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Predicting a fatal outcome in patients with pneumonia caused by carbapenem-resistant *Klebsiella pneumoniae* by hematological indices

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ABSTRACT

Aim. To determine the most significant indicators for predicting a fatal outcome in patients with pneumonia caused by carbapenem-resistant *K. pneumoniae*.

Materials and methods. A total of 114 cases of pneumonia caused by *K. pneumoniae*, including those associated with COVID-19, were retrospectively analyzed. Depending on the outcome of the disease, two groups were formed: group 1 included 54 patients discharged from the hospital upon completion of treatment; group 2 encompassed 60 patients with an unfavorable (fatal) outcome. Patients who did not have a concomitant COVID-19 infection were analyzed separately. The profile of concomitant diseases, hemogram parameters, C-reactive protein (CRP) level, and hematological indices (neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR)) were studied, and the risk of death according to the CURB-65 score was assessed.

Results. Patients with an unfavorable outcome were characterized by higher leukocyte and neutrophil counts, higher NLR, MLR, PLR, and CRP levels, higher risk according to the CURB-65 score, and lower lymphocyte and platelet concentrations. According to the results of the ROC analysis, the most significant prognostic indicators of an unfavorable outcome were lymphocytes, neutrophils, NLR, CURB-65, CRP, and TLR. The diagnostic value of the CURB-65 score (3–5 points) in predicting the risk of an unfavorable outcome was the following: test sensitivity was 47.5%, specificity was 98.2%, positive predictive value was 96.6%, negative predictive value was 63.1%, accuracy was 71.7%. For NLR (at a threshold value > 6), sensitivity was 85.0%, specificity was 87.0%, positive predictive value was 87.9%, negative predictive value was 83.9%, accuracy was 86.0%. For MLR, the diagnostic accuracy was 79.0%, and for PLR – 73.7%.

Conclusion. The parameter of choice that can be used at the early stage to predict the fatal outcome of pneumonia caused by carbapenem-resistant *K. pneumoniae* should be NLR (> 6) due to its high sensitivity (85%) and specificity (87%) and ease of use. In addition, the CURB-65 score can be used at NLR > 3.

Keywords: prediction of a fatal outcome, carbapenem-resistant *Klebsiella pneumoniae*, COVID-19, CURB-65 score, hematological indices

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Прогнозирование летального исхода у пациентов с пневмонией, вызванной карбапенем-резистентной *Klebsiella pneumoniae*, при помощи гематологических индексов

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РЕЗЮМЕ

Цель. Определение наиболее значимых показателей для прогнозирования летального исхода у пациентов с пневмонией, вызванной карбапенем-резистентной *K. pneumoniae.*

Материалы и методы. Ретроспективно проанализировано 114 случаев пневмонии, вызванной *K. pneumoniae*, в том числе на фоне коронавирусной инфекцией (COVID-19). В зависимости от исхода заболевания сформировано две группы: группа 1 – 54 пациента, выписанных из стационара по завершении лечения; группа 2 – 60 пациентов с неблагоприятным (летальным) исходом. Отдельно проанализированы пациенты, у которых не выявлено сопутствующей инфекции COVID-19. Изучена структура сопутствующих заболеваний, определены показатели гемограммы, С-реактивного белка (СРБ), а также гематологические индексы: отношение нейтрофилов и лимфоцитов (НЛИ), моноцитов и лимфоцитов (МЛИ), тромбоцитов и лимфоцитов (ТЛИ). Риск летального исхода оценивался по шкале CURB-65.

Результаты. Для пациентов с неблагоприятным исходом характерны более высокие показатели лейкоцитов в общем анализе крови, нейтрофилов, значения НЛИ, МЛИ, ТЛИ, СРБ, более высокий риск по шкале CURB-65 и низкий уровень лимфоцитов, тромбоцитов. По результатам проведенного ROC-анализа, наиболее значимыми прогностическими показателями неблагоприятного исхода является уровень лимфоцитов, нейтрофилов, НЛИ, показатели CURB-65, СРБ, ТЛИ. Диагностическая значимость шкалы CURB-65 (3–5 баллов) в прогнозировании риска неблагоприятного исхода составляет: чувствительность теста – 47,5%, специфичность – 98,2; положительная прогностическая ценность – 96,6; отрицательная прогностическая ценность – 63,1; точность – 71,7%. Для НЛИ (при пороговом значении более 6) получены следующие данные: по чувствительности (85,0%), специфичности (87,0%), положительной прогностической ценности (87,9%), отрицательной прогностической ценности (83,9%), точности (86,0%). Диагностическая точность для МЛИ составила 79,0%, для ТЛИ – 73,7%.

Заключение. Предпочтительным показателем, который можно использовать на первом этапе для прогнозирования летального исхода пневмонии, вызванной карбапенем-резистентной *K. pneumoniae*, следует считать НЛИ (при уровне более 6) ввиду высокой чувствительности (85%) и специфичности (87%), а также простоты применения. В дополнение к этому можно использовать расчет баллов по шкале CURB-65 при значениях 3 балла и выше.

Ключевые слова: прогнозирование летального исхода, карбапенем-резистентная *K. pneumoniae*, COVID-19, шкала CURB-65, гематологические индексы

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

K.pneumoniae is the most common pathogen of healthcare-associated infections worldwide. These pathogens belong to the group of clinically significant ESKAPE pathogens – *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp.*, which is associated with the development of severe infections and the difficulty of selecting an effective antibiotic (AB) regimen [1–3]. In the profile of nosocomial pneumonia, there is an increase in the prevalence of carbapenem-resistant *K.pneumoniae*. Carbapenem resistance is a marker of multidrug and extensive antibiotic resistance [4, 5].

K. pneumoniae, previously almost never seen among the causative agents of community-acquired pneumonia, is now often isolated from the biomaterial of patients diagnosed with pneumonia in the first 48 hours of hospital stay. High frequency of an unfavorable outcome has been noted among patients with pneumonia associated with K. pneumoniae and other ESKAPE pathogens, especially in combination with COVID-19 infection [2, 6, 7]. Detection of carbapenem-resistant *K. pneumoniae* in patients' biomaterial increases the risk of an unfavorable outcome [8, 9].

Risk factors for a fatal outcome of community-acquired pneumonia have been identified: late hospitalization (5 days or more after the onset of the disease); underestimation of the severity of the patient's condition during the initial examination; concomitant somatic symptom pathology, bilateral nature of pneumonia; errors in initial antibacterial therapy. In order to predict an unfavorable outcome, the levels of procalcitonin, C-reactive protein (CRP), presepsin, pro-adrenomedullin, and progranulin are assessed. However, to date it is difficult to identify a single marker with an absolute predictive ability regarding a fatal outcome in a patient with pneumonia [10].

Researchers from Saint Petersburg reported that it is possible to accurately predict the likelihood of a fatal outcome in patients with severe community-acquired pneumonia upon their admission to the intensive care unit (ICU) by assessing serum markers, such as surfactant protein D, hypoxia-inducible factor 1α, angiotensin-converting enzyme 2, and levels of interleukins 6 and 10 [11].

At the stage of diagnosis, important tasks for the physician include determining the risk of an adverse outcome and deciding whether to treat the patient in the internal medicine department or in the ICU. Currently, the CURB-65 score (confusion, uremia, respiratory rate, blood pressure, age ≥ 65 years) and the Pneumonia severity index (PSI) are widely used and recommended for predicting 30-day mortality and a need for intensive care in a hospital setting. However, the CURB-65 assessment system may be preferable for identifying high-risk patients and due to its ease of use [12].

Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) are biomarkers used for prediction of adverse outcomes in many diseases. NLR has high practical significance for predicting mortality in patients with pneumonia, as it correlates with mortality in patients with community-acquired pneumonia better than traditional assessment systems (PSI, CURB-65), leukocyte count, and CRP [13–16]. NLR has been shown to be an independent risk factor for death from nosocomial pneumonia during the COVID-19 pandemic [17]. MLR and PLR are increasingly recognized as markers of inflammation and have good prognostic value in patients with cancer, cardiovascular disease, and some infectious diseases, but the prognostic value of these parameters for hospitalized patients with pneumonia is questionable [16, 18]. For early diagnosis and assessment of the disease severity as well as for prediction of the disease outcome, preference is given to non-invasive prediction methods that do not require additional costs.

The aim of this study was to determine the most significant indicators for predicting a fatal outcome in patients with pneumonia caused by carbapenem-resistant *K. pneumoniae*.

MATERIALS AND METHODS

A retrospective analysis of 114 cases of pneumonia caused by *K.pneumoniae* was conducted. The object of the study were adult patients treated at the Gomel Regional Tuberculosis Clinical Hospital (GRTCH) for pneumonia caused by *K.pneumoniae* in 2021–2024, including those with COVID-19 co-infection, confirmed in the laboratory before and during hospitalization. Inclusion criteria: age 18 years and older, isolation of carbapenem-resistant *K.pneumoniae* from sputum, bronchoalveolar lavage fluid (BALF) in diagnostically significant quantities (10^6 CFU / ml or more).

The profile of concomitant diseases, hemogram parameters, and CRP were studied. Hematological indices were calculated based on a complete blood count, which was taken on the day of sputum and BALF specimen collection for microbiological testing, before the initiation of antibacterial therapy (19 patients) and thereafter (95 patients). The median detection of *K. pneumoniae* in the studied samples was 17.0 [11.0–27.0] days from the onset of the disease, 13.0 [6.0–20.0] days from the date of hospitalization.

The study group consisted of 45 women and 69 men. The median age of patients was 68.0 [59.0–75.8] years (minimum age – 21 years, maximum age – 91 years). Fifty-five people (48.2%; 38.8–57.8) were patients of pulmonology departments, and 59 patients (51.8%; 42.2–61.2) were treated in the ICU. Mechanical ventilation was used in 28 patients (24.6%; 17.0–33.5). COVID-19 infection was detected in 65 patients (57.0%; 47.4–66.3). A fatal outcome was observed in 60 patients (52.6%; 43.1–62.3).

Depending on the outcome of the disease, two groups were formed: group 1 included 54 patients discharged from the hospital upon completion of treatment. Group 2 encompassed 60 patients with an unfavorable (fatal) outcome. Patients who did not have concomitant COVID-19 infection were analyzed separately. The characteristics of the groups are presented in Table 1.

Table 1

Characteristics of the Groups of Patients Hospitalized with Pneumonia Caused by *K. Pneumoniae*

Parameter	Group 1, $n = 54$	Group 2, $n = 60$	p
Sex: male/female	39/15	30/30	0.016*
Age, *Me* [Q_{25}–Q_{75}]	61.0 (52.5–70.8)	70.0 (62.0–77.3)	0.001*
Treatment in the ICU, abs. (%)	10 (18.5)	29 (48.3)	<0.001*
Mechanical ventilation used, abs. (%)	2 (3.7)	26 (43.3)	<0.001*
COVID-19 infection, abs. (%)	22 (40.7)	43 (71.7)	<0.001*
Aggravated premorbid background, abs. (%)	51 (94.4)	59 (98.3)	0.26

* differences are statistically significant.

Cardiovascular diseases (ischemic heart disease, arterial hypertension, arrhythmias) were present in 55 people (91.7%; 81.6–97.2) in group 2 and in 38 patients (70.4%; 56.4-82.0) in group 1 ($\chi^2 = 8.58$, $p = 0.004$). Metabolic disorders (obesity, diabetes mellitus) were present in 21 patients (38.9%; 25.9–53.1) in group 1 and in 28 patients (46.7%; 33.7–60.0) in group 2 without statistically significant differences ($p = 0.40$). Chronic nonspecific lung diseases were present in 9 patients (16.7%; 7.9–29.3) in group 1 and in 8 patients (13.3%; 5.9–24.6) in group 2 without statistically significant differences ($p = 0.62$).

Cancer was detected in 11 patients (20.4%; 10.6–33.5) in group 1 and in 8 patients (13.3%; 5.9–24.6) in group 2 without statistically significant differences ($p = 0.32$). Chronic liver diseases were present in 5 patients (7.9%; 3.7–14.5) in group 1 and in 4 patients (6.7%; 1.9–16.2) in group 2 ($p = 0.61$). Chronic kidney diseases were observed in 9 patients (16.7%; 7.9–29.3) in group 1 and in 7 patients (11.7%; 4.8–22.6) in group 2 ($p = 0.44$). To predict 30-day mortality, the CURB-65 pneumonia severity assessment score was used [12].

Statistical processing of the obtained data was performed using the Statistica v. 12.5 and MedCalc, v. 18.9.1 software packages. The median and the interquartile range *Me* [Q_{25}–Q_{75}] were calculated to present the data. Comparison of groups by quantitative characteristics was performed using the Mann – Whitney U-test. For relative values, the 95% confidence interval (95% CI) was determined using the Clopper – Pearson method. The significance of differences in the relative values was calculated using the Pearson's χ^2 test. To assess the impact of various factors on hospital mortality, the odds ratio (OR) was calculated with 95% CI. To study the relationship between variables, the Spearman's rank correlation coefficient (r_s) was calculated. To assess the significance of quantitative variables in predicting a certain outcome, the ROC analysis was used with the calculation of area under the curve (AUC), 95% CI for AUC, and determination of the cutoff point using the Youden criterion and sensitivity and specificity for this cutoff point. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The hemogram parameters obtained on the day of sputum and BALF specimen collection and the calculated hematological indices are presented in Table 2.

Table 2 shows that patients in group 2 were characterized by higher WBC and neutrophil counts, NLR, MLR, PLR, and CRP, lower levels of lymphocytes and platelets, and a higher risk according to the CURB-65 score.

Table 2

Laboratory Parameters of Patients in the Analyzed Groups, *Me* [Q_{25}–Q_{75}]

Parameter	Group 1, *n* = 54	Group 2, *n* = 60	*p*
White blood cells (WBC), × 10^9 / L	8.9 [7.6–12.3]	13.4 [9.6–17.2]	0.0003*
Neutrophils, %	68.0 [61.2–75.0]	88.0 [82.0–91.0]	<0.0001*
Lymphocytes, %	18.5 [15.0–27.0]	7.0 [4.0–11.8]	<0.0001*
Monocytes, %	6.5 [4.0–8.0]	5.0 [3.0–7.9]	0.147
Platelets, × 10^9 / l	279.5 [211.0–331.0]	213.0 [163.0–255.0]	0.004*
Hemoglobin, g / l	116.5 [97.0–131.0]	108.5 [94.5–123]	0.19
Red blood cells, × 10^{12} / l	3.8 [3.1–4.4]	3.8 [3.3–4.4]	0.982
CRP, mg / l	41.8 [23.0–88.0]	140.0 [95.0–140.0]	<0.0001*
MLR	0.32 [0.19–0.42]	0.94 [0.41–1.25]	<0.0001*
NLR	3.74 [2.37–5.07]	12.25 [7.31–22.38]	<0.0001*
PLR	12.36 [9.11–20.64]	33,53 [18.44–55.67]	<0.0001*
CURB-65 score	1.0 [0.0–1.0]	2.0 [2.0–4.0]	<0.0001*
CURB-65, *n* (%)			
0–1 points	45 (83.3)	13 (21.7)	χ^2 = 46.5; <0.0001
2 points	8 (14.8)	18 (30.0)	
3–5 points	1 (1.9)	28 (46.7)	

* differences are statistically significant.

Various factors that could affect the mortality of hospitalized patients were analyzed. Risk factors associated with a fatal outcome were the presence of COVID-19 infection (OR 3.68; 95% CI 1.69–8.03), CURB-65 scores of 3–5 (OR 46.37; 95% CI 6.02–357.5), the use of mechanical ventilation (OR 19.88; 95% CI 4.43–89.27), and hospitalization in the ICU (OR 4.12; 95% CI 1.75–9.66), which does not contradict the data of foreign authors [19, 20].

A direct correlation was established between the CURB-65 score and WBC count (r_s = 0.33, p = 0.0004), neutrophil count (r_s = 0.65, p < 0.001), CRP (r_s = 0.42, p < 0.001), PLR (r_s = 0.64, p < 0.001), MLR (r_s = 0.60, p < 0.001), and NLR (r_s = 0.78, p < 0.001). An inverse correlation was established between the CURB-65 score and the lymphocyte count (r_s = –0.79, p < 0.001).

The ROC analysis was performed to determine the prognostic value and threshold values of the parameters. The parameters that have significant differences when compared in the study groups were included (WBC, neutrophils, lymphocytes, platelets, CRP, NLR, MLR, PLR, CURB-65 score).

For WBC, the AUC values were 0.69 (0.60–0.77), test sensitivity was 71.2%, specificity was 68.5% at a cutoff point of > 10.4, and the Youden index was 0.40. For neutrophils, the AUC values were 0.93 (0.87–0.97), test sensitivity was 85.0%, specificity was 94.4% at a cutoff point of > 79, and the Youden index was 0.79. For lymphocytes, the AUC values were 0.92 (0.85–0.96), test sensitivity was 93.3%, specificity was 77.8% at a cutoff point ≤ 14.37, and the Youden index was 0.71. For platelets, the AUC values were 0.66 (0.56–0.74), test sensitivity was 76.7%, specificity was 55.6% at a cutoff point ≤ 255, and the Youden index was 0.32. The AUC values obtained for CRP were 0.80 (0.71–0.87), test sensitivity was 75.0%, specificity was 77.8% at a cutoff point > 97, and the Youden index was 0.53.

The AUC values for MLR (Fig. 1) were 0.79 (0.70–0.86), test sensitivity was 70.0%, specificity was 85.2% at a cutoff point > 0.55, and the Youden index was 0.55. For NLR, the AUC values were (Fig. 2) 0.93 (0.86–0.97), test sensitivity was 85.0%, specificity was 87.0% at a cutoff point of > 6, and the Youden index was 0.72. For PLR, the AUC values were 0.80 (0.72–0.87), test sensitivity was 56.7%, specificity was 92.6% at a cutoff point of > 28.15, the Youden index was 0.49 (Fig. 3). For the CURB-65 score, the AUC values were 0.87 (0.80–0.93), test sensitivity was 46.7%, specificity was 98.2% at a cutoff point of > 2, the Youden index was 0.60 (Fig. 4).

According to the results of the analysis, the most significant prognostic indicators of an unfavorable outcome were lymphocytes, neutrophils, NLR, CURB-65, CRP, and PLR. To exclude the influence of COVID-19 co-infection on the threshold values of prognostic indicators, the ROC analysis was performed including the NLR values calculated for patients who did not have confirmed COVID-19 co-infection (*n* = 49). The AUC values were 0.92 (0.81–0.98), test sensitivity was 82.4%, specificity was 87.5% at a cutoff point of > 6, the Youden index was 0.73.

The diagnostic value of the CURB-65 score (3–5 points) in predicting the risk of an unfavorable outcome in patients was calculated using the Medcalc Diagnostic Test Evaluation Online Calculator (https://www.medcalc.org/calc/diagnostic_test.php). The test sensitivity was 47.5%, specificity was 98.2%, positive predictive value was 96.6%, negative predictive value was 63.1%, and accuracy was 71.7%.

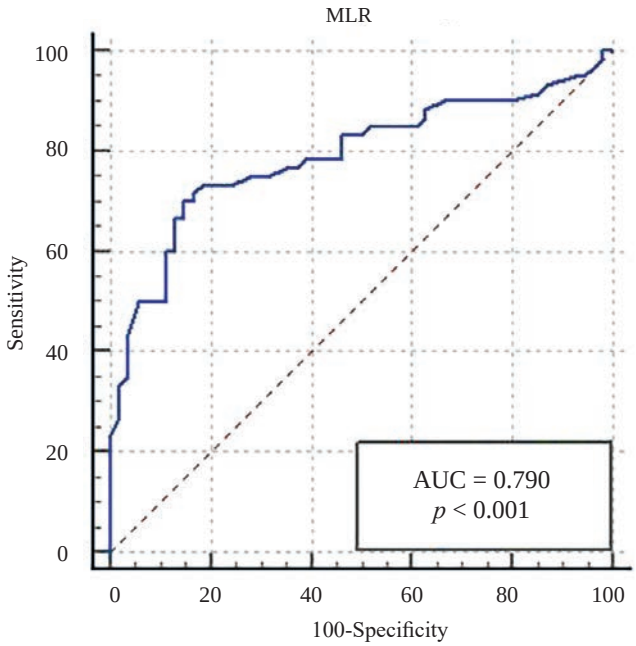


Fig. 1. ROC-curve for the prognostic value of MLR

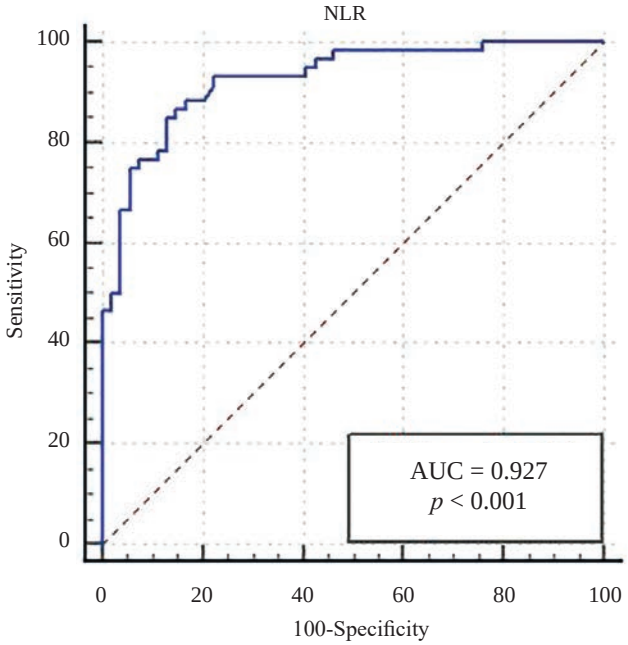
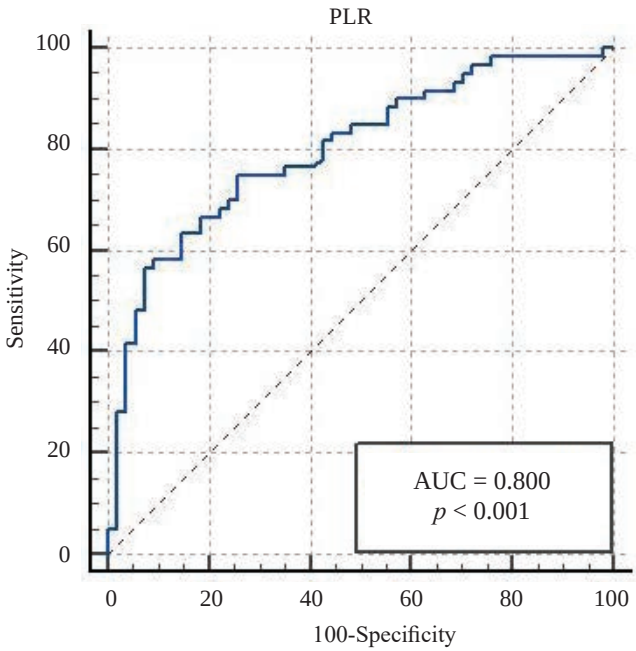


Fig. 2. ROC-curve for the prognostic value of NLR



Figю 3. ROC-curve for the prognostic value of PLR

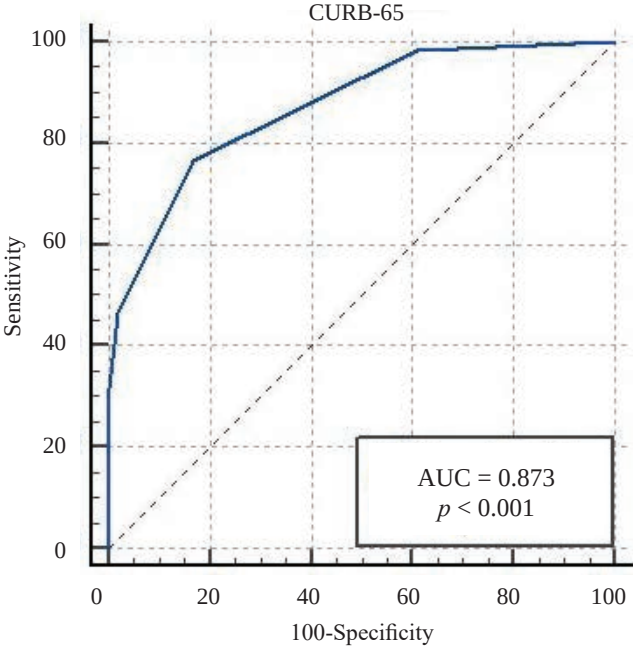


Fig. 4. ROC-curve for the prognostic value of CURB-65 score

For NLR (at a threshold value > 6), sensitivity was 85.0%, specificity was 87.0%, positive predictive value was 87.9%, negative predictive value was 83.9%, and accuracy was 86.0%. For MLR, the diagnostic accuracy was 79.0%, and for PLR – 73.7%.

DISCUSSION

To predict a fatal outcome in patients with pneumonia caused by carbapenem-resistant *K. pneumoniae*, including those with COVID-19 co-infection, various laboratory parameters, scores, and indices can be used. In a similar study conducted by A. Singh et al., the average values of NLR, PLR, and CRP were higher in the group of patients with severe COVID-19 infection and a fatal outcome than in those with moderate disease and discharged, respectively. It is proposed to consider these indicators for predicting a fatal outcome. MLR is not a reliable prognostic biomarker, since when analyzing the ROC curve, the AUC 95% CI was < 0.50. NLR, on the contrary, had

the highest AUC (0.923), with the highest specificity (0.83%) and sensitivity (0.88%) [21], which is consistent with our data.

According to the study by O. Bardakci, the group of deceased patients had higher CURB-65 scores compared to survivors, both in patients with COVID-19-associated pneumonia and in patients with community-acquired pneumonia without COVID-19 infection. It was assumed that NLR and PLR are as reliable as the CURB-65 risk assessment score [22]. Z. Wang et al. reported that NLR was an easily accessible biomarker for predicting mortality in patients with carbapenem-resistant K. pneumoniae infection [23].

In a study by E. Cataudella et al., NLR predicted 30-day mortality in elderly patients with pneumonia ($p < 0.001$) and showed better results than the PSI score ($p < 0.05$), CURB-65 score, CRP, and leukocyte count ($p < 0.001$) [15]. However, there is also somewhat different information. According to Y. Kaya et al., deceased patients with community-acquired pneumonia had higher NLR levels compared to survivors (13.5 ± 9 versus 7.9 ± 6.8, $p = 0.010$). Still, when comparing ROC curves, the prognostic value of NLR did not exceed the CURB-65 and PSI scores [24]. According to our data, NLR is a more sensitive indicator in assessing the risk of an unfavorable outcome than the CURB-65 score, and PLR and MLR are inferior to the CURB-65 score in diagnostic accuracy. Considering that NLR has greater sensitivity and the CURB-65 score has greater specificity, we believe it is optimal to use them in combination.

CONCLUSION

In patients with pneumonia caused by carbapenem-resistant *K. pneumoniae*, the prognosis of a fatal outcome can be determined using laboratory parameters (leukocytes, neutrophils, lymphocytes, platelets, NLR, MLR, and PLR), as well as CURB-65 score. Although this scoring system is widely used and has proven itself as a simple way to assess the patient's condition and predict mortality and the need for intensive care, it showed low specificity (47%) and diagnostic accuracy (71.7%). Therefore, NLR (at a level > 6) should be considered as the indicator of choice that can be used at the first stage to predict a fatal outcome of pneumonia caused by carbapenem-resistant *K. pneumoniae* due to its high sensitivity (85%) and specificity (87%) as well as due to ease of use. In addition, the calculation of the CURB-65 score can be used at NLR > 3.

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Author Contribution

Levchenko K.V. – review of publications on the article topic, study design, collection of material, drafting of the article, statistical processing, analysis and interpretation of the data. Mitsura V.M. – study design, statistical processing, analysis and interpretation of the data, editing of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication.

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