Multicenter Development and Validation of a Novel Risk Nomogram for Early Prediction of Severe 2019-Novel Coronavirus Pneumonia

Abstract:
Background
Severe cases of coronavirus disease 2019 (COVID-19) rapidly develop acute respiratory distress leading to respiratory failure, with remarkably high short-term mortality rates. At present, there is no reliable risk stratification tool for COVID-19 patients. We aimed to construct and validate a model for early identification of severe cases of COVID-19.

Methods
SARS-CoV-2 infected patients from two centers in Guangzhou and one center in Wuhan were included retrospectively, and divided into the train and external validation cohorts. All patients with non-severe COVID-19 during hospitalization were followed for more than 15 days following admission and patients who deteriorated to severe COVID-19 were assigned to the severe group. Least absolute shrinkage and selection operator (LASSO) algorithm and logistic regression model were used to construct a nomogram for risk prediction in the train cohort. The predictive accuracy and discriminative ability of nomogram were evaluated by area under the curve (AUC) and calibration curve. Decision curve analysis (DCA) and clinical impact curve analysis (CICA) were conducted to evaluate the clinical applicability of our nomogram.

Findings
The train cohort consisted of 189 patients, while the two independent validation cohorts consisted of 165 and 18 patients. Among all cases, 72 (19.35%) patients developed severe COVID-19. We generated the nomogram containing one clinical and six serological indicators (age, serum lactate dehydrogenase, C-reactive protein, the coefficient of variation of red blood cell distribution width, blood urea nitrogen, albumin, direct bilirubin) that could early identify severe COVID-19 patients. The nomogram showed remarkably high diagnostic accuracy in distinguishing individuals with severe COVID-19 from non-severe COVID-19 (AUC 0.914 [95% CI 0.852–0.976] in the train
cohort; 0.856 [0.795-0.916] in validation cohort 1. The calibration curve for probability of severe COVID-19 showed optimal agreement between prediction by nomogram and actual observation. DCA and CICA further indicated that our nomogram conferred significantly high clinical net benefit.

Interpretation
Our nomogram is a potentially useful prediction tool for risk assessment of COVID-19 patients and early identification of severe COVID-19 patients. Risk stratification will enable better management and optimal use of medical resources via patient prioritization and thus significantly reduce mortality rates.
Multicenter Development and Validation of a Novel Risk Nomogram for Early Prediction of Severe 2019-Novel Coronavirus Pneumonia

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Summary:

Background

Severe cases of coronavirus disease 2019 (COVID-19) rapidly develop acute respiratory distress leading to respiratory failure, with remarkably high short-term mortality rates. At present, there is no reliable risk stratification tool for COVID-19 patients. We aimed to construct and validate a model for early identification of severe cases of COVID-19.

Methods

SARS-CoV-2 infected patients from two centers in Guangzhou and one center in Wuhan were included retrospectively, and divided into the train and external validation cohorts. All patients with non-severe COVID-19 during hospitalization were followed for more than 15 days following admission and patients who deteriorated to severe COVID-19 were assigned to the severe group. Least absolute shrinkage and selection operator (LASSO) algorithm and logistic regression model were used to construct a nomogram for risk prediction in the train cohort. The predictive accuracy and discriminative ability of nomogram were evaluated by area under the curve (AUC) and calibration curve. Decision curve analysis (DCA) and clinical impact curve analysis (CICA) were conducted to evaluate the clinical applicability of our nomogram.

Findings

The train cohort consisted of 189 patients, while the two independent validation cohorts consisted of 165 and 18 patients. Among all cases, 72 (19.35%) patients developed severe COVID-19. We generated the nomogram containing one clinical and six serological indicators (age, serum lactate dehydrogenase, C-reactive protein, the coefficient of variation of red blood cell distribution width, blood urea nitrogen, albumin, direct bilirubin) that could early identify severe COVID-19 patients.
The nomogram showed remarkably high diagnostic accuracy in distinguishing individuals with severe COVID-19 from non-severe COVID-19 (AUC 0.914 [95% CI 0.852-0.976] in the train cohort; 0.856 [0.795-0.916] in validation cohort). The calibration curve for probability of severe COVID-19 showed optimal agreement between prediction by nomogram and actual observation. DCA and CICA further indicated that our nomogram conferred significantly high clinical net benefit.

**Interpretation**

Our nomogram is a potentially useful prediction tool for risk assessment of COVID-19 patients and early identification of severe COVID-19 patients. Risk stratification will enable better management and optimal use of medical resources via patient prioritization and thus significantly reduce mortality rates.

**Key Words:**

COVID-19; Nomogram; Severe COVID-19 prediction; Risk stratification

**Funding**

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Introduction

Since the outbreak of novel coronavirus pneumonia (COVID-19) in December 2019, the number of reported cases has surpassed 100,000 with over 3600 deaths worldwide, as of March 8, 2020. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of coronaviruses known to cause common colds and severe illnesses such as the severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), is the cause of COVID-19. Compared with much higher overall case-fatality rates (CFR) for SARS and MERS, COVID-19 is being responsible for more total deaths because of the increased transmission speed and the growing numbers of cases. Until now, SARS-CoV-2 transmission via person to person has caused the largest outbreaks of COVID-19 worldwide, owing to increasing imported and secondary contact infection risk. Up to now, the World Health Organization (WHO) has raised global Coronavirus Disease (COVID-19) outbreak risk to “Very High”, and SARS-CoV-2 infection has become a serious threat to public health.

According to a report recently released by the Chinese Center for Disease Control and Prevention that included approximately 44,500 confirmed cases of SARS-CoV-2 infections, up to 15.8% were severe or critical. Among of the cases, CFR was significantly higher in critical cases than in other cases (49.0% vs 2.3%)². Most COVID-19 patients have a mild disease course, while some patients experience rapid deterioration (particularly within 7-14 days) from onset of symptoms into severe COVID-19 with or without acute respiratory distress syndrome (ARDS)⁶. Current epidemiological data suggests that the mortality rate of severe COVID-19 patients is about 20 times higher than that of non-severe COVID-19 patients⁷.⁸ This situation highlights the need to identify COVID-19 patients at risk of developing ARDS and other serious complications of COVID-19.
These severe illness patients often require utilization of intensive medical resources. Therefore, early identification of patients at high risk for severe COVID-19 will not only alleviate shortage of medical resources, but also facilitate appropriate supportive care and reduce the mortality rate, unnecessary or inappropriate healthcare utilization via patient prioritization.

At present, an early warning model for predicting COVID-19 patients at-risk of developing a costly condition is scarce. In our study, non-severe COVID-19 patients were enrolled on admission from all three cohorts and observed for at least 15 days to assess the clinical characteristics, hematology indices and outcomes of patients with non-severe and severe COVID-19. Furthermore, we developed and validated an effective prognostic nomogram, for accurate individualized assessment of the incidence of severe COVID-19.

**Material and method**

**Data collection**

Data on COVID-19 inpatients between January 20th 2020 and March 2nd 2020 was retrospectively collected from three clinical centers: Guangzhou Eighth People's Hospital, Zhongnan Hospital of Wuhan University and the Third Affiliated Hospital of Sun Yat-sen University. A total of 372 patients with COVID-19 were enrolled, 9 patients younger than 15 years of age were excluded from the study. Upper respiratory swab samples were collected on all suspected cases of SARS-CoV-2 infection on admission and immediately placed into sterile tubes with viral transport medium, which were tested in Zhongnan Hospital of Wuhan University or sent to the Center for Disease Control and Prevention for laboratory diagnosis in Guangzhou. Clinical laboratory test results, including biochemical indices, blood routine results, were collected from routine clinical practice. The study
was approved by the Ethics Committee of the Eighth People's Hospital of Guangzhou (20200547). Written informed consent was waived by the Ethics Commission of the Third Affiliated Hospital of Sun Yat-sen University for emerging infectious diseases.

The diagnosis of SARS-CoV-2 infection was based on the Guidelines for Diagnosis and Treatment of Novel Coronavirus Pneumonia (5th version), released by National Health Commission of China. Suspected cases of COVID-19 requires meeting any of the following epidemiology history criteria or any two of the following clinical manifestations: (A) Epidemiological history: a history of travel to or residence in Wuhan, China in the last 14 days prior to symptom onset; contact with a confirmed or suspected case of 2019-nCOV infection in the last 14 days prior to symptom onset; aggressive disease onset. (B) Clinical manifestation: Fever and/or respiratory infection, or with normal/decreased white blood cells counts and normal/decreased lymphocyte counts. In the absence of the above mentioned criteria for epidemiological history, the suspected case should meet with all of the above mentioned criteria for clinical manifestation. A confirmed case was defined as an individual with laboratory confirmation of SARS-CoV-2 which required positive PCR on specific nucleic acid sequences of SARS-CoV-2, irrespective of clinical signs and symptoms. For diagnosis of Severe COVID-19, at least one of the following conditions should be met: (1) Shortness of breath, Respiratory rate (RR) ≥30times/min, (2) Arterial oxygen saturation (Resting status) ≤93%, or (3) the ratio of Partial pressure of oxygen to Fraction of inspiration O₂/ FiO₂ ≤300mmHg.

**Laboratory Methods**

Clinical laboratory test results, including biochemical indices, blood routine results, were collected from routine clinical practice. Clinical laboratory test results included albumin (ALB), aspartate aminotransferase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), creatine kinase...
creatine kinase-MB (CK-MB), creatinine (Crea), C-reactive protein (CRP), total bilirubin (TBIL), direct bilirubin (DBIL), globulin (GLB), lactate dehydrogenase (LDH), procalcitonin (PCT), total bile acid (TBA), hemoglobin (HB), lymphocyte count, monocyte count, neutrophil count, platelet distribution width (RDW), platelet (PLT), red blood cell (RBC), RDW-CV (red blood cell distribution width-coefficient variation). All biochemical parameters were obtained via standard automated laboratory methods and using commercially available kits following to the manufacturers protocols.

**Statistical Analysis**

Categorical variables were expressed as frequency and percentage, and Fisher’s exact test was performed to analyze significance. Continuous variables were expressed as mean (standard deviation [SD]), or median (interquartile range [IQR]), as appropriate. Parametric test (T test) and non-parametric test (Mann-Whitney U) were used for continuous variables with or without normal distribution, respectively. A value of p < 0.05 was considered statistically significant. Except for filling missing values, all the statistical analyses were analyzed using R (version 3.6.2) with default parameters.

Of all potential predictors in the dataset, 0.09 % of the fields had missing values. Predictor exclusion was limited to those with more than 7% missing rate to minimize the bias of the regression coefficient. [16]. Little’s MCAR test (R package BaylorEdPsych) was used to assess the suitability of the remaining missing values for imputation. This test is used to test whether missing values are “missing completely at random” (MCAR) or biased. The missing values were imputed by expectation-maximization (EM) method using SPSS statistical software, version 25 (SPSS, Inc., Chicago, IL, USA).
To identify the relative importance of each feature, feature selection was performed using least absolute shrinkage and selection operator (LASSO) regression method prediction models were built using logistic regression, decision tree, random forest (RF) and support vector machine (SVM) using R package Caret, using 300-time repeated random sub-sampling validation for diverse parameter conditions, respectively. As described previously, Nomograms were established with the rms package and performance of nomogram was evaluated by discrimination (Harrell’s concordance index) and calibration (calibration plots and Hosmer-Lemeshow calibration test) in R. During the external validation of the nomogram, the total points for each patient in the validation cohort were calculated based on the established nomogram.

**Results**

The selection of the study population is illustrated in Figure 1. A total of 372 COVID-19 patients were enrolled after admission from three centers in Guangzhou and Wuhan (Figure 1). All patients with non-severe COVID-19 during hospitalization were followed for more than 15 days following admission and patients who deteriorated to severe COVID-19 were assigned to the severe group. There were no significant differences in age, sex, disease type between the train cohort and validation cohorts (Table 1). In the train cohort, the non-severe COVID-19 group consisted of 159 (86.41%) patients, with a median age of 45 years of age (range 33-61 years) while 25 patients (13.59%), with a median age of 64 years of age (range 55-72 years) progressed to severe COVID-19. By the end of Feb 25, one patient with severe COVID-19 in the train group died. None of the 184 patients from the train group had a history of exposure to Huanan seafood market in Wuhan, 55 of them (29.1%) had not left Guangzhou recently, but had a close exposure history with COVID-19
patients, and the rest (70.9%) were Wuhan citizens or visited Wuhan recently. Other baseline characteristics in train cohort were shown in Table 2.

A total of 49 features were collected from each patient in the train cohort. After excluding irrelevant and redundant features, 39 features remained for LASSO regression analysis. The results showed that age, DBIL, RDW-CV, BUN, CRP, LDH and ALB from the 189 patients were predictive factors for severe COVID-19 when the Area Under Curve (AUC) was maximal (Figure 2B and 2C). Then we built prediction models using logistic regression, decision tree, random forest (RF) and support vector machine (SVM), and evaluated their performance by the receiver operating characteristic curve (ROC) and the precision-recall curve (appendix p1). There were no big difference in performance of these models except for decision tree. Therefore, logistic regression model was used for further analysis owing to its high predictive power and interpretability.

The predictive nomogram that integrated all selected features for the incidence of severe COVID-19 in the train cohort is shown (Figure 2C). To evaluate clinical applicability of our risk prediction nomogram, decision curve analysis (DCA) and clinical impact curve analysis (CICA) were performed. The DCA and CICA visually showed that the nomogram had a superior overall net benefit within the wide and practical ranges of threshold probabilities and impacted patient outcomes (Figure 2D and 2E). In Figure 3A and 3B, the calibration plot for severe illness probability showed a good agreement between the prediction by nomogram and actual observation in the train cohort 1 and validation cohort 1, respectively.

In the train cohort, the nomogram had a significantly high AUC 0.914 (95% CI 0.852-0.976) to discriminate individuals with severe COVID-19 from non-severe COVID-19, with a sensitivity of 89.29% and specificity of 81.99% (Figure 3C, Table 2). Cutpoint R package was used to calculate
optimal cutpoints by bootstrapping the variability of the optimal cutpoints, which was 102.8915 for our nomogram (corresponding to a threshold probability of 0.154). Then patients in the validation cohorts were divided into the low group (score ≤102.8915) and the high group (score>102.8915) for further analysis. In consistent with the train cohort, in validation cohort 1, AUC was 0.856 for nomogram of patients with severe COVID-19 versus non-severe COVID-19 with a sensitivity of 77.5% and specificity of 74.4% (Figure 3D, Table 3). In validation cohort 2, the sensitivity and the specificity of the nomogram were observed to be 75% and 100%, respectively.

Discussion

Since the outbreak of COVID-19 in December 2019, the number of reported cases has reached 100,000 and over 3600 deaths worldwide in March, 2020. Recently, the WHO has raised its risk assessment of COVID-19 to "Very High At A Global Level". Early identification of severe COVID-19 patients will lead to better management and optimal use of medical resources at a time where resources available to Intensive Care Units to cope with the epidemic, are scarce. In this research, we retrospectively evaluated clinical characteristics, hematology indices and outcomes of patients with non-severe or severe COVID-19 patients. Furthermore, we developed and validated an effective prognostic nomogram. The nomogram composed of seven features, had significantly high sensitivity to distinguish individuals with severe COVID-19 from non-severe COVID-19, which is of great value for accurate individualized assessment of the incidence of severe COVID-19.

Our findings suggest that nomogram is a promising predictor for risk stratification of severe COVID-19. Liu et al showed that NLR might be a predictor of disease severity in COVID-19 patients and developed a nomogram from a single center with a small sample size and no external
Our nomogram has a significantly higher AUC in the train and validation cohorts than Liu’s nomogram (0.914/0.856 vs 0.849). Our nomogram predicted a total of 120.8915 points at a 15.4% probability threshold, which was close to the prevalence of severe COVID-19 (14.8%) in the training cohort and hence consistent with the reality. This cut-off value may lead to high false positive rates but in the setting of this COVID-19 outbreak, high false positive rates are acceptable in order to minimize risks of missed diagnosis. Meanwhile, application of the nomogram in the training cohort and validation cohort showed good differentiation with AUC values of 0.914 and 0.856 respectively, as well as high sensitivity and specificity. Our study has several strengths: first, the seven features of nomogram were relatively inexpensive and easy to be obtained directly from the routine blood tests. Second, to guarantee the robustness of the conclusion, we included the data from three centers. A clinical prognostic marker research needs a large sample size and validation in independent cohorts. So far, no published studies have recruited SARS-CoV-2 infected patients from three centers and performed validation in independent cohorts. The performance of our nomogram to predict prognosis of COVID patients was validated in two independent cohorts in this study.

Three cohorts of the COVID-19 patients in the hospital were from Guangzhou and Wuhan. The prevalence of severe COVID-19 was 14.8% in train cohort 1, 24.24% in the validation cohort 1 and 22.22% in validation cohort 2. In our study, patients with severe illness had a median age of 64 (range from 55 to 72) years. We found that older patients were more likely to develop severe illness. Our results were consistent with other reports in the literature, which suggest that age might be risk a factor for the rapid progression of disease\textsuperscript{9,10}. NLR, a widely used marker for the assessment of system inflammation, has been reported to be a prognostic predictor for patients with SARS-CoV-
2 infection. Although NLR was higher in severe COVID-19 patients than in non-severe COVID-19 patients, it was not identified by LASSO as an important feature instead of LDH and CRP. Reportedly, the level of LDH is useful as a marker in determining diagnosis or prognosis of multiple pneumonia, such as pneumocystis jiroveci pneumonia, community acquired pneumonia, and serum LDH levels correlates positively with NLR levels. We also observed that NLR has a moderately correlation with CRP (r, 0.57) and LDH (r, 0.52). Like NLR, CRP and LDH also are associated with the systemic inflammatory response. Li et al has reported that LDH is an important clinical feature for prediction of criticality in patients with severe SARS-CoV-2 infection. Therefore, we speculate that this might be one of the reasons why the lasso model did not identified NLR as a more important feature. Our study showed the increased LDH and CRP were related to the progress of the COVID-19 and were important risk prediction factors for severe COVID-19 disease. Therefore, our results indicate that patients with higher levels of inflammation at admission might be at higher risk for severe COVID-19.

RDW-CV, one of the numbers or blood cell indices, was also included in our nomogram. RDW-CV reflects the variation in the size of RBC (red blood cells) and correlates with mortality and bloodstream infection risk in the critically. RDW-CV is very helpful in distinguishing between the different types of anemia and predicting prognosis of the patient with acute exacerbation of interstitial pneumonia. RDW can be regarded as an index of enhanced patient fragility and higher vulnerability to adverse outcomes. The elevated RDW-CV may explain fatigue experienced by severe COVID-19 patients.

There were some limitations in the study. First, this is a retrospective study, including 372 patients with non-severe COVID-19 on admission. Second, some patients are still in hospital and
their condition may change with follow-up. More comprehensive investigation needs to be conducted to evaluate the performance of our nomogram.

In summary, our data suggest that our nomogram could early identify the severe COVID-19 patients, and it is especially valuable for risk stratification management, which will be helpful for alleviating insufficient medical resources and reducing mortality.

References


Contributors

BH, YLS and FZ designed the study and had full access to all data in the study and take
responsibility for the integrity of the data and the accuracy of the data analysis. JG, JYO XPQ, YSJ, YQC and MKT contributed to collect data, analyze data, and write the paper. LXY, JC, MKT and WYX contributed to the statistical analysis. All authors contributed to data interpretation, and reviewed and approved the final version.

Conflict of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

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Figure legends

Figure 1. Flow chart of study participants in train and validation groups.

Figure 2. Construction of prediction nomogram in patients with COVID-19. The nomogram composed of age, DBIL, RDW_CV, BUN, CRP, LDH and ALB was developed. (A) LASSO coefficient profiles (y-axis) of the 39 features. The lower x-axis indicated the log (λ). The top x-axis has the average numbers of predictors. (B) Identification of the optimal penalization coefficient (λ) in the LASSO model was performed via 3-fold cross-validation based on minimum criteria. The area under the receiver operating characteristic (AUC) was plotted verse log (λ). The y-axis indicated AUC. Red dots represent average AUC for each model with a given λ, and vertical bars through the red dots showed the upper and lower values of the AUC. The dotted vertical lines represent the optimal values of λ. When the optimal λ value of 0.68 with log (λ) = - 4.82 was selected, the AUC reached the peak. The upper and lower x-axis indicated the same meaning as in Figure 2A. LASSO, least absolute shrinkage and selection operator. (C) Nomogram predicting the severe COVID-19 probability in patients with COVID-19 infection was plotted. To use this nomogram in clinical management, an individual patient’s value is located on each variable axis, and a line is plotted upward to calculate the number of points received for each variable value. The sum of these scores is located on the Total points axis and draw a line straight down to get the probability of severe COVID-19. (D) Decision curve compares the net clinical benefits of three scenarios in predicting the severe COVID-19 probability: a perfect prediction model (grey line), screen none (horizontal solid black line), and screen based on the nomogram (blue line). (E) Clinical impact curve of the nomogram plot the number of COVID-19 patients classified as high risk, and the number of cases classified high risk with severe NCAP at each high risk threshold. RDW_CV,
red blood cell distribution width-coefficient variation; BUN, blood urea nitrogen; DBIL, direct bilirubin; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALB, albumin.

**Figure 3. The calibration and ROC curves of the nomogram**

The calibration curve and ROC for performance to distinguish individuals with severe COVID-19 from non-severe COVID-19 in the train cohort (A, C) and validation cohort 1 (B, D), respectively.
Total screened patients with COVID-2019 infection

- Guangzhou Eighth People's Hospital (Development cohort) n=192
  - Excluded due to Age (n=3)
  - Eligible patients with COVID-2019 INFECTION included (n=189)

- Zhongnan Hospital of Wuhan University (Validation cohort 1) n=171
  - Excluded due to Age (n=6)
  - Eligible patients with COVID-2019 INFECTION included (n=165)

- Third Affiliated Hospital of Sun Yat-sen University (Validation cohort 2) n=18
  - Eligible patients with COVID-2019 INFECTION included (n=18)
Figure 3

Development cohort

Validation cohort

C

Development cohort

Sensitivity

Specificity

AUC: 0.914

D

Validation cohort

Sensitivity

Specificity

AUC: 0.856

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Table 1. Baseline characteristics of the study cohort

<table>
<thead>
<tr>
<th></th>
<th>Train cohort (n=189)</th>
<th>Validation cohort 1 (n=165)</th>
<th>Validation cohort 2 (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.0 (35.0, 63.0)</td>
<td>52.0 (37.0, 64.0)</td>
<td>41.5 (29.0, 50.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>Female</td>
<td>101 (53.4%)</td>
<td>93 (56.4%)</td>
<td>9 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>88 (46.6%)</td>
<td>72 (43.6%)</td>
<td>9 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Basic.disease</td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>No</td>
<td>134 (70.9%)</td>
<td>117 (70.9%)</td>
<td>14 (77.8%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>55 (29.1%)</td>
<td>48 (29.1%)</td>
<td>4 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Non-severe</td>
<td>161 (85.2%)</td>
<td>125 (75.8%)</td>
<td>14 (77.8%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>28 (14.8%)</td>
<td>40 (24.2%)</td>
<td>4 (22.2%)</td>
<td></td>
</tr>
</tbody>
</table>

"Yes" of Basic.disease means patients with one of the following disease: hypertension, diabetes, cardiovascular disease, chronic respiratory disease, tuberculosis disease.
Table 2. Demographics and characteristics of COVID-19 patients in the train cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-severe (n=161)</th>
<th>Severe (n=28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>45.0 (33.0, 62.0)</td>
<td>63.5 (54.5, 72.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Female</td>
<td>89 (55.3%)</td>
<td>12 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72 (44.7%)</td>
<td>16 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>Exposure</td>
<td></td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Patients in Guangzhou</td>
<td>51 (27.0%)</td>
<td>7 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Close contact with Wuhan</td>
<td>110 (58.2%)</td>
<td>21 (11.1%)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>No</td>
<td>119 (73.9%)</td>
<td>16 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (26.1%)</td>
<td>12 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>No</td>
<td>156 (96.9%)</td>
<td>25 (89.3%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (3.1%)</td>
<td>3 (10.7%)</td>
<td></td>
</tr>
<tr>
<td>Basic disease</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>120 (74.5%)</td>
<td>14 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41 (25.5%)</td>
<td>14 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23.4 (21.4, 25.7)</td>
<td>23.4 (22.3, 24.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>No</td>
<td>119 (73.9%)</td>
<td>16 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (26.1%)</td>
<td>12 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>No</td>
<td>156 (96.9%)</td>
<td>25 (89.3%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (3.1%)</td>
<td>3 (10.7%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (breaths/ min)</td>
<td>20.0 (20.0, 20.0) (n=160)</td>
<td>20.0 (20.0, 22.0) (n=28)</td>
<td>0.04</td>
</tr>
<tr>
<td>Laboratory test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>12.9 (10.7, 15.7)</td>
<td>10.9 (9.6, 13.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>97.9 (96.7, 98.8)</td>
<td>96.8 (95.2, 97.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>WBC (10E9/L)</td>
<td>4.6 (3.7, 5.6)</td>
<td>5.2 (4.4, 6.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>RBC (10E12/L)</td>
<td>4.5 (0.6)</td>
<td>4.2 (0.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>136.8 (16.7)</td>
<td>128.9 (17.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Platelet (10E9/L)</td>
<td>180.0 (147.0, 221.0)</td>
<td>167.0 (139.5, 200.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2.8 (2.0, 3.6)</td>
<td>3.7 (2.8, 5.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Monocyte (10E9/L)</td>
<td>0.4 (0.3, 0.5)</td>
<td>0.3 (0.3, 0.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>Lymphocyte (10E9/L)</td>
<td>1.3 (1.0, 1.8)</td>
<td>1.0 (0.8, 1.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NLR</td>
<td>1.9 (1.4, 2.9)</td>
<td>3.7 (2.0, 6.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PLR</td>
<td>131.0 (96.6, 177.4)</td>
<td>174.8 (117.7, 210.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>SII</td>
<td>360.5 (229.1, 562.9)</td>
<td>561.7 (320.1, 1019.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RDW-SD (fL)</td>
<td>39.9 (38.5, 42.0)</td>
<td>42.7 (39.6, 44.1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
### Summary of Blood Tests

**RDW-CV (%)**  
12.2 (11.8, 12.7)  
12.8 (12.3, 13.1)  
<0.01

**PDW**  
11.9 (10.6, 14.1)  
14.9 (10.9, 16.2)  
0.03

**AST (U/L)**  
20.8 (17.4, 27.1)  
33.5 (27.4, 46.5)  
<0.01

**ALT (U/L)**  
21.0 (14.2, 32.4)  
23.0 (15.1, 40.5)  
0.33

**ALB (g/L)**  
39.7 (4.3) (n=158)  
34.2 (5.1) (n=28)  
<0.01

**Globulin (g/L)**  
28.3 (26.2, 30.2) (n=157)  
29.3 (27.8, 32.0) (n=26)  
0.07

**BUN (mmol/L)**  
3.9 (3.2, 4.6)  
4.7 (3.1, 7.2)  
0.08

**Creatine (umol/L)**  
58.8 (47.6, 76.7)  
57.0 (42.5, 80.7)  
0.52

**TBIL (umol/L)**  
9.6 (6.5, 14.1) (n=158)  
12.3 (8.6, 20.4) (n=28)  
0.03

**DBIL (umol/L)**  
3.9 (2.7, 5.2) (n=157)  
5.2 (3.4, 7.8) (n=26)  
<0.01

**TBA (umol/L)**  
2.7 (1.5, 4.1) (n=157)  
3.9 (2.3, 7.7) (n=26)  
0.01

**Creatine kinase-MB (U/L)**  
11.6 (5.0) (n=150)  
16.4 (16.8) (n=27)  
<0.01

**Creatine kinase (U/L)**  
76.5 (50.0, 111.0) (n=160)  
111.5 (72.5, 168.5) (n=28)  
<0.01

**LDH (U/L)**  
175.5 (148.5, 219.5) (n=160)  
296.0 (203.0, 407.0) (n=28)  
<0.01

**CRP (mg/L)**  
5.0 (5.0, 19.5)  
35.5 (21.6, 72.3)  
<0.01

**Glucose (mmol/L)**  
6.1 (2.4) (n=149)  
8.2 (4.4) (n=26)  
<0.01

**Lactate mmol/L**  
1.8 (1.4, 2.1) (n=152)  
1.9 (1.4, 2.3) (n=25)  
0.19

**INR**  
1.0 (1.0, 1.1) (n=159)  
1.1 (1.0, 1.1) (n=28)  
0.59

**APTT (s)**  
39.1 (4.4) (n=159)  
40.0 (5.4) (n=28)  
0.32

**D-Dimer (μg/L)**  
990.0 (600.0, 1380.0) (n=158)  
1225.0 (6.6, 1720.0) (n=28)  
0.25

**SAA (mg/L)**  
1.0 (0.0, 2.0) (n=104)  
4.0 (4.0, 4.0) (n=20)  
<0.01

**PCT (ng/ml)**  
0.0 (0.0, 0.1) (n=32)  
0.2 (0.1, 0.3) (n=12)  
<0.01

ALL features with missing values are labeled with a specific number of samples.

Abbreviations: BMI, body mass index; PaO2, partial pressure of oxygen; SaO2, oxygen saturation; WBC, white blood cell; RBC, red blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; RDW-SD, red blood cell distribution width-standard deviation; RDW-CV, red blood cell distribution width-coefficient variation; PDW, platelet distribution width; AST, aspartate aminotransferase; ALT, alanine transaminase; ALB, albumin; BUN, blood urea nitrogen; TBIL, total bilirubin; DBIL, direct bilirubin; TBA, total bile acids; LDH, lactate dehydrogenase; CRP, C-reactive protein; INR, international normalized ratio; APTT, partial thromboplastin time; SAA, Serum amyloid A; PCT, procalcitonin.

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Table 3. Performance of nomogram for early prediction of severe COVID-19

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% CI)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development cohort (n=189)</td>
<td>0.914 (0.852-0.976)</td>
<td>89.29</td>
<td>81.99</td>
</tr>
<tr>
<td>Validation cohort 1 (n=165)</td>
<td>0.856 (0.795-0.916)</td>
<td>77.5</td>
<td>74.4</td>
</tr>
<tr>
<td>Validation cohort 2(^5) (n=18)</td>
<td>75</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

\(^5\) Owing to the limited sample size, AUC was not calculated in validation cohort 2.