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RESEARCH ARTICLE

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# Simple nomogram based on initial laboratory data for predicting the probability of ICU transfer of COVID-19 patients: Multicenter retrospective study

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## Abstract

This retrospective, multicenter study investigated the risk factors associated with intensive care unit (ICU) admission and transfer in 461 adult patients with confirmed coronavirus disease 2019 (COVID-19) hospitalized from 22 January to 14 March 2020 in Hunan, China. Outcomes of ICU and non-ICU patients were compared, and a simple nomogram for predicting the probability of ICU transfer after hospital admission was developed based on initial laboratory data using a Cox proportional hazards regression model. Differences in laboratory indices were observed between patients admitted to the ICU and those who were not admitted. Several independent predictors of ICU transfer in COVID-19 patients were identified including older age (≥65 years) (hazard ratio [HR] = 4.02), hypertension (HR = 2.65), neutrophil count (HR = 1.11), procalcitonin level (HR = 3.67), prothrombin time (HR = 1.28), and D-dimer level (HR = 1.25). The lymphocyte count and albumin level were negatively associated with mortality (HR = 0.08 and 0.86, respectively). The developed model provides a means for identifying, at hospital admission, the subset of patients with COVID-19 who are at high risk of progression and would require transfer to the ICU within 3 and 7 days after hospitalization. This method of early patient triage allows a more effective allocation of limited medical resources.

KEYWORDS

COVID-19, ICU transfer, laboratory examination, nomogram

## 1 | INTRODUCTION

In December 2019, an outbreak of a new disease that was eventually named coronavirus disease 2019 (COVID-19) was reported in Wuhan (Hubei, China).[1] The spread of COVID-19 was designated as a pandemic by the World Health Organization (WHO) on 11 March 2020. As of 3 April 2020, there were 960 000 confirmed cases of COVID-19 in 204 countries, with 50 000 deaths. The causative agent of COVID-19 was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 11 February 2020 by the WHO.[2]

COVID-19 can progress rapidly in critically ill patients; a meta-analysis of 50 466 patients with COVID-19 showed that 18.1% were severe cases.[3] Without timely and appropriate care, the outcome of patients can be very poor.[4] It is therefore essential to identify at an early stage those patients who will require admission to the intensive care unit (ICU). However, ICUs in hospitals around the world are over capacity because of the scale of this pandemic.[4,5] A simple model for predicting COVID-19 progression can guide clinical decision-making with regard to critical-care capacity and resource allocation. Although numerous differences in laboratory indices have been reported between patients with and those without ICU care,[6,7] there are no models for predicting the risk of progression and need for ICU admission based on these data.

To address this issue, this study investigated the laboratory indices and factors associated with ICU admission and transfer in COVID-19 patients in Hunan, China, and used this information to develop a nomogram for predicting the probability of ICU transfer after hospital admission.

## 2 | METHODS

### 2.1 | Ethics approval

The ethics committee of Xiangya Hospital (Changsha, China) approved the study protocol (2020-010). Written, informed consent was obtained from participants or their families for retrospectively collected data.

### 2.2 | Study population and data collection

This was a retrospective, multicenter study involving 461 adult patients (aged ≥ 18 years) confirmed as having COVID-19 according to WHO interim guidance,[8] who were admitted to the First Hospital of Changsha, Zhuzhou Lukou District People's Hospital, Xiangtan Central Hospital, Yueyang Second People's Hospital, and Shaoyang Central Hospital from 22 January to 14 March 2020. A diagnosis of COVID-19 was confirmed by fluorescent reverse transcription PCR detection of SARS-CoV-2 RNA. The patients' clinical, demographic, laboratory, and outcome data were obtained from electronic medical records and interviews with attending physicians. A trained team of physicians and medical students were responsible for data collection.

### 2.3 | Outcomes

Patients were divided into two groups based on ICU transfer status—namely, the ICU care (ICUC) group (n = 55) and non-(N)ICUC group (n = 406 patients). Patients were followed up for 30 days after hospital admission, until the end of the observation period (29 March 2020), or until referral to the ICU. Time-to-event was defined as the time from hospitalization to ICU admission.

### 2.4 | Construction and calibration of nomograms

The Cox proportional hazard model was used to generate nomograms for predicting the risk of ICU transfer using rms (http://www.rms.com). A score based on regression coefficients was assigned to factors that would be convenient for clinical decision-making. The discrimination and predictive abilities of the nomogram were assessed with Harrell's concordance index (C-index), where a larger index reflected a more accurate prediction of prognosis. To validate the nomogram, calibration curves plotted based on nomogram-predicted and actual probabilities of ICU transfer were analyzed.

### 2.5 | Statistical analysis

Descriptive data are presented as the interquartile range (IQR) for continuous variables and as numbers (%) for categorical variables. Differences in the distribution of patient characteristics between the ICUC and NICUC groups are presented with 95% confidence intervals

**TABLE 1** Demographic characteristics of COVID-19 patients

| Study population | Number (%) |
|---|---|
| No. of patients | 461 |
| Age, median (IQR), y | 45.00 (34.50-57.00) |
| ≥65 | 69 (14.97%) |
| <65 | 392 (85.03%) |
| Sex | |
| Male | 239 (51.84%) |
| Female | 222 (48.16%) |
| Comorbidities | |
| Hypertension | 83 (18.00%) |
| Diabetes mellitus | 48 (10.41%) |
| Cardiovascular disease | 25 (5.42%) |
| Nervous system disease | 12 (2.60%) |
| Liver disease | 17 (3.69%) |
| Chronic lung disease | 11 (2.39%) |
| Chronic kidney disease | 1 (2.17%) |
| Endocrine system disease | 5 (10.85%) |
| Tumor | 6 (13.02%) |
| ICU admission | 55 (11.93%) |

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range.

(CIs). Continuous variables were analyzed with the Mann-Whitney *U* test, and categorical variables were compared between subgroups with the $\chi^2$ test or Fisher's exact test. The Cox proportional hazards model was used to determine the hazard ratio (HR) and 95% CI between individual factors and ICU transfer status. Statistical analyses were performed using SPSS v25.0 (IBM, Armonk, NY) or R v3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

## 3 | RESULTS

### 3.1 | Demographics and laboratory findings

A total of 461 hospitalized patients with confirmed COVID-19 were included in this study (Table 1). The median age of patients was 45 years (IQR, 34.5-57 years), and 239 (51.48%) were male. The most common comorbidity was hypertension (n = 84 [18%]).

Table 2 shows the laboratory findings upon hospital admission. Most patients presented with elevated infection-related indices including erythrocyte sedimentation rate (ESR; 276 of 386 [71.5%]), C-reactive protein (CRP; 248 of 430 [57.67%]), and procalcitonin (PCT) level (37 of 453 [8.17%]). More than half of the cohort had lymphocytopenia (245 of 461 [53.15%]) and hypoalbuminemia (230 of 458 [50.22%]), and about one-third of patients had leukopenia (149 of 461 [32.32%]). Some patients had liver injury, as evidenced by increased levels of aspartate aminotransferase (AST; 96 of 461 [20.82%]) and alanine aminotransferase (57 of 461 [12.36%]). Myocardial indices were also elevated: 76 of 375 (20.27%) had increased lactate dehydrogenase (LDH) and 21 of 376 (5.59%) had increased creatine kinase muscle-brain isoform. A few patients had kidney injury, as indicated by increased plasma urea (11 of 419 [2.63%]) and serum creatinine (52 of 461 [11.28%]). A few patients showed abnormal coagulation function, which was reflected by an increased level of D-dimer (47 of 451 [10.42%]) or prolonged prothrombin (PT; 13 of 427 [3.04%]) or activated partial thromboplastin (41 of 427 [9.6%]) times.

### 3.2 | Risk factors associated with ICU admission

A total of 55 (11.93%) patients were admitted to the ICU; these patients (ICUC group) were significantly older (median age, 60 years

**TABLE 2** Initial laboratory indices of COVID-19 patients

| Test | Number of patients tested | Value (median) (IQR) | Number of patients with a value deviating from the reference value, % |
|---|---|---|---|
| Hematology | | | |
| White blood cell count, $\times10^9$/mL | 461 | 4.76 (3.64-5.96) | 32.32* |
| Neutrophil count, $\times10^9$/mL | 433 | 2.96 (2.22-3.84) | 5.54 |
| Lymphocyte count, $\times10^9$/mL | 461 | 1.13 (0.81-1.60) | 53.15* |
| Hemoglobin, g/L | 461 | 132 (121-145) | 7.81* |
| Platelet count $\times10^9$/mL | 461 | 192 (147-244) | 5.21* |
| Biochemistry | | | |
| Total bilirubin, μmol/L | 460 | 11.05 (8.14-17.26) | 12.39 |
| AST, U/L | 461 | 24.00 (19.10-31.45) | 20.82 |
| ALT, U/L | 461 | 21.00 (14.86-31.94) | 12.36 |
| Albumin, g/L | 458 | 39.91 (36.07-43.43) | 50.22* |
| Urea, mM | 419 | 4.1 (3.27-5.07) | 2.63 |
| Creatinine, μM | 461 | 63.00 (49.45-76.40) | 11.28 |
| Creatine kinase, U/L | 461 | 69.07 (46.35-107.70) | 7.38 |
| CK-MB, U/L | 376 | 10.53 (7.20-14.78) | 5.59 |
| Lactate dehydrogenase, U/L | 375 | 179.30 (144.30-230.00) | 20.27 |
| Infection-related indices | | | |
| CRP, mg/L | 430 | 7.69 (2.50-25.73) | 57.67 |
| Procalcitonin, ng/mL | 453 | 0.50 (0.50-0.50) | 8.17 |
| ESR, mm/h | 386 | 35.00 (14.00-62.25) | 71.5 |
| Coagulation function | | | |
| PT, s | 427 | 12.00 (11.10-12.70) | 3.04 |
| APTT, s | 427 | 32.60 (29.50-36.00) | 9.6 |
| D-dimer, μg/mL | 451 | 0.31 (0.17-0.52) | 10.42 |

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK-MB, creatine kinase muscle-brain isoform; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; LDH, lactate dehydrogenase; PT, prothrombin time.
*Below reference.

[IQR, 50-70 years] vs 43 years [IQR, 34-53 years]; $P < .001$) and were more likely to have hypertension (n = 19 [34.55%] vs n = 64 [13.88%]) than those who did not receive ICU care (NICUC group; n = 406). Differences in laboratory findings between the two groups are summarized in Table 3. White blood cell (WBC) and neutrophil counts were higher in the ICUC group than in the NICUC group ($P < .001$). Lymphocyte and platelet counts were lower in the ICUC group than in the NICUC group ($P < .001$ and < .001, respectively). Indices of liver damage (AST and LDH), renal dysfunction (urea), infection (CRP, PCT, and ESR), and coagulation function (PT and D-dimer) were significantly elevated in the ICUC group compared to the NICUC group. Patients who were later admitted to the ICU had lower levels of albumin.

A bivariate Cox proportional hazard model identified several independent predictors of ICU transfer in COVID-19 patients (Table 4), including older age (≥ 65 years) (HR = 4.02), hypertension (HR = 2.65), neutrophil count (HR = 1.11), PCT level (HR = 3.67), PT (HR = 1.28), and D-dimer level (HR = 1.25). Lymphocyte count and albumin level were negatively associated with ICU transfer (HR = 0.08 and 0.86, respectively).

**TABLE 3** Laboratory findings of patients with COVID-19 upon hospital admission

| | No ICU care | ICU care | *P* |
|---|---|---|---|
| No. of patients | 406 | 55 | |
| Age, median (IQR), y | 43.00 (34.00-53.25) | 60.00 (50.00-70.00) | <.001 |
| Sex | | | |
| Male | 206 (47.8%) | 33 (60.00%) | .197 |
| Female | 200 (52.2%) | 22 (40.00%) | |
| Comorbidities | | | |
| Hypertension | 64 (13.88%) | 19 (34.55%) | .001 |
| Diabetes mellitus | 40 (8.68%) | 8 (14.55%) | .285 |
| Cardiovascular disease | 19 (4.12%) | 6 (10.91%) | .056 |
| Hematology | | | |
| White blood cell count, $\times 10^9$/mL | 4.70 (3.61-5.79) | 5.26 (4.27-7.10) | .035 |
| Neutrophil count, $\times 10^9$/mL | 2.90 (2.18-3.72) | 3.96 (2.98-6.05) | <.001 |
| Lymphocyte count, $\times 10^9$/mL | 1.20 (0.90-1.62) | 0.72 (0.50-1.02) | <.001 |
| Hemoglobin, g/L | 133.00 (121.00-145.00) | 131.00 (120.00-142.00) | .304 |
| Platelet count, $\times 10^9$/mL | 198.50 (149.00-247.00) | 151.00 (130.00-186.00) | <.001 |
| Biochemistry | | | |
| Total bilirubin, μmol/L | 11.00 (8.16-17.36) | 11.30 (7.61-15.99) | .821 |
| AST, U/L | 23.22 (18.84-30.18) | 30.80 (25.52-49.39) | <.001 |
| ALT, U/L | 20.90 (14.92-30.93) | 21.71 (14.80-37.09) | .444 |
| Albumin, g/L | 40.40 (36.64-43.90) | 35.38 (32.93-38.63) | <.001 |
| Urea, mM | 4.06 (3.20-4.96) | 4.69 (3.65-6.02) | .009 |
| Creatinine, μM | 63.00 (49.98-76.40) | 56.00 (46.99-77.40) | .411 |
| Creatine kinase, U/L | 66.65 (45.00-101.25) | 104.70 (67.90-214.00) | <.001 |
| CK-MB, U/L | 10.50 (7.00-14.43) | 12.25 (7.50-16.10) | .187 |
| Lactate dehydrogenase, U/L | 172.85 (141.75-213.00) | 280.10 (196.90-352.95) | <.001 |
| Infection-related indices | | | |
| CRP, mg/L | 5.45 (2.50-19.72) | 44.08 (26.44-77.12) | <.001 |
| Procalcitonin, ng/mL | 0.05 (0.05-0.05) | 0.05 (0.05-0.08) | <.001 |
| ESR, mm/h | 30.00 (13.00-57.75) | 61.00 (33.75-78.50) | <.001 |
| Coagulation function | | | |
| PT, s | 11.90 (11.10-12.70) | 12.60 (11.80-13.00) | .001 |
| APTT, s | 32.50 (29.50-35.97) | 33.50 (31.10-36.80) | .1 |
| D-dimer, μg/mL | 0.29 (0.17-0.49) | 0.51 (0.36-0.85) | .004 |

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK-MB, creatine kinase muscle-brain isoform; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; PT, prothrombin time.

**TABLE 4** Bivariate Cox regression of factors associated with ICU admission

| | HR (95%CI) | P |
|---|---|---|
| Age (≥65 vs <65), y | 4.02 (2.32-6.95) | <.001 |
| Sex ratio (male vs female) | 0.68 (0.39-1.18) | .169 |
| Comorbidities | | |
| Hypertension | 2.65 (1.52-4.64) | .001 |
| Diabetes mellitus | 1.55 (0.73-3.29) | .25 |
| Cardiovascular disease | 2.30 (0.99-5.38) | .054 |
| Hematology | | |
| White blood cell count, $\times10^9$/mL | 1.07 (1.00-1.15) | .4 |
| Neutrophil count, $\times10^9$/mL | 1.11 (1.05-1.18) | <.001 |
| Lymphocyte count, $\times10^9$/mL | 0.08 (0.04-0.18) | <.001 |
| Hemoglobin, g/L | 0.99 (0.97-1.0) | .112 |
| Platelet count, $\times10^9$/mL | 0.99 (0.99-0.99) | <.001 |
| Biochemistry | | |
| Total bilirubin, μmol/L | 1.01 (1.00-1.03) | .148 |
| AST, U/L | 1.02 (1.02-1.03) | <.001 |
| ALT, U/L | 1.00 (0.99-1.01) | .83 |
| Albumin, g/L | 0.86 (0.82-0.91) | <.001 |
| Urea, mM | 1.16 (1.09-1.24) | <.001 |
| Creatinine, μM | 1.00 (1.00-1.00) | .19 |
| Creatine kinase, U/L | 1.00 (1.00-1.00) | <.001 |
| CK-MB, U/L | 1.01 (1.00-1.04) | .313 |
| Lactate dehydrogenase, U/L | 1.01 (1.01-1.01) | <.001 |
| Infection-related indices | | |
| CRP, mg/L | 1.02 (1.01-1.02) | <.001 |
| Procalcitonin, ng/mL | 3.67 (2.44-5.49) | <.001 |
| ESR, mm/h | 1.02 (1.00-1.02) | <.001 |
| Coagulation function | | |
| PT, s | 1.28 (1.15-1.43) | <.001 |
| APTT, s | 1.05 (1.00-1.09) | .032 |
| D-dimer, μg/mL | 1.25 (1.14-1.37) | <.001 |

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CI, confidence interval; CK-MB, creatine kinase muscle-brain isoform; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HR, hazard ratio; ICU, intensive care unit; LDH, lactate dehydrogenase; PT, prothrombin time.

### 3.3 | Nomogram for predicting the probability of ICU transfer after hospital admission

A total of 286 patients with complete data for all variables (18 in the ICUC group and 268 in the NICUC group) were included in the multivariable Cox proportional hazard model. Multivariate HRs were calculated for the prognostic factors used to develop the nomogram (Table 5). The results showed that lymphocyte count (HR = 0.37 [0.15-0.91]; $P$ = .03), platelet count (HR = 0.99 [0.99-1.00]; $P$ = .041), AST level (HR = 1.03 [1.01-1.05]; $P$ = .001), LDH level (HR = 1.00 [1.00-1.01]; $P$ = .017), and CRP level (HR = 1.01 [1.01-1.02]; $P$ < .001) were independent predictors of ICU transfer. These factors were used to develop a nomogram for predicting the probability of ICU transfer after hospital admission (Figure 1). Each point of an independent variable was determined according to the intersection of the vertical line drawn from the variable to the point axis. The total risk score was then calculated by adding each variable point; the probability of ICU admission was obtained from the total point axis. The C-index of the nomogram was 0.848. Calibration curves indicated that the probability predicted using the nomogram showed good concordance with real-world data (Figure 2).

**TABLE 5** Multivariate COX proportional hazard model for ICU admission

| | HR (95% CI) | P |
|---|---|---|
| Lymphocyte count, $\times10^9$/mL | 0.37 (0.15-0.91) | .03 |
| Platelet count, $\times10^9$/mL | 0.99 (0.99-1.00) | .041 |
| AST, U/L | 1.03 (1.01-1.05) | .001 |
| LDH, U/L | 1.00 (1.00-1.01) | .017 |
| CRP, mg/L | 1.01 (1.01-1.02) | <.001 |

Abbreviations: AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; ICU, intensive care unit; LDH, lactate dehydrogenase.

## 4 | DISCUSSION

In this study, blood biochemistry, coagulation function, and infection-related biomarkers were examined in 461 adult patients with laboratory-confirmed COVID-19, and several risk factors associated with ICU admission of COVID-19 patients using the Cox proportional hazard model were identified. Based on these factors, a simple nomogram was developed for predicting the probability of ICU transfer 3 and 7 days after hospitalization. This is the first model for predicting the probability of ICU transfer in patients with COVID-19.

The clinical presentation of COVID-19 varies from asymptomatic to mild upper respiratory tract symptoms and severe viral pneumonia

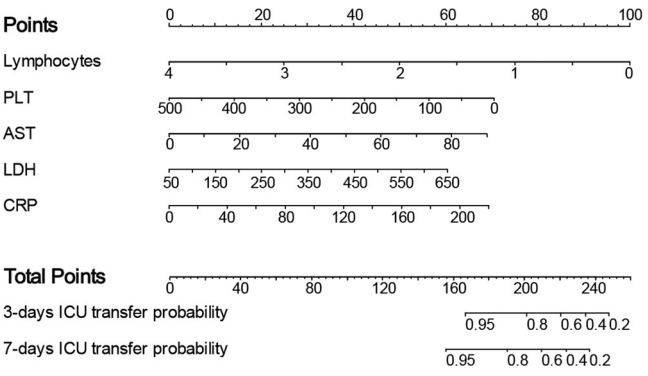


**FIGURE 1** Nomogram predicting the probability of ICU transfer. All 5 prognostic factors must be available for this model to be used. AST, aspartate aminotransferase; CRP, C-reactive protein; ICU, intensive care unit; LDH, lactate dehydrogenase; PLT, platelet

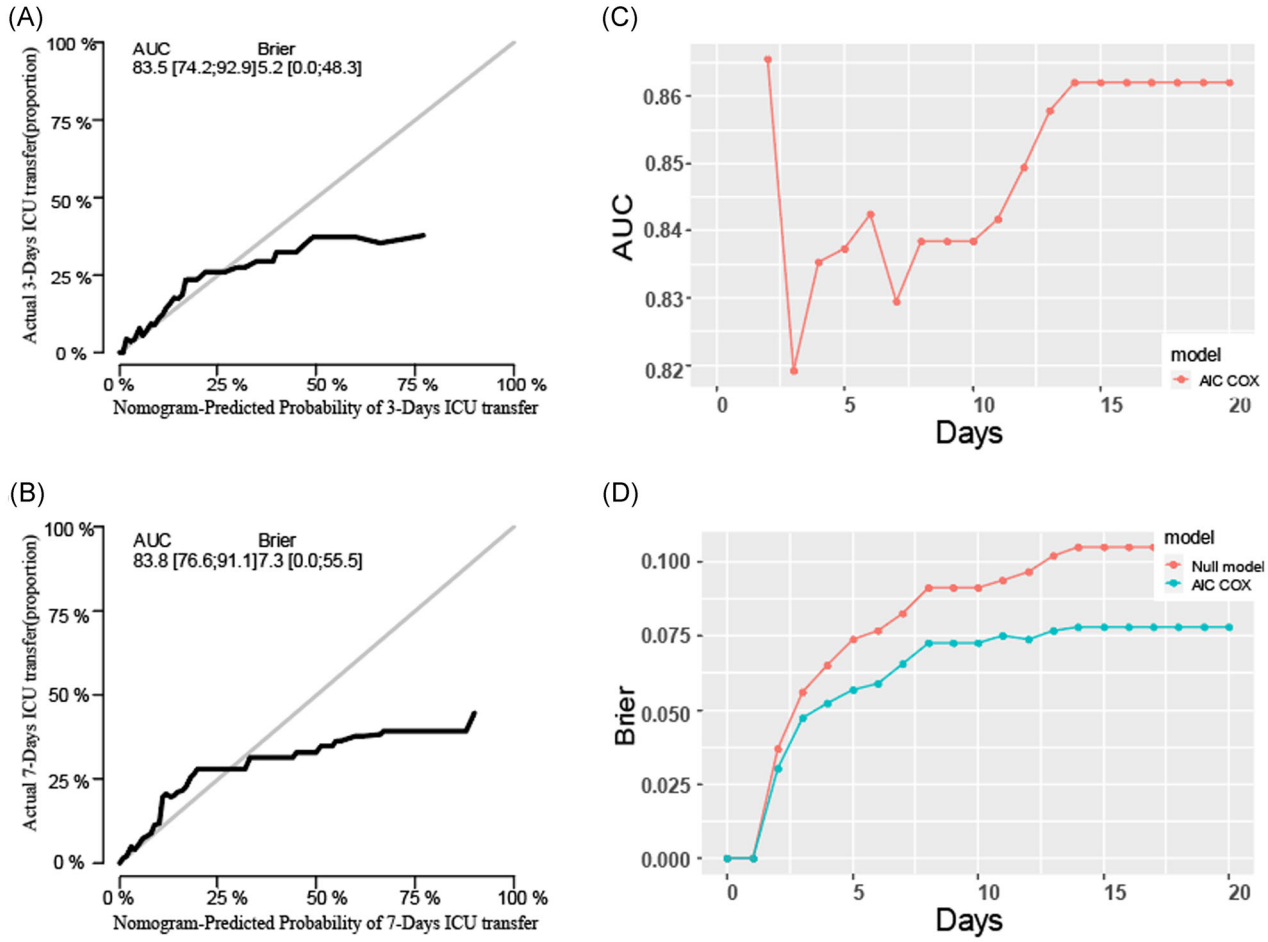


**FIGURE 2** Discrimination and calibration of the nomogram. A,B, Calibration curve for predicting ICU transfer 3 days (A) and 7 days (B) after hospital admission. C, Time-dependent area under the receiver operating characteristic curve (AUC) plot. (D) Time-dependent Brier score plot

with respiratory failure, and death[9,10]; 20.3% of patients with COVID-19 require ICU admission.[11] Predicting which patients are at risk of COVID-19 progression and thus require ICU transfer at the time of hospital admission could improve patient outcomes by ensuring that those who are most likely to become critically ill can receive appropriate care early on, thereby alleviating pressure on ICU capacity.

In terms of laboratory findings, high levels of ESR and CRP as well as hypoalbuminemia and lymphopenia were observed in over half of the patients, which is consistent with other reports.[12] There were also numerous differences between the ICUC and NICUC groups. The ICU patients had an increased WBC count, neutrophilia, lymphopenia, thrombocytopenia, and elevated indices of liver damage (AST and LDH), renal dysfunction (urea), infection (CRP, PCT, and ESR), and coagulation function (PT and D-dimer), which is in agreement with previous studies.[6,7,13] The univariate and multivariate Cox regression models showed that lymphopenia was a significant predictor of ICU transfer; lymphopenia has been shown to be a feature of severe COVID-19.[14,15] These data suggest that severe cases of SARS-CoV-2 infection are likely associated with bacterial infection; immune deficiency; activation of coagulation; and impaired myocardial, hepatic, and kidney functions.

Immune dysregulation was found to be associated with the critical illness caused by SARS-CoV-2 infection. Elevated infection-related indices and poor coagulation functions were also found to be risk factors for ICU transfer, as previously reported.[13,16] CRP is widely used as a biochemical indicator for inflammation because it reflects the acute severe systemic inflammatory response caused by viral infections; it has been suggested that a cytokine storm is involved in severe disease.[17] Interestingly, a higher PCT level was associated with a higher probability of ICU transfer in the present study. As demonstrated in a recent meta-analysis,[18] PCT levels may predict evolution to a more severe form of the disease. Moreover, moderately or markedly increase D-dimer levels suggest the activation of coagulation in patients who are later admitted to the ICU. Platelet-to-lymphocyte ratio was shown to be associated with prognosis in patients with COVID-19[19]; here it was shown that thrombocytopenia was related to COVID-19 severity.

A nomogram was established to guide clinical decision-making with regard to critical-care resource allocation. Five variables were included in the model including lymphocyte and platelet counts and

AST, LDH, and CRP levels. The C-index of the nomogram was 0.848, suggesting that the model was effective in identifying patients at risk for ICU transfer. In addition, the calibration curves indicated that the probability of ICU transfer predicted using the nomogram matched well with real-world data.

This study had two major limitations. Firstly, because of its retrospective design, not all laboratory tests were performed for all patients, which reduced the sample size for constructing the nomogram. Secondly, prospective studies were not carried out to validate the model; this will be done in the future in a larger cohort of COVID-19 patients.

In conclusion, although it requires verification and validation in a larger number of patients, the predictive model developed in this study can aid physicians in identifying early on (ie, at the time of admission) patients who are at risk of COVID-19 progression and therefore require transfer to the ICU, so that medical resources can be more effectively allocated and patient outcomes improved.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

The study was designed by ZZ, YM, and YC. PH, WL, MJ, XX, DD, XL, and PC were responsible for data collection. ZZ, YM, and HZ were responsible for the data analysis. ZZ drafted the first draft and all other authors provided guidance on the revision of the manuscript. All authors read and approved the final manuscript.

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