ORIGINAL ARTICLE

CONTENTS

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

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

ABSTRACT

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

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

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

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

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

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INTRODUCTION

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

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

In our previous stages of research and relevant pub-

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

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

AIM

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

MATERIALS AND METHODS

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

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

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

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

RESULTS

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

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

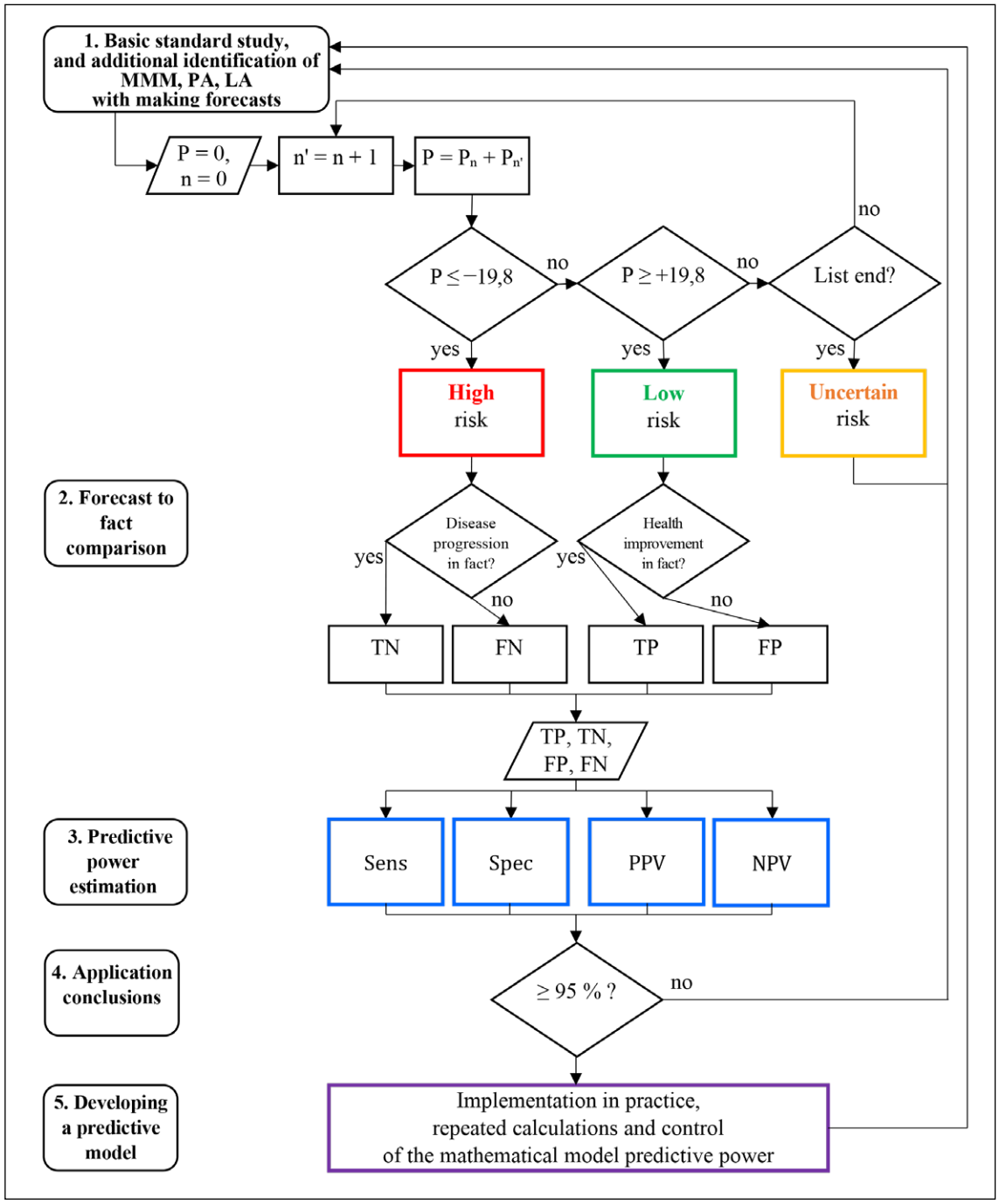

Fig. 1. Methodology for assessing the prognostic power and clinical effectiveness of a method (algorithm) for clinical course predicting in patients with chronic myeloid leukemia

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

CONCLUSIONS

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

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

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

CONFLICT OF INTEREST

The Author declare no conflict of interest

CORRESPONDING AUTHOR

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

ORCID AND CONTRIBUTIONSHIP

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

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

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