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# Prediction of Mortality in ICU Patients with SARS-CoV-2-Associated Pneumonia

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## Summary

**Aim:** to determine the predictive value of selected routine clinical and laboratory parameters and to assess their prognostic significance for modeling mortality risk in intensive care unit (ICU) patients with SARS-CoV-2-associated pneumonia.

**Materials and Methods.** A retrospective case-control analysis of 73 medical records was performed. The control group included 20 records of surviving patients, while the primary group comprised 53 records of non-survivors treated between January and February 2022. The study parameters included leukocyte differential count, C-reactive protein (CRP), ferritin, blood oxygen saturation ($SpO_2$) via pulse oximetry, and the neutrophil ratio (NR) defined as the percentage of band neutrophils divided by the percentage of segmented neutrophils. The prognostic value of identified predictors was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), 95% confidence interval (CI), sensitivity (Se), specificity (Sp), and cutoff point (CP) were determined, with CP defined as the predictor value yielding the highest sum of sensitivity and specificity.

**Results.** The most informative predictors of mortality in SARS-CoV-2-associated pneumonia were:

On the day of hospital admission: Ferritin levels (AUC=0.826; 95% CI: 0.717–0.905; $P<0.001$, CP⩽0.473 mg/L; Se=78%; Sp=75%). On ICU day 1: Granulocyte count (GRA, AUC=0.711; 95% CI: 0.589–0.814; $P<0.002$, CP>$6\times10^9$/L; Se=94%; Sp=75%), NR (AUC=0.713; 95% CI: 0.541–0.850; $P<0.016$, CP>18; Se=91%; Sp=62%). On the final day in ICU: CRP (AUC=0.825; 95% CI: 0.522–0.973; $P<0.013$, CP>14 mg/L; Se=75%; Sp=100%); NR (AUC=0.862; 95% CI: 0.724–0.947; $P<0.0001$, CP>16; Se=94%; Sp=82%); $SpO_2$ (AUC=0.909; 95% CI: 0.819–0.963; $P<0.0001$, CP⩽91%; Se=77%; Sp=100%); White blood cell count (WBC, AUC=0.833; 95% CI: 0.725–0.912; $P<0.001$, CP>$12.2\times10^9$/L; Se=80%; Sp=81%). Using a stepwise elimination approach, a mathematical model was proposed for predicting mortality probability *(P)* in SARS-CoV-2-associated pneumonia.

**Conclusion.** The most valuable prognostic model for predicting mortality risk is represented by the equation: $P=1/(1+e^{-Z})\times100\%$ using routine laboratory parameters such as ferritin, neutrophil ratio and blood oxygen saturation. The model showed a sensitivity of 84.0% and a specificity of 94.1%.

***Keywords: SARS-CoV-2-associated pneumonia, mortality predictors, prognostic model***

**Conflict of interest.** The authors declare no conflict of interest.

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## Introduction

The emergence of COVID-19, caused by the SARS-CoV-2 virus, has highlighted the unpreparedness of modern medicine to effectively combat such infections, despite advances in therapeutic strategies [1]. This has necessitated the search not only for novel pharmacological agents [2] and medical technologies [3, 4], but also for reliable prognostic criteria to predict disease outcome. Researchers have investigated the impact of comorbid conditions on COVID-19 survival [5, 6] and evaluated the diagnostic value of both routine [7, 8] and specialized medical examinations [9, 10]. Attempts have been made to predict in-hospital mortality in COVID-19 patients based on disease severity [10]. However, these predictive models were primarily constructed using sociodemographic and anamnestic parameters.

In critically ill COVID-19 patients requiring high-flow oxygen therapy, proposed predictors of mortality risk included age, serum albumin levels,

interleukin-6 (IL-6), and D-dimer concentrations [11]. However, each of these predictors was analyzed independently and showed only moderate prognostic accuracy, and no comprehensive predictive algorithm for estimating the probability of mortality was formulated in this study.

Some investigators have used the severity of lung involvement on computed tomography (CT) as a prognostic marker for COVID-19 mortality [12]. However, the degree of lung damage was assessed visually rather than quantitatively using dedicated software. In addition, evidence suggests that partial pressure of oxygen ($PO_2$), blood pH, and the number of antibiotics administered during treatment may serve as significant risk factors for mortality, varying by type of health care facility (community, federal, or private clinics) [13]. However, the prognostic value of these parameters was not explicitly defined, and only odds ratios were reported. In severe SARS-CoV-2-associated pneumonia, serum and urinary cystatin C concentrations have demonstrated high prognostic utility [14]. However, this biomarker is not included in the standard panel of routine clinical and laboratory tests used in clinical practice.

Currently, a nomogram has been developed based on a multifactorial analysis of predictors of 30-day mortality in hospitalized COVID-19 patients. By assessing patient age, comorbidities, serum C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels at the time of ICU admission, the authors obtained a model with relatively high prognostic accuracy (AUC=0.811 [0.733–0.874], $P<0.001$) [15]. However, the model did not include changes in leukocyte differentials and ferritin levels during hospitalization, which could have further improved its predictive performance.

Other studies have demonstrated the potential utility of certain leukocyte differential parameters as outcome predictors in COVID-19 patients [16]. However, these studies did not take into account the duration of ICU stay, the level and type of oxygen support, including at the time of death, or the relationship between leukocyte differentials and acute-phase blood proteins [16].

Given these limitations, further investigation of the prognostic value of routine blood parameters for predicting COVID-19 outcomes is warranted.

The aim of this study was to evaluate the predictive value of selected routine clinical and laboratory parameters and their prognostic utility in modeling mortality risk in ICU patients with SARS-CoV-2-associated pneumonia.

## Materials and Methods

A total of 262 medical records of patients diagnosed with COVID-19 and treated in the intensive care unit (ICU) of the Tambov Central District Hospital, which had been temporarily converted to a COVID-19 facility, were analyzed for the study (Fig. 1). From this cohort, 100 medical records were randomly selected, including both male and female patients with confirmed disease.

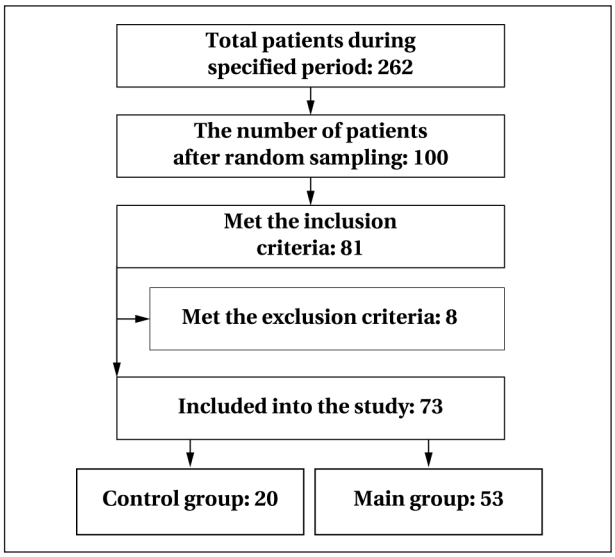


**Fig. 1. Diagram of patient selection for the study.**

The COVID-19 severity classification and treatment protocols followed the official interim clinical guidelines of the Russian Ministry of Health in effect at the time of the study (January–February 2022).

Inclusion criteria:

— SARS-CoV-2-associated pneumonia confirmed by computed tomography (CT) scan

— Age ⩾ 18 years

Exclusion criteria:

— Comorbidities, including

- Cancer (including cases after recent chemotherapy or radiotherapy prior to hospitalization), *N*=4
- Systemic lupus erythematosus, *N*=1
- Rheumatoid arthritis, *N*=1
- History of recent intestinal surgery, *N*=2.

The duration of ICU stay was not included in the analysis.

The study was conducted as a retrospective case-control analysis with a random selection of medical records. The selected cases were divided into two groups:

— Control group: 20 medical records of survivors (10 males and 10 females).

— Main group: 53 medical records of non-survivors (26 men and 27 women) who were in the ICU at the time of death.

The extent of lung involvement was assessed based on computed tomography (CT) findings at hospital admission. Serial chest radiographs were performed to monitor disease progression. At the time of death, all ICU patients in the main group had radiographic evidence of multilobar pneumonia.

Patients were admitted to the ICU if they met at least two of the following criteria:

**Table 1. Distribution of Patients by Disease Duration at Hospital Admission, Age, and Lung CT Findings [*Me (Q25, Q75)*].**

| Parameter | Values in groups | |
|---|---|---|
| | Control group, *N*=20 | Main group, *N*=53 |
| Disease duration at admission (days) | 7.0 [5.0; 12.0] | 7.5 [5.0; 9.0] |
| Mean age (years) | 66 [57; 72] | 70 [65; 82]* |
| Lung CT Severity | | |
| CT 1–2 | 12 (60%) | 30 (57%) |
| CT 3 | 7 (35%) | 12 (22%) |
| CT 4 | 1 (5%) | 11 (21%) |

**Note.** * — statistically significant difference compared to the control group ($P<0.05$).

— Impaired consciousness

— Respiratory rate >35 breaths/min

— Oxygen saturation ($SpO_2$) ⩽ 92% as measured by pulse oximetry, despite oxygen therapy via nasal cannula or oxygen mask.

On admission to the ICU, patients in both groups were started on non-invasive ventilation (NIV) using MEKICS MV 2000 (South Korea, Belarus) or ZISLINE MV300 K1.22 (Triton-Electronics, Russia) ventilators. NIV was delivered in the following modes:

— Continuous positive airway pressure (CPAP) at 7–10 $cmH_2O$.

— Pressure support (PS) at 14–24 $cmH_2O$.

— Inspiratory oxygen fraction ($FiO_2$) typically set between 0.6 and 1.0.

Patients were intubated and placed on MV if they exhibited:

— Persistent hypoxemia ($SpO_2$<92%) with accessory respiratory muscle involvement.

— Rapid deep breathing.

— Respiratory fatigue.

— Respiratory arrest.

— Hemodynamic instability.

Patients were discharged from the ICU when they no longer required NIV, as evidenced by:

— Clear consciousness and stable hemodynamics.

— Sustained $SpO_2$⩾93% with $FiO_2$⩽40%.

— Positive end-expiratory pressure (PEEP) ⩽ 5 cm $H_2O$.

— Respiratory rate (RR) < 30 breaths/min.

The study aimed to identify potential predictors of mortality risk based on routine hematologic parameters. These included complete blood count (CBC) indices, specifically leukocyte differentials, measured using the Drew 3 Hematology Analyzer (USA). In addition, leukocyte subpopulations in peripheral blood smears were assessed manually under a microscope. C-reactive protein (CRP) and ferritin levels were quantified using the ACCENT-200 analyzer (Poland). Oxygen saturation ($SpO_2$) was measured by pulse oximetry.

Data for analysis were collected at four time points:

— On hospital admission.

— On ICU day 1.

— On the last ICU day.

— At hospital discharge (for survivors).

For each parameter, sensitivity, specificity, and predictive accuracy were determined as predictors of mortality risk. The prognostic value was assessed by receiver operating characteristic (ROC) curve analysis. Binary logistic regression modeling was used to estimate the probability of mortality, including predictors with an area under the ROC curve (AUC) greater than 80%.

Model validation was performed by constructing ROC curves to assess overall model significance, sensitivity, and specificity, with statistical significance confirmed for AUC values significantly greater than 0.5.

Data were processed using Statistica 10.0 (Dell Inc., USA) and MedCalc 12.4 (MedCalc Software, Belgium). As most variables had non-normal distribution (Shapiro–Wilk test), results were expressed as medians with interquartile ranges *(Me [Q25; Q75])*.

Statistical comparisons were performed using

— Wilcoxon test (for paired data)

— Mann–Whitney *U* test (for independent groups)

— Spearman correlation coefficient (to assess relationships between variables).

Statistical significance was set at $P<0.05$, with Bonferroni correction for multiple comparisons.

## Results

At the time of hospital admission, both groups had similar disease duration. However, the mean age of the main group (non-survivors) was significantly higher than that of the control group (survivors) ($Z$=2.31, $P$=0.021).

A statistically significant positive Spearman correlation was found between patient age and mortality in COVID-19 cases complicated by SARS-CoV-2-associated pneumonia ($R$=0.270, $P$=0.020).

In the group of non-survivors who were on mechanical ventilation (CMV/VCV; CMV/PCV, $FiO_2$>60%, PEEP 6–10 cm $H_2O$) at the time of death, $SpO_2$ values on the day of death were significantly higher compared to the values on admission. However, they remained below the generally accepted lower normal limit of 95% (Table 2).

The highest prognostic value (AUC: 0.909; 95% CI: 0.819– 0.963, $P$<0.001) as a predictor of imminent mortality risk in patients with SARS-CoV-2-associated

**Table 2. Levels of C-reactive protein, serum ferritin, and saturation in patients with SARS-CoV-2-associated pneumonia *(Me (Q25, Q75))*.**

| Parameter | Values at study stages | | | | *P value* | | |
|---|---|---|---|---|---|---|---|
| | Day of admission (1) | Day 1 in the ICU (2) | Last day in the ICU (3) | Day of discharge from the hospital (4) | 1–2 | 1–3 | 1–4 |
| **Control group (survivors), *N*=20** | | | | | | | |
| $SpO_2$ | 86.0 | 78.0 | 95.0 | 95.0 | 0.084 | <0.001 | <0.001 |
| | (80.0; 87.0) | (74.0; 88.0) | (92.0; 97.0)# | (92.0; 98.0)# | | | |
| CRP, mg/L | 82.00 | 112.00 | 5.00 | 5.00 | 0.374 | 0.012 | 0.068 |
| | (57.00; 112.00) | (62.00; 140.00) | (5.00; 14.00) | (5.00; 28.00) | | | |
| Ferritin, μg/L | 0.529 | 0.509 | 0.394 | 0.228 | 0.176 | 0.068 | 0.109 |
| | (0.403; 0.573) | (0.426; 0.601) | (0.352; 0.444) | (0.228; 0.405) | | | |
| **Main group (non-survivors), *N*=53** | | | | | | | |
| $SpO_2$ | 85.0 | 80.0 | 88.0 | — | 0.148 | 0.007 | — |
| | (80.0; 87.0) | (74.0; 88.0) | (82.0; 91.0)# | | | | |
| CRP, mg/L | 89.00 | 89.50 | 49.00 | — | 0.351 | 0.225 | — |
| | (50.00; 132.00) | (39.00; 150.50) | (11.00; 103.00) | | | | |
| Ferritin, μg/L | 0.401 | 0.420 | 0.448 | — | 0.136 | 0.715 | — |
| | (0.340; 0.465)* | (0.354; 0.480)* | (0.410; 0.612) | | | | |
| ***P* values for the intergroup differences** | | | | | | | |
| $SpO_2$ | 0.769 | 0.636 | <0.001 | | | | |
| CRP, mg/L | 0.875 | 0.719 | 0.057 | | | | |
| Ferritin, μg/L | 0.004 | 0.015 | 0.186 | | | | |

**Note.** $SpO_2$ — blood oxygen saturation by pulse oximetry; CRP – C-reactive protein; * — $P<0.05$, statistically significant difference between survivors and non-survivors groups; # — $P<0.05$, statistically significant difference from values on the day of admission; *N* — number of patients in the group.

pneumonia was the $SpO_2$ level measured on the day of death (Fig. 2, *a*). In addition, the presence of patients with SARS-CoV-2-associated pneumonia on mechanical ventilation at the time of death in CMV/VCV or CMV/PCV modes with $FiO_2$>60% and PEEP 6–10 cm $H_2O$ influenced the cut-off point, which in this case was 91%. Below this threshold, the prognostic accuracy for imminent mortality in patients with SARS-CoV-2-associated pneumonia on mechanical ventilation was 83.8%.

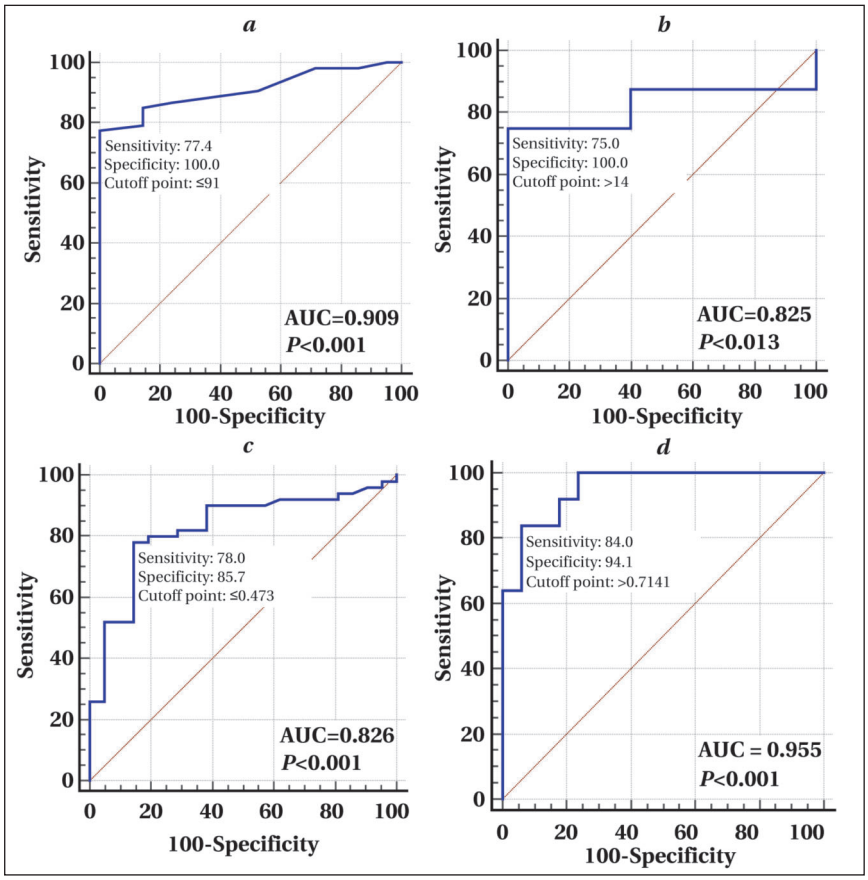


**Fig. 2. Informative value of routine parameters in predicting the probability of mortality in patients with SARS-CoV-2-associated pneumonia admitted to the ICU.**
**Note.** *a* — Blood oxygen saturation on the last day in the ICU; *b* — C-reactive protein level in blood on the last day in ICU; *c* — Blood ferritin level on the day of admission; *d* — Result of the quality assessment of the logit model for prognosis.

As shown in Table 2, the serum CRP levels of patients in both groups were significantly above the established normal range (0–3 mg/L) at hospital admission. However, only in the survivors did CRP levels decrease significantly on the last day in the ICU. During this period, a significant positive correlation ($R$=0.553, $P$=0.049) was observed between mortality and CRP levels. Furthermore, the probability of mortality was 82.1% when the CRP level exceeded 14 mg/L on the last day in the ICU (Fig. 2, *b*).

On the day of admission and the first day in the ICU, ferritin levels were significantly lower in non-survivors than in survivors, by 24% and 17%, respectively (Table 2). Negative

**Table 3. Parameters of WBC differential in patients with SARS-CoV-2 associated pneumonia *(Me (Q25, Q75))*.**

| Parameter | Values at study stages | | | | *P value* | | |
|---|---|---|---|---|---|---|---|
| | Day of admission (1) | Day 1 in the ICU (2) | Last day in the ICU (3) | Day of discharge from the hospital (4) | 1–2 | 1–3 | 1–4 |
| **Control group (survivors), *N*=20** | | | | | | | |
| WBCs, ×10⁹/L | 6.2 (4.0; 11.7) | 7.7 (5.3; 12.8) | 9.7 (7.40; 12.2) | 9.4 (7.30; 10.7) | 0.109 | 0.095 | 0.191 |
| Lymphocytes | | | | | | | |
| Absolute count, ×10⁹/L | 1.3 (0.8; 1.9) | 0.9 (0.7; 1.5) | 0.8 (0.7; 1.3) | 1.6 (1.0; 2.1) | 0.090 | 0.191 | 0.552 |
| Percentage, % | 16.6 (10.4; 43.9) | 9.5 (7.5; 16.4)# | 10.0 (6.7; 11.5)# | 17.6 (8.8; 21.5) | 0.004 | 0.006 | 0.079 |
| MLC | | | | | | | |
| Absolute count, ×10⁹/L | 0.5 (0.4; 0.9) | 1.1 (0.5; 1.3)# | 1.2 (0.7; 1.4)# | 1.1 (0.7; 1.3) | 0.006 | 0.008 | 0.014 |
| Percentage, % | 8.5 (7.3; 9.4) | 9.1 (8.3; 11.0) | 10.9 (8.5; 14.5)# | 10.5 (9.4; 13.1)# | 0.158 | 0.006 | 0.002 |
| Granulocytes | | | | | | | |
| Absolute count, ×10⁹/L | 3.5 (2.2; 9.7) | 8.8 (5.4; 10.7)# | 7.9 (5.8; 9.4) | 6.0 (5.1; 8.5) | 0.005 | 0.092 | 0.266 |
| Percentage, % | 70.8 (47.3; 81.6) | 79.4 (70.9; 83.7) | 78.2 (70.3; 83.9) | 70.3 (66.8; 79.4) | 0.026 | 0.073 | 0.274 |
| Eosinophils, % | 1.0 (1.0; 2.0) | 1.0 (1.0; 2.0) | 1.0 (1.0; 1.0) | 1.0 (1.0; 2.0) | 0.686 | 0.735 | 0.990 |
| Band neutrophils, % | 4.0 (2.0; 9.0) | 6.0 (6.0; 10.0) | 7.0 (6.0; 9.0) | 6.0 (6.0; 8.0) | 0.043 | 0.107 | 0.128 |
| Segmented neutrophils, % | 63.0 (41.0; 66.0) | 65.0 (61.0; 66.0) | 64.0 (63.0; 67.0) | 62.5 (58.5; 65.0) | 0.176 | 0.093 | 0.753 |
| BSNR | 0.07 (0.05; 0.16) | 0.10 (0.08; 0.16) | 0.11 (0.09; 0.14) | 0.11 (0.09; 0.12) | 0.176 | 0.374 | 0.128 |
| **Main group (non-survivors), *N*=53** | | | | | | | |
| WBCs, ×10⁹/L | 9.1 (5.2; 14.4) | 11.7 (7.2; 15.7)#* | 16.2 (13.0; 24.7)#* | | 0.001 | <0.001 | |
| Lymphocytes | | | | | | | |
| Absolute count, ×10⁹/L | 1.1 (0.8; 1.5) | 1.0 (0.8; 1.5) | 1.1 (0.8; 1.5) | | 0.808 | 0.591 | |
| Percentage, % | 10.7 (7.1; 20.2)* | 7.6 (6.8; 11.7)# | 6.4 (4.3; 9.1)#* | | 0.004 | <0.001 | |
| MLC | | | | | | | |
| Absolute count, ×10⁹/L | 0.7 (0.4; 1.0) | 0.9 (0.6; 1.4)# | 1.4 (0.9; 2.2)#* | | 0.001 | <0.001 | |
| Percentage, % | 7.0 (4.4; 9.3)* | 7.7 (5.5; 9.9)# | 7.5 (5.8; 10.9)* | | 0.005 | 0.123 | |
| Granulocytes | | | | | | | |
| Absolute count, ×10⁹/L | 7.4 (4.6; 12.6)* | 10.4 (6.3; 14.7)#* | 13.6 (10.4; 21.6)#* | | 0.001 | <0.001 | |
| Percentage, % | 81.3 (70.2; 86.7)* | 82.8 (78.6; 86.7)* | 85.6 (81.1; 88.5)#* | | 0.055 | 0.011 | |
| Eosinophils, % | 2.00 (1.00; 2.00) | 2.00 (1.00; 2.00) | 1.00 (1.00; 2.00) | | 0.950 | 0.068 | |
| Band neutrophils, % | 7.0 (4.0; 9.5) | 9.5 (6.0; 17.0) | 12.0 (8.0; 20.0)#* | | 0.030 | 0.014 | |
| Segmented neutrophils, % | 63.5 (59.0; 65.0) | 63.0 (57.0; 65.0) | 59.0 (53.0; 63.0)* | | 0.726 | 0.890 | |
| BSNR | 0.11 (0.07; 0.16) | 0.18 (0.09; 0.30)#* | 0.21 (0.16; 0.39)#* | | 0.016 | 0.012 | |
| ***P* values for the intergroup differences** | | | | | | | |
| WBCs, ×10⁹/L | 0.057 | 0.046 | <0.001 | | | | |
| Lymphocytes | | | | | | | |
| Absolute count, ×10⁹/L | 0.476 | 0.794 | 0.228 | | | | |
| Percentage, % | 0.015 | 0.172 | 0.002 | | | | |
| MLC | | | | | | | |
| Absolute count, ×10⁹/L | 0.376 | 0.886 | 0.215 | | | | |
| Percentage, % | 0.027 | 0.099 | 0.004 | | | | |
| Granulocytes | | | | | | | |
| Absolute count, ×10⁹/L | 0.016 | 0.032 | <0.001 | | | | |
| Percentage, % | 0.007 | 0.038 | <0.001 | | | | |
| Eosinophils, % | 0.683 | 0.175 | 0.736 | | | | |
| Band neutrophils, % | 0.131 | 0.060 | 0.001 | | | | |
| Segmented neutrophils, % | 0.709 | 0.076 | 0.011 | | | | |
| BSNR | 0.356 | 0.043 | <0.001 | | | | |

**Note.** Statistically significant difference ($P<0.05$): * — intergroup; # — compared to the values on the day of admission. BSNR — band-to-segmented neutrophil ratio; MLC — myeloid lineage cells.

correlations between ferritin levels and mortality risk were found on these days ($R$=–0.343, P = 0.003; $R$=–0.331, $P$ = 0.014, respectively). As shown in Fig. 2, *c*, ferritin concentration at admission was the most potent prognostic predictor of mortality risk (AUC=0.826; 95% CI: 0.717–0.905; $P<0.001$), with a cutoff of ⩽0.473 μg/L. Ferritin levels below this threshold indicated an 80.2% probability of death (prognostic accuracy).

Table 3 shows that in the comparison group, there were no significant changes in the absolute WBC count during hospitalization. In contrast, in the main group, the WBC count increased by 29% on the first day and by 86% on the last day in the ICU compared with the day of admission. Notably, on both the first and last days in the ICU, non-survivors had significantly higher WBC counts than survivors, by 52% and 67%, respectively (Table 3).

A significant positive correlation was found between mortality and blood leukocyte count in patients with SARS-CoV-2-associated pneumonia on both the first and last day of ICU stay ($P$=0.045 and $P<0.0001$, respectively). At the time of admission, the percentage of lymphocytes was lower than the normal range (25–50%) in both groups, with a significantly greater reduction (by 36%) in

the main group compared with the control group (Table 3). On the first and last day of ICU stay, a significant decrease in relative lymphocyte count (%) was observed in both groups compared to the day of hospitalization (Table 2). However, in non-survivors, this parameter was 36% lower on the last day of ICU stay than in survivors during the same period (Table 3).

As shown in Table 3, the absolute number of monocytes, eosinophils, basophils, and immature cells (myeloid lineage cells, MLC) in non-survivors at the time of hospitalization was almost identical to that in survivors (Table 3). On the first ICU day, there was a significant increase in the MLC count in both groups compared with the day of admission, and it remained elevated until the last day of ICU stay (Table 3). However, on the last ICU day, the absolute MLC count was significantly (17%) higher in non-survivors (Table 3).

However, the relative percentage of MLC (%) showed a totally different trend. In survivors, it increased on the last day of ICU stay and on the day of discharge compared to the day of admission, whereas in non-survivors, no significant changes were observed during the same period (Table 3).

As shown in Table 2, the absolute granulocyte count in the blood of non-survivors with SARS-CoV-2-associated pneumonia was significantly higher (by 105%) on the day of hospitalization compared with survivors during the same observation period. On the first day of ICU stay, granulocyte counts increased in both survivors and non-survivors by 151% and 40%, respectively, compared with the day of admission. In non-survivors, the granulocyte count remained significantly elevated on the last ICU day compared to the day of admission (Table 3). Compared to the survivors, the granulocyte count in the main group was increased by 17% and 52% on the first and last day of ICU stay, respectively (Table 3).

A positive correlation was found between mortality and granulocyte count on admission, on the first ICU day, and on the last ICU day, with correlation coefficients of $R$=0.287 ($P$=0.015), $R$=0.259 ($P$=0.031), and $R$=0.552 ($P$<0.0001), respectively. Regarding the relative granulocyte percentage, its value in non-survivors significantly exceeded that of survivors on the day of hospitalization and on the first and last ICU days by 18%, 5%, and 10%, respectively (Table 3). In survivors, the relative granulocyte percentage remained almost unchanged compared to the day of admission, whereas in non-survivors it increased on the last day of ICU stay (Table 3).

On the last day of ICU stay, the percentage of band neutrophils in the blood of non-survivors was 71% higher than on the day of hospitalization (Table 2). Meanwhile, the percentage of segmented neutrophils in non-survivors was significantly reduced (by 8%) on the last ICU day (Table 3).

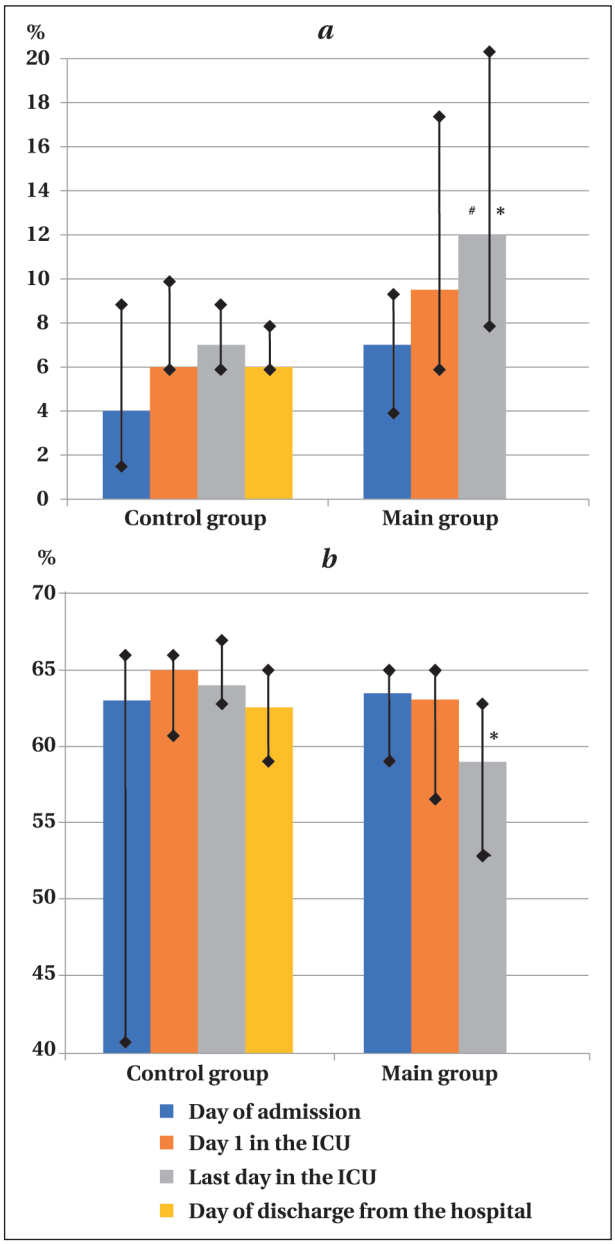


**Fig. 3. Changes in the percentage of band neutrophils (*a*) and segmented neutrophils (*b*) in the blood of ICU patients.**
**Note:** Statistically significant difference ($P$<0.05): * — between groups; # — compared with the values on the day of admission. Vertical lines represent the range Q25-Q75.

In the main group, an abnormal neutrophil shift with a significant decrease in percentage of segmented neutrophils along with an increase in band neutrophils was most pronounced on the last ICU day, i. e. the day of death (Fig. 3).

Among all leukocyte differential parameters, the band-to-segmented neutrophil ratio showed the highest prognostic value as a predictor of mortality risk in patients with SARS-CoV-2-associated pneumonia (Table 4). It was a significant predictor on both the first and last day of ICU stay. As death approached, its predictive value increased, as indicated by an increased prognostic accuracy from 61.6% to 82.4%.

**Table 4. Results of prognostic value assessment of WBC differential parameters (based on ROC analysis) for predicting mortality risk in patients with SARS-CoV-2-associated pneumonia in the ICU.**

| Parameter | Area under the curve (AUC) ROC | 95% CI | *P value* (AUC = 0.5) | Sensitivity, % | Specificity, % | Prognostic accuracy, % | Cutoff |
|---|---|---|---|---|---|---|---|
| **Day 1 in the ICU** | | | | | | | |
| Granulocytes, $\times10^9$/L | 0.711 | от 0.589 до 0.814 | 0.002 | 93.7 | 42.9 | 79.3 | >6 |
| BSNR | 0.713 | от 0.541 до 0.850 | 0.016 | 50 | 90.9 | 61.6 | >0.18 |
| **Last day in the ICU (day of death in patients of the main group)** | | | | | | | |
| WBC count, $\times10^9$/L | 0.833 | от 0.725 до 0.912 | 0.001 | 79.6 | 81 | 79.9 | >12.2 |
| Granulocytes, $\times10^9$/L | 0.848 | от 0.742 до 0.923 | <0.0001 | 71.4 | 90.5 | 76.8 | >11.3 |
| PMNs, % | 0.830 | от 0.687 до 0.926 | <0.0001 | 66.7 | 88.2 | 72.8 | >10 |
| BSNR | 0.862 | от 0.724 до 0.947 | <0.0001 | 77.8 | 94.1 | 82.4 | >0.16 |

**Table 5. Parameters of prediction model for estimating the probability of death in patients with SARS-CoV-2-associated pneumonia admitted to the ICU.**

| Parameter | Regression coefficient | Mean squared error (MSE) | *P value* | Odds ratio (OR) |
|---|---|---|---|---|
| Ferritin (μg/mL) at the day of admission | –0.951 | 4.992 | 0.849 | 0.386 |
| $SpO_2$ at the last day in the ICU | –0.493 | 0.192 | 0.010 | 287.3 |
| BSNR at the last day in the ICU | 24.081 | 10.979 | 0.028 | 0.611 |
| Intercept | 41.477 | 15.848 | 0.009 | |

According to the presented ROC analysis results (Fig. 2, *a–c* and Table 4), each parameter shows good or satisfactory prognostic value. Although many parameters showed statistically significant informativeness ($P \leqslant 0.05$), it is impractical to rely on a single criterion as a predictor of mortality risk because its prognostic accuracy is far from 100%. Therefore, a unified mathematical model incorporating the assessment of multiple parameters simultaneously was developed (Table 5).

Two of the three predictors characterized the patient's condition on the «last day in the ICU». Since this determination is possible only retrospectively, it is clinically advisable to calculate the probability of mortality on a daily basis, taking into account the clinical and laboratory parameters corresponding to the day of assessment.

Based on the calculations performed, the equation for estimating the probability *(P)* of mortality is as follows

$$\mathbf{P=1/(1+e^{-Z}) \times 100\%,}$$

where

$Z=41.477-0.951\times X_1+24.081\times X_2-0.493\times X_3$.

Here,

— $X_1$ is the serum ferritin concentration (mg/L) at hospital admission,

— $X_2$ is the band-to-segmented neutrophil ratio on the day of the ICU assessment, and

— $X_3$ is the oxygen saturation (%) on the day of ICU assessment.

The developed mathematical model accounts for 86.3% of the experimental values ($R^2$=0.863), with an overall prediction accuracy of 85.7%.

In logistic regression, predicted values for the dependent variable range from 0 to 100, independent of the values of the independent variables. When $y>0.5$, there is a high probability of death.

The model was validated by receiver operating characteristic (ROC) curve analysis of the predicted values (Fig. 2, *d*). The constructed model demonstrated substantial prognostic power in identifying mortality risk, with a sensitivity of 84.0% and a specificity of 94.1%. The area under the ROC curve (AUC) was 0.955 with $Z$=16.1 ($P<0.001$).

## Discussion

There was no significant difference in $SpO_2$ levels between the two groups at hospital admission and on the first day in the ICU (Table 1), indicating similar impairment of lung oxygenation at these time points. However, in the main group, the treatment administered, including respiratory support by MV in CMV/VCV and CMV/PCV modes with $FiO_2$>60% and PEEP of 6–10 cm $H_2O$, did not prevent pulmonary disease progression, resulting in a fatal outcome.

Post-mortem examinations revealed that patients in the main group had diffuse alveolar damage, as evidenced by massive fibrin deposition in the alveolar spaces and interalveolar septal fibrosis. As previously reported in the literature [15], these histopathological changes indicate the progression of inflammation in the lung tissue associated with SARS-CoV-2 pneumonia. This may explain why the $SpO_2$ level at death was higher than at admission, but did not reach the low limit of normal range (Table 2).

The progression of lung inflammation in SARS-CoV-2-associated pneumonia, often complicated by secondary bacterial infections, may contribute to the development of refractory hypoxemia. This condition is seen in mechanically ventilated patients with ARDS, where changes in ventilatory settings do not correct hypoxemia [18]. Mechanical ventila-

tion could not restore $SpO_2$ to normal levels in the main group, indicating the presence of refractory hypoxemia (see Table 1).

One of the key markers of systemic inflammation is an elevated level of CRP in the blood. As a soluble pattern recognition receptor (PRR), CRP binds to danger-associated molecular patterns (DAMPs) and plays a crucial role in regulating both inflammatory and immune responses [19]. Its production is primarily driven by the pro-inflammatory cytokine interleukin-6 (IL-6) [19], which is known to contribute to lung injury in COVID-19 [20]. Therefore, persistently high CRP levels in critically ill patients at the time of death not only suggest ongoing inflammation in the lungs despite treatment but also indicate excessive production of pro-inflammatory cytokines, particularly IL-6.

CRP also functions as an opsonin, recognizing specific ligands on bacterial pathogen-associated molecular patterns (PAMPs) and endogenous DAMPs. This interaction triggers both the classical and, to a lesser extent, the alternative complement activation pathways [19]. The complement system, a key component of innate immunity, has evolved as a primary defense mechanism against infections [21]. Given this, persistently elevated CRP levels in COVID-19 patients strongly suggest the presence of a secondary bacterial infection.

Currently, there is no consensus on the role of hyperferritinemia in the pathogenesis of COVID-19 [22, 23]. Specifically, it remains unclear whether ferritin in COVID-19 serves merely as a byproduct of the inflammatory response or acts as a pathogenetic mediator [23]. Some researchers have identified an association between mortality and a rapid increase in ferritin levels ($\geqslant$1,000 μg/L) [23]. Others have reported that the restoration of pulmonary gas exchange function in SARS-CoV-2-associated pneumonia during hyperbaric oxygen therapy was accompanied by a reduction in hyperferritinemia, although ferritin levels did not fully normalize [24].

The conflicting data on the role of ferritin in COVID-19 may be attributed to the unique structure of its protein molecule, which consists of light (L) and heavy (H) chains. Notably, only the H subunit possesses redox activity. The quantitative ratio of L and H chains varies depending on tissue type and homeostatic conditions, influencing the functional properties of ferritin [25].

Our findings indicate a high probability of fatal outcomes in SARS-CoV-2-associated pneumonia when ferritin levels at the time of hospitalization are $\leqslant$0.473 μg/L. This suggests that, unlike the control group, patients in the main group had a delayed development of hyperferritinemia as a systemic response to SARS-CoV-2-induced lung injury. Consequently, this delay may have contributed to an increased risk of mortality as the disease progressed.

Since the degree of leukocytosis reflects the intensity of the inflammatory response [20], the observed increase in leukocytosis in the main group (Table 2) suggests the development of secondary bacterial infection driving the progression of pulmonary inflammation. This is further supported by the predominance of granulocytic lineage cells within the peripheral blood leukocyte pool, leading to the development of relative lymphocytopenia. The progressive decrease in lymphocyte percentage observed in critically ill patients from the main group in the ICU (Table 2) can be considered a prognostically unfavorable marker for mortality. This conclusion is supported by the negative correlation between lymphocyte percentage and mortality, both on the day of admission ($R$=–0.288, $P$=0.014) and on the last day in the ICU ($R$=–0.378, $P$=0.001).

Regarding granulocytes, a notable finding in the main group was the progression of neutrophilia due to an increased presence of immature neutrophil forms, which occurred alongside a reduction in segmented neutrophils (Table 2). This biological marker should be considered an adverse prognostic indicator of mortality risk in SARS-CoV-2-associated pneumonia. Notably, on the last day of ICU stay, a significant positive correlation was found between mortality and the percentage of band neutrophils ($R$=0.508, $P<0.001$), while a significant negative correlation was observed between mortality and the percentage of segmented neutrophils ($R$=–0.387, $P$=0.010).

An elevated blood neutrophil count was associated with poor outcome in patients with suppurative lung disease, regardless of whether they had a history of COVID-19. Meanwhile, separate analyses showed that this association was statistically significant only in those without a history of COVID-19 [26]. The available data suggest that the authors of this study examined the total number of circulating neutrophils without considering the proportion of band and segmented neutrophils.

However, our research demonstrated that shifts in the ratio of these neutrophil subtypes — expressed as the band-to-segmented neutrophil ratio — could serve as an early predictor of mortality in SARS-CoV-2-associated pneumonia, as early as the first day of ICU admission.

Furthermore, the prognostic value of the band-to-segmented neutrophil ratio increased as the fatal outcome approached (Table 3).

The mechanism behind the prognostic significance of the neutrophil ratio may be related to an impaired immune response to bacterial infection in the presence of SARS-CoV-2. This dysfunction leads to uncontrolled production of neutrophils by the bone marrow. In response to microbial agents,

these neutrophils produce excessive free radicals and cytokines — not only to eliminate pathogens within phagosomes, but also by releasing them into the extracellular environment. This uncontrolled response causes collateral tissue damage, particularly to the vascular endothelium [26].

As a result, disruption of the endothelial glycocalyx and increased permeability of the tissue-blood barrier [27] contribute to pulmonary edema and abnormal deposition of blood proteins, such as fibrinogen, in the lung interstitial tissue [15]. In addition, endothelial damage in pulmonary capillaries impairs endothelial antithrombotic function, leading to the formation of microthrombi [28], a process that has been well documented in SARS-CoV-2-associated pneumonia [15].

**Study limitations.** The results of this study should be interpreted with caution because of several limitations. First, the authors used random sampling with a small sample size, which reduces the strength of the evidence. In addition, inclusion and exclusion criteria were applied after the random selection of medical records, which further reduces the reliability of the study. Another limitation is the lack of internal cross-validation or external validation to confirm the accuracy of the model.

## Conclusion

This study suggests that common blood inflammation markers — such as CRP, ferritin, absolute leukocyte and granulocyte counts, percentage of granulocytes and band neutrophils, as well as band-to-segmented neutrophil ratio and oxygen saturation measured by pulse oximetry — can help assess the risk of poor outcome in patients with SARS-CoV-2-associated pneumonia admitted to or already in the ICU.

In addition, an association was found between these parameters and specific hospitalization time points, including the day of admission, the first day in the ICU, and the last day in the ICU.

Among these factors, the most valuable prognostic tool was a mathematical model incorporating ferritin levels, band-to-segmented neutrophil ratio, and oxygen saturation. This model had a sensitivity of 84.0% and a specificity of 94.1% for predicting adverse outcomes in ICU patients with SARS-CoV-2-associated pneumonia.

To determine whether this prediction model is specific to SARS-CoV-2-associated pneumonia, further studies are needed to assess its applicability to lung inflammation caused by other pathogens.

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