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Coronavirus Pandemic

Clinical characteristics and risk factors for prediction of severity in patients with COVID-19: a retrospective multicentre study

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Abstract

Introduction: This study aimed to investigate the clinical characteristics of patients infected with coronavirus disease 2019 (COVID-19) and to identify risk factors associated with severe infection among Chinese patients.

Methodology: We collected demographic data, clinical characteristics, and laboratory test results at admission for COVID-19 patients hospitalized in one of two designated tertiary hospitals in Yili Prefecture, Xinjiang Province, between July 2022 and October 2022. Patients were categorized into Group A (asymptomatic, mild, and moderate cases) and Group B (severe and critical cases) based on disease severity. Multivariate regression analysis was conducted to identify risk factors for severe disease, and a nomogram prediction model was developed using these factors. Additionally, stratified analyses were performed by comorbidity status.

Results: Multivariate analysis indicated that older age, male sex, elevated urea nitrogen, higher D-dimer levels, and combined laboratory parameters at admission were positively associated with disease severity. The predictive performance of these factors, measured by area under the curve, was 0.872 (95% CI: 0.819–0.925), 0.613 (95% CI: 0.514–0.712), 0.813 (95% CI: 0.724–0.902), 0.790 (95% CI: 0.717–0.862), and 0.931 (95% CI: 0.891–0.971), respectively. Conversely, vaccination appeared to mitigate progression to severe disease to some extent.

Conclusions: Patient age, sex, urea nitrogen, D-dimer, and serum creatinine levels at admission, as well as vaccination status and comorbidities, significantly influence disease progression in COVID-19 patients. Clinical management can be optimized by tailoring early warning systems and intervention strategies based on these patient-specific risk factors, thereby supporting informed decisions for diagnosis, treatment, prevention, and control.

Key words: COVID-19 infection; clinical characteristics; risk factors; disease severity; comorbidity.

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Introduction

Coronavirus disease 2019 (COVID-19) continues to pose a global public health challenge since its emergence in 2019. Over time, multiple mutant strains have appeared, exhibiting varying degrees of transmissibility, pathogenicity, and immunogenicity [1]. The B.1.1.529 variant, first identified in South Africa in November 2021, was classified by the World Health Organisation (WHO) as a variant "of concern" and named Omicron. Its numerous sublineages have gradually become the dominant circulating severe acute respiratory syndrome (SARS-CoV-2) variants worldwide. According to a report published on June 25, 2024, in the Health Day section of U.S. News & World Report, COVID-19 infections are rising again in the United States, driven by hot weather, increased travel, and family gatherings. Data from the U.S. Centres for Disease Control and Prevention (CDC) indicate a 25% increase in hospitalizations from May 26 to June 1, suggesting no clear decline in case numbers. Similarly, Spain's Instituto de Salud Carlos III, through its surveillance system for acute respiratory infections, reported that the COVID-19 incidence rate rose from 136.9 to 151 cases per 100,000 people between June 17 and 23, 2024. In China, the Chinese CDC recorded 157 new severe cases and eight deaths from May 1 to May 31, 2024, including two deaths from respiratory failure due to COVID-19 and six deaths from COVID-19 combined with underlying conditions. The positive rate for SARS-CoV-2 among influenza-like illness cases also increased, from 8.9% during July 1–7 to 18.7% during July 22–28. These data underscore that COVID-19 remains a significant ongoing threat to global health.

The clinical severity of COVID-19 ranges from asymptomatic or mild symptoms to severe and critical illness [2]. Although most patients experience mild symptoms and the overall morbidity and mortality are lower than those of Middle East respiratory syndrome

and SARS, COVID-19 is highly contagious, largely due to asymptomatic and presymptomatic transmission. In China, among 72,314 reported cases, approximately 81% were classified as mild, 14% as severe, and 5% as critical [3]. Studies have also indicated that asymptomatic or mildly symptomatic cases account for 30%–60% of all infections [4,5]. While most cases are mild and self-limiting, a subset of patients may progress rapidly to acute respiratory distress syndrome (ARDS) [6] and subsequently develop multiorgan dysfunction syndrome, which can involve concurrent cardiovascular impairment, acute kidney injury (AKI), hepatic dysfunction, and coagulopathy. Multiple studies have identified advanced age (≥ 65 years) and pre-existing conditions such as hypertension, diabetes mellitus, or cardiovascular disease as significant risk factors for severe COVID-19 outcomes [7]. Vaccination has been shown to play a critical role in reducing both morbidity and mortality [8].

Although immunity, vaccination, and the natural attenuation of viral virulence have reduced overall disease severity, risk prediction remains critical for identifying patients at high risk of developing severe COVID-19, including ARDS [9]. Early and rapid identification of high-risk individuals is essential to guide timely preventive measures and therapeutic interventions. Without prompt and appropriate care, outcomes for these patients can be poor, underscoring the importance of targeted risk stratification in clinical management.

Therefore, the timely identification of clinical warning signs is crucial for the early intervention of patients at risk of progressing to severe or critical illness. While previous studies have described the epidemiological features and clinical characteristics of COVID-19, well-defined risk factors for adverse clinical outcomes remain limited.

Objectives

This study aimed to characterize the clinical and laboratory features of COVID-19 patients and to examine their association with disease severity in two tertiary hospitals in Yili Prefecture.

Methodology

Study Design

We conducted a retrospective, multicenter study of consecutive patients with suspected COVID-19 (n = 1,110) admitted to two national-level sentinel tertiary hospitals between July 30 and October 19, 2022. Inclusion criteria were: (1) positive nasopharyngeal swab results by reverse transcriptase polymerase chain reaction (RT-PCR); and (2) availability of complete clinical data. Exclusion criteria were: (1) negative RT-PCR results from nasopharyngeal swabs; and (2) incomplete clinical data. SARS-CoV-2 infection was confirmed by RT-PCR using DaAn Gene assays (Cat# DA0931; target genes: ORF1ab/N). Positivity was defined as cycle threshold (Ct) values ≤ 35 for the ORF1ab and/or N gene(s), with single-target positivity requiring retest confirmation, in accordance with the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 9) issued by China's National Health Commission [10].

All procedures involving human participants were conducted in accordance with the ethical standards of the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region and the 1964 Helsinki Declaration, including its later amendments or comparable ethical standards. The study protocol was approved by the hospital's ethical review board (Ethical Approval No. KY2024051001). Written informed consent to participate was obtained from all participants or their legal guardians.

COVID-19 patients were classified according to the 9th edition of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia issued by China's National Health Commission [10]. Asymptomatic infection: Patients with a positive RT-PCR test for SARS-CoV-2 in respiratory or other specimens, but without clinical symptoms such as fever, sore throat, or dry cough, and no radiological features of COVID-19 on computed tomography (CT) imaging. Mild type: Patients exhibiting mild clinical symptoms without evidence of pneumonia on imaging. Moderate type: Patients presenting with fever and respiratory symptoms, along with radiological signs of pneumonia. Severe type: Patients meeting any of the following criteria: (1) Respiratory rate ≥ 30 breaths/min; (2) Resting oxygen saturation ≤ 93%; (3) PaO_2/FiO_2 (partial pressure of arterial oxygen/fraction of inspired oxygen) ≤ 300 mmHg (1 mmHg = 0.133 kPa); (4) Rapid progression of lung lesions on imaging, with an increase > 50% within 24–48 hours. Critical type: Patients meeting any of the following conditions: (1) Respiratory failure requiring mechanical ventilation; (2) Shock; (3) Multiple organ failure requiring intensive care unit (ICU) treatment.

Patients were discharged when they met all of the following criteria: (1) Body temperature returned to normal and remained stable for more than three days; (2) Respiratory symptoms showed significant improvement; (3) Chest CT imaging demonstrated a reduction in pulmonary exudative lesions.

Data Collection

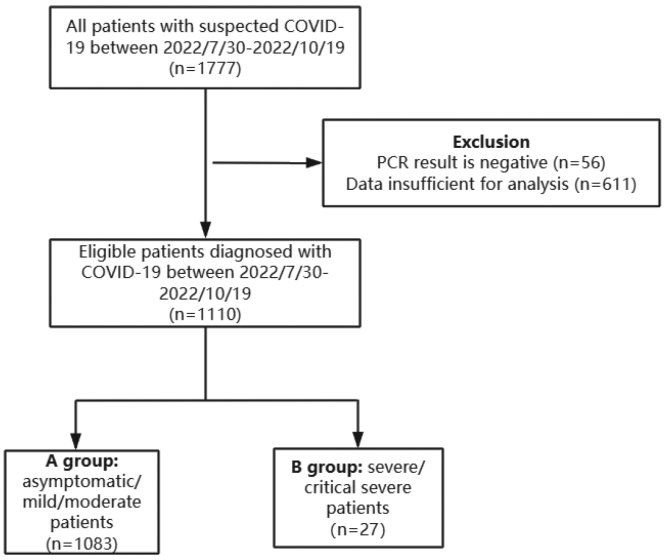
Clinical, demographic, and laboratory data were collected from electronic medical records and through interviews with attending physicians. Data collection was conducted by a team of trained physicians and medical students. To protect patient privacy, each participant was assigned a unique identifier, and all digital records were stored on a password-protected computer. Nasopharyngeal swab samples were obtained from all patients at admission and tested for SARS-CoV-2 using RT-PCR.

Demographic and laboratory variables recorded on the first day of hospitalization included: Demographic data: age, sex, duration of hospitalization, comorbidities, disease-related anxiety, and vaccination status. Vaccination status was categorized as unvaccinated or vaccinated (at least one dose). Hematological parameters: lymphocyte count (Lyc), platelet count (PLT), white blood cell count (WBC), and neutrophil count. Infection markers: procalcitonin (PCT) and C-reactive protein (CRP). Coagulation profile: D-dimer. Liver and kidney function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (Cr), and blood urea nitrogen (BUN). These variables were analyzed to evaluate their association with COVID-19 disease severity.

Statistical Analysis

Data were entered using Microsoft Excel 2013 and analyzed using SPSS version 24.0 and R version 4.1.0 (Vienna, Austria).

Figure 1. COVID-19 patient enrollment and group stratification.



COVID-19: coronavirus disease 2019; PCR: polymerase chain reaction.

Categorical variables were presented as counts and (%), while continuous variables were expressed as medians with interquartile ranges (IQRs). The normality of continuous variables was assessed using the Shapiro–Wilk test.

Univariate analyses were conducted using the Chi-square (χ^2) test for categorical variables and the Mann–Whitney U test for continuous variables to identify statistically significant factors. Variables showing significance in univariate analysis were then included in multivariate logistic regression models to identify independent risk factors associated with disease severity. Results of the logistic regression were reported as odds ratios (ORs) with 95% confidence intervals (95% CIs).

Collinearity among continuous variables was assessed using the variance inflation factor (VIF), with a threshold of VIF < 10 indicating acceptable collinearity. Given the substantial differences in sample sizes between groups, a less stringent significance level of $p < 0.10$, rather than the conventional $p < 0.05$, was adopted, consistent with recommendations for exploratory analyses involving unequal group sizes. Significant risk factors identified in multivariate analysis were used to construct a nomogram predictive model using the rms package in R. The predictive performance of each parameter was evaluated by plotting receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC). Calibration curves were subsequently generated to assess the reliability and accuracy of the predictive model. To examine whether comorbidities, including hypertension, diabetes mellitus, and chronic obstructive pulmonary disease (COPD), modified these associations, stratified analyses were performed. For these analyses, $p < 0.10$ was considered statistically significant.

Results

Patients' demographics analysis

A total of 1,777 patients suspected of having COVID-19 were initially screened, and after applying exclusion criteria, 1,110 patients meeting the enrollment criteria were included in the study. Patients were assigned to Group A (asymptomatic/mild/moderate; coded as 0) or Group B (severe/critical; coded as 1) based on disease severity (Figure 1). Of these, 1,083 patients were classified into Group A, and 27 patients into Group B. Baseline characteristics of the two groups are summarized in Table 1. In Group A, 568 patients (52.4%) were male and 515 (47.6%) were female, yielding a near 1:1 male-

Table 1. Baseline Characteristics of Patients Infected With COVID-19.

Characteristic	Asymptomatic / Mild / Moderate patients	Severe / Critical Severe patients	χ^2/Z	*p*
Age (years)	37.00 (22.00,60.00)	79.00 (65.00, 82.00)	-6.803	< 0.001***
Duration of treatment (days)	9.00 (7.00,12.00)	7.00 (4.00,13.00)	-1.743	0.081†
Gender, n (%)				
Male	568 (52.4%)	20 (74.1%)	4.946	0.026*
Female	515 (47.6%)	7 (25.9%)		
Fear of illness				
Yes	713 (65.8%)	26 (96.3%)	10.984	< 0.001***
No	370 (34.2%)	1 (3.7%)		
Vaccinate				
Yes	946 (87.3%)	13 (48.1%)	31.191	< 0.001***
No	137 (12.7%)	14 (51.9%)		

Categorical variables are presented as counts (%) and continuous variables are presented as medians (interquartile spacing, IQR). *P* values comparing two groups are derived from χ^2 test, Fisher's exact test, or Mann-Whitney U test. Statistical significance was primarily defined as †$p < 0.1$ (primary threshold), with conventional significance levels denoted as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. COVID-19: coronavirus disease 2019.

to-female ratio, with a median age of 37 years (IQR, 22–60). In Group B, 20 patients (74.1%) were male and 7 (25.9%) were female, with a median age of 79 years (IQR, 65–82). The median duration of hospitalization was 9 days (IQR, 7–12) in Group A and 7 days (IQR, 4–13) in Group B. Disease-related anxiety was reported in 713 patients (65.8%) in Group A and 26 patients (96.3%) in Group B. Regarding vaccination status, 946 patients (87.3%) in Group A and 13 patients (48.1%) in Group B had received at least one dose of a COVID-19 vaccine.

Prognostic Risk Factors for disease severity in COVID-19 patients

To identify risk factors associated with severe COVID-19, univariate and multivariable logistic regression analyses were performed. As shown in Table 1, patients in Group B were significantly older than those in Group A (median age, 79 vs. 37 years) and had a higher proportion of males (74.1% vs. 52.4%), both statistically significant differences. Disease-related anxiety was more prevalent in Group B than in Group A (96.3% vs. 65.8%), whereas vaccination rates were significantly lower in Group B (48.1% vs. 87.3%). Laboratory comparisons between the two groups are summarized in Table 2. Compared with Group A, patients in Group B exhibited significantly higher median values for WBC, 6.60 vs. 5.33 × 109/L, $p = 0.016$), D-dimer (1.66 vs. 0.36 mg/L, $p < 0.001$), PCT, 0.50 vs. 0.30 ng/mL, $p < 0.001$), AST (32.00 vs. 24.10 U/L, $p = 0.002$), BUN, 10.01 vs. 4.69 mmol/L, $p < 0.001$), and Cr, 127.00 vs. 62.00 μmol/L, $p < 0.001$). In contrast, Lyc (1.12 vs. 1.85 × 109/L, $p < 0.001$) and PLT (75.00 vs. 200.00 × 109/L, $p = 0.009$) were significantly lower in Group B. These findings highlight both demographic and laboratory factors that are associated with progression to severe or critical COVID-19.

Thirteen variables identified in univariate analysis were included in the multivariate logistic regression model. Collinearity diagnostics confirmed that all variables had VIF < 10 (Supplementary Table 1), indicating no significant multicollinearity. Although BUN and Cr exhibited moderate collinearity (VIF ~5.7), sensitivity analyses excluding BUN and/or Cr confirmed that the effect estimates for key predictors remained robust (Supplementary Tables 2–4). Multivariate analysis revealed that older age, higher D-

Table 2. Laboratory Findings of Patients Infected With COVID-19.

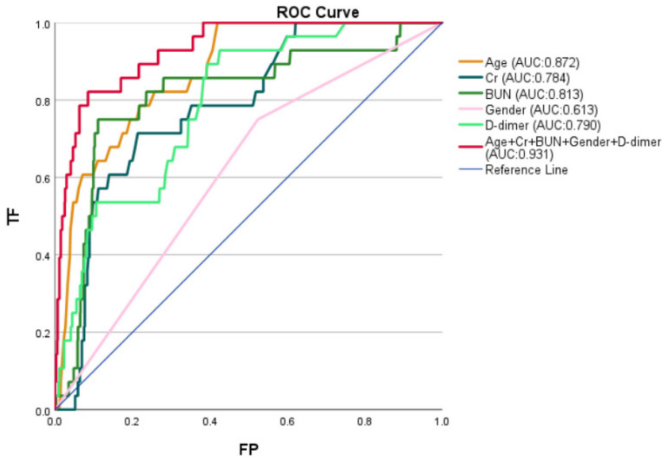
Test	Asymptomatic / Mild / Moderate patients	Severe / Critical Severe patients	Z value	*p*
WBC, *10^9/L	5.33 (4.15, 6.81)	6.60 (4.53, 9.43)	-2.417	0.016*
Lyc, *10^9/L	1.85 (1.2, 3.34)	1.12 (0.69, 1.57)	-4.426	< 0.001***
Neutrophil count, *10^9/L	3.62 (2.28, 7.43)	4.92 (2.91, 8.95)	-1.444	0.149
D-dimer (μg/L)	0.36 (0.20, 0.849)	1.66 (0.59, 3.24)	-5.339	< 0.001***
PCT (ng/mL)	0.30 (0.23, 0.47)	0.50 (0.34, 1.7)	-3.850	< 0.001***
CRP (mg/dL)	6.14 (1.50, 13.00)	6.8 (3.03, 17.30)	-1.035	0.300
PLT, *10^9/L	200 (163.00, 249.00)	175.00 (108.00, 227.00)	-2.604	0.009**
ALT (U/L)	19.00 (13.00, 30.00)	19.00 (11.00, 32.00)	-0.117	0.907
AST (U/L)	24.10 (18.00, 34.00)	32.00 (23.00, 55.00)	-3.027	0.002**
BUN (mmol/L)	4.69 (3.70, 6.06)	10.01 (8.05, 16.32)	-6.026	< 0.001***
Cr (μmol/L)	62.00 (49.00, 79.00)	127.00 (72.50, 166.00)	-5.278	< 0.001***

Data are presented as medians (interquartile spacing, IQR). *p* values comparing two groups are from Mann-Whitney U test. Statistical significance was primarily defined as †$P < 0.1$ (primary threshold), with conventional significance levels denoted as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. COVID-19: coronavirus disease 2019; Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: alanine aminotransferase; ALT: alanine aminotransferase; Cr: creatinine (referring to serum creatinine); BUN: urea nitrogen.

dimer levels, and elevated BUN were associated with increased disease severity (age: OR 1.065, 95% CI 1.032–1.098, $p < 0.001$; D-dimer: OR 1.187, 95% CI 0.978–1.441, $p = 0.083$; BUN: OR 1.291, 95% CI 1.134–1.471, $p < 0.001$). Interestingly, higher Cr levels were inversely associated with disease severity (OR 0.993, 95% CI 0.989–0.997, $p < 0.001$). Male patients were more likely to develop severe disease than female patients (OR 3.924, 95% CI 1.383–11.129, $p = 0.010$). Vaccination was associated with reduced disease severity (OR 0.323, 95% CI 0.108–0.961, $p < 0.001$) (Table 3). The predictive performance of each factor, assessed by ROC curves, showed AUC values of 0.872 (95% CI 0.819–0.925) for age, 0.813 (95% CI 0.724–0.902) for BUN, 0.784 (95% CI 0.709–0.858) for Cr, 0.613 (95% CI 0.514–0.712) for gender, and 0.790 (95% CI 0.717–0.862) for D-dimer (Figure 2). Vaccination was excluded from the combined model due to its negligible discriminative power in univariate ROC analysis (AUC = 0.313; Supplementary Figure 1). The combined model incorporating all selected predictors achieved an AUC of 0.931 (95% CI 0.891–0.971) (Figure 2). Collinearity diagnostics for the predictors in the ROC model are presented (Supplementary Table 5). Sensitivity analyses excluding BUN and/or Cr showed no significant decrease in AUC (all $p > 0.05$, DeLong's test), confirming the stability of the model (Supplementary Figure 2).

A nomogram was subsequently constructed to predict disease severity in COVID-19 patients using the six independently identified risk and protective factors: age, D-dimer, BUN, Cr, gender, and vaccination status (Figure 3). The nomogram assigns points to each predictor based on its value, age (0–100 years, 0–33 points), D-dimer (0–16 μg/mL, 0–23 points), BUN (0–60 mg/dL, 0–100 points), Cr (0–2400 μmol/L, 0–95 points), gender (male: 8 points; female: 0), and vaccination status (unvaccinated: 10 points; vaccinated: 0). The total points, with a theoretical range of 0–289 (displayed as 0–200), correspond to the predicted probability of severe outcomes. By drawing a vertical line from the total points to the "Risk of Event" axis, clinicians can obtain the estimated risk, which is categorized into Low Risk (< 5%), Medium Risk (5–

Figure 2. Receiver operating characteristic (ROC) curves for predicting severe COVID-19 using individual biomarkers and a combined model.



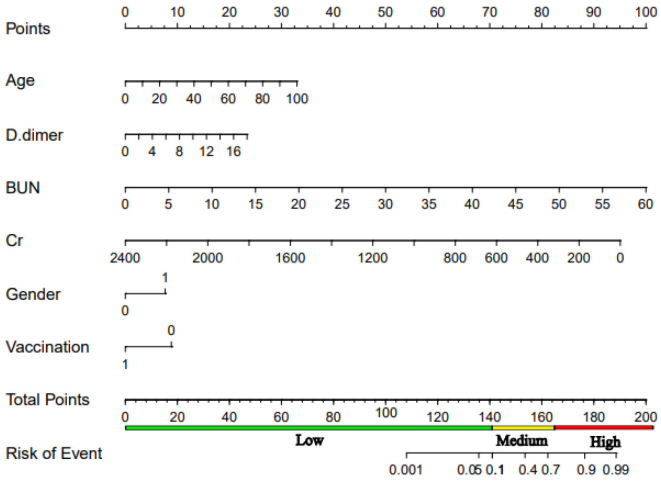
COVID-19: coronavirus disease 2019; AUC: area under the curve; BUN: blood urea nitrogen; Cr: creatinine (referring to serum creatinine); ROC: receiver operating characteristic.

Table 3. Multivariate Logistic regression model for the severity of COVID-19.

Items	Regression coefficient	Standard error	*p*	OR value	OR value with 95%CI
Age (years)	0.063	0.016	< 0.001***	1.065	(1.032,1.098)
WBC, *10^9/L	0.057	0.093	0.538	1.059	(0.882, 1.271)
Lyc, *10^9/L	-0.191	0.295	0.826	0.788	(0.464, 1.473)
D-dimer (μg/L)	0.172	0.099	0.083†	1.187	(0.978, 1.441)
PCT (ng/mL)	-0.001	0.021	0.954	0.999	(0.959, 1.040)
PLT, *10^9/L	-0.002	0.003	0.586	0.998	(0.991, 1.005)
AST (U/L)	0.003	0.005	0.517	1.003	(0.993, 1.014)
BUN (mmol/L)	0.256	0.066	< 0.001***	1.291	(1.134, 1.471)
Cr (μmol/L)	-0.007	0.002	< 0.001***	0.993	(0.989, 0.997)
Duration of treatment (days)	-0.059	0.047	0.214	0.943	(0.860,1.034)
Fear of illness					
Yes	-2.330	1.836	0.204	0.097	(0.003, 3.557)
No*	Reference	Reference	Reference	Reference	Reference
Vaccine					
Yes	-0.678	0.169	< 0.001***	0.323	(0.108, 0.961)
No*	Reference	Reference	Reference	Reference	Reference
Gender					
Male	1.367	0.532	0.010*	3.924	(1.383, 11.129)
Female*	Reference	Reference	Reference	Reference	Reference

*: Control Group. Statistical significance was primarily defined as †$p < 0.1$ (primary threshold), with conventional significance levels denoted as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. COVID-19: coronavirus disease 2019; Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: alanine aminotransferase; ALT: alanine aminotransferase; Cr: creatinine (referring to serum creatinine); BUN: urea nitrogen; CI: confidence interval.

Figure 3. Nomogram for predicting the risk of progression to severe COVID-19 based on six clinical variables.



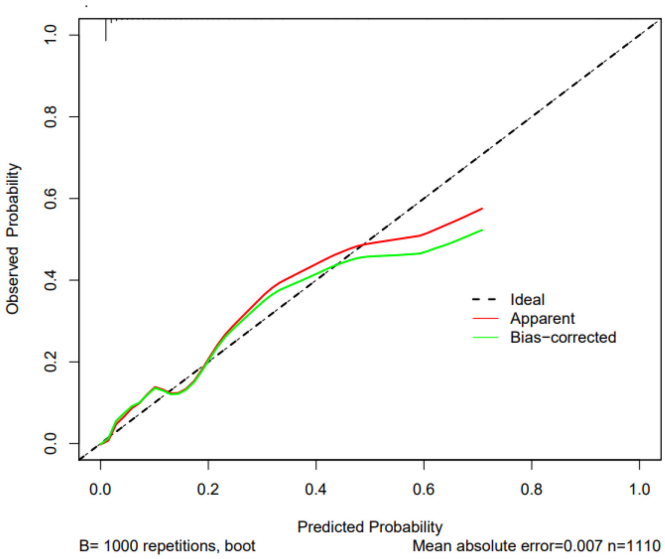
AUC: area under the curve; COVID-19: coronavirus disease 2019; BUN: blood urea nitrogen; Cr: creatinine (referring to serum creatinine).

40%), or High Risk (> 40%) zones as defined on the nomogram. The prognostic performance of COVID-19 severity was best predicted using the combination of age, gender, BUN, D-dimer, and Cr. Calibration curves indicated excellent agreement between predicted and observed outcomes, with no significant deviation from the reference line, confirming the reliability and accuracy of the nomogram (Figure 4).

The relationship between comorbidities and the severity of COVID-19.

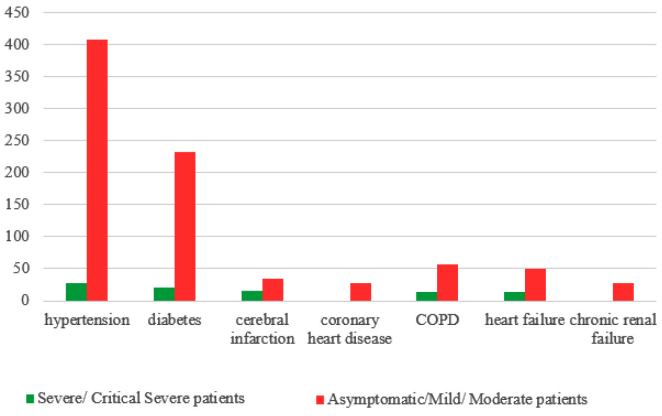
Table 4 summarizes the distribution of comorbidities across the two groups. Among Group A patients, 546 (50.4%) had at least one comorbidity, compared to all 27 patients (100%) in Group B, with all differences statistically significant. Hypertension was the most common comorbidity in both groups, followed by diabetes, COPD, cerebral infarction, and heart failure (Figure 5). To assess the robustness of associations between potential predictors and disease severity in patients with specific comorbidities, subgroup analyses were performed for hypertension,

Figure 4. Calibration curves of the nomogram for predicting severe COVID-19 in the modelling cohort (n = 1,110). The ideal line (grey diagonal) represents perfect agreement between predicted and observed probabilities.



COVID-19: coronavirus disease 2019; MAE: mean absolute error.

Figure 5. Distribution of Severe/Critical Severe Patients (Green Bars) and Asymptomatic/Mild/Moderate Patients (Red Bars) Across Different Comorbidities.



COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019.

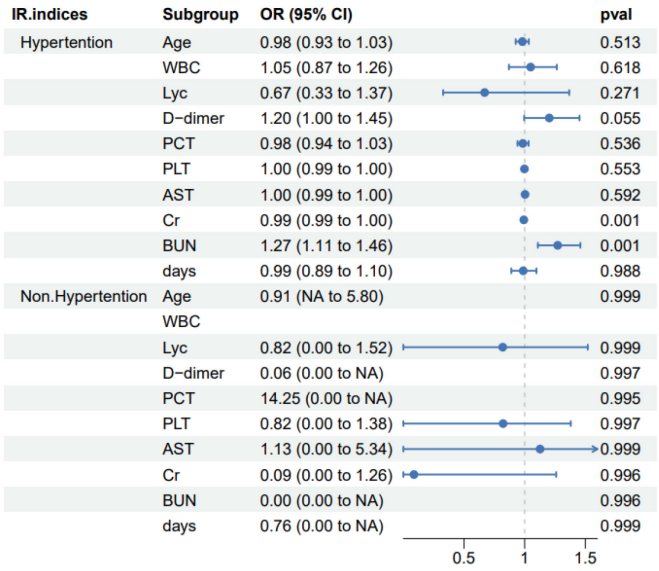
Table 4. Distribution of comorbidities in patients with COVID-19.

Comorbidities	Asymptomatic / Mild / Moderate patients (n = 1083)	Severe / Critical Severe patients (n = 27)	χ^2/Z	p
Any	546 (50.4%)	27 (100%)	25.935	< 0.001***
Hypertension	407 (40.6%)	27 (100%)	38.076	< 0.001***
Diabetes	233 (21.5%)	20 (74.1%)	41.354	< 0.001***
COPD	57 (5.3%)	13 (48.1%)	74.899	< 0.001***
Cerebral infarction	35 (3.2%)	15 (55.6%)	155.720	< 0.001***
Heart failure	50 (4.6%)	14 (51.29%)	99.657	< 0.001***

Variables are presented as counts (%). *p* comparing two groups are derived from χ^2 test. Statistical significance was primarily defined as †$p < 0.1$ (primary threshold), with conventional significance levels denoted as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. COVID-19: coronavirus disease 2019; COPD: Chronic Obstructive Pulmonary Disease.

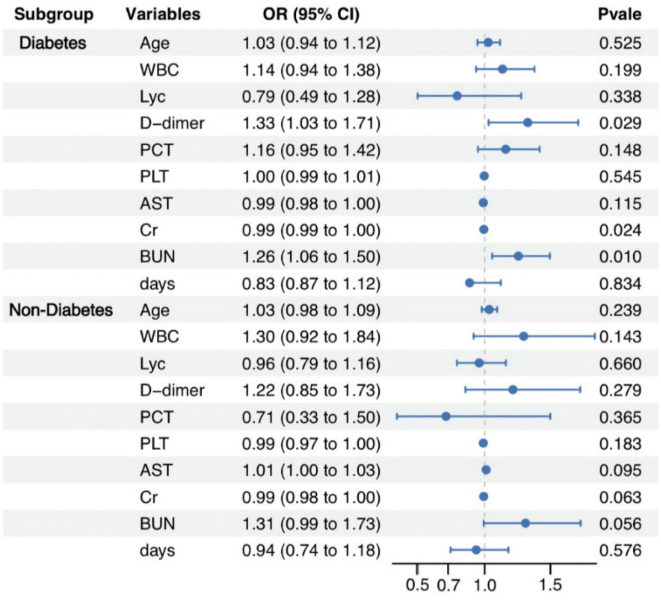
diabetes, and COPD. Hypertensive patients (Figure 6): BUN (OR 1.27, 95% CI 1.11–1.46, p = 0.001) and D-dimer levels (OR 1.20, 95% CI 1.00–1.45, p = 0.055) were positively associated with disease severity, whereas Cr levels (OR 0.99, 95% CI 0.99–1.00, p = 0.001) were negatively associated. No significant associations were observed among non-hypertensive patients. Diabetic patients (Figure 7): D-dimer (OR 1.33, 95% CI 1.03–1.71, p = 0.029) and BUN (OR 1.26, 95% CI 1.06–1.50, p = 0.010) were positively associated with severity, whereas Cr (OR 0.99, 95% CI 0.99–1.00, p = 0.024) was negatively associated. Among non-diabetic patients, AST (OR 1.01, 95% CI 1.00–1.03, p = 0.095) and BUN (OR 1.31, 95% CI 0.99–1.73, p = 0.056) showed positive associations, and Cr (OR 0.99, 95% CI 0.98–1.00, p = 0.063) was negatively associated. COPD patients (Figure 8): BUN (OR 2.45, 95% CI 1.15–5.24, p = 0.021) and D-dimer (OR 4.51, 95% CI 1.14–17.93, p = 0.032) were positively associated with severity, while PCT (OR 0.58, 95% CI 0.35–0.97, p = 0.037) and PLT, OR 0.97, 95% CI 0.94–1.00, p = 0.023) were negatively associated. In non-COPD patients, age (OR 1.06, 95% CI 1.02–1.11, p = 0.006), AST (OR 1.02, 95% CI 1.01–

Figure 6. Forest plot of odds ratios (OR) with 95% confidence intervals (CI) and p values for indices in Hypertention and Non - Hypertention subgroups, highlighting significant associations in each subgroup to compare their predictive roles.



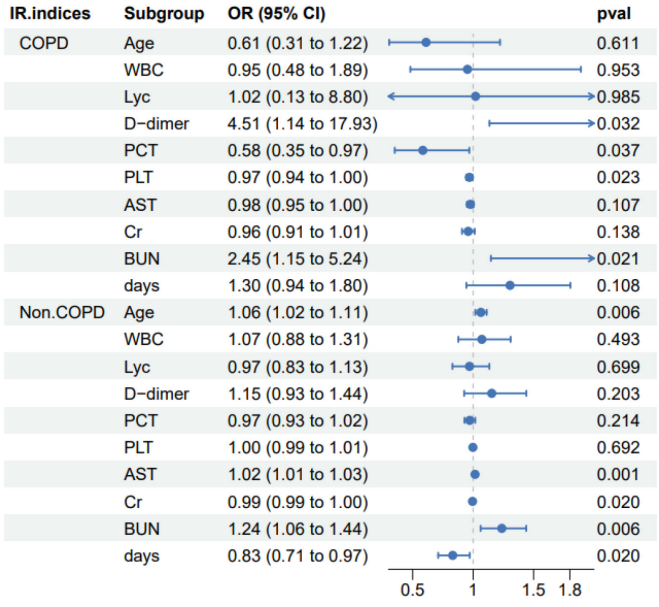
Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine (referring to serum creatinine); BUN: blood urea nitrogen; days: duration of treatment days; NA: not applicable.

Figure 7. Forest plot of odds ratios (OR) with 95% confidence intervals (CI) and p values for indices in Diabetes and Non - Diabetes subgroups, highlighting significant associations in each subgroup to compare their predictive roles.



Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine (referring to serum creatinine); BUN: blood urea nitrogen; days: duration of treatment days.

Figure 8. Forest plot of odds ratios (OR) with 95% confidence intervals (CI) and p values for indices in COPD and Non - COPD subgroups, highlighting significant associations in each subgroup to compare their predictive roles.



Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine (referring to serum creatinine); BUN: urea nitrogen; days: duration of treatment days.

1.03, p = 0.001), and BUN (OR 1.24, 95% CI 1.06–1.44, p = 0.006) were positively associated, whereas duration of treatment (OR 0.83, 95% CI 0.71–0.97, p = 0.020) and Cr (OR 0.99, 95% CI 0.99–1.00, p = 0.020) were negatively associated. These findings highlight that the predictive value of laboratory and demographic factors for COVID-19 severity may be modified by the presence of specific comorbidities.

Discussion

In this retrospective cohort study, we evaluated risk factors associated with disease severity among COVID-19 patients admitted to two tertiary care hospitals between July 30 and October 19, 2022. Our findings indicate that older age, male sex, elevated D-dimer, and increased BUN levels on admission were independently associated with greater disease severity. Conversely, vaccination conferred a protective effect, reducing the risk of progression to severe or critical illness. These risk factors were integrated into a predictive model with direct clinical applicability, facilitating early identification of high-risk patients and enabling timely monitoring and intervention to improve outcomes.

Consistent with established evidence, age was a significant predictor of COVID-19 severity in our cohort. The median age in the severe group was substantially higher than in the mild group (79 vs. 37 years), aligning with prior studies that reported higher median ages in severe cases (e.g., 52 vs. 45 years [11]; 60 vs. 49 years [12]). Age is a well-recognized major risk factor for severe COVID-19 [13,14], likely reflecting both the higher prevalence of comorbidities and age-related declines in immune resilience observed in older patients, as demonstrated in ICU cohorts [15].

Male sex was strongly associated with severe disease, reinforcing its inclusion in our predictive model. While the mild group exhibited a near-equal sex distribution, males were significantly overrepresented in the severe group. This observation aligns with meta-analyses reporting that males constitute approximately 60% of hospitalized COVID-19 cases (95% CI [0.54, 0.65]) [16] and are at higher risk of infection and progression to severe disease [17,18]. The observed sex disparity may be attributable to biological differences, including variations in immune and hormonal responses [19, 20]. Mechanistic studies suggest that elevated ACE2 receptor expression in males facilitates viral entry [21,22], whereas estrogen has been shown to downregulate ACE2 expression in vitro and in animal models [23], providing a plausible biological explanation for the lower risk of severe outcomes in females and supporting its predictive value in clinical risk assessment. Although numerous biomarkers, such as blood counts, liver and kidney function tests, and coagulation factors, have been associated with COVID-19 severity and poor outcomes [24-30], our multivariate analysis identified only a subset as independent predictors suitable for inclusion in our model. Specifically, leukocyte, lymphocyte, and PLT did not differ significantly between severity groups after adjustment. This discrepancy with prior reports may reflect the predominance of asymptomatic or mild cases in our cohort, as well as large group sizes that could dilute observable effects. Consistent with established pathophysiology, univariate analysis revealed marked alterations in Group B (severe/critical), including significantly decreased absolute Lyc and PLT, alongside elevated CRP, PCT, and D-dimer levels. Lymphocytopenia is a well-documented indicator of severity [31], associated with T-cell depletion during the antiviral response [30], and has been reported in a higher proportion of severe cases (e.g., 80% vs. 25% in mild cases) [32,33], with confirmation from meta-analyses [34]. Elevated CRP reflects intense inflammation and cytokine storm, a critical driver of disease progression [35], whereas increased PCT may indicate bacterial co-infection and independently predict progression to severe disease [36]. Notably, although PCT and other markers were significant in univariate analyses, they did not retain independent predictive value in our final multivariate model.

Although thrombocytopenia is frequently associated with critical illness and mortality [34,37-39], potentially resulting from mechanisms such as bone marrow suppression or microthrombosis [34,40], our adjusted analysis found no significant association between PLT and COVID-19 severity. This finding is consistent with studies reporting either no association or no significant differences at admission [41]. Consequently, PLT was not included [42] in our predictive model. This discrepancy may reflect the composition of our cohort, which was predominantly asymptomatic or mild cases, and the large group sizes may have diluted subtle effects. Therefore, while PLT may be relevant in more severe populations, it was excluded from our current prediction model.

D-dimer emerged as a robust, independent predictor in our model. Our analysis confirmed significantly higher D-dimer levels in patients with severe disease, which were positively associated with COVID-19 severity. This finding aligns with prior evidence indicating that elevated D-dimer predicts poor prognosis, 28-day mortality in sepsis and COVID-19 [43], critical illness [44], and, specifically, in-hospital

mortality when levels exceed 2.0 μg/mL [11]. The inclusion of D-dimer in our predictive model enhances its clinical utility by enabling early identification of high-risk patients who may benefit from timely anticoagulation assessment and intervention.

Consistent with early reports linking comorbidities such as hypertension, diabetes mellitus, and COPD to critical COVID-19 outcomes [45,46], our study confirmed statistically significant differences in these conditions between severity groups, in agreement with prior research [47-50]. Renal dysfunction emerged as a particularly critical factor. Pre-existing chronic kidney disease (CKD) is a well-established risk factor for severe COVID-19 [51-54], and renal injury occurs in over 30% of hospitalized patients, including those without prior kidney disease [55]. Vulnerability is especially pronounced in dialysis patients, who experience COVID-19 mortality rates approximately 20 times higher than the general population in Japan, findings supported by studies from the US and Europe [38,39]. The mechanisms linking CKD to severe COVID-19 likely involve dysregulation of both innate and adaptive immunity. AKI is also common at admission; prospective studies report elevated Cr (14.4%) and BUN (13.1%) in COVID-19 patients, with AKI developing in 5.1%, particularly among critically ill patients or those with elevated admission Cr [56]. Elevated baseline Cr or BUN has been identified as an independent risk factor for mortality [57]. Beyond renal function, BUN is increasingly recognized as a prognostic marker in cardiovascular disease and pneumonia [58]. Our findings reinforce this: BUN levels differed significantly between severity groups, and logistic regression confirmed BUN as an independent predictor of poor prognosis. Notably, BUN demonstrated strong predictive performance (AUC-ROC = 0.813), supporting its inclusion in our clinical prediction model for early identification of high-risk patients who may benefit from intensified renal monitoring and management. In contrast, although elevated Cr is generally associated with AKI and adverse outcomes [56,57], our analysis revealed a negative correlation with disease severity (OR 0.993). This unexpected finding may be influenced by the large baseline differences between groups and warrants further investigation, which likely explains why Cr was not prioritized in the final predictive model.

Vaccination status emerged as a significant protective factor against severe COVID-19 in our study, reinforcing its inclusion in the clinical prediction model. Vaccinated patients demonstrated a substantially reduced risk of disease progression (OR = 0.323). This finding aligns with large cohort studies showing that vaccination is associated with decreased mortality [59], suggesting that immunization helps prevent clinical deterioration and hospitalization. By incorporating vaccination status, our model can identify patients at lower baseline risk, potentially allowing healthcare resources to be prioritized for unvaccinated or otherwise high-risk individuals. Although some studies report high rates of severe disease among vaccinated inpatients (e.g., 45.3% [60]), this likely reflects the vulnerability of specific subgroups, particularly elderly patients and those with comorbidities, who may have lower vaccination coverage or diminished immune responses. These observations underscore the importance of intensifying vaccination efforts, especially in high-risk populations, and highlight the utility of our model in identifying vulnerable individuals for targeted intervention. Importantly, evidence indicates that most COVID-19 vaccines effectively reduce hospitalization, disease severity, and mortality, with even a single dose generally sufficient to confer protection, though individual immune responses may vary [61].

Strengths and Limitations

This study has several notable strengths. Its multicenter design within the Xinjiang region and substantial sample size help address the underrepresentation of this population in COVID-19 severity research. Additionally, the detailed subgroup analyses of comorbidities identified specific disease-related risks for severe illness, enhancing the clinical utility of our predictive model by enabling early identification and proactive management of high-risk patients to potentially mitigate disease progression. However, several limitations should be acknowledged. The retrospective design limits causal inference, and the marked imbalance in group sizes may introduce bias. Data collection was restricted to admission parameters, without serial measurements to capture disease progression or dynamic predictors. Comprehensive biomarker testing, including lactate dehydrogenase, interleukin-6, and serum ferritin, was not uniformly performed, potentially underestimating their predictive contribution and limiting the model's scope. Furthermore, the nomogram requires rigorous internal and external validation to confirm its generalizability and clinical reliability; it is currently presented as an initial tool based on readily available admission data (age, sex, vaccination status, D-dimer, and BUN). The absence of in-hospital mortality data also precludes assessment of the model's performance for this critical

endpoint. Despite these limitations, our findings and the proposed model provide a practical foundation for early risk stratification. Future prospective studies incorporating serial measurements, additional biomarkers, and mortality outcomes are warranted to refine and validate the model's clinical applicability.

Conclusions

In conclusion, our analysis identified older age, male sex, elevated BUN, and elevated D-dimer on admission as key independent risk factors for severe COVID-19. Based on these factors, we developed a clinical prediction model that demonstrated strong prognostic value and practical applicability. The resulting nomogram offers clinicians a useful tool for early identification of high-risk patients, enabling prioritized monitoring and timely interventions, such as intensified renal assessment for elevated BUN or prompt anticoagulation evaluation for high D-dimer. While comorbidities such as hypertension, diabetes, and COPD were confirmed as risk indicators for poor outcomes, this study primarily included patients with asymptomatic or mild disease. Therefore, further prospective studies are needed to validate the model's performance and clarify the precise impact of comorbidities in cohorts with more severe illness.

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Authors 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.

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Conflict of interest

No conflict of interest is declared.

References

1. Volz E, Hill V, McCrone JT, Price A, Jorgensen D, O'Toole Á, Southgate J, Johnson R, Jackson B, Nascimento FF, Rey SM, Nicholls SM, Colquhoun RM, da Silva Filipe A, Shepherd J, Pascall DJ, Shah R, Jesudason N, Li K, Jarrett R, Pacchiarini N, Bull M, Geidelberg L, Siveroni I, Goodfellow I, Loman NJ, Pybus OG, Robertson DL, Thomson EC, Rambaut A, Connor TR (2021) Evaluating the effects of SARS-CoV-2 spike mutation D614G on transmissibility and pathogenicity. Cell 184: 64-75.e11. doi: 10.1016/j.cell.2020.11.020.
2. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, Haagmans BL, Lauber C, Leontovich AM, Neuman BW, Penzar D, Perlman S, Poon LLM, Samborskiy DV, Sidorov IA, Sola I, Ziebuhr J (2020) The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 5: 536-544. doi: 10.1038/s41564-020-0695-z.
3. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G (2020) Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 368: m1091. doi: 10.1136/bmj.m1091.
4. Yamahata Y, Shibata A (2020) Preparation for quarantine on the cruise ship Diamond Princess in Japan due to COVID-19. JMIR Public Health Surveill 6: e18821. doi: 10.2196/18821.
5. Yang R, Gui X, Xiong Y (2020) Comparison of clinical characteristics of patients with asymptomatic vs symptomatic coronavirus disease 2019 in Wuhan, China. JAMA Netw Open. 3: e2010182. doi: 10.1001/jamanetworkopen.2020.10182.
6. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395: 565-574. doi: 10.1016/S0140-6736(20)30251-8.
7. World Health Organization (WHO) (n.d.) Coronavirus disease (COVID-19) advice for the public: Mythbusters. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public. Accessed: 18 March 2023.
8. Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, Casado I, Navascués A, Burgui C (2023) Risk reduction of hospitalisation and severe disease in vaccinated COVID-19 cases during the SARS-CoV-2 variant Omicron BA.1-predominant period, Navarre, Spain, January to March 2022. Euro Surveill. 28: 2200337. doi: 10.2807/1560-7917.ES.2023.28.5.2200337.
9. Zhang HP, Sun YL, Wang YF, Yazici D, Azkur D, Ogulur I (2023) Recent developments in the immunopathology of COVID-19. Allergy 78: 369-388. doi: 10.1111/all.15593.
10. National Health Commission of the People's Republic of China (n.d.) Diagnosis and treatment of pneumonia of new coronavirus infection (Trial Version 9). Available: http://en.nhc.gov.cn/. Accessed: March 2023.

11. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX (2020) Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382: 1708-1720. doi: 10.1056/NEJMoa2002032.
12. Qu R, Ling Y, Zhang YHZ, Wei LY, Chen X, Li XM (2020) Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol 92: 1533-1541. doi: 10.1002/jmv.25767.
13. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centred, retrospective, observational study. Lancet Respir Med 8: 475-481. doi: 10.1016/S2213-2600(20)30079-5.
14. Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 323: 1239-1242. doi: 10.1001/jama.2020.2648.
15. Güçlü E, Kocayiğit H, Okan HD, Erkorkmaz U, Yürümez Y, Yaylacı S (2020) Effect of COVID-19 on platelet count and its indices. Rev Assoc Med Bras 66: 1122-1127. doi: 10.1590/1806-9282.66.8.1122.
16. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB (2020) COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 92: 577-583. doi: 10.1002/jmv.25757.
17. Albitar O, Ballouze R, Ooi JP, Sheikh Ghadzi SM (2020) Risk factors for mortality among COVID-19 patients. Diabetes Res Clin Pract 166: 108293. doi: 10.1016/j.diabres.2020.108293.
18. Damayanthi HDWT, Prabani KIP, Weerasekara I (2021) Factors associated for mortality of older people with COVID-19: a systematic review and meta-analysis. Gerontol Geriatr Med 7: 23337214211057392. doi: 10.1177/23337214211057392.
19. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC (2020) Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). JAMA 324: 782-793. doi: 10.1001/jama.2020.12839.
20. Ambrosino I, Barbagelata E, Ortona E, Ruggieri A, Massiah G, Giannico OV (2020) Gender differences in patients with COVID-19: a narrative review. Monaldi Arch Chest Dis 90: 1389. doi: 10.4081/monaldi.2020.1389.
21. Alwani M, Yassin A, Al-Zoubi RM, Aboumarzouk OM, Nettleship J, Kelly D (2021) Sex-based differences in severity and mortality in COVID-19. Rev Med Virol 31: e2223. doi: 10.1002/rmv.2223.
22. Liu J, Ji H, Zheng W, Wu X, Zhu JJ, Arnold AP (2010) Sex differences in renal angiotensin converting enzyme 2 (ACE2) activity are 17β-oestradiol-dependent and sex chromosome-independent. Biol Sex Differ 1: 6. doi: 10.1186/2042-6410-1-6.
23. Stelzig KE, Canepa-Escaro F, Schiliro M, Berdnikovs S, Prakash YS, Chiarella SE (2020) Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. Am J Physiol Lung Cell Mol Physiol 318: L1280-L1281. doi: 10.1152/ajplung.00153.2020.
24. Huang I, Pranata R (2020) Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care 8: 36. doi: 10.1186/s40560-020-00453-4.
25. Loomba RS, Villarreal EG, Farias JS, Aggarwal G, Aggarwal S, Flores S (2022) Serum biomarkers for prediction of mortality in patients with COVID-19. Ann Clin Biochem 59: 15-22. doi: 10.1177/00045632211014244.
26. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y (2020) Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol 92: 2152-2158. doi: 10.1002/jmv.26003.
27. Battaglini D, Lopes-Pacheco M, Castro-Faria-Neto HC, Pelosi P, Rocco PRM (2022) Laboratory biomarkers for diagnosis and prognosis in COVID-19. Front Immunol 13: 857573. doi: 10.3389/fimmu.2022.857573.
28. Edinger F, Edinger S, Koch C, Markmann M, Hecker M, Sander M (2022) Peak plasma levels of mtDNA serve as a predictive biomarker for COVID-19 in-hospital mortality. J Clin Med 11: 7161. doi: 10.3390/jcm11237161.
29. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS (2021) Predictors of COVID-19 severity: a literature review. Rev Med Virol 31: 1-10. doi: 10.1002/rmv.2146.
30. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T (2020) Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 57: 389-399. doi: 10.1080/10408363.2020.1770685.
31. Esper FP, Adhikari TM, Tu ZJ, Cheng YW, El-Haddad K, Farkas DH (2023) Alpha to Omicron: disease severity and clinical outcomes of major SARS-CoV-2 variants. J Infect Dis 227: 344-352. doi: 10.1093/infdis/jiac411.
32. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395: 1054-1062. doi: 10.1016/S0140-6736(20)30566-3.
33. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395: 507-513. doi: 10.1016/S0140-6736(20)30211-7.
34. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G (2020) Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 58: 1021-1028. doi: 10.1515/cclm-2020-0369.
35. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S (2020) Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180: 934-943. doi: 10.1001/jamainternmed.2020.0994.
36. Lippi G, Plebani M (2020) Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chim Acta 505: 190-191. doi: 10.1016/j.cca.2020.03.004.
37. Bao C, Tao X, Cui W, Yi B, Pan T, Young KH (2020) SARS-CoV-2 induced thrombocytopenia as an important biomarker significantly correlated with abnormal coagulation function, increased intravascular blood clot risk and mortality in COVID-19 patients. Exp Hematol Oncol 9: 16. doi: 10.1186/s40164-020-00172-4.
38. Kikuchi K, Nangaku M, Ryuzaki M, Yamakawa T, Oshima Y, Hanafusa N (2021) Survival and predictive factors in dialysis patients with COVID-19 in Japan: a nationwide cohort study. Ren Replace Ther 7: 59. doi: 10.1186/s41100-021-00378-0.
39. James MT, Quan H, Tonelli M, Manns BJ, Faris P, Laupland KB (2009) CKD and risk of hospitalization and death with pneumonia. Am J Kidney Dis 54: 24-32. doi: 10.1053/j.ajkd.2009.04.005.
40. Wool GD, Miller JL (2021) The impact of COVID-19 disease on platelets and coagulation. Pathobiology 88: 15-27. doi: 10.1159/000512007.

41. Asrie F, Tekle E, Gelaw Y, Dagnew M, Gelaw A, Negash M (2022) Baseline thrombocytopenia and disease severity among COVID-19 patients, Tibebe Ghion Specialized Hospital COVID-19 treatment centre, Northwest Ethiopia. J Blood Med 13: 315-325. doi: 10.2147/JBM.S366478.
42. Hana C, Aboulenain S, Dewaswala N, Narendran V (2020) Does thrombocytopenia truly correlate with COVID-19 severity? Blood 136: 39-40. doi: 10.1182/blood-2020-142440.
43. Rodelo JR, De la Rosa G, Valencia ML, Ospina S, Arango CM, Gómez CI (2012) D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. Am J Emerg Med 30: 1991-1999. doi: 10.1016/j.ajem.2012.04.033.
44. Price LC, McCabe C, Garfield B, Wort SJ (2020) Thrombosis and COVID-19 pneumonia: the clot thickens! Eur Respir J 56: 2001608. doi: 10.1183/13993003.01608-2020.
45. Augusto O, Ge E, Li Y, Wu S, Candido E, Wei X (2021) Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in Canada: a population-based cohort study. PLoS One 16: e0258154. doi: 10.1371/journal.pone.0258154.
46. Wang L, He W, Yu X, Hu D, Bao M, Liu H (2020) Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect 80: 639-645. doi: 10.1016/j.jinf.2020.03.019.
47. Zhang Y, Li H, Zhang J, Cao Y, Zhao X, Yu N (2020) The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: a single-centre, retrospective, observational study in Wuhan. Diabetes Obes Metab 22: 1443-1454. doi: 10.1111/dom.14086.
48. Huang I, Lim MA, Pranata R (2020) Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 14: 395-403. doi: 10.1016/j.dsx.2020.04.018.
49. Barrera FJ, Shekhar S, Wurth R, Moreno-Pena PJ, Ponce OJ, Hajdenberg M (2020) Prevalence of diabetes and hypertension and their associated risks for poor outcomes in Covid-19 patients. J Endocr Soc 4: bvaa102. doi: 10.1210/jendso/bvaa102.
50. Attaway AA, Zein J, Hatipoğlu US (2020) SARS-CoV-2 infection in the COPD population is associated with increased healthcare utilization: an analysis of Cleveland Clinic's COVID-19 registry. EClinicalMedicine 26: 100515. doi: 10.1016/j.eclinm.2020.100515.
51. Lu G, Zhang Y, Zhang H, Ai J, He L, Yuan X (2022) Geriatric risk and protective factors for serious COVID-19 outcomes among older adults in Shanghai Omicron wave. Emerg Microbes Infect 11: 2045-2054. doi: 10.1080/22221751.2022.2109517.
52. Ortiz A, Cozzolino M, Fliser D, Fouque D, Goumenos D, Massy ZA (2021) Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. Nephrol Dial Transplant 36: 87-94. doi: 10.1093/ndt/gfaa314.
53. Legrand M, Bell S, Forni L, Joannidis M, Koyner JL, Liu K (2021) Pathophysiology of COVID-19-associated acute kidney injury. Nat Rev Nephrol 17: 751-764. doi: 10.1038/s41581-021-00452-0.
54. Nadim MK, Forni LG, Mehta RL, Connor MJ, Liu KD, Ostermann M, Rimmelé T (2020) COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 16: 747-764. doi: 10.1038/s41581-020-00356-5.
55. Uribarri A, Núñez-Gil IJ, Aparisi A, Becerra-Muñoz VM, Feltes G, Trabattoni D, Fernández-Rozas I, Viana-Llamas MC, Pepe M, Cerrato E, Capel-Astrua T, Romero R, Castro-Mejía AF, El-Battrawy I, López-País J, D'Ascenzo F, Fabregat-Andres O, Bardají A, Raposeiras-Roubin S, Marín F, Fernández-Ortiz A, Macaya C, Estrada V, HOPE COVID-19 Investigators (2020) Impact of renal function on admission in COVID-19 patients: an analysis of the international HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID-19) Registry. J Nephrol 33: 737-745. doi: 10.1007/s40620-020-00790-5.
56. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L (2020) Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 97: 829-838. doi: 10.1016/j.kint.2020.03.005.
57. Cheng Y, Luo R, Wang X, Wang K, Zhang N, Zhang M (2020) The incidence, risk factors, and prognosis of acute kidney injury in adult patients with coronavirus disease 2019. Clin J Am Soc Nephrol 15: 1394-1402. doi: 10.2215/CJN.04650420.
58. Du J, Niu J, Ma L, Sui Y, Wang S (2022) Association between blood urea nitrogen levels and length of stay in patients with pneumonic chronic obstructive pulmonary disease exacerbation: a secondary analysis based on a multicentre, retrospective cohort study. Int J Chron Obstruct Pulmon Dis 17: 2847-2856. doi: 10.2147/COPD.S381872.
59. Baker TB, Bolt DM, Smith SS, Piasecki TM, Conner KL, Bernstein SL (2023) The relationship of COVID-19 vaccination with mortality among 86,732 hospitalized patients: subpopulations, patient factors, and changes over time. J Gen Intern Med 38: 1248-1255. doi: 10.1007/s11606-022-08007-0.
60. Chen CL, Teng CK, Chen WC, Liang SJ, Tu CY, Shih HM (2024) Clinical characteristics and treatment outcomes among the hospitalized elderly patients with COVID-19 during the late pandemic phase in central Taiwan. J Microbiol Immunol Infect 57: 257-268. doi: 10.1016/j.jmii.2024.01.006.
61. Rotshild V, Hirsh-Raccah B, Miskin I, Muszkat M, Matok I (2021) Comparing the clinical efficacy of COVID-19 vaccines: a systematic review and network meta-analysis. Sci Rep 11: 22777. doi: 10.1038/s41598-021-02321-z.

Annex – Supplementary Items

Supplementary Table 1. Variance Inflation Factors (VIF) and tolerance for predictors in the multivariable logistic regression model.

Items	VIF	1/VIF
Age (years)	1.588	0.630
WBC, $*10^9$/L	1.371	0.730
Lyc, $*10^9$/L	1.852	0.540
D-dimer (μg/L)	1.200	0.833
PCT (ng/mL)	1.238	0.808
PLT, $*10^9$/L	1.391	0.718
AST (U/L)	1.054	0.948
BUN (mmol/L)	5.752	0.174
Cr (μmol/L)	5.350	0.187
Duration of treatment (days)	1.065	0.939
Fear of illness	2.526	0.396
Vaccine	1.212	0.825
Gender	1.384	0.723

Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine (referring to serum creatinine); BUN: blood urea nitrogen.

Supplementary Table 2. Multivariate Logistic Regression Models for COVID-19 Severity (with BUN removed).

Items	Regression coefficient	Standard error	*p*	OR value	OR value with 95% CI
Age (years)	0.047	0.017	0.005**	1.048	(1.015, 1.083)
WBC, $*10^9$/L	0.152	0.076	0.047*	1.164	(1.002, 1.352)
Lyc, $*10^9$/L	-0.067	0.089	0.451	0.935	(0.785, 1.114)
D-dimer (μg/L)	0.164	0.090	0.068†	1.178	(0.988, 1.404)
PCT (ng/mL)	-0.003	0.023	0.889	0.997	(0.953, 1.040)
PLT, $*10^9$/L	-0.005	0.004	0.175	0.175	(0.991, 1.043)
AST (U/L)	0.005	0.005	0.286	1.005	(0.996, 1.015)
Cr (μmol/L)	0.000	0.001	0.667	1.000	(0.998, 1.001)
Duration of treatment(days)	-0.022	0.053	0.674	0.978	(0.882, 1.084)
Fear of illness					
Yes	0.207	1.541	0.893	1.230	(0.060, 25.210)
No*	Reference	Reference	Reference	Reference	Reference
Vaccine					
Yes	-1.054	0.548	0.055†	0.349	(0.119, 1.021)
No*	Reference	Reference	Reference	Reference	Reference
Gender					
Male	1.229	0.519	0.018*	3.418	(1.235, 9.457)
Female*	Reference	Reference	Reference	Reference	Reference

*: Control Group. Statistical significance was primarily defined as †$p < 0.1$ (primary threshold), with conventional significance levels denoted as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. COVID-19: coronavirus disease 2019; Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cr: creatinine (referring to serum creatinine); BUN: blood urea nitrogen; CI: confidence interval.

Supplementary Table 3. Multivariate Logistic Regression Models for COVID-19 Severity (with Cr removed).

Items	Regression coefficient	Standard error	*p*	OR value	OR value with 95%CI
Age (years)	0.055	0.016	< 0.001***	1.057	(1.023, 1.092)
WBC, *10^9/L	0.129	0.080	0.109	1.137	(0.972, 1.331)
Lyc, *10^9/L	-0.070	0.090	0.439	0.932	(0.781, 1.113)
D-dimer (μg/L)	0.163	0.089	0.067†	1.178	(0.989, 1.403)
PCT (ng/mL)	-0.012	0.023	0.607	0.988	(0.944, 1.034)
PLT, *10^9/L	-0.004	0.004	0.338	0.996	(0.989, 1.004)
AST (U/L)	0.005	0.005	0.268	1.005	(0.996, 1.021)
BUN (μmol/L)	0.038	0.026	< 0.001***	1.039	(0.987, 1.094)
Duration of treatment(days)	-0.035	0.053	0.510	0.966	(0.870, 1.071)
Fear of illness					
Yes	0.000	1.567	1.000	1.000	(0.046, 21.571)
No*	Reference	Reference	Reference	Reference	Reference
Vaccine					
Yes	-0.866	0.525	0.099†	0.421	(0.150, 1.178)
No*	Reference	Reference	Reference	Reference	Reference
Gender					
Male	1.171	0.520	0.024**	3.227	(1.163, 8.948)
Female*	Reference	Reference	Reference	Reference	Reference

*: Control Group. Statistical significance was primarily defined as †$p < 0.1$ (primary threshold), with conventional significance levels denoted as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. COVID-19: coronavirus disease 2019; Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Cr: creatinine (referring to serum creatinine); CI: confidence interval.

Supplementary Table 4. Multivariate logistic regression models for COVID-19 severity (with Cr and BUN removed).

Items	Regression coefficient	Standard error	*p*	OR value	OR value with 95% CI
Age (years)	0.050	0.016	0.002**	1.051	(1.019, 1.084)
WBC, *10^9/L	0.151	0.076	0.048*	1.163	(1.001, 1.350)
Lyc, *10^9/L	-0.070	0.090	0.435	0.932	(0.782, 1.112)
D-dimer (μg/L)	0.162	0.089	0.068*	1.176	(0.988, 1.400)
PCT (ng/mL)	-0.005	0.023	0.839	0.995	(0.952, 1.041)
PLT, *10^9/L	-0.005	0.004	0.192	0.995	(0.987, 1.003)
AST (U/L)	0.005	0.005	0.273	1.005	(0.996, 1.015)
Duration of treatment(days)	-0.025	0.052	0.631	0.975	(0.880, 1.080)
Fear of illness					
Yes	0.110	1.529	0.942	1.117	(0.056, 22.375)
No*	Reference	Reference	Reference	Reference	Reference
Vaccine					
Yes	-0.998	0.528	0.059†	0.368	(0.131,1.037)
No*	Reference	Reference	Reference	Reference	Reference
Gender					
Male	1.213	0.518	0.019*	3.363	(1.218, 9.282)
Female*	Reference	Reference	Reference	Reference	Reference

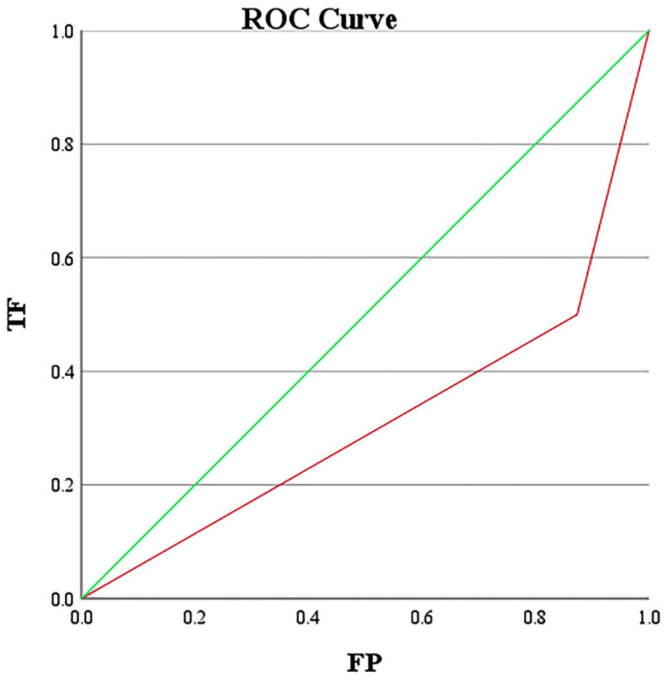
*: Control Group. Statistical significance was primarily defined as †$p < 0.1$ (primary threshold), with conventional significance levels denoted as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. COVID-19: coronavirus disease 2019; Lyc: lymphocyte count; PLT: platelet count; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Cr: creatinine (referring to serum creatinine); CI: confidence interval.

Supplementary Table 5. Variance Inflation Factors (VIF) and tolerance for predictors in the final ROC model.

Items	VIF	1/VIF
Age (years)	1.084	0.630
BUN (mmol/L)	5.075	0.197
Cr (μmol/L)	4.803	0.208
D-dimer	1.046	0.956
Gender	1.037	0.964

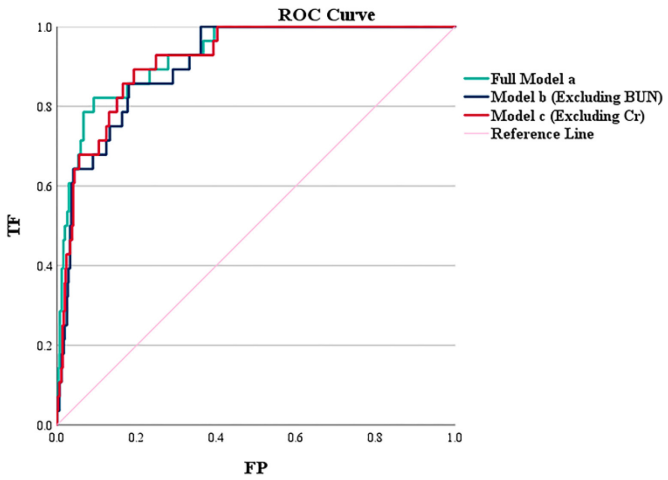
Cr: creatinine (referring to serum creatinine); BUN: blood urea nitrogen; ROC: receiver operating characteristic.

Supplementary Figure 1. ROC curve for vaccination status predicting COVID-19 severity. AUC = 0.313 (95% CI: 0.198-0.428) indicates inverse discrimination capacity.



COVID-19: coronavirus disease 2019; AUC: area under the curve; ROC: receiver operating characteristic.

Supplementary Figure 2. ROC curves under different models.



ROC: receiver operating characteristic.