the deployment of modern primary healthcare. Meanwhile, the implementation of a unified telemedicine space is based on World Bank projects aimed at enabling specialised healthcare institutions in metropolises and regional centers to provide such services to patients referred from primary and specialised care facilities.

In the context of decentralisation and the introduction of the subsidiarity mechanism, the function of coordinating patient routes in a certain way removes patients from a chaotic pattern of healthcare-seeking behavior and coordinates this process accordingly through family doctors, general practitioners, or pediatricians. According to the Ministry of Health of Ukraine, 75% of citizens have already chosen their primary care physician and signed the corresponding agreement with them through the National Health Service of

Table 3. Number of primary healthcare physicians, proportion of pensioners in the average annual population of the Dnipro metropolitan area, as well as patients (18 years and older), as well as prevalence of hypertension, stroke, heart attack, ischemic heart disease; HIV/AIDS and AIDS mortality per 10,000 average annual population of the metropolitan area

Metropolis	Number of primary care doctors	Pensioners	Number of patients with hypertension	Number of patients with stroke	Number of patients with heart attack	Number of patients with ischemic heart disease	Number of patients with HIV/AIDS	AIDS-related mortality rate
2010								
Dnipro	-	21,5	3243,0	13,7	4,9	2044,1	45,7	2,92
2013								
Dnipro	5,2	22,5	3221,0	10,4	4,8	1824,0	69,6	2,8
2014								
Dnipro	5,6	22,9	3514,0	13,2	5,0	1958,0	64,7	2,2
2018								
Dnipro	5,9	24,6	3915,0	10,0	4,8	2408,0	58,2	2,7
2019								
Dnipro	4,9	31,4	*	*	*	*	215,2	2,4
2020								
Dnipro	4,7	31,7	*	*	*	*	243,5	*

Note: * data for 2019–2020 were not provided by the city; data for 2021–2022 are unavailable

Source: compiled by the authors based on [21]

Ukraine [19].

Thus, the spatial monopolised medical dependence of patients on healthcare facilities, primarily primary healthcare, specialised care in general and cluster facilities, and specialised care in supra-cluster institutions in metropolitan areas or regional centres, if necessary, is replaced by their conscious choice of a facility in a metropolitan centre that is capable of providing appropriate care.

The application of the functional approach in studying the characteristics of the healthcare sector in metropolitan areas indicates that the provision of primary healthcare services does not depend on the size of the city or other settlement, nor on the metropolitan region itself, but is determined by the efforts and activities of community leadership to create appropriate conditions for the work of this category of physicians and the conclusion of agreements with the National Health Service of Ukraine.

The availability of specialised medical services in metropolitan cities or regional centers, as well as in communities, depends on the number of individuals whose income is equal to or exceeds that of the middle-class incomes. According to the State Statistics Service of Ukraine, up to 40% of the population does not seek necessary medical care due to financial constraints. [20].

The dynamics of metropolitan changes in the healthcare sector will likely indicate an increase in the metropolitan function at both regional and global levels. This will likely be evidenced by an increase in the provision

of specialised medical services in metropolises or regional centers to foreign legal entities and individuals, as well as the expansion of medical education for international students.

The metropolitan healthcare space of the city of Dnipro includes healthcare facilities across three zones of influence, within the jurisdictions of communities, districts and regions that are part of its metropolitan area of influence.

The characteristics of the healthcare system within the metropolitan space of the city of Dnipro, which includes Dnipropetrovsk, Zaporizhzhia, and Kirovohrad regions, were examined through a comparative analysis for the years 2010, 2013–2014, and 2018–2020 (Table 1), based on the rate of emergency medical service (EMS) calls per 100,000 population. This indicator is one of the indicators of the accessibility and quality of primary health care, as well as the level of medical literacy of the population.

In the metropolis of Dnipro, the lowest emergency medical service (EMS) call rates were recorded in 2010, 2013, and 2014. The Kirovohrad region demonstrated the most favorable trend in reducing EMS calls [22] (Fig. 2). In 2014 (excluding the city of Dnipro and the Kirovohrad region) and in 2018 (excluding the Kirovohrad region), the call rates in the metropolitan region exceeded the national average (23477,1 and 21107,56, respectively).

As for 2019–2020, due to the incorrect information from the city of Dnipro, it is not possible to perform calcula-

tions for the metropolitan region. Notably, in 2020, the indicator for Dnipropetrovsk region (22272,0) was 17.1% higher than the national average (19017,0), while in Zaporizhzhia (18497,5) and Kirovohrad regions (16014,4), it was lower by 2.7% and 15.8%, respectively [21].

In 2018, compared to 2010, the city of Dnipro showed a 5.4% increase in emergency medical service calls. The same trend is observed when comparing these indicators with those of the metropolis of Kharkiv (Table 2).

The decrease in this indicator over several years, while meeting the standards of emergency medical care, may to some extent indicate an improvement in the provision of primary health care.

An analysis of the incidence of socially dangerous diseases – hypertension, heart attack, stroke, HIV/AIDS, and AIDS-related mortality, which pose risks of premature death (among the population aged 18 and older), was conducted for the years 2010, 2013–2014, and 2018–2020 per 10,000 average annual population (Table 3).

This analysis takes into account the decrease in the number of family doctors in 2019–2020 compared to 2013 and 2018, as well as the increase in the proportion of pensioners.

In 2018, compared to 2010, the proportion of people with hypertension in the city increased by 20.7% (from 3915 to 3243). At the same time, the share of pensioners in the average annual population increased from 21.5 % in 2010 to 22.9 % in 2017.

The incidence of ischemic heart disease in the city increased by 17.8% between 2010 and 2019 [21].

There was a persistent trend of the highest AIDS-related mortality in Dnipro compared to other metropolitan areas in both 2010 and 2019 (2,9 and 2,4 per 10,000 population, respectively). The city also recorded the highest incidence rate of HIV/AIDS among Ukraine's metropolitan areas in 2019 (215,2) and 2020 (243,5) [21].

In 2018, compared to 2010, mortality rates due to hypertension increased by 14.5% (220,3 vs. 192,3), ischemic heart disease by 27.6% (762,7 vs. 597,8) (in 2020, compared to 2019, an 11% increase), heart attack compared to 2019, an increase of 11%), heart attack by 29% (35,6 and 27,6) (in 2020, an increase of 14.4% compared to 2019) and stroke by 8.2% (81,6 and 75,4) (in 2020, an increase of 19.5% compared to 2019) [21].

DISCUSSION

In the course of providing specialised medical care, high-cost medical equipment is used by healthcare institutions in the regional centers of Dnipropetrovsk, Zaporizhzhia, and Kirovohrad regions. Due to the lack of proper load, this equipment often remains idle,

leading to inefficient and unjustified expenditures of financial resources. The reason for this is the lack of legal mechanisms that would enable the Department of Health of the metropolis of Dnipro to coordinate the activities of healthcare facilities in communities, towns, villages, and settlements within the metropolitan zone of influence. In advanced countries, such coordination is regulated by laws and government resolutions under the framework of “metropolisation”.

For the city of Dnipro, a comparable example is the successful metropolis of Lyon. The alignment of master development plans among the communities of Lyon's metropolitan region enabled the creation of joint coordination bodies involving managers, economists, legal experts, and entrepreneurs. This facilitated highly favorable conditions for investment, including in healthcare projects. This has helped to eliminate duplication of funding for the construction of facilities and to ensure proper statistical support of processes, including in the healthcare sector.

When substantiating the perspective tasks for the development of the healthcare system in the metropolis of Dnipro, the positive changes associated with the expansion of primary healthcare based on family medicine and emergency medical care infrastructure should be taken into account.

To develop the Dnipro metropolitan area in line with European and international standards, it is advisable to design and implement a competitive model for the healthcare system's development. In addition, the central government should facilitate the adoption of the Law of Ukraine “On the Development of Metropolitan Areas”. This is particularly relevant in the context of the full-scale war.

In the long term, it is important to delineate the zones of influence of metropolitan areas in the healthcare sector in relation to morbidity rates and to assess how well specialised healthcare facilities meet the needs of these populations. It is especially important to identify the so-called “uncovered zones”, which include settlements whose population has difficulty accessing the services of specialised medical care in metropolitan or regional centres of a particular metropolis. This lack of access may result in increased mortality and disability rates among the working-age population, especially among men.

Significant challenges in the provision of specialised medical care are associated with the preservation of outdated district hospitals, maintained not based on criteria of consolidation for scaling and improving service quality, but for political motives, specifically, preserving obsolete staffing structures. This occurs despite the fact that modern European practices are

shifting towards the creation of multi-profile hospitals at the district level, serving populations of no less than 120,000-150,000 residents. Legislative preservation of outdated general hospitals poses a threat of delayed and low-quality services, which leads to excessive spending from both public budgets and households and increasing mortality rates.

Legislative efforts to preserve the human resources of medical personnel should be based on mechanisms that prioritise the preservation and promotion of public health, as well as the provision of high-quality and timely treatment by healthcare professionals who meet international standards and criteria of professional competence. This becomes possible only under conditions of a high workload for medical staff that enables them to continuously improve their professional competence. The laws "On a Capable Network of Hospitals" and "On Public Health" adopted in 2022 preserve the ineffective network of district hospitals with low capacity and increase centralisation by transferring functions from the local and regional levels to the Ministry of Health [23], [24]. The current policy of prioritising salary payments to medical personnel for the sake of job preservation without accounting for actual efficiency and combined with fixed wage increases demotivates healthcare staff and significantly undermines their ability to provide high-quality medical care.

CONCLUSIONS

Ukraine faces a need to establish a modern, European-style metropolitan healthcare space, building on the successful decentralisation reform. In the context of decentralisation, Ukraine requires the consolidation of governmental authorities, businesses, science, and the media within metropolitan areas to develop contemporary and competitive strategies for metropolitan regional development, including healthcare systems at both national and regional levels. This process must be based on the genuine devolution of powers from the central government to local communities, specifically, entrusting communities with the organisation of primary healthcare services, newly established districts

with responsibility for the operation of general and cluster-based specialised healthcare institutions, and metropolitan cities with the provision of specialised care through supracluster medical facilities. In this transformation, the scientific and expert community, civil society, Parliament, and the government, as well as individual citizens, are expected to retain their roles as leading forces in finalising decentralisation reform and initiating the subsequent stage of metropolitan development.

Two of the three regions of the Dnipro metropolitan area – Dnipropetrovsk and Zaporizhzhia are currently located within the immediate zone of active hostilities in the ongoing Russo-Ukrainian war. Moreover, a significant part of Zaporizhzhia region is occupied. This requires accelerating the integration of the Dnipro metropolitan area by combining human, financial, intellectual, scientific, entrepreneurial, and humanitarian resources to generate high added value in the economic domain and to establish an effective healthcare system in each of the three zones of metropolitan influence. Such integration must be underpinned by effective coordination among levels of local governance, adhering strictly to the principle of subsidiarity.

A priority task is the development of five-year programs for the healthcare system of the Dnipro metropolitan area, focusing on reducing mortality from non-communicable diseases, particularly under conditions of large-scale military aggression.

This goal is to be achieved by promoting projects within metropolitan area and facilitating their funding, primarily in the healthcare sector. These initiatives must be grounded in the principle of full compliance and autonomy at all levels of medical service delivery within a unified electronic system for healthcare management, centered on the use of an electronic patient card to which the patient should have access.

Looking ahead, it is essential to study international best practices in the development of metropolitan healthcare spaces and the organisation of their infrastructure to ensure the delivery of high-quality and accessible medical care. Relevant case studies include countries such as France, Poland, Canada, and others.

REFERENCES

1. Shliakh ME. *Za maibutnie liudstva [The Way. For the Future of Humanity]*. Translated from French by Ye. Maricheva. Kyiv: NikaTsentr. 2014, p.256. (Ukrainian)
2. Hill RC. Separate and unequal: governmental inequality in the metropolis. *Am Polit Sci Rev.* 1974;68(4):1557-1568. DOI: 10.2307/1959941.
3. Rennie TA, Srole L, Opler MK, Langner TS. Urban life and mental health: socioeconomic status and mental disorder in the metropolis. *Am J Psychiatry.* 1957;113(9):831-837. doi: 10.1176/ajp.113.9.831. DOI 
4. Ursebach J, O'Connell ME, Kirk A et al. Evidence for measurement bias of the short form health survey based on sex and metropolitan influence zone in a secondary care population. *Health Qual Life Outcomes.* 2020;18. doi: 10.1186/s12955-020-01318-y. DOI 

5. Sibley LM, Weiner JP. An evaluation of access to health care services along the ruralurban continuum in Canada. *BMC Health Serv Res.* 2011;11(1). doi: 10.1186/1472-6963-11-20. [DOI](#)
6. Heisler M, Kovtonyuk P, De Vos C. Attacks on health care used as a weapon of war in Ukraine and globally: the demand for accountability. *JAMA.* 2023;329(12):973974. doi: 10.1001/jama.2023.2787. [DOI](#)
7. Stepanova N. War in Ukraine: the price of dialysis patients' survival. *J Nephrol.* 2022;35(3):717718. doi: 10.1007/s40620-022-01308-x. [DOI](#)
8. Jankowski M, Gujski M. The public health implications for the refugee population, particularly in Poland, due to the war in Ukraine. *Med Sci Monit.* 2022;28:e9368081. doi: 10.12659/MSM.936808. [DOI](#)
9. Fontanarosa PB, Flanagan A, Golub RM. Catastrophic health consequences of the war in Ukraine. *JAMA.* 2022;327(16):15491550. doi: 10.1001/jama.2022.6046. [DOI](#)
10. Armitage R. War in Ukraine: the impacts on child health. *Br J Gen Pract.* 2022;72(719):272273. doi: 10.3399/bjgp22X719621. [DOI](#)
11. Murphy A, Fuhr D, Roberts B et al. The health needs of refugees from Ukraine. *BMJ.* 2022;377. doi: 10.1136/bmj.o864. [DOI](#)
12. Savchuk IG. Rol' mizhnarodnykh ekonomichnykh vidnosyn u formuvanni metropoliyinoho rehionu. [The role of international economic relations in the formation of the metropolitan region]. *Visnyk KNU im. Tarasa Shevchenka. Seriya Heohrafiya.* 2018;(1):1014. (Ukrainian)
13. Melnyk MI. Metropoliyini funktsii velykykh mist Ukrainy: potentsial rozvytku ta perspektyvy realizatsii. [Metropolitan functions of large cities of Ukraine: potential for development and prospects for implementation.]. *Lviv: Natsionalna akademiya nauk Ukrainy, Instytut rehionalnykh doslidzhen im. M. I. Dolishnoho.* 2016, p.552. (Ukrainian)
14. Pitiurenko YI. Systemy rozselennia i terytorial'na orhanizatsiia narodnoho hospodarstva. [Systems of settlement and territorial organization of the national economy]. *Kyiv: Naukova dumka.* 1983, p.140. (Ukrainian)
15. "Yakisna medytsyna dlia vsiiei sim'i – pidpyshy deklaratsiiu z terapevtamy, pediatriamy ta simeinymy likariamy. ["Good medicine for all families – signed declarations with therapists, pediatricians and family doctors"]. *Medicover.* <https://medicover.ua/deklaranty/deklaratsiya.html> [Accessed 11 July 2025] (Ukrainian)
16. Natsional'na sluzhba zdorov'ia: elektronna medychna kartka. [National Health Service: electronic health card]. *Natsional'na sluzhba zdorov'ya Ukrayiny.* <https://www.facebook.com/nszu.ukr/posts/1179888065822942> [Accessed 11 July 2025] (Ukrainian)
17. Tkachuk AF. Chorna kishka detsentralizatsii [The Black Cat of Decentralization]. *Dzerkalo Tyzhnia.* <https://zn.ua/ukr/internal/chorna-kishka-detsentralizatsiji.html> [Accessed 11 July 2025]
18. Hanushchak Yu. Reforma terytorial'noi orhanizatsyi vlyady. [Reform of the territorial organization of government.]. *Kyiv: SofiyaA, SwissUkrainian DESPRO project.* 2013, p.160. (Ukrainian)
19. Na s'ohodni svoikh likariv obralo blyzko 75 % ukrayintsiv. [Nearly 75% of Ukrainians chose their own medicines]. *Natsional'na sluzhba zdorov'ya Ukrayiny.* <https://nszu.gov.ua/novini/nacionalna-sluzhba-zdorovya-proponuye-pidvishchiti-stavku-si-335> [Accessed 11 July 2025] (Ukrainian)
20. Ylvisaker PN. Innovation and evolution: Bridge to the future metropolis. *Ann Am Acad Pol Soc Sci.* 1957;314(1):156164. doi: 10.1177/000271625731400117. [DOI](#)
21. Center for Medical Statistics, Ministry of Health of Ukraine. [Tsentr medychnoyi statystyky Ministerstva okhorony zdorov'ya Ukrayiny]. <http://medstat.gov.ua/ukr/main.html>. [Accessed 11 July 2025] (Ukrainian)
22. Blumenfeld H. The economic base of the metropolis: Critical remarks on the "basicnonbasic" concept. *J Am Inst Planners.* 1955;21(4):114132.
23. Law of Ukraine No. 2494IX of July 29, 2022. "On amendments to laws to increase accessibility of medical and rehabilitation care during martial law." As of July 29, 2022. [Zakon Ukrayiny № 2494 IX vid 29 lypnya 2022 roku. «Pro vnesennya zmin do zakoniv shchodo pidvyshchennya dostupnosti medychnoyi ta reabilitatsiynoyi dopomohy pid chas voyennoho stanu». Stanom na 29 lypnya 2022 roku]. *Verkhovna Rada of Ukraine.* (Ukrainian)
24. Law of Ukraine No. 2573 of September 6, 2022. "On the public health system." [Zakon Ukrayiny № 2573 vid 6 veresnya 2022 roku. «Pro systemu okhorony zdorov'ya»]. *Verkhovna Rada of Ukraine.* (Ukrainian)

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Vladyslav Smiianov

Sumy State University

116 Kharkivska St., 40007 Sumy, Ukraine

e-mail: v.smiyanov@med.sumdu.edu.ua

ORCID AND CONTRIBUTIONSHIP

Vladyslav Smiiianov: 0000-0002-4240-5968 **A** **B**

Oleksander Korniiichuk: 0000-0001-7357-0598 **C** **D**

Iryna Khomenko: 0000-0002-8412-6393 **E** **F**

Anatolii Tsarenko: 0000-0002-1617-3673 **A** **C**

Oleksandra Ivakhno: 0000-0002-9721-5088 **B** **D**

Viktoriia Yasenok: 0000-0003-3250-2112 **A** **E**

Olha Smiiianova: 0000-0002-5400-773X **B** **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: 10.05.2025

ACCEPTED: 29.08.2025



Key drivers of antibiotic resistance in *Escherichia coli* in a One Health context: A literature review

Alicja Polak¹, Kinga Kosiń², Wojciech Liszka³, Maria Malina⁴, Jakub Kiwior¹

¹FACULTY OF MEDICINE, MEDICAL UNIVERSITY OF SILESIA, KATOWICE, POLAND

²PRIVATE DENTAL PRACTICE – KINGA KOSIŃ, CRACOW, POLAND

³PRIVATE DENTAL PRACTICE – WOJCIECH LISZKA, CRACOW, POLAND

⁴FACULTY OF MEDICINE, JAGIELLONIAN UNIVERSITY MEDICAL COLLEGE, CRACOW, POLAND

ABSTRACT

Aim: To summarize the key factors driving *E. coli* resistance in Europe, with reference to global data and the One Health context.

Materials and Methods: A narrative literature review was conducted based on 14 peer-reviewed articles and institutional reports addressing resistance mechanisms and the epidemiology of *E. coli* strains in Europe and globally.

Conclusions: Resistance in *E. coli* is driven by complex, cross-sectoral dynamics. Effective containment strategies should include rational antibiotic use in primary care, restrictions on veterinary antimicrobial use, improved diagnostics, modernized wastewater infrastructure, and inclusion of travel history in AMR risk assessments. The persistent detection of *bla*_{CTX-M} and *mcr-1* in all reservoirs highlights the need for a unified One Health approach.

KEY WORDS: *Escherichia coli*, drug resistance, beta-lactamases, gene transfer, One Health

Wiad Lek. 2025;78(9):1909-1914. doi: 10.36740/WLek/209473 DOI

INTRODUCTION

Escherichia coli is a natural component of the human gut microbiota and a leading cause of urinary tract, intraabdominal and bloodstream infections in Europe. Although in 2023 the most common *E. coli* resistance was observed for aminopenicillins, European Centre for Disease Prevention and Control data from 2016–2020 indicate that the most severe clinical cases and the highest number of deaths were associated with resistance to third-generation cephalosporins. Given the serious health consequences of infections caused by antibiotic-resistant *E. coli* strains, comprehensive preventive measures are essential – extending beyond hospital care to encompass the broader healthcare system. [1]. One of the key resistance mechanisms of *Escherichia coli* is the ability to produce enzymes that inactivate β-lactam antibiotics. These bacteria can easily transfer resistance genes via plasmids and mobile genetic ele-

ments, such as transposons and insertion sequences, through the process of horizontal gene transfer (HGT). HGT is one of the major mechanisms facilitating the copying and dissemination of genes – including resistance genes such as *bla*_{CTX-M-15} gene – between bacteria of different species. This gene has been identified in multiple reservoirs: human, animal, and environmental [2]. Although carbapenem resistance in *Escherichia coli* remains uncommon, the emergence of hard-to-detect mechanisms – such as the OXA-244 carbapenemase – raises growing concern. These enzymes may evade standard diagnostics, increasing the risk of unnoticed spread within healthcare settings [3].

AIM

This review synthesises the main factors contributing to the emergence and spread of antibiotic-resistant

Escherichia coli in Europe, taking into account the interconnected human, animal, and environmental dimensions of the One Health perspective.

MATERIALS AND METHODS

This literature review was conducted to identify and synthesize scientific evidence on the mechanisms and epidemiology of antibiotic resistance in *Escherichia coli* in Europe, with a particular focus on the One Health perspective.

A structured literature search was performed using keywords such as “*Escherichia coli*”, “antibiotic resistance”, “ESBL”, “carbapenemase”, “CTX-M”, “OXA-244”, “fluoroquinolone resistance”, “veterinary antibiotics”, “horizontal gene transfer”, “mcr-1”, and “One Health”.

Inclusion criteria encompassed peer-reviewed articles focusing on *E. coli* resistance in human, animal, and environmental reservoirs within the European region.

A total of 14 scientific articles were selected and analyzed. The selection process followed the principles of narrative review methodology, aiming to provide a comprehensive yet structured overview of the most relevant mechanisms and drivers of resistance.

REVIEW AND DISCUSSION

INAPPROPRIATE ANTIBIOTIC PRESCRIBING IN HUMAN MEDICINE

Data from recent years indicate that antibiotic prescribing by primary care physicians significantly contributes to bacterial resistance to antimicrobial agents. A study conducted in 14 European countries revealed notable differences in prescribing practices across nations. Countries such as Spain, Poland, and Italy exhibited particularly high rates of broad-spectrum antibiotic use, reflected in elevated Antibiotic Spectrum Index (ASI) values. The study demonstrated a clear correlation between the volume of antibiotics prescribed and the prevalence of resistant microorganisms. Notably, the role of primary care physicians emerged as crucial, with approximately 90% of the antibiotic selection pressure (ASP) originating from primary care rather than hospital settings. Interestingly, it was not merely the number of prescriptions that mattered, but rather the breadth of antimicrobial activity. The broader the antibiotic spectrum, the higher the associated risk of resistance development. Although some general practitioners still believe that antimicrobial resistance (AMR) is primarily driven by hospital or veterinary antibiotic use, this study highlights the substantial influence of prescribing practices in family medicine on the growing AMR crisis [4].

This shift toward broad-spectrum antibiotic prescribing is not a new phenomenon. As early as the early 2000s, a cross-national study conducted in 26 European countries already highlighted a decline in the use of narrow-spectrum agents in favor of newer broad-spectrum antibiotics, especially in Southern and Eastern Europe [5].

A relevant example is the outpatient use of fluoroquinolones in the treatment of urinary tract infections (UTIs), which are most commonly caused by *Escherichia coli*. Antibiotics such as ciprofloxacin and levofloxacin are frequently prescribed empirically for cystitis and pyelonephritis. However, recent years have seen a notable increase in *E. coli* resistance to this antibiotic class, particularly in Southern and Eastern Europe, with resistance rates in Poland *previously reported* at approximately 30%. This trend highlights the importance of monitoring regional resistance patterns and promoting responsible antibiotic prescribing practices [6].

VETERINARY AND AGRICULTURAL ANTIBIOTIC USE

The practice of frequent antibiotic use by animal-based food producers is a serious factor contributing to antimicrobial resistance [9].

In 2023, EU member states, along with Iceland and Norway, jointly reported data on the sale and use of antimicrobials in animals for the first time. Coordinated by the EMA, the ESUAvet report showed that 98% of veterinary antimicrobials sold were intended for food-producing animals. The most frequently used classes included penicillins, tetracyclines, and sulfonamides. Usage data, mostly collected by veterinarians, focused on cattle, pigs, poultry, and turkeys [7].

The Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA IV) report indicates that reducing the use of antimicrobials in food-producing animals is associated with a higher proportion of *Escherichia coli* isolates fully susceptible to the tested antimicrobial agents. This pattern was observed both in animal and human isolates, particularly in countries that have significantly decreased overall antimicrobial consumption [8].

The increase in resistance to colistin – an antibiotic used in the treatment of severe infections caused by carbapenemase-producing *E. coli* strains – is closely linked to its widespread use in food-producing animals. A particular concern is the emergence of the plasmid-mediated resistance gene *mcr-1*, which facilitates horizontal transfer of this trait between bacteria. In many cases, *E. coli* isolates from both animals and humans have carried both *mcr-1* and *bla*CTX-M, suggesting the potential for co-transfer of resistance to colistin and cephalosporins [9].

Emerging evidence demonstrates that the use of antibiotics in livestock farming fosters the gastrointestinal colonization of poultry and mammals by *E. coli* strains carrying *bla*CTX-M resistance genes. These strains can be transmitted to humans through both the food chain and direct contact [12].

Recent data from Thailand indicate that both companion animals and individuals working closely with them may carry *E. coli* strains resistant to multiple antimicrobial agents. These strains were often found to possess extended-spectrum beta-lactamase (ESBL) genes, including *bla*CTX-M, *bla*TEM, *bla*SHV, along with tetracycline resistance markers (*tetA*, *tetB*). This highlights the potential role of household pets as reservoirs of resistance genes and supports the need for integrated antimicrobial resistance surveillance within a One Health framework [10].

1 HOSPITAL TRANSMISSION AND INFECTION CONTROL GAPS

A 2-year study in a tertiary care hospital found that many patients carried ESBL-producing *E. coli* at admission or acquired it during hospitalization. Most infections (60%) were endogenous, but transmission between patients also occurred, revealing infection-control gaps. The study highlights the need for antibiotic stewardship to limit antibiotic overuse and lower ESBL-E infection rates [11].

Although carbapenem resistance in *Escherichia coli* remains relatively low in the EU/EEA – with fewer than 1.5% of invasive isolates exhibiting resistance in 2022— it is becoming an increasing concern due to the emergence of difficult-to-detect resistance mechanisms and the critical importance of carbapenems as last-resort antibiotics. One such mechanism involves the OXA-244 carbapenemase, an enzyme with low hydrolytic activity that often escapes detection through standard screening methods and fails to grow on selective CPE media. This diagnostic limitation was exemplified by a large-scale hospital outbreak in Poland in 2023, where *E. coli* ST38 strains carrying the *bla*OXA-244 gene were identified in 38 patients across 13 wards. Despite extensive epidemiological investigation, no definitive source of transmission was established. The spread was likely facilitated by intra-hospital movement of patients and healthcare personnel, further highlighting the importance of improved detection and containment strategies for emerging carbapenemase producers [3].

2 INTERNATIONAL TRAVEL AND POPULATION MOBILITY

A multinational study conducted across several countries confirmed that international travel constitutes a

major risk factor for colonization with extended-spectrum β -lactamase-producing *Escherichia coli* (ESBL-EC). Individuals who traveled at least once per year to Asia, Sub-Saharan Africa, or Northern Africa exhibited an approximately fourfold increased likelihood of ESBL-EC carriage compared to those who had not traveled to these regions. This association remained statistically significant after adjustment for potential confounders [14].

3 HORIZONTAL GENE TRANSFER AND MOBILE GENETIC ELEMENTS

On a global scale, *bla* CTX-M-15 is the most frequently identified CTX-M gene variant in *Escherichia coli*. The extraintestinal pathogenic clone ST131 has emerged as the leading strain worldwide, with its H30-Rx sublineage being particularly widespread. This subclone is notable for carrying both fluoroquinolone resistance and the *bla* CTX-M-15 gene, which has contributed to its success. The dissemination of this resistance gene is largely driven by horizontal gene transfer via conjugative plasmids, especially those belonging to the IncF family, which act as primary vectors. Importantly, ST131 has not only been found in clinical human samples but also in animals and the environment, reflecting its broad adaptability and relevance in One Health contexts [12].

ENVIRONMENTAL RESERVOIRS AND WASTEWATER INTERFACES

The natural environment serves as a significant reservoir of antimicrobial resistance genes, including *bla*CTX-M, primarily due to pollution linked to human activities. ESBL-producing *Escherichia coli* have been increasingly identified in a variety of environmental settings.

The presence of mobile genetic elements – especially class I integrons and transposons – facilitates the horizontal transfer of resistance traits between bacteria, enabling their persistence across ecological boundaries.

Environmental contamination with residual antibiotics supports the survival of resistant strains that may eventually transfer their resistance to humans and animals.

For instance, fluoroquinolone pollution favors the selection of bacterial strains carrying integrons that harbor both *bla*CTX-M and *qnr* genes, contributing to the long-term maintenance and environmental spread of ESBL resistance [12].

Inadequate treatment processes in wastewater treatment plants (WWTPs) contribute significantly to the dissemination of antimicrobial-resistant bacteria and resistance genes in the environment. These facilities

receive human excreta containing unmetabolized antibiotics, as well as a wide range of chemicals, including pharmaceuticals and personal care products. If not effectively removed, these substances create selective pressure that promotes the survival and spread of resistant strains. Studies have detected multidrug-resistant *Escherichia coli* isolates, including those carrying resistance genes such as *mcr-1* and *ermA*, in treated effluents released into natural water bodies [13].

DISCUSSION

This literature review reveals that antibiotic-resistant *Escherichia coli* is an increasingly complex public health challenge in Europe, driven by a constellation of interrelated factors across human, animal, and environmental domains. The reviewed evidence shows that resistance is no longer confined to hospitals but is instead propagated through interconnected ecosystems. Understanding the multifactorial dynamics of resistance transmission is therefore crucial for designing effective mitigation strategies across all sectors of the One Health interface.

The role of primary care practitioners is particularly concerning, given their significant contribution to antimicrobial selection pressure. The shift toward broad-spectrum agents, such as fluoroquinolones, has likely contributed to the regional increase in resistance, especially in Southern and Eastern Europe. These findings support the need for continued education and stewardship programs tailored specifically to outpatient care.

In the veterinary and agricultural sectors, the widespread use of antimicrobials—especially in food-producing animals – has enabled the persistence and dissemination of resistance genes such as *mcr-1* and *blaCTX-M*. The identification of these genes in both human and animal isolates, as well as in companion animals, highlights the permeability of the One Health interface and the necessity of coordinated surveillance across sectors.

Hospital-based transmission remains an ongoing concern, particularly in light of the emergence of elusive resistance mechanisms such as OXA-244 carbapenemase. The inability of standard diagnostic tests to detect certain carbapenemase producers presents a serious threat, as undetected carriers may facilitate silent outbreaks. This calls for the incorporation of more sensitive molecular diagnostics in clinical microbiology laboratories.

Horizontal gene transfer further complicates containment efforts. Plasmids, integrons, and transposons have accelerated the spread of resistance across species and ecosystems, with environmental contamination –

particularly via wastewater – providing ideal conditions for persistence and exchange of resistance traits. These findings underscore the urgent need to improve wastewater treatment standards and reduce pharmaceutical residues in the environment.

One important but often underappreciated factor is international travel. The AWARE study demonstrated that frequent travelers to high-prevalence regions face significantly higher risks of ESBL-EC colonization. This highlights the global dimension of resistance dissemination and suggests that travel history should be more routinely considered in clinical risk assessments and screening protocols.

Key summary points:

- Antibiotic resistance in *E. coli* is driven by interconnected pressures across the One Health spectrum.
- Inappropriate outpatient prescribing, particularly of broad-spectrum antibiotics, remains a critical issue in many European countries.
- Antimicrobial use in agriculture contributes to resistance gene dissemination, including in household pets.
- Hospital outbreaks caused by hard-to-detect carbapenemases, such as OXA-244, illustrate the diagnostic limitations of current protocols.
- Environmental contamination and wastewater interfaces create persistent reservoirs of resistance.
- Frequent international travel to high-risk regions significantly increases the likelihood of ESBL-EC carriage.

CONCLUSIONS

Antibiotic resistance in *Escherichia coli* presents an escalating public health challenge that transcends hospital walls and reflects the interconnectivity of human, animal, and environmental health domains. This literature review demonstrates that resistance is fueled by multiple factors: excessive broad-spectrum antibiotic use in primary care, the overuse of antimicrobials in food-producing animals, inadequate infection control in healthcare settings, environmental contamination, and global travel.

A coordinated and multisectoral approach is urgently required. Strategies should include:

- Strengthening antimicrobial stewardship in outpatient settings;
- Restricting non-therapeutic antibiotic use in agriculture;
- Improving diagnostic capacities to detect hard-to-identify resistance mechanisms;
- Enhancing wastewater treatment standards;
- Integrating travel history into risk assessment protocols.

Finally, the consistent presence of *bla*CTX-M and *mcr*-1 genes across human, animal, and environmental reservoirs reinforces the critical importance of adopting a One Health perspective in tackling antibiotic

resistance. Future efforts must prioritize surveillance, prevention, and international collaboration to limit the spread of multidrug-resistant *E. coli* and protect public health.

REFERENCES

1. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARSNet): annual epidemiological report 2023. Stockholm: ECDC; 2024.
2. Zhang S, Yang J, Abbas M, Yang Q, et al. Threats across boundaries: the spread of ESBL-positive Enterobacteriaceae bacteria and its challenge to the "one health" concept. *Front Microbiol*. 2025 Feb 21;16:1496716. doi: 10.3389/fmicb.2025.1496716. [DOI](#)
3. Izdebski R, Biedrzycka M, Urbanowicz P, et al. Large hospital outbreak caused by OXA-244-producing *Escherichia coli* sequence type 38, Poland, 2023. *Euro Surveill*. 2024 May;29(22):2300666. doi: 10.2807/1560-7917.ES.2024.29.22.2300666. [DOI](#)
4. Sijbom M, Büchner FL, Saadah NH, Numans ME, De Boer MGJ. Trends in antibiotic selection pressure generated in primary care and their association with sentinel antimicrobial resistance patterns in Europe. *J Antimicrob Chemother*. 2023 May 3;78(5):1245-1252. doi: 10.1093/jac/dkad082. [DOI](#)
5. Goossens H, Ferech M, Vander Stichele R, Elseviers M; ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005 Feb 12-18;365(9459):579-87. doi: 10.1016/S0140-6736(05)17907-0. [DOI](#)
6. Ruiz-Lievano AP, Cervantes-Flores F, Nava-Torres A, Carbajal-Morales PJ, Villaseñor-García LF, Zavala-Cerna MG. Fluoroquinolone Resistance in *Escherichia coli* Causing Community-Acquired Urinary Tract Infections: A Systematic Review. *Microorganisms*. 2024; 12(11):2320. doi: 10.3390/microorganisms12112320. [DOI](#)
7. European Medicines Agency. First report on EUwide sales and use of antimicrobials in animals (ESUAvet). Amsterdam: EMA; 2025.
8. European Centre for Disease Prevention and Control; European Food Safety Authority; European Medicines Agency. Antimicrobial consumption and resistance in bacteria from humans and food-producing animals: Fourth joint inter-agency report JIACRA IV – 2019–2021. *EFSA J*. 2024;22(2):e8589. doi:10.2903/j.efsa.2024.8589. [DOI](#)
9. Van TTH, Yidana Z, Smooker PM, Coloe PJ. Antibiotic use in food animals worldwide, with a focus on Africa: Pluses and minuses. *J Glob Antimicrob Resist*. 2020 Mar;20:170-177. doi: 10.1016/j.jgar.2019.07.031. [DOI](#)
10. Buranasinsup S, Wiratsudakul A, Chantong B, Maklon K, Suwanpakdee S, Jiemtaweeboon S, Sakcamduang W. Prevalence and characterization of antimicrobial-resistant *Escherichia coli* isolated from veterinary staff, pets, and pet owners in Thailand. *Journal of Infection and Public Health*. doi:10.1016/j.jiph.2023.11.006. [DOI](#)
11. Nguyen MN, Gladstone BP, De Angelis G, et al. Tracing carriage, acquisition, and transmission of ESBL-producing *Escherichia coli* over two years in a tertiary care hospital. *Genome Med*. 16, 151 (2024). doi: 10.1186/s13073-024-01424-2. [DOI](#)
12. Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M β -lactamases: temporal and geographical shifts in genotype. *J Antimicrob Chemother*. 2017 Aug 1;72(8):2145-2155. doi: 10.1093/jac/dkx146. [DOI](#)
13. Meradji S, Basher NS, Sassi A, Ibrahim NA, Idres T, Touati A. The Role of Water as a Reservoir for Antibiotic-Resistant Bacteria. *Antibiotics*. 2025;14(8):763. doi: 10.3390/antibiotics14080763. [DOI](#)
14. Rodríguez-Molina D, Berglund F, Blaak H, et al. International Travel as a Risk Factor for Carriage of Extended-Spectrum β -Lactamase-Producing *Escherichia coli* in a Large Sample of European Individuals-The AWARE Study. *Int J Environ Res Public Health*. 2022 Apr 14;19(8):4758. doi: 10.3390/ijerph19084758. [DOI](#)

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Alicja Polak

Faculty of Medicine

Medical University of Silesia

Katowice, Poland

e-mail: ala038718@gmail.com

ORCID AND CONTRIBUTIONSHIP

Alicja Polak: 0009-0009-7324-4675 [A](#) [D](#)

Kinga Kosiń: 0009-0009-4569-3633 [B](#)

Wojciech Liszka: 0009-0005-6511-8039 **B**

Maria Malina: 0009-0001-7205-2788 **F**

Jakub Kiwior: 0009-0000-0901-8117 **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: 12.05.2025

ACCEPTED: 13.08.2025





SAVE A LIFE
ŚWIATOWY ZJAZD

POLONIJNYCH
ŚRODOWISK
MEDYCZNYCH



21–22 listopada
2025 roku

CENTRUM DYDAKTYCZNE
WARSZAWSKIEGO UNIwersYTETU MEDYCZNEGO,
UL. KS. TROJDENA 2A, WARSZAWA

PIERWSZY ZJAZD
POLONIJNYCH ŚRODOWISK MEDYCZNYCH

Zarejestruj się już dziś!



W programie:



Basic Life Support
– kursy i szkolenia



Innowacje w medycynie
ratunkowej



Medycyna pola
walki



Profilaktyka
i styl życia



Badania profilaktyczne
dla uczestników
i osób towarzyszących



Networking
Wieczorny koncert gwiazdy
Zwiedzanie Warszawy z przewodnikiem

Szczegóły na stronie Zjazdu:

www.swiatowyzjazdpsm.pl

Znajdziesz nas na:



[zjazdpoloniimed](https://www.instagram.com/zjazdpoloniimed)

Organizatorzy



Naczelna
Izba Lekarska



Polskie
Towarzystwo
Lekarskie



Ministerstwo
Zdrowia

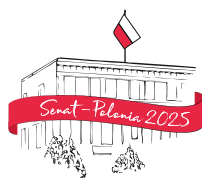
Partnerzy



WARSZAWSKI
UNIwersYTET
MEDYCZNY



NACZELNA IZBA
PIELĘGNIAREK I POŁOŻNYCH



STOWARZYSZENIE
„WSPÓLNOTA POLSKA”



DOFINANSOWANO ZE ŚRODKÓW BUDŻETU PAŃSTWA

Dotacja celowa na dofinansowanie realizacji
zadania publicznego z zakresu opieki Senat RP
nad Polonią i Polakami za granicą

Światowy Zjazd Polonijnych
Środowisk Medycznych Save a Life

DOFINANSOWANIE
493 400 zł

CAŁKOWITA WARTOŚĆ
563 400 zł

DATA PODPISANIA UMOWY
sierpień 2025 r.