Хирургия. Журнал имени Н.И. Пирогова
2024, №8, с. 15–20
https://doi.org/10.17116/hirurgia202408115

Pirogov Russian Journal of Surgery
2024, No. 8, pp. 15–20
https://doi.org/10.17116/hirurgia202408115

Факторы, связанные с нормальным количеством лейкоцитов и уровнем С-реактивного белка у взрослых больных с острым аппендицитом: ретроспективное когортное исследование

© CARLOS SALAZAR YAMIR[1], JOSÉ CABALLERO-ALVARADO[1, 2], KATHERINE LOZANO-PERALTA[1], CARLOS ZAVALETA-CORVERA[1]

[1]Медицинский факультет, Частный университет Антенор Оррего, Трухильо, Перу;
[2]Хирургическое отделение, Региональная больница Трухильо, Трухильо, Перу

Резюме

Цель исследованя. Выявить факторы, связанные с нормальным количеством лейкоцитов и уровнем С-реактивного белка (СРБ) у взрослых с острым аппендицитом.

Материал и методы. В ретроспективное когортное исследование были включены пациенты в возрасте 18—60 лет, перенесшие операции по поводу острого аппендицита. Оценили такие переменные, как возраст, пол, вес, рост, происхождение, самолечение, диабет (СД2), высокое артериальное давление, тип аппендицита, продолжительность заболевания, предоперационный период. Анализировали тип аппендэктомии, продолжительность операции и срок пребывания в стационаре. Пациенты были разделены 2 группы: больные с нормальными и аномальными значениями параметров воспаления. Для анализа использовали программное обеспечение SPSS версии 28.

Результаты. Мы включили 333 пациента. У 11,11% показатели воспаления были нормальными. Больные обеих групп имели средний возраст около 33 лет. Мужчины составили 56,76 и 57,43% в обеих группах соответственно. В группе аномальных значений средний предоперационный период был короче, а катаральный аппендицит чаще встречался в группе нормальных значений. Многофакторный анализ показал, что сельское происхождение и самолечение были в значительной степени связаны с нормальными параметрами воспаления.

Вывод. Распространенность нормальных показателей воспаления у больных острым аппендицитом составила 11,11%. Сельское происхождение, самолечение, более короткий предоперационный период и катаральный аппендицит были значимо связаны с нормальными параметрами воспаления.

Ключевые слова: *острый аппендицит, лейкоциты, СРБ, воспалительные параметры.*

Информация об авторах:
Carlos Zavaleta-Corvera — https://orcid.org/0000-0001-5918-8261
Автор, ответственный за переписку: Carlos Zavaleta Corvera — e-mail: czavaletac3@upao.edu.pe

Как цитировать:
Carlos Salazar Yamir, José Caballero-Alvarado, Katherine Lozano-Peralta, Carlos Zavaleta-Corvera. Факторы, связанные с нормальным количеством лейкоцитов и уровнем С-реактивного белка у взрослых больных с острым аппендицитом: ретроспективное когортное исследование. *Хирургия. Журнал им. Н.И. Пирогова*. 2024;8:15–20. https://doi.org/10.17116/hirurgia202408115

Factors associated with normal leukocyte count and C-reactive protein in adults with acute appendicitis: a retrospective cohort study

© CARLOS SALAZAR YAMIR[1], JOSÉ CABALLERO-ALVARADO[1, 2], KATHERINE LOZANO-PERALTA[1], CARLOS ZAVALETA-CORVERA[1]

[1]School of Medicine, Antenor Orrego Private University, Trujillo, Peru;
[2]Surgery Department, Regional Hospital of Trujillo, Trujillo, Peru

Abstract

Objective. To identify the factors associated with normal leukocyte count and C-reactive protein (CRP) in adults with acute appendicitis.

Material and methods. A retrospective cohort study included patients aged 18-60 years after surgeries for acute appendicitis. Convenience sampling was used to select medical records, and variables such as age, sex, weight, height, origin, self-medication, diabetes (DM2), high blood pressure (HBP), type of appendicitis, duration of illness, preoperative time, type of appendectomy, operative time, and hospital stay were analyzed. Patients were categorized into those with normal and abnormal inflammatory parameters. The SPSS version 28 software was used for analysis.

Results. We included 333 patients; 11.11% ones had normal inflammatory parameters. Both groups had mean age of approximately 33 years. Men comprised 56.76% and 57.43%in both groups, respectively. The abnormal group had shorter mean preoperative time, and catarrhal appendicitis was more common in the normal group. Multivariate analysis revealed that rural origin and self-medication were significantly associated with normal inflammatory parameters.

Conclusion. The prevalence of normal inflammatory parameters in acute appendicitis patients was 11.11%. Rural origin, self-medication, shorter preoperative time, and catarrhal appendicitis were significantly associated with normal inflammatory parameters in this context.

Keywords: *acute appendicitis, white blood cells, CRP, inflammatory parameters.*

Information about the authors:
Carlos Zavaleta-Corvera — https://orcid.org/0000-0001-5918-8261
Corresponding author: Carlos Zavaleta Corvera — e-mail: czavaletac3@upao.edu.pe

To cite this article:
Carlos Salazar Yamir, José Caballero-Alvarado, Katherine Lozano-Peralta, Carlos Zavaleta-Corvera. Factors associated with normal leukocyte count and C-reactive protein in adults with acute appendicitis: a retrospective cohort study. *Pirogov Russian Journal of Surgery*. 2024;8:15–20. https://doi.org/10.17116/hirurgia202408115

Introduction

Acute appendicitis is an inflammation of the appendix. Mainly affects young people and men worldwide [1]. The frequency of this condition varies by region, in Europe there are 12.4 annual cases per 10,000 people [2]. In 2016, the US spent $9.3 billion on its treatment [3].

An accurate diagnosis of acute appendicitis is crucial for proper treatment and preventing complications. Although the clinical history and physical examination are the first tools used, their accuracy may be limited [4, 5]. Therefore, techniques such as ultrasonography, computed tomography [6, 7] and various serum biomarkers, such as C-reactive protein and leukocyte count, are used to improve diagnostic accuracy [8—11].

The clinical diagnosis has an accuracy of 88%, which results in 12% of appendectomies where appendicitis is not found [12]. Inflammatory markers are used to improve the accuracy in the diagnosis of acute appendicitis. The most common tests are white blood cell count and C-reactive protein (CRP) [13]. However, it is also common to see an increase in the leukocyte count, a sign of an inflammatory response to an infection or irritation of the appendix [14]. On the other hand, CRP is a protein that the liver produces when there is systemic inflammation. If it is present in the blood, it may indicate inflammation, infections or organ damage. In addition, it is an indicator of acute response, which implies that its level can rise rapidly if there is inflammation [14].

Potential complications make the appendicitis a surgical emergency. That´s why it is crucial to improve its diagnosis and treatment in adults. Although white blood cell counts and C-reactive protein levels are common indicators, there are patients with appendicitis who show normal values in these tests. This can cause late diagnoses and suboptimal treatments, increasing the risk of complications. Therefore, it is essential to identify the factors related to these normal values in people with appendicitis, to improve diagnostic accuracy.

Methods

Retrospective cohort study investigation included all patients over 18 years of age undergoing surgery for acute appendicitis between January 2022 and July 2023. The diagnosis of acute appendicitis was confirmed by histopathology. Upon admission to the hospital, it was essential that patients present laboratory tests, specifically white blood cell count and CRP. Patients with incidental appendectomy, cecum cancer, peritonitis, appendiceal masses or abscesses were excluded. For the leukocyte count, normal values were considered those that ranged between 4 and 10 thousand/L. Regarding CRP, any value less than 5 mg/l was established as normal.

The patients' medical records were exhaustively reviewed, extracting clinical and surgical data that were recorded in files designed specifically for this study.

Data analysis was carried out with SPSS software version 28. Descriptive statistics such as mean, standard deviation, frequencies and percentages were calculated. For the inferential analysis, the Chi Square test and Student's t test were applied. In addition, logistic regression was used to determine the variables related to normal leukocyte count and CRP in cases of acute appendicitis.

The study was approved by the Ethics Committee of the Antenor Orrego Private University. Although explicit consent was not requested from the patients due to the retrospective nature of the study, the confidentiality of the information was guaranteed following international ethical standards, by coding each patient.

Table 1. **Distribution of adults according to clinical characteristics and inflammatory parameters**

Clinical characteristics	Leukocyte count + CRP		OR CI 95%	*p*-value
	Normal (37)	Abnormal (296)		
Age (years)	33.03±11.69	32.89±11.35	—	0.943
Gender			0.97 [0.49—1.94]	0.938
Male	21 (56.76%)	170 (57.43%)		
Female	16 (43.24%)	126 (42.57%)		
BMI (Kg/m2)	24.93±2.18	25.30±2.60	—	0.402
Procedence			2.18 [1.05—4.53]	0.034
Rural	13 (35.14%)	59 (19.93%)		
Urban	24 (64.86%)	237 (80.07%)		
AutomedicationYes	16 (43.24%)	77 (26.01%)	2.17 [1.08—4.37]	0.028
No	21 (56.76%)	219 (73.99%)		
Hypertension			0.62 [0.14—2.73]	0.523
Yes	2 (5.41%)	25 (8.45%)		
No	35 (94.59%)	271 (91.55%)		
Diabetes Mellitus 2			0.55 [0.12—2.40]	0.417
Yes	2 (5.41%)	28 (9.46%)		
No	35 (94.59%)	268 (90.54%)		
Length of the disease	17.62 ± 8.34	20.56 ± 9.77	—	0.081

Note. CRP: C reactive protein. BMI: Body mass index. CI: Confidence interval.

Table 2. **Distribution of adults according to surgical characteristics and inflammatory parameters**

Clinical characteristics	Leukocyte count + CRP		OR CI 95%	*p*-value
	Normal (37)	Abnormal (296)		
Preoperative time	11.97±4.06	9.24±5.68	—	0.005
Type of appendicitis			—	0.037
Catarrhal	8 (21.62%)	22 (7.43%)		
Suppurated	26 (70.27%)	240 (81.08%)		
Gangrenous	1 (2.70%)	18 (6.08%)		
Perforated	2 (5.41%)	16 (5.41%)		
Type of appendectomy			0.61[0.17—2.20]	0.441
Open	34 (91.89%)	281 (94.93%)		
Laparoscopic	3 (8.11%)	15 (5.07%)		
Operating time	77.24±25.45	77.63±28.11	—	0.937
Hospital stays	1.49±1.22	1.76±1.38	—	0.244
White blood cell count	7649.46±1414.62	14516.35±4516.14	—	0.001
CRP	3.59±1.02	158.87±88.70	—	0.001

Note. CRP: C reactive protein, BMI: Body mass index, CI: Confidence interval, OR: Odds Ratio.

Results

We included 333 patients aged 18 to 60 years operated on for pathologically confirmed acute appendicitis were evaluated, finding that 11.11% presented normal inflammatory parameters in leukocyte count and CRP. The average age was 33.03 years for those with normal parameters and 32.89 years for those with abnormal parameters. The only clinical characteristic with a significant association with normal inflammatory parameters was urban origin (p=0.034). Regarding surgical characteristics, those with normal parameters showed a longer preoperative time (11.97 hours) and predominance of suppurative appendicitis (70.27%). Despite similar operative times and hospital stays between groups, there were notable differences in leukocyte count and CRP. Additionally, the multivari-

Table 3. **Multivariate analysis of the factors associated with normal inflammatory parameters in patients with acute appendicitis**

	B	Wald	Valor *p*	ORa	CI 95%	
					IL	SL
Rural procedence	0.75	3.93	0.048	2.12	1.01	4.42
Automedication	0.75	4.30	0.038	2.11	1.04	4.28

Note. B: Regression coefficient, ORa: Adjusted Odds Ratio, IL: Inferior Limit, SL: Superior Limit.

ate analysis revealed that rural origin (aOR=2.12; p=0.048) and self-medication (aOR=2.11; p=0.038) were significantly associated with the normality of the inflammatory parameters.

Discussion

Acute appendicitis occurs with a frequency of 100 new cases per 100,000 individuals annually, being the main reason for a suddenly painful abdomen. Although men are slightly more likely to develop acute appendicitis compared to women (8.6% versus 6.7%), women are more likely to require an appendectomy over their lifetime (23, 1% versus 12.0%) [15].

Acute appendicitis has been reported to be one of the predominant causes of an acute abdomen. Although its main identification is through clinical evaluation, additional diagnostic methods are sometimes used, such as leukocyte analysis, measurement of C-reactive protein, ultrasound, and computed tomography. Early diagnosis and timely surgical intervention with appendectomy usually have a positive outcome. However, if treatment is delayed, serious complications may arise, such as peritonitis due to rupture of the appendix or the development of abscesses [16].

On some occasions, emergency doctors treat patients with abdominal pain, but the examination is not conclusive and in addition to the physical examination, laboratory results may also be obtained, specifically the most common, a normal white blood cell count and CRP, which could lead us to exclude a diagnosis of acute appendicitis. However, the literature has reported a proportion of patients with normal inflammatory parameters; A notable observation in this study was the prevalence of normal inflammatory parameter results of 11.11% in patients with acute appendicitis; an Australian study by N. Dayawansa et al. [14]; found a prevalence of 8.54% of these normal inflammatory parameters in this population of patients with acute appendicitis; Another study carried out in Sub Africa by A. Withers et al. [17], also reported normality figures greater than 20%. These findings are intriguing, as inflammation is generally expected to be elevated in appendicitis.

Additionally, the prolonged preoperative time in the group with normal inflammatory parameters could suggest a less acute or severe manifestation of the disease. This could sometimes lead to an atypical presentation of the condition. Therefore, it is preferable to keep these patients under observation for a longer period. This is the reason why patients with normal inflammatory parameters experienced a longer preoperative time. S. Echevarria et al. [18], in Bolivia, highlighted the presence of atypical appendicitis, which causes delays in diagnosis, because clinical evaluation, clinical scoring systems and inflammatory markers do not discriminate the diagnosis and it must be opt for imaging studies, the latter was also corroborated by S. Borruel Nacenta et al. [19].

The multivariate analysis offered two crucial findings: origin and self-medication as factors significantly associated with the presence of normal inflammatory parameters. These results suggest the possible influence of external or behavioral factors on the clinical presentation of acute appendicitis. Specifically, the relationship between self-medication and normal inflammatory parameters may suggest that certain medications taken prior to hospital admission could be moderating the inflammatory response; A study conducted in Pakistan by S. Asad et al. [20], found that 23.08% of patients with acute appendicitis had self-medication at home and it influenced their diagnosis.

The presence of normal inflammatory parameters in cases of acute appendicitis may be surprising, given that this inflammatory condition usually manifests clear signs of inflammation, such as increased leukocytes and high CRP levels. However, in the early stages of appendicitis, clinical symptoms may be evident without inflammatory markers exceeding normal values. Additionally, some individuals may have a reduced inflammatory response due to genetic factors, comorbidities, or the intake of certain medications, such as nonsteroidal anti-inflammatory drugs. Likewise, in cases where appendicitis has not spread or perforated, the systemic inflammatory response may be limited, maintaining inflammatory indicators within a normal range [21, 22].

We consider that future studies can address topics such as the effect of self-medication on inflammation and clinical presentation, that is, research that focuses on the type, dose and duration of medications taken by patients before hospital admission. These investigations could determine whether specific medications, or combinations of them, play a role in moderating the inflammatory response in cases of appendicitis. Another topic could be epidemiological studies of origin and appendicitis, given that origin (urban or rural) showed a significant association with inflammatory parameters. Therefore, it would be beneficial to conduct detailed epidemiological studies to better understand the differences in clinical presentation and inflammatory response between urban and rural populations. These investigations could consider factors such as access to medical care, diet, lifestyle and environmental exposures that may vary

between urban and rural areas and finally investigate alternative biomarkers in acute appendicitis, although white blood cell count and CRP are standard biomarkers to evaluate inflammation, the existence of normal inflammatory parameters in some patients suggests the need to explore other biomarkers. Future research could focus on identifying and validating new biomarkers that could be more sensitive or specific for the early detection and management of appendicitis, especially in those cases where traditional parameters may not be as revealing.

This study has several limitations that must be considered. First, it was conducted at a single hospital center, which could limit the generalizability of the results to other populations or clinical settings. Furthermore, sole reliance on WBC counts and CRP as inflammatory parameters may not reflect the entire inflammatory landscape in patients with acute appendicitis. It is also possible that there were unidentified or uncontrolled confounding factors that could have influenced the results. The lack of correlation with imaging tests, such as ultrasound or computed tomography, in determining the severity and extent of appendicitis may have limited diagnostic accuracy. Finally, the possible presence of biases, such as selection bias or information bias, cannot be completely ruled out.

Conclusion

The prevalence of normal inflammatory parameters in patients with acute appendicitis was 11.11%. Rural origin, self-medication, preoperative time and catarrhal appendicitis are significantly associated with normal inflammatory parameters in patients with acute appendicitis.

Funding Sources: The authors declare that this work has not received any funding from funding agencies in the public, commercial, or non-profit sectors.

Ethical aspects: All authors certify that they meet the current authorship criteria of the International Committee of Medical Journal Editors (ICMJE).

The authors declare no conflicts of interest.

ЛИТЕРАТУРА/REFERENCES

1. Carratalá-Munuera C, Pilco JDR, Orozco-Beltrán D, Compañ A, Quesada JA, Nouni-García R, Gil-Guillén VF, García-Ortíz L, López-Pineda A. Hospitalization Trends for Acute Appendicitis in Spain, 1998 to 2017. *Int J Environ Res Public Health*. 2021;18(23):12718. https://doi.org/10.3390/ijerph182312718
2. Saren R, Aspegren S, Paajanen H, Ukkonen M, Käkelä P. Incidence of acute diverticulitis compared to appendicitis in emergency wards: a 10-year nationwide register and cohort study from Finland. *Scand J Gastroenterol*. 2023;58(2):151-156. https://doi.org/10.1080/00365521.2022.2111225
3. Stukalin I, Jogiat UM, Ahmed NS, Guo H, Laffin M, Ma C. Age-related disparities and trends in national healthcare spending for management of appendicitis in the United States: A retrospective cost-analysis. *Surgery*. 2023;173(4):896-903. https://doi.org/10.1016/j.surg.2022.12.003
4. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, Boermeester M, Sartelli M, Coccolini F, Tarasconi A, De' Angelis N, Weber DG, Tolonen M, Birindelli A, Biffl W, Moore EE, Kelly M, Soreide K, Kashuk J, Ten Broek R, Gomes CA, Sugrue M, Davies RJ, Damaskos D, Leppäniemi A, Kirkpatrick A, Peitzman AB, Fraga GP, Maier RV, Coimbra R, Chiarugi M, Sganga G, Pisanu A, De' Angelis GL, Tan E, Van Goor H, Pata F, Di Carlo I, Chiara O, Litvin A, Campanile FC, Sakakushev B, Tomadze G, Demetrashvili Z, Latifi R, Abu-Zidan F, Romeo O, Segovia-Lohse H, Baiocchi G, Costa D, Rizoli S, Balogh ZJ, Bendinelli C, Scalea T, Ivatury R, Velmahos G, Andersson R, Kluger Y, Ansaloni L, Catena F. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg*. 2020;15(1):27. https://doi.org/10.1186/s13017-020-00306-3
5. Snyder MJ, Guthrie M, Cagle S. Acute Appendicitis: Efficient Diagnosis and Management. *Am Fam Physician*. 2018;98(1):25-33.
6. Benedetto G, Ferrer Puchol MD, Llavata Solaz A. Suspicion of acute appendicitis in adults. The value of ultrasound in our hospital. *Radiologia (Engl Ed)*. 2019;61(1):51-59. https://doi.org/10.1016/j.rx.2018.08.007
7. Rud B, Vejborg TS, Rappeport ED, Reitsma JB, Wille-Jørgensen P. Computed tomography for diagnosis of acute appendicitis in adults. *Cochrane Database Syst Rev*. 2019;2019(11):CD009977. https://doi.org/10.1002/14651858.CD009977.pub2
8. Hodge SV, Mickiewicz B, Lau M, Jenne CN, Thompson GC. Novel molecular biomarkers and diagnosis of acute appendicitis in children. *Biomark Med*. 2021;15(12):1055-1065. https://doi.org/10.2217/bmm-2021-0108
9. Orellana-Henriquez J, Robalino-Rodriguez I, Sanchez-Alban H, Franco-Orellana J, Oleas R, Baquerizo-Burgos J, Patiño-Aquin M, Torres-Herrera C, Puga-Tejada M. Predictive biomarkers for complicated acute appendicitis: A prospective Ecuadorian study. *Cir Cir*. 2020;88(5):599-607. https://doi.org/10.24875/CIRU.20000256
10. Güngör A, Göktuğ A, Güneylioğlu MM, Yaradılmış RM, Bodur I, Öztürk B, Karaman İ, Karacan CD, Tuygun N. Utility of biomarkers in predicting complicated appendicitis: can immature granulocyte percentage and C-reactive protein be used? *Postgrad Med*. 2021;133(7):817-821. https://doi.org/10.1080/00325481.2021.1948306
11. Sengul S, Guler Y, Calis H, Karabulut Z. The Role of Serum Laboratory Biomarkers for Complicated and Uncomplicated Appendicitis in Adolescents. *J Coll Physicians Surg Pak*. 2020;30(4):420-424. https://doi.org/10.29271/jcpsp.2020.04.420
12. Kumar S, Maurya J, Kumar S, Patne SK, Dwivedi AND. A study of C-reactive protein and D-dimer in patients of appendicitis. *J Family Med Prim Care*. 2020;9(7):3492-3495. https://doi.org/10.4103/jfmpc.jfmpc_197_20
13. Halaseh SA, Kostalas M, Kopec C, Nimer A. Bilirubin as a Predictor of Complicated Appendicitis in a District General Hospital: A Retrospective Analysis. *Cureus*. 2022;14(9):e29036. https://doi.org/10.7759/cureus.29036
14. Dayawansa NH, Segan JDS, Yao HHI, Chong HI, Sitzler PJ. Incidence of normal white cell count and C-reactive protein in adults with acute appendicitis. *ANZ J Surg*. 2018;88(6):E539-E543. https://doi.org/10.1111/ans.13760

15. Téoule P, Laffolie J, Rolle U, Reissfelder C. Acute Appendicitis in Childhood and Adulthood. *Dtsch Arztebl Int.* 2020;117(45):764-774. https://doi.org/10.3238/arztebl.2020.0764
16. Ribeiro AM, Romero I, Pereira CC, Soares F, Gonçalves Á, Costa S, da Silva JB. Inflammatory parameters as predictive factors for complicated appendicitis: A retrospective cohort study. *Ann Med Surg (Lond).* 2022;74:103266. https://doi.org/10.1016/j.amsu.2022.103266
17. Withers AS, Grieve A, Loveland JA. Correlation of white cell count and CRP in acute appendicitis in paediatric patients. *S Afr J Surg.* 2019;57(4):40.
18. Echevarria S, Rauf F, Hussain N, Zaka H, Farwa UE, Ahsan N, Broomfield A, Akbar A, Khawaja UA. Typical and Atypical Presentations of Appendicitis and Their Implications for Diagnosis and Treatment: A Literature Review. *Cureus.* 2023;15(4):e37024. https://doi.org/10.7759/cureus.37024
19. Borruel Nacenta S, Ibáñez Sanz L, Sanz Lucas R, Depetris MA, Martínez Chamorro E. Update on acute appendicitis: Typical and untypical findings. *Radiologia (Engl Ed).* 2023;65(suppl 1):S81-S91. https://doi.org/10.1016/j.rxeng.2022.09.010
20. Asad S, Ahmed A, Ahmad S, Ali S, Ahmed S, Ghaffar S, Khattak IU. Causes of delayed presentation of acute appendicitis and its impact on morbidity and mortality. *J Ayub Med Coll Abbottabad.* 2015;27(3):620-623.
21. Kim JJY, Dobson BH, L H Ng C, Thong DW, Arthur T, Parker D; QUEST Collaboration. Can normal inflammatory markers rule out acute appendicitis? The reliability of biochemical investigations in diagnosis. *ANZ J Surg.* 2020;90(10):1970-1974. https://doi.org/10.1111/ans.15559
22. Sushruth S, Vijayakumar C, Srinivasan K, Raj Kumar N, Balasubramaniyan G, Verma SK, Ramesh A. Role of C-Reactive Protein, White Blood Cell Counts, Bilirubin Levels, and Imaging in the Diagnosis of Acute Appendicitis as a Cause of Right Iliac Fossa Pain. *Cureus.* 2018;10(1):e2070. https://doi.org/10.7759/cureus.2070

Поступила 12.11.2023
Received 12.11.2023
Принята к печати 12.12.2023
Accepted 12.12.2023