

PREDICTION IN INTENSIVE CARE MEDICINE

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Predictors and risk factors for mortality in patients with severe COVID-19: a retrospective single-center study

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Abstract

INTRODUCTION: The high prevalence of severe disease and in-hospital mortality (IHM) during the COVID-19 pandemic represented a major clinical challenge, highlighting the need to improve risk stratification tools. **OBJECTIVE:** To develop prognostic models for risk stratification of in-hospital mortality (IHM) in patients with severe COVID-19. **MATERIALS AND METHODS:** A retrospective single-center study was conducted at Regional Clinical Hospital No. 2. in Vladivostok. Medical records of 98 patients with severe COVID-19 who were treated in the intensive care unit (ICU) in 2024 were analyzed. Two groups were identified: the first group comprised 43 patients (43.9 %) with a favorable outcome, and the second group included 55 patients (56.1 %) who died during hospitalization. Methods of univariate and multifactorial logistic regression (MLR) were used to develop predictive models of IHM. **RESULTS:** The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores demonstrated high predictive accuracy for adverse outcomes in patients with severe COVID-19, both at the initial stage of the study during assessment of clinical and functional status in the ICU and when incorporated as predictors in multivariable logistic regression models. Procalcitonin, creatinine, urea, C-reactive protein, and lactate dehydrogenase levels were positively associated with mortality, whereas glomerular filtration rate was negatively

ПРОГНОЗИРОВАНИЕ В ИНТЕНСИВНОЙ ТЕРАПИИ

Предикторы и факторы риска летального исхода у пациентов с тяжелым течением новой коронавирусной инфекции: ретроспективное одноцентровое исследование

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Реферат

АКТУАЛЬНОСТЬ: Наиболее значимой клинической проблемой во время пандемии новой коронавирусной инфекции (COronaVirus Disease 2019 — COVID-19) была высокая распространенность тяжелых форм заболевания и госпитальной летальности, что актуализирует необходимость совершенствования рискометрических инструментов. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Разработка прогностических моделей для стратификации риска госпитальной летальности у больных с тяжелым течением COVID-19. **МАТЕРИАЛЫ И МЕТОДЫ:** Проведено ретроспективное одноцентровое исследование на базе Краевой клинической больницы № 2 г. Владивостока. Обработаны данные медицинских карт 98 пациентов с тяжелым течением COVID-19, находящихся на лечении в отделении реанимации и интенсивной терапии (ОРИТ) в 2024 г. Выделено 2 группы лиц, первую составили 43 (43,9 %) больных с благоприятным исходом лечения, вторую — 55 (56,1 %) пациентов, умерших в стационаре. Для разработки прогностических моделей госпитальной летальности использовали методы однофакторной и многофакторной логистической регрессии. **РЕЗУЛЬТАТЫ:** Шкалы Acute Physiology and Chronic Health Evaluation II (APACHE II) и Sequential Organ Failure Assessment (SOFA) показали высокую точность прогнозирования неблагоприятного исхода у пациентов с тяжелым течением COVID-19

associated with mortality. D-dimer, aspartate aminotransferase, and alanine aminotransferase values had no statistically significant effect on the endpoint. **CONCLUSIONS:** Based on a multistep selection process, demographic and clinical variables were identified, most of which demonstrated predictive value and were used to develop prognostic models for adverse outcomes in patients with severe COVID-19. The APACHE-II and SOFA scales are reliable tools in stratifying the risk of an adverse outcome in severe COVID-19.

KEYWORDS: new coronavirus infection, COVID-19, mortality predictors, intensive care, machine learning, APACHE II, SOFA

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как на первом этапе исследования при оценке клинико-функционального статуса больных в ОРИТ, так и при использовании балльных оценок этих шкал в качестве предикторов прогностических моделей многофакторной логистической регрессии. Положительную взаимосвязь с летальным исходом имели показатели прокальцитонина, креатинина, мочевины, С-реактивного белка, лактатдегидрогеназы (ЛДГ), а отрицательную — скорость клубочковой фильтрации (СКФ). Показатели D-димера, аспаратаминотрансферазы (АСТ) и аланинаминотрансферазы (АЛТ) не оказывали статистически значимого влияния на конечную точку. **ВЫВОДЫ:** На основе многоступенчатого отбора были выделены демографические и клинические признаки, большинство из которых обладали предиктивным потенциалом и использовались при разработке прогностических моделей неблагоприятного исхода у тяжелых пациентов с COVID-19. Шкалы APACHE II и SOFA являются надежными инструментами в стратификации риска неблагоприятного исхода при тяжелом течении COVID-19.

КЛЮЧЕВЫЕ СЛОВА: новая коронавирусная инфекция, COVID-19, предикторы летального исхода, реанимация и интенсивная терапия, машинное обучение, APACHE II, SOFA

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Introduction

In recent years, a significant decline and stabilization in the incidence of coronavirus disease 2019 (COVID-19) have been observed. So, in 2024, more than 1.1 million cases of this disease were registered in the Russian Federation,

with a peak in September-October. However, timely stratification of disease severity and assessment of the risk of adverse outcomes remain important clinical challenges, particularly among patients requiring treatment in intensive care units (ICUs). A review of the literature indicates that demographic, clinical history, clinical, instrumen-

tal, and laboratory parameters are most commonly used to identify predictors of fatal outcomes. Adverse outcomes in COVID-19 were found to be frequently associated with alterations in blood cell counts (white blood cells, neutrophils, lymphocytes, eosinophils, monocytes, and platelets), hemoglobin levels, coagulation parameters (D-dimer and prothrombin time), markers of liver function (albumin, total bilirubin, alanine aminotransferase), renal function (urea and creatinine), and inflammatory markers (C-reactive protein, interleukin-6, lactate dehydrogenase, procalcitonin, ferritin, and cardiac troponin) [1–4]. Increased in-hospital mortality was observed in cohorts of male patients, older and elderly individuals, and those with comorbidities, including chronic diseases of the lungs, cardiovascular system, brain, kidneys, and liver, as well as diabetes mellitus and malignancies [5–20]. In intensive care units, validated and widely used scoring systems are employed to stratify disease severity and assess the risk of adverse outcomes. These include the Simplified Acute Physiology Score II (SAPS II), Acute Physiology and Chronic Health Evaluation II (APACHE II), and Sequential Organ Failure Assessment (SOFA) score [18]. At the same time, a number of studies indicate the need to improve risk-based tools for a more accurate assessment of the prognosis in patients with COVID-19. Clinical and laboratory characteristics and prognostic indicators in patients have changed over the five years of the pandemic. In recent years, machine learning (ML) methods, which represent a core technology of artificial intelligence, have been increasingly used to address this task. The development of prognostic models based on these parameters, taking into account regional characteristics, improves the quality of generated predictions, and

their implementation into clinical decision support systems enhances reliability and physician confidence.

Objective

To develop prognostic models for risk stratification of in-hospital mortality in patients with severe COVID-19.

Materials and methods

A single-center retrospective cohort study was conducted on the basis of the Regional Clinical Hospital No. 2 in Vladivostok. Medical records of 163 patients (Figure 1), including 70 women and 93 men, who were treated in the ICU for severe COVID-19 were analyzed. The diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) testing of biomaterial obtained from the nasopharynx and oropharynx. The data was extracted from the BARS Healthcare MIS (medical information system). Indications for ICU admission included severe respiratory failure and the requirement for respiratory support in patients with clinically significant lung involvement exceeding 50 %, as assessed using a visual percentage scale. The study endpoint was all-cause in-hospital mortality in patients with COVID-19, analyzed as a binary categorical variable (absence or occurrence). The study was approved by the local Ethics committee of the Regional Clinical Hospital No. 2 — Protocol No. 05 dated March 05, 2025.

All patients were treated in accordance with the current Interim Guidelines for the Prevention, Diagnosis,

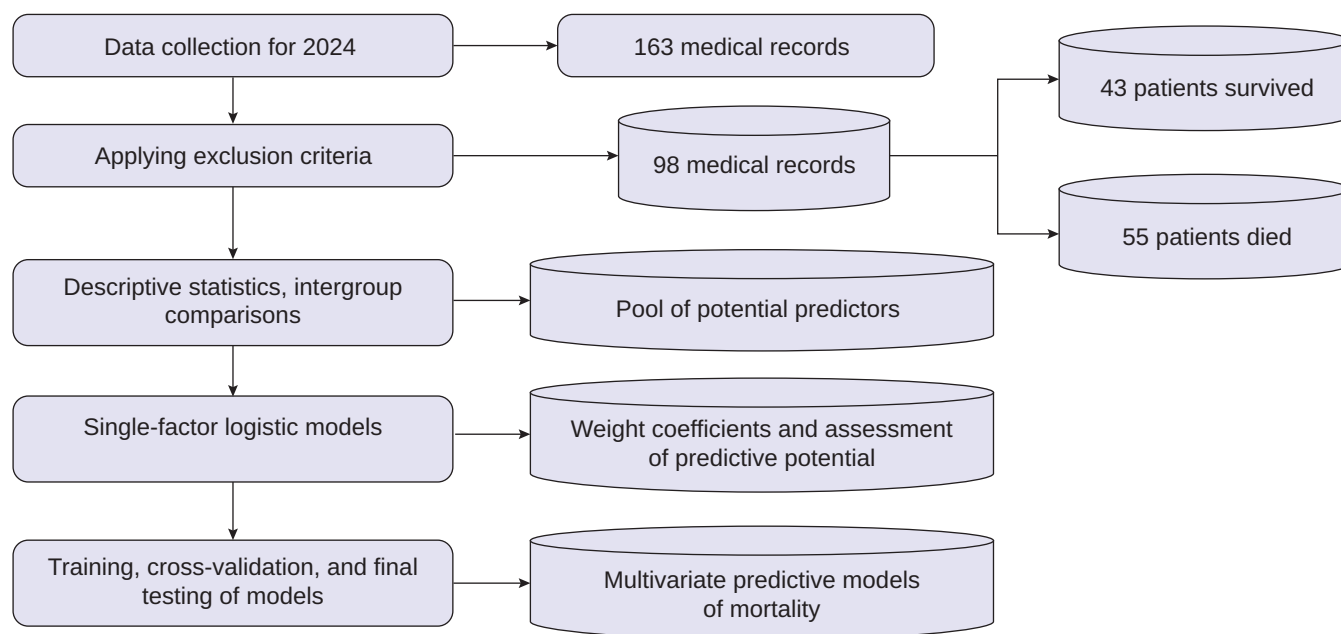


Fig. 1. Flow chart of study design

and Treatment of Coronavirus Disease (COVID-19) issued by the Ministry of Health of the Russian Federation (Version 18, October 26, 2023).

The **inclusion criteria** for medical records were as follows:

- Severe course of COVID-19.
- Severe respiratory failure requiring respiratory support.
- Over the age of 18.
- Concomitant diseases not included in the exclusion criteria.

The study **non-inclusion criteria**:

- Immunodeficiency conditions.
- Oncological and hematological diseases.
- Pregnancy.
- Addiction.

Taking into account the above criteria, a structured set of processed and categorized data was formed, including 98 medical records of patients, which were divided into 2 groups. The first group included 43 (43.9 %) patients with a favorable treatment outcome, and the second group included 55 (56.1 %) patients who died in the ICU.

Demographic (age, sex) and anthropometric parameters (height, body weight, and body mass index [BMI]), laboratory findings (white blood cell count, platelet count, creatinine, C-reactive protein, procalcitonin, urea, D-dimer, lactate dehydrogenase, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and glomerular filtration rate [GFR]) were analyzed. GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Initial respiratory support modalities, including invasive mechanical ventilation, noninvasive ventilation, and high-flow oxygen therapy, were also assessed. During the first 24 hours of ICU stay, the APACHE II and SOFA scoring systems were used to assess patient condition and stratify the risk of adverse outcomes. The severity of comorbid pathology was assessed using Charlson Comorbidity Index (CCI). Scores on these scales, along with other variables, were considered potential predictors of in-hospital mortality (Table 1).

Statistical methods

The input features (potential predictors) were presented as continuous and categorical variables. Mathematical statistics and machine learning methods were used for data processing and analysis. The former included chi-square, Fisher's exact, and Mann-Whitney tests, as well as univariable logistic regression (ULR). The indicators were represented by median values (Me), their 25 % and 75 % percentiles (Q1; Q3) and 95% confidence intervals (CI). The chi-square criterion and the odds ratio (OR) were used to compare categorical variables. Continuous variables were compared using the Mann-Whitney U-test, as the Kolmogorov-Smirnov test indicated a deviation from normal distribution ($p < 0.05$). Using ULR, the weighting coefficients corresponding to the degree of influence of individ-

ual factors on the endpoint were determined. Additionally, the prognostic significance of each potential predictor was assessed using the area under the ROC curve (AUC).

Multifactorial logistic regression was used to develop predictive models of hospital mortality. The model structure was incrementally expanded by adding potential predictors, with model performance metrics evaluated at each step; improvements in these metrics indicated the prognostic value of the analyzed factors. To develop models, the dataset was randomly divided into 2 parts: 80 % of the data was used for training and cross-validation of models using the stratified K-Fold method on 5 subsamples, and 20 % for final testing. The procedure of random division, subsequent training, cross-validation, and final testing was repeated 100 times using the parameters and hyperparameters set at the first iteration step. The metrics AUC, sensitivity (Sen), and specificity (Spec) were used to evaluate and improve the models. The Hosmer-Lemeshow test and the Brier score were used to evaluate the calibration of the models. The results were considered statistically significant at p -value < 0.05 . Data processing and analysis were performed in Python version 3.9.16 using pandas, numpy, scipy, matplotlib, seaborn, statsmodels, and sklearn libraries.

Results

At the first stage of the study, statistical analysis of 22 variables characterizing the clinical and functional status of patients in the comparison groups showed that only 11 of them differed significantly (Table 1). Comparable values were observed between the groups for age, anthropometric parameters (height, body weight, and BMI), and the CCI. At the same time, in the group of patients who died in hospital, there was a significant (2.5 times) predominance of males compared with the group of patients with a favorable treatment outcome (87.3 % vs 34.9 %, p -value < 0.000001). In the analyzed cohort, the odds of in-hospital mortality were nearly 13-fold higher in men than in women (OR 12.8). No statistically significant differences were observed between the groups in white blood cell count, platelet count, AST, ALT, or D-dimer levels. However, non-survivors exhibited higher blood urea and creatinine levels and lower glomerular filtration rate, indicating progressive renal dysfunction in patients with severe COVID-19. In this patient cohort, elevated levels of systemic inflammatory markers, including C-reactive protein and procalcitonin, were observed. Analysis of initial respiratory support during the first 24 hours of ICU stay showed that, compared with the control group, patients in the main group more frequently required invasive mechanical ventilation (OR 38.8, $p < 0.000001$) and high-flow oxygen therapy (OR 7.47, $p = 0.000016$). These findings indicate the presence of severe respiratory failure at ICU admission, requiring invasive respiratory support. In other words, it can be said that in the main group of patients, the severity of respiratory failure

Table 1. Clinical and functional characteristics of patients in the comparison groups during the first 24 hours of ICU stay (Me (Q1; Q3))

Indicators	Total number of patients, n = 98	Deceased, n = 55	Survivors, n = 43	OR (95% CI)	p
Age, years	72 (63; 81)	73 (67; 83)	69 (59; 80)	—	0.11
Gender: men	63 (64.3 %)	48 (87.3 %)	15 (34.9 %)	12.8 (4.7; 35.2)	< 0.000001
Gender: female	35 (35.7 %)	7 (12.7 %)	28 (65.1 %)	—	
Body weight, kg	74 (64; 84.25)	75 (64; 90)	71 (64.5; 80)	—	0.263
BMI, kg/m ²	25.9 (22.9; 30.5)	28.1 (23.4; 31.2)	25.3 (22.7; 29.2)	—	0.219
CCI, points	7 (5; 10)	7 (5; 10)	8 (5; 9.75)	—	0.944
GFR, ml/min	56 (27.25; 86)	49 (15.5; 76.5)	77 (40.5; 98.5)	—	0.002
Without high-flow oxygen therapy	59 (60.2 %)	44 (80 %)	15 (34.9 %)	7.47 (3; 18.6)	0.000016
Ventilation during the first 24 hours in ICU	38 (38.8 %)	36 (65.5 %)	2 (4.7 %)	38.8 (8.5; 178.4)	< 0.000001
Leukocytes, ×10 ⁹ /l	11.45 (8.42; 18.2)	12.22 (8.75; 19.33)	10.5 (7.23; 16.54)	—	0.165
Platelets, ×10 ⁹ /l	212 (148; 290)	205 (146.25; 289)	219 (151.5; 288.5)	—	0.98
Creatinine, μmol/L	99 (61.9; 176.2)	124 (77.55; 296.55)	81 (57.15; 116.95)	—	0.0027
CRP, mg/l	96.8 (37.4; 140.4)	121 (76.6; 159.8)	59.45 (20.73; 103.6)	—	0.001
Procalcitonin, ng/ml	0.68(0.25; 4.29)	1.95 (0.52; 10)	0.36 (0.12; 0.83)	—	0.00003
Urea, mmol/l	11.6 (6.63; 20.6)	15.7 (8; 27.5)	8.3 (5.6; 15.7)	—	0.0026
D-dimers, ng/ml	2128 (1344; 3422)	2838 (1462; 4211)	1993 (1315; 2849)	—	0.119
LDH, U/l	258.65 (185.9; 504.5)	317 (191; 456.1)	287 (167.54; 287.65)	—	0.022
ALT, U/l	26.25 (15.48; 43)	25 (17; 43.15)	28 (13.5; 42.6)	—	0.805
AST, U/l	39.15 (24.7; 76.18)	38 (26.75; 72.5)	39.3 (21.5; 72.45)	—	0.614
SO, min, %	89.8 (85.0; 95.1)	88.4 (84.2; 94.3)	91.3 (85.4; 96.9)	—	0.27
SOFA, points	7 (5; 8)	8 (6; 10)	5 (4; 6.5)	—	0.000002
APACHE II, points	17 (13; 21.75)	20 (17; 27)	13 (10; 15)	—	< 0.000001

Note: 95% CI — 95% confidence interval; ALT — alanine aminotransferase; APACHE II — Acute Physiology and Chronic Health Evaluation II; AST — aspartate aminotransferase; BMI — body mass index; CCI — Charlson Comorbidity Index; CRP — C-reactive protein; GPR — glomerular filtration rate; ICU — intensive care unit; LDH — lactate dehydrogenase; OR — odds ratio; SO — oxygen saturation (blood oxygen saturation of arterial blood); SOFA — Sequential Organ Failure Assessment.

was more significant. Analysis of the functional status of patients based on APACHE II and SOFA scores demonstrated statistically significant intergroup differences, indicating the informative value of these risk assessment tools.

It the second stage of the study, multivariable logistic regression models were developed using normalized data to assess the impact of individual variables on the study endpoint. Weight coefficients were calculated to characterize the predictive value of the analyzed factors (Table 2). It was found that of the 11 indicators identified at the previous stage, the higher median values of the weighting coefficients were demonstrated by the scores of the APACHE II and SOFA scales: Me 3.15, 95% CI (3.13; 3.17) and Me 2.13, 95% CI (2.09; 2.16), respectively. These results were confirmed by high AUC levels (0.936 and 0.779) (Figure 2). The

use of invasive mechanical ventilation demonstrated high predictive value, as reflected by a regression coefficient of 2.4 (2.37–2.43) and an AUC of 0.815. In the developed ULR models, most of the weighting coefficients had a positive value, which indicated an increase in the unfavorable outcome probability in the presence of these signs or their increase. A negative value of the GFR weighting coefficient indicates an increased risk of mortality with a decrease in the value of this indicator.

At the final stage of the study, prognostic models for in-hospital mortality in patients with COVID-19 were constructed using multivariable logistic regression based on the predictors listed in Table 2. This objective was achieved by expanding the structure of the baseline univariable SOFA and APACHE II models, in which the scale scores were

used as the sole predictors (Table 3). Incorporation of invasive mechanical ventilation as a predictor improved model performance, increasing the AUC from 0.779 to 0.875 for the SOFA model and from 0.936 to 0.960 for the APACHE II model. Sequential addition of C-reactive protein and lactate dehydrogenase levels to the SOFA model predictors increased the AUC to 0.908 (95% CI 0.896–0.920). A novel prognostic model for in-hospital mortality in COVID-19 was developed that did not include SOFA or APACHE II scores. The predictors of this model included

seven previously selected variables: patient age, male sex, procalcitonin, urea, lactate dehydrogenase, use of invasive mechanical ventilation, and absence of indication for high-flow oxygen therapy. The model demonstrated high prognostic accuracy based on the AUC parameter — 0.935 (0.925; 0.946). The absence of multicollinearity was confirmed by variance inflation factor (VIF) values, which were below 1.35 for all predictors. The Brier score demonstrated good calibration for all three models: Brier Score — 0.105. 0.117. 0.13. At the same time, the Hosmer-Lemeshow test

Table 2. Weighting coefficients of one-factor logistic regression models characterizing the predictive potential of the analyzed factors (Me, 95% CI)

Indicators	Weight factor	AUC
Gender: men	1.97 (1.94; 2)	0.758 (0.743; 0.773)
Without high-flow oxygen therapy	1.61 (1.58; 1.65)	0.72 (0.702; 0.82)
Creatinine	1.21 (1.18; 1.23)	0.679 (0.659; 0.7)
GFR, ml/min	-1.32 (-1.36; -1.28)	0.682 (0.661; 0.702)
Ventilation on the Day 1	2.4 (2.37; 2.43)	0.815 (0.8; 0.83)
CRP, mg/l	1.33 (1.29; 1.38)	0.683 (0.663; 0.704)
Procalcitonin, ng/ml	1.35 (1.31; 1.38)	0.772 (0.754; 0.79)
Urea, mmol/l	1.48 (1.44; 1.51)	0.677 (0.657; 0.698)
LDH, U/l	1.09 (1.05; 1.12)	0.636 (0.609; 0.663)
SOFA, points	2.13 (2.09; 2.16)	0.779 (0.76; 0.798)
APACHE II, points	3.15 (3.13; 3.17)	0.936 (0.929; 0.944)

Note: APACHE II — Acute Physiology and Chronic Health Evaluation-II; AUC — area under the ROC-curve; CI — confidence interval; CRP — C-reactive protein; GFR — glomerular filtration rate; LDH — lactate dehydrogenase; SOFA — Sequential Organ Failure Assessment.

Table 3. Prognosis of hospital mortality patterns in COVID-19 patients

Predictors	Cross-validation		Final testing	
	AUC	AUC	Sen	Spec
SOFA				
SOFA	0.78 (0.775; 0.786)	0.779 (0.76; 0.798)	0.715 (0.688; 0.741)	0.713 (0.683; 0.732)
SOFA + MV	0.858 (0.856; 0.863)	0.875 (0.859; 0.89)	0.797(0.773; 0.822)	0.797 (0.765; 0.82)
SOFA + MV + CRP	0.899 (0.894; 0.903)	0.896 (0.883; 0.91)	0.8 (0.774; 0.827)	0.802 (0.778; 0.827)
SOFA + MV + CRP + LDH	0.901 (0.896; 0.905)	0.908 (0.896; 0.92)	0.81 (0.785; 0.835)	0.804 (0.775; 0.832)
APACHE II				
APACHE II	0.929 (0.925; 0.933)	0.936 (0.929; 0.944)	0.836 (0.815; 0.86)	0.839 (0.818; 0.86)
APACHE II + MV	0.953 (0.949; 0.956)	0.96 (0.952; 0.968)	0.871 (0.848; 0.893)	0.887 (0.874; 0.9)
Age, MV, lack of indications for high-flow oxygen therapy, male sex, procalcitonin, urea, LDH				
	0.921 (0.918; 0.925)	0.935 (0.925; 0.946)	0.837 (0.812; 0.862)	0.825 (0.798; 0.852)

Note: APACHE II — Acute Physiology and Chronic Health Evaluation II; AUC — area under the receiver operating characteristic curve; CRP — C-reactive protein; LDH — lactate dehydrogenase; MV — mechanical ventilation; Sen — sensitivity; SOFA — Sequential Organ Failure Assessment; Spec — specificity.

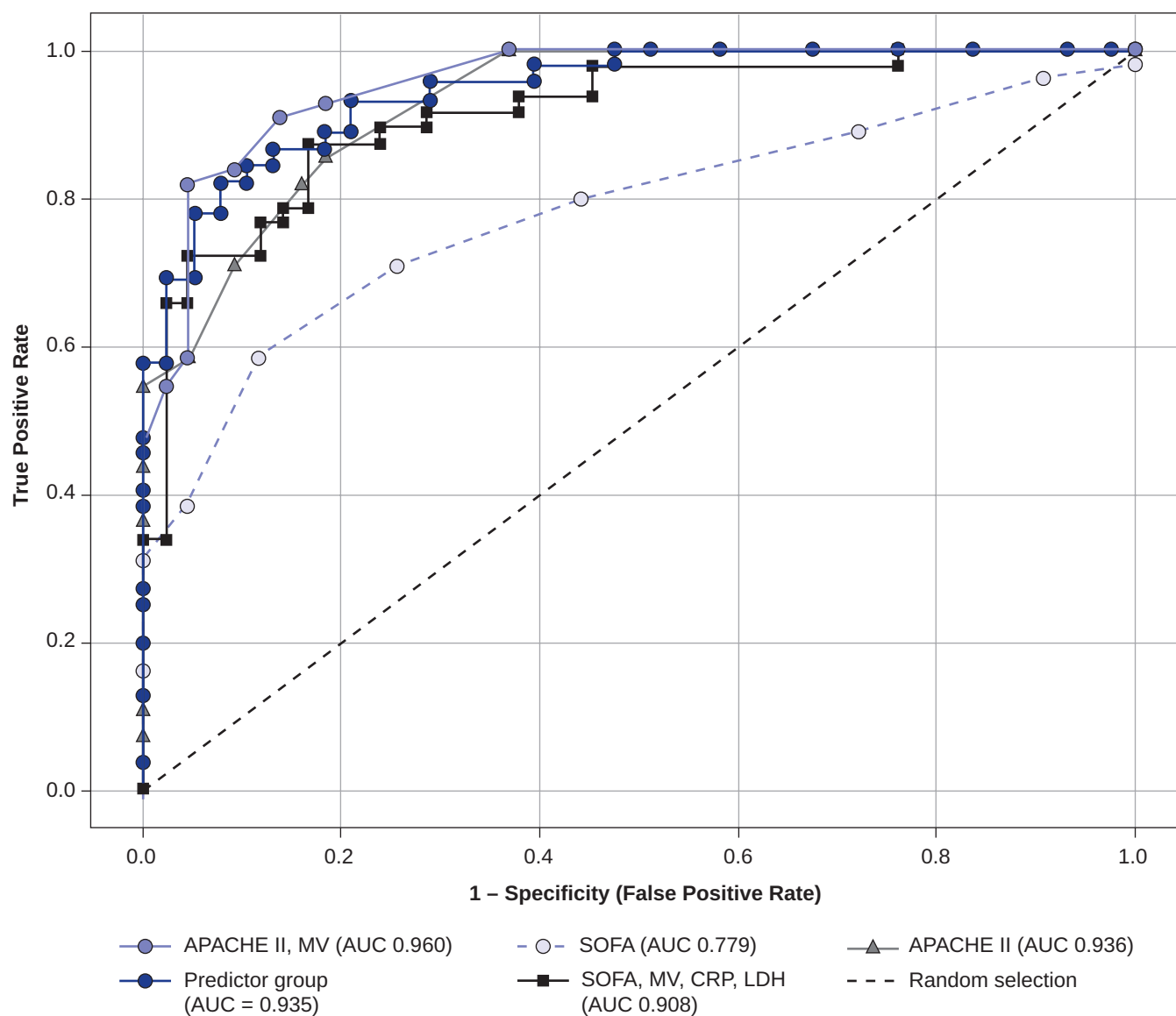


Fig. 2. ROC curves of five predictive models

Note: APACHE II — Acute Physiology and Chronic Health Evaluation II; AUC — area under the ROC curve; CRP — C-reactive protein; LDH — lactate dehydrogenase; MV — mechanical ventilation; SOFA — Sequential Organ Failure Assessment.

demonstrated excellent calibration for the best SOFA-based model ($p = 0.6$) and good calibration for the authors' Model 3 ($p = 0.373$), whereas Model 2 based on APACHE showed a statistically significant discrepancy between observed and predicted values ($p = 0.035$).

Discussion

In recent years, predictive analytics methods have been increasingly used in clinical medicine, which is confirmed by an increasing number of scientific studies on this issue. Most of the current predictive models have been developed using modern machine learning methods and are characterized by good ($0.8 < \text{AUC} < 0.9$) and excellent ($\text{AUC} > 0.9$)

accuracy of the generated conclusions. An important area of risk stratification is the development of prognostic tools for assessing the risk of adverse outcomes in patients treated in the ICU [7, 8, 13, 21]. In our study, the SOFA and APACHE II scores demonstrated high predictive accuracy for adverse outcomes in patients with severe COVID-19, both during initial ICU assessment and when incorporated as predictors in prognostic models. These data are also confirmed by the results of other studies. So, in a meta-analysis including 27 studies and 6 clinical case series ($n = 42,219$), Qian Z. et al. reported a negative mean difference (MD) between survivors and non-survivors for both the APACHE II score (MD -4.90 ; 95% CI from -6.54 to -3.27) and the SOFA score (MD -2.27 ; 95% CI from -2.95 to -1.59) [22]. Eldaboosy S. et al. reported a positive correlation between

mortality and APACHE II score. In critically ill patients, an APACHE II score ≥ 25 was associated with a mortality rate of 50 %, whereas scores > 35 were associated with an increased mortality rate of up to 80 % [23]. In our study, analysis of demographic characteristics showed that mortality from COVID-19 was 6.8 times higher in men than in women, whereas age was not significantly associated with adverse outcomes. However, analysis of mortality in the initial cohort of patients ($n = 163$) in 2024 revealed the following sex distribution: 54 men (33.1 %) and 30 women (23.3 %). Further investigation of the association between sex and mortality requires a larger patient cohort. The results of the meta-analysis of Bepouka B. et al. [24], which included 12 studies ($n = 42,219$), demonstrate that hospital mortality in males with COVID-19 is significantly higher (OR 1.52; 95% CI 1.04–2.00). In another meta-analysis, the risk of death was also closely related to the male sex: OR 1.45; 95% CI 1.41–1.51; relative risk 1.24; 95% CI 1.07–1.41 [25].

In our study, all patients admitted to the ICU with severe respiratory failure and hypoxemia received respiratory support within the first 24 hours, including invasive mechanical ventilation (40 %), noninvasive ventilation (21 %), and high-flow oxygen therapy (39 %). The overall mortality rate in patients was 57 %, while the mortality rate in patients on mechanical ventilation reached 99.4 % ($p < 0.000001$). The results of a meta-analysis conducted by Lim Z. et al. [26] according to 69 studies ($n = 57,420$), showed that in patients with severe COVID-19 on mechanical ventilation, mortality is 45 % (39–52 %). Notably, in-hospital mortality in COVID-19 varied across studies from 47.9 % (46.4–49.4 %) to 84.4 % (83.3–85.4 %), depending on patient cohorts, healthcare resource availability, and other factors. In the meta-analysis of Chang R. et al. [27] performed on the data of 28 studies ($n = 12,437$), the mortality rate in cohorts of patients on mechanical ventilation ranged from 43 % (29–58 %) to 69 % (61–75 %). Procalcitonin, creatinine, urea, C-reactive protein, and lactate dehydrogenase levels were positively associated with mortality, while glomerular filtration rate showed a negative association. In a meta-analysis by Zheng Z. et al. [28], which included 13 studies ($n = 3,027$), the risk of adverse outcomes was significantly higher in patients with procalcitonin levels > 0.5 ng/mL (OR 43.24; 95% CI 9.92–188.49; $p < 0.00001$) and creatinine levels ≥ 133 $\mu\text{mol/L}$ (OR 5.30; 95% CI 2.19–12.83; $p = 0.0002$). It should also be noted that D-dimer, AST, and ALT levels did not have a statistically significant association with the study endpoint, distinguishing our findings from those of several other studies [28, 29].

Comparative analysis of prognostic models for in-hospital mortality demonstrated that the model in-

cluding APACHE II score and invasive mechanical ventilation achieved the highest predictive performance (AUC 0.96). Multivariable models incorporating SOFA score, invasive mechanical ventilation, C-reactive protein, and lactate dehydrogenase (AUC 0.908), as well as models including age, male sex, invasive mechanical ventilation, oxygen therapy, procalcitonin, urea, and lactate dehydrogenase (AUC 0.936), demonstrated slightly lower but comparable predictive accuracy, corresponding to an excellent level of discrimination. Calibration analysis showed that the SOFA-based model and the authors' model exhibited no statistically significant deviation from ideal calibration, indicating that their predicted probabilities were reliable. At the same time, the APACHE-based model has statistically significant deviations from the ideal calibration with a good Brier estimate, which may indicate calibration problems in certain probability ranges.

Conflicting findings and evolving temporal trends of established risk factors reported in the literature suggest that the clinical presentation of severe COVID-19, patient characteristics, and potentially the virulence of the pathogen have changed over time, contributing to variability in predictors of adverse outcomes throughout the course of the pandemic. During the first and second pandemic waves, isolated acute respiratory failure was the predominant clinical presentation and was not associated with sex or age. In contrast, during subsequent waves, patients were more likely to present with multiple comorbidities, multiorgan dysfunction, and advanced age.

The limitations of the study are related to the insufficient sample size, the retrospective nature of the study, and the need to expand the range of analyzed indicators and machine learning methods.

Conclusion

Through a multistep selection process, key demographic and clinical-laboratory variables with predictive value were identified and incorporated into prognostic models for in-hospital mortality in patients with severe COVID-19. The APACHE II and SOFA scores are reliable tools for risk stratification of adverse outcomes in this disease. Indicators of renal injury, CRP and LDH were also found to be reliable markers of an unfavorable outcome. Further analysis of the predictive value of risk factors for adverse outcomes in severe COVID-19 and the development of new prognostic models based on modern machine learning methods remain important tasks in clinical medicine.

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