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ORIGINAL RESEARCH

Clinical Characteristics and Prognostic Factors of Severe COVID-19

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Purpose: Coronavirus disease-2019 (COVID-19) has high mortality and has caused heavy economic burden worldwide. In this study, we investigated the clinical characteristic and prognostic factors of patients with severe COVID-19. We aimed to identify the severe cases in early stages to improve the prognosis and mortality.

Patients and Methods: We collected the clinical data of 98 patients with severe COVID-19, who were admitted to the Second Affiliated Hospital of Soochow University (Jiangsu, China) from December 2022 to November 2023. The patients were divided into two groups, namely survivors and non-survivors, based on the outcomes of hospitalization. The risk factors affecting the prognosis of severe COVID-19 patients were identified by univariate analysis and multivariate logistic regression analysis. The predictive value of the individual and combined risk factors for the prognosis of severe COVID-19 was evaluated by the area under the receiver operating characteristic curve (AUROC).

Results: Compared with survivors, non-survivors had higher white blood cell (WBC) count, neutrophil count, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and platelet (PLT) count. Moreover, non-survivors exhibited a higher propensity to develop acute kidney injury (AKI) and receive mechanical ventilation (MV) and continuous renal replacement therapy (CRRT). Multivariate logistic regression analysis showed that WBC count, PLT count, APACHE II score, and MV were independent risk factors affecting the prognosis of severe COVID-19 patients, with AUC values of 0.807, 0.690, 0.761, and 0.751, respectively. The AUC of the combined risk factors was 0.897.

Conclusion: WBC count, PLT count, APACHE II score, and MV were independent risk factors for the poor prognosis of severe COVID-19 patients. High WBC count, PLT count, and APACHE II score, as well as the use of MV, showed good predictive value for the mortality of severe COVID-19 cases, especially when combined.

Keywords: COVID-19, white blood cell, platelet count, APACHE II score, mechanical ventilation

Introduction

In December 2019, a large number of people contracted unexplained pneumonia in Wuhan, China.[1] Patients exhibited fever, cough, and myalgia or fatigue during the disease onset. Due to the lack of specific treatment options in the early stages, an increasing number of similar cases were identified in China and across the world, with some patients rapidly developing dyspnea or even acute respiratory distress syndrome (ARDS). Deep sequencing analysis from the lower respiratory tract samples of the patients led to the identification of a novel coronavirus.[2] In February 2022, the World Health Organization (WHO) coined the term "COVID-19" for the pneumonia caused by the novel coronavirus. Based on the severity of the disease, COVID-19 could be classified as mild (laboratory confirmed, without pneumonia), moderate (laboratory confirmed and with pneumonia), severe, and critical (respiratory failure requiring mechanical ventilation, shock, or other organ failure that requires intensive care).[3] Severe COVID-19 patients had poor prognosis and high mortality rates, which imposed a heavy burden on the global healthcare systems and economy.[4] Previous studies had discovered partial clinical and laboratory characteristics which were associated with mortality in COVID-19. WBC count, neutrophil count, PLT count, APACHE II

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score, AKI and the use of MV and CRRT are associated with COVID-19.[5–11] However, not enough studies discovered the predictive value of WBC count, PLT count, APACHE II score and the use of MV in severe COVID-19 and the combined diagnostic value of these four risk factors has not yet been reported. Therefore, in this study, we analyzed the clinical characteristics and prognostic risk factors of severe COVID-19 to improve our understanding of severe COVID-19 and to develop effective treatments to prevent and minimize its progression.

Materials and Methods

Study Design and Patients

We retrospectively analyzed 98 adult patients diagnosed with severe COVID-19, who were admitted to the Second Affiliated Hospital of Soochow University (Jiangsu, China) between December 2022 to November 2023. According to the guidelines provided by the China National Health Commission,[12] COVID-19 diagnosis was based on the results of real-time reverse transcription–polymerase chain reaction (RT-PCR) test. Patients were considered to have severe COVID-19 if they satisfied any of the following criteria: (a) exhibited respiratory distress (respiratory rate ≥ 30 beats/min); (b) had ≤ 93% mean oxygen saturation in the resting state; (c) had a ≤ 300 mmHg (1 mmHg = 0.133 kPa) ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2); (d) exhibited respiratory failure and required mechanical ventilation (MV); (e) exhibited shock; (f) exhibited organ dysfunction and required ICU admission.

Data Collection

The following data was collected for each patient: age, body mass index (BMI), gender, chronic medical histories (hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease [COPD], malignancy, chronic kidney disease, neurological disease, immune system disease, and long-term glucocorticoid administration), symptoms from onset to hospital admission (fever, cough, hemoptysis, chest tightness, and chest pain), laboratory values on admission (white blood cells [WBC] count, neutrophil count, platelet [PLT] count, PaO2/FiO2, lactate dehydrogenase [LDH] level, D-dimer level, C-reactive protein [CRP] concentration, interleukin-6 [IL-6] level, procalcitonin [PCT] concentration, brain natriuretic peptide [BNP] level, and APACHE II score), comorbidities (acute kidney injury [AKI], liver dysfunction, Aspergillus infection, and hypoalbuminemia), and treatments (mechanical ventilation [MV], continuous renal replacement therapy [CRRT], antiviral treatment, antifungal treatment, glucocorticoid treatment, sivelestat sodium treatment, and tocilizumab treatment). This study was granted ethical approval (JD-LK2023025-I01) by the Ethics Committee of the Second Affiliated Hospital of Soochow University. Informed consent was obtained by all living patients. For patients who died, informed consent was obtained from a family member.

Statistical Analysis

Statistical analysis was performed using the SPSS v26 software (SPSS, Inc., Chicago, IL, USA). Normally distributed measurement data were presented as the mean ± standard deviation and compared using the independent samples *t* test; otherwise, the data were presented as the median and interquartile range and Wilcoxon rank sum test was used. Count data were presented as n or n (%) and compared using the Chi-squared (χ^2) test or Fisher's exact test. The independent risk factors influencing the adverse outcomes of severe COVID-19 patients were analyzed using the multivariate logistic regression analysis. MedCalc was used to draw the receiver operating characteristic (ROC) curves to evaluate the predictive value of the risk factors. The P value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 98 patients included in the study, 27 had died. The survivor and non-survivor groups showed no significant difference in age, BMI, gender, underlying disease, long-term glucocorticoid administration, neutrophil count, PaO2/FiO2, LDH level, CRP concentration, D-dimer level, IL-6 level, PCT concentration, and BNP level (P > 0.05; Tables 1 and 2). However, the survivor and non-survivor groups showed a significant difference in the WBC count, PLT count,

Table 1 Demographic and Baseline Characteristics of Severe COVID-19 Patients

Indicators	Survivors (n = 71)	Non-survivors (n = 27)	t/Z/χ^2	P-value
Age (y)	78.00 (69.00, 84.00)	76.62 ± 6.40	−0.08	0.937
BMI	22.84 ± 3.33	23.70 ± 4.37	−1.051	0.296
Gender			0.333	0.564
Male	54 (76.1%)	19 (70.4%)		
Female	17 (23.9%)	8 (29.6%)		
Underlying diseases				
Hypertension	51 (71.8%)	23 (85.2%)	1.886	0.170
Diabetes	22 (31.0%)	10 (37.0%)	0.326	0.568
Cardiovascular disease	6 (8.5%)	2 (7.4%)	0.000	1.000
COPD	3 (4.2%)	0 (0.0%)	-	0.559
Malignancy	10 (14.1%)	4 (14.8%)	0.000	1.000
Chronic kidney disease	5 (7.0%)	5 (18.5%)	1.699	0.192
Neurological disease	19 (26.8%)	9 (33.3%)	0.414	0.520
Immune system disease	9 (12.7%)	1 (3.7%)	0.879	0.349
Long-term glucocorticoid administration	4 (5.6%)	0 (0.0%)	0.473	0.491

Note: -: Fisher's exact test.
Abbreviations: BMI, body mass index; COPD, Chronic obstructive pulmonary disease.

Table 2 Laboratory Values of Severe COVID-19 Patients

	Survivors (n = 71)	Non-survivors (n = 27)	Z/χ^2	P-value
WBC count (× 10^9/L)	13.60 (9.70, 16.70)	23.16 ± 9.02	−4.680	<0.001
Neutrophil count (× 10^9/L)	12.00 (7.60, 15.40)	21.26 ± 8.42	−4.775	<0.001
PLT count (× 10^9/L)	164.00 (128.00, 221.00)	228.22 ± 85.83	−2.891	0.004
PaO_2/FiO_2 (mmHg)	203.00 (164.00, 251.00)	182.78 ± 90.69	−1.678	0.093
LDH (mmol/L)	297.00 (249.00, 365.00)	336.00 (236.00, 454.00)	−1.344	0.179
CRP (mg/dL)	68.20 (30.10, 122.10)	94.20 (37.10, 207.90)	−1.223	0.221
D-dimer (ng/mL)	1.41 (0.78, 3.01)	2.01 (1.07, 2.96)	−1.181	0.238
IL-6 (pg/mL)	26.62 (12.10, 59.47)	45.54 (17.16, 262.91)	−1.809	0.070
PCT (ng/mL)	0.25 (0.79, 1.26)	0.38 (0.12, 1.50)	−1.117	0.264
BNP (pg/mL)	570.00 (200.00, 1352.00)	733.00 (268.00, 3370.00)	−1.240	0.215
APACHE II score	9.00 (7.00, 13.00)	14.00 (11.00, 21.00)	−3.999	<0.001

Abbreviations: WBC, white blood cell; PLT, platelet; PaO2/FiO2, partial pressure of arterial oxygen to the fraction of inspired oxygen; LDH, lactate dehydrogenase; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; BNP, brain natriuretic peptide; APACHE II, Acute Physiology and Chronic Health Evaluation II.

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Table 3 Symptoms, Comorbidities, and Treatments of Severe COVID-19 Patients

	Survivors (n = 71)	**Non-survivors (n = 27)**	**Z/χ^2**	**P-value**
Symptoms				
Fever	53 (74.6%)	23 (85.2%)	1.248	0.264
Cough	53 (74.6%)	15 (55.6%)	3.357	0.067
Hemoptysis	2 (2.8%)	1 (3.7%)	-	1.000
Chest tightness	49 (69.0%)	18 (66.7%)	0.050	0.823
Chest pain	4 (5.6%)	1 (3.7%)	0.000	1.000
Comorbidities				
AKI	19 (26.8%)	13 (48.1%)	4.069	0.044
Liver dysfunction	30 (42.3%)	6 (22.2%)	3.377	0.066
Aspergillus infection	19 (26.8%)	7 (25.9%)	0.007	0.933
Hypoalbuminemia	56 (78.9%)	23 (85.2%)	0.499	0.480
Treatment				
MV	9 (12.7%)	17 (63.0%)	25.378	<0.001
CRRT	2 (2.8%)	6 (22.2%)	7.408	0.006
Antiviral treatment	66 (93.0%)	23 (85.2%)	0.638	0.424
Antifungal treatment	36 (50.7%)	19 (70.4%)	3.072	0.080
Glucocorticoid dose for the initial 10 d (mg)	50.00 (37.50, 66.75)	56.33 ± 40.30	−0.235	0.814
Sivelestat sodium treatment	11 (15.5%)	7 (25.9%)	0.809	0.368
Tocilizumab treatment	6 (8.5%)	1 (3.7%)	0.142	0.707

Note: -: Fisher's exact test.
Abbreviations: AKI, acute kidney injury; MV, mechanical ventilation; CRRT, continuous renal replacement therapy.

and APACHE II score ($P < 0.05$; Table 2). AKI was more common in non-survivors than in survivors ($P < 0.05$). Moreover, compared to survivors, non-survivors were more likely to receive MV and CRRT ($P < 0.05$). The glucocorticoid dose for the initial 10 d was generally higher for non-survivors compared to survivors, although the difference was not statistically significant ($P > 0.05$). Furthermore, the survivor and non-survivor groups showed no significant difference in symptoms (fever, cough, hemoptysis, and chest pain), comorbidities (liver dysfunction, Aspergillus infection, and hypoalbuminemia), and treatments (antiviral, antifungal, sivelestat sodium, and tocilizumab treatments) ($P > 0.05$; Table 3).

Prognostic Risk Factors for Severe COVID-19

The variance inflation factor (VIF) test results ranged from 1.119 to 1.647 (<10), indicating that there was no multicollinearity among the variables. Logistic regression analysis showed that WBC count (odds ratio [OR] = 1.272), PLT count (OR = 1.006), APACHE II score (OR = 1.207), and MV (OR = 6.960) were independent risk factors for the poor prognosis of severe COVID-19 patients (Table 4).

Table 4 Multivariate Logistic Regression Analysis of Risk Factors Associated with the Prognosis of Severe COVID-19

Variables	B	SE	Waldχ^2	P-value	OR	95% Confidence Interval
WBC count	0.241	0.070	11.663	0.001	1.272	1.108–1.461
Neutrophil count	−0.053	0.036	2.214	0.137	0.948	0.885–1.017
PLT count	0.006	0.003	4.218	0.040	1.006	1.000–1.013
APACHE II score	0.188	0.080	5.545	0.019	1.207	1.032–1.411
AKI	−0.852	0.867	0.964	0.326	0.427	0.078–2.336
MV	1.940	0.800	5.880	0.015	6.960	1.451–33.392
CRRT	−0.019	1.129	0.000	0.986	0.981	0.107–8.962

Abbreviations: B, regression coefficient; SE, standard error of mean; WBC, white blood cell; PLT, platelet; APACHE II, Acute Physiology and Chronic Health Evaluation II; AKI, acute kidney injury; MV, mechanical ventilation; CRRT, continuous renal replacement therapy.

Predictive Value of the Prognostic Risk Factors

The ROC curve analysis showed that the WBC count, APACHE II score, and MV had good predictive value for the outcomes of severe COVID-19 patients, with the area under the curve (AUC) values of 0.807, 0.761, and 0.751, respectively. PLT count also exhibited a predictive value for the prognosis of severe COVID-19 patients, with an AUC value of 0.690. The AUC of all four risk factors was 0.897, which was higher than that of any single factor ($Z = 2.235$, 3.452, 2.604, and 3.374, $P < 0.05$; Table 5 and Figure 1).

Discussion

This retrospective study identified clinical characteristics and prognostic risk factors of severe COVID-19. The identified risk factors may enable the identification of potential severe COVID-19 patients in the early stages. Our results showed that high WBC count, neutrophil count, PLT count, and APACHE II score at baseline were associated with worse outcomes in COVID-19 patients. Additionally, COVID-19 patients who underwent MV and CRRT treatments had a greater chance of mortality. In addition to being independent risk factors, WBC count, PLT count, APACHE II score, and MV showed good predictive value for the outcomes of severe COVID-19 patients. The novelty of our study is that we confirmed the combination of these four risk factors had a higher value and accuracy in predicting the prognosis of severe COVID-19 cases.

Previous studies have found that elevated WBC and neutrophil levels are related to higher mortality of COVID-19 patients and that WBC is an independent risk factor for the death of COVID-19 patients.[5,9] Upon infection, the immune system recognizes the coronavirus particles, triggering a WBC and neutrophil-induced cytokine storm, contributing to

Table 5 ROC Curve Analysis of the Risk Factors Associated with the Prognosis of Severe COVID-19

Variables	AUC	95% Confidence Interval	P-value	Cutoff	Sensitivity (%)	Specificity (%)
WBC count	0.807	0.715–0.880	< 0.01	15.90	81.50	73.20
PLT count	0.690	0.588–0.779	< 0.01	179.00	70.40	62.00
APACHE II score	0.761	0.665–0.842	< 0.01	12.00	66.70	73.20
MV	0.751	0.654–0.833	< 0.01	-	62.96	87.30
Combination	0.897	0.819–0.949	< 0.01	0.30	81.50	87.30

Abbreviations: WBC, white blood cell; PLT, platelet; APACHE II, Acute Physiology and Chronic Health Evaluation II; MV, mechanical ventilation.

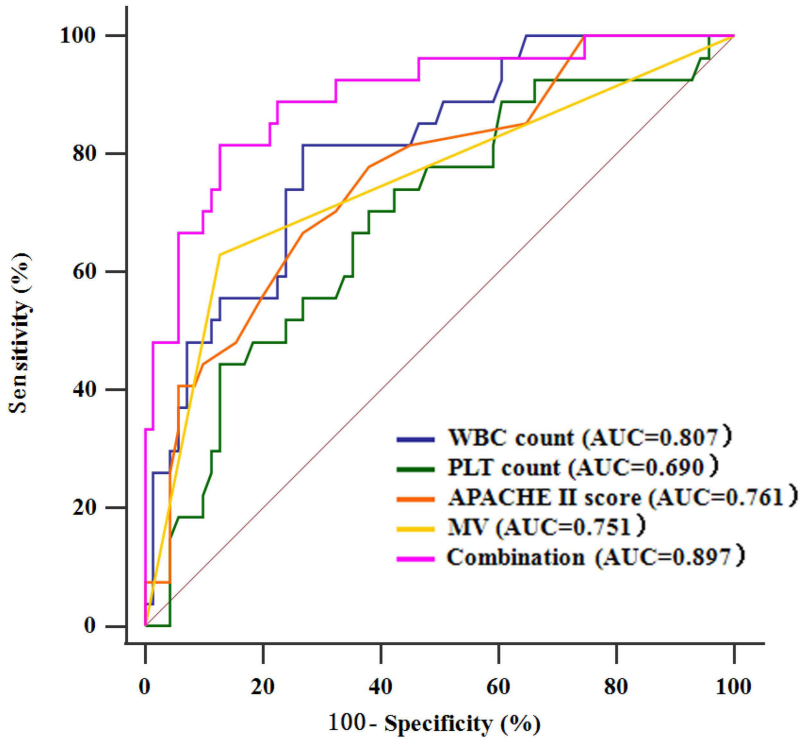

Figure 1 Predictive values of individual risk factors alone and in combination for severe COVID-19 prognosis.
Abbreviations: WBC, white blood cell; PLT, platelet; APACHE II, Acute Physiology and Chronic Health Evaluation II; MV, mechanical ventilation.

severe lung damage or ARDS in extreme cases.[13,14] Our study confirmed that WBC and neutrophils were elevated in the non-survivor group. Additionally, our results showed that high WBC level was an independent risk factor (OR = 1.272) and a reliable predictive parameter for the mortality of severe COVID-19 patients. Specifically, for each unit increase in WBC count, the risk of death of severe COVID-19 patients increased by 1.272 times. Therefore, paying close attention to the changes in WBC and neutrophil levels may reduce the mortality rate of severe COVID-19 patients by ensuring timely treatment.

Previous studies reported lower PLT counts in severe COVID-19 cases.[15–18] In contrast, our study found that PLT count was elevated among the non-surviving severe COVID-19 patients, consistent with the results of Yang et al.[6] One explanation for this may be that as China announced new measures in December 2022, while rolling back COVID-19 restrictions, the novel coronavirus mutated during transmission.[5] Besides, previous study has found that the PLT count of COVID-19 patients increased rapidly before the development of severe symptoms, reaching the highest level at 11–15 d after admission, and then declined rapidly,[16] indicating that PLT count may decrease after the development of severe symptoms. In our study, PLT count was recorded upon admission. Therefore, dynamic changes in PLT count in severe COVID-19 cases may be more meaningful for predicting their prognosis. Our study showed that PLT count was an independent risk factor for the prognosis of severe COVID-19 patients (OR = 1.006). Specifically, for each unit increase in PLT count, the risk of death increased by 1.006 times in severe COVID-19 cases. Therefore, PLT count may serve as a predictive factor for the prognosis of severe COVID-19 patients.

APACHE II score is a scoring system based on age, physiologic measurements, and past medical history, and it is widely used to evaluate disease severity and hospital mortality in patients with serious diseases.[19–21] Zou et al[22] found that the APACHE II score can predict hospital mortality, with an APACHE II score > 17 indicating the possibility of particularly poor outcomes. Tameshkel et al[23] found that a high APACHE II score is associated with intubation as well as prolonged intubation time. Consistent with previous research,[21] our results revealed that the APACHE II score was significantly higher in the non-survivor group compared to the survivor group and that it may predict the risk of mortality in severe COVID-19 (OR = 1.207) cases. For each unit increase in the APACHE II score, the risk of death increased by 1.207 times in the severe COVID-19

cases. Notably, our research subjects were severe cases, these patients had more severe symptoms and higher mortality, so it was crucial to identify them, especially in the early time when medical resources were scarce. The APACHE II score calculated within 24 h of hospital admission showed a good predictive value in severe COVID-19 cases. Further research is required to explore whether the APACHE II score may be used to decrease mortality and improve the clinical outcomes of severe COVID-19 patients.

Dyspnea can result in respiratory failure and ARDS in severe COVID-19 patients during hospitalization.[24] Long-term low oxygen saturation in multiple organ systems and MV are associated with high mortality and increased hospital stay duration in patients with COVID-19.[8,25–28] MV plays an important role in the treatment of severe COVID-19 patients.[29] Our findings showed that MV was more frequently used for non-survivor patients and that it was an independent risk factor for the outcomes of severe COVID-19 patients (OR = 6.960), with good predictive value. Specifically, the risk of death increased by 6.960 times when severe COVID-19 patients received MV treatment. MV is used to provide adequate gas exchange and to avoid ventilator-induced lung injury. However, there are a few complications to MV treatment. Late intubation causes aggravated lung injury and increases the risk of mortality among patients. While early intubation exposes the patients to unnecessary deep sedation, neuromuscular blockade, and ventilator-associated complications.[30] Therefore, further studies are required to determine the effective use of MV for hypoxemic patients with severe COVID-19.

COVID-19 is a systemic disease that affects multiple organ systems.[31,32] Our study found that AKI was an independent risk factor for the mortality of severe COVID-19 patients. AKI can be induced by inflammatory stress, including angiotensin II and hypertensive stress, diabetes-related metabolic stress, cytokine storm, high CRP level, over-reactive TGF-β signaling, complement activation, and lung-kidney crosstalk.[10] Among the severe COVID-19 patients with AKI, CRRT was more frequently used for patients receiving MV. MV may affect kidney function by reducing kidney perfusion and glomerular filtration.[11] Our study found that AKI was more common in non-survivors compared to survivors, consistent with a previous study.[33] Notably, we found that CRRT was associated with poor outcomes in severe COVID-19 patients. One possible explanation for this may be the delayed application of CRRT for beneficial outcomes. However, whether CRRT can improve the progression of AKI in COVID patients remains to be determined. Early detection and treatment of kidney abnormalities, such as avoidance of nephrotoxic drugs and adequate hemodynamic support, as well as appropriate CRRT application time need to be investigated further.

Previous studies have reported that WBC count, PLT count, APACHE II score, and MV are associated with COVID-19. The combination of fibrinogen-to-albumin ratio and PLT level can predict the development of severe COVID-19 cases (AUC = 0.754).[16] However, the combined diagnostic value of WBC count, PLT count, APACHE II score, and MV has not yet been demonstrated up to now. The results of our study showed that the combination of these four risk factors had a higher value and accuracy in predicting the prognosis of severe COVID-19 cases (AUC = 0.897) compared to the individual factors, with sensitivity and specificity of 81.50% and 87.30%, respectively. Consequently, a combination of WBC count, PLT count, APACHE II score, and MV can be used to identify potential severe COVID-19 cases in the early stages.

Our study has some limitations. First, because the OR value of PLT count was slight, its value as a prognostic indicator alone may be limited. Our study is a single-center retrospective study with a small sample size, which may limit the reliability and universality of our results. Second, there was limited information on the clinical outcomes of the patients owing to the retrospective nature of this study. Further studies should explore the effect of more specific information such as IL-10, CD4 T lymphocyte, and CD8 T lymphocyte levels in the prognosis of severe COVID-19 patients. Third, there were no records of the clinical data of patients after discharge, so we could not investigate the factors associated with the long-term outcomes of COVID-19.

Conclusions

Our study found that WBC count, PLT count, APACHE II score, and MV were independent risk factors for the prognosis of severe COVID-19 cases. These four indicators could be used independently or in combination to predict the outcomes of severe COVID-19 patients; moreover, they showed a higher predictive value upon combined application. Notably, COVID-19 has not been eliminated, and long COVID remains a challenge worldwide.[34] The results of our study may enable the identification of potential severe COVID-19 patients in the early stages, which may contribute to the decrease

in COVID-19-related mortality in China as well as other countries. Further studies need to be conducted to explore whether WBC count, PLT count, APACHE II score, and MV are associated with long COVID.

Abbreviations

COVID-19, Coronavirus disease 2019; AUROC, area under the receiver operating characteristic curve; WBC, white blood cell; APACHE II, Acute Physiology and Chronic Health Evaluation II; PLT, platelet; AKI, acute kidney injury; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; ARDS, acute respiratory distress syndrome; RT-PCR, real-time reverse-transcriptase–polymerase-chain-reaction; PaO2/FiO2, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin; BNP, brain natriuretic peptide; ROC, receiver operating characteristic; OR, odds ratio; AUC, area under the curve; B, regression coefficient; SE, standard error of mean.

Data Sharing Statement

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was performed in accordance with the Declaration of Helsinki and granted ethical approval (JD-LK2023025-I01) by the Ethics Committee of the Second Affiliated Hospital of Soochow University. Informed consent was obtained by all living patients. For patients who died, informed consent was obtained from a family member.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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