Establishment of a clinical nomogram model to predict the progression of COVID-19 to severe disease

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Research

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Abstract

Background

Coronavirus disease 2019 (COVID-19) is a worldwide public health pandemic with a high mortality rate, among severe cases. The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. It is important to ensure early detection of the virus to curb disease progression to severe COVID-19. This study aimed to establish a clinical-nomogram model to predict the progression to severe COVID-19 in a timely, efficient manner.

Methods

This retrospective study included 202 patients with COVID-19 who were admitted to the Fifth Affiliated Hospital of Sun Yat-sen University and Shiyan Taihe Hospital from January 17 to April 30, 2020. The patients were randomly assigned to the training dataset (n = 163, with 43 progressing to severe COVID-19) or the validation dataset (n = 39, with 10 progressing to severe COVID-19) at a ratio of 8:2. The optimal subset algorithm was applied to filter for the clinical factors most relevant to the disease progression. Based on these factors, the logistic regression model was fit to distinguish severe (including severe and critical cases) from non-severe (including mild and moderate cases) COVID-19. Sensitivity, specificity, and area under the curve (AUC) were calculated using the R software package to evaluate prediction performance. A clinical nomogram was established and performance assessed with the discrimination curve.

Results

Risk factors, including demographics data, symptoms, laboratory and image findings were recorded for the 202 patients. Eight of the 52 variables that were entered into the selection process were selected via the best subset algorithm to establish the predictive model; they included gender, age, BMI, CRP, D-dimer, TP, ALB, and involved-lobe. Sensitivity, specificity and AUC were 0.91, 0.84 and 0.86 for the training dataset, and 0.87, 0.66, and 0.80 for the validation dataset.

Conclusions

We established an efficient and reliable clinical nomogram model which showed that gender, age, and initial indexes including BMI, CRP, D-dimer, involved-lobe, TP, and ALB could predict the risk of progression to severe COVID-19.

Introduction

Many novel coronavirus disease 2019 (COVID-19) cases have been detected in Wuhan, Hubei Province since December 2019. The rapid spread of the COVID-19 outbreak has caused a global pandemic. Until 11 June 2020, there were 83,064 confirmed patients and 4,634 deaths in 31 provinces in China, with a mortality rate of

5.58% [1]. Up to 11 June 2020, there were 7,273,958 cases confirmed globally with 413,372 deaths in 216 countries [2], with a mortality rate of 5.68%. According to Chinese epidemic statistics, the distribution of critical, severe and mild types of COVID-19 was 5%, 14%, and 81% respectively in the population [3]. Studies [4] have shown that mortality rates for severe COVID-19, common pneumonia, and absence of pneumonia are 5.88%, 0.12%, and 0% respectively, among patients diagnosed with COVID-19. Our objective was to establish a clinical nomogram to predict the risk of patient progression to severe disease, based on their initial examination, including clinical and imaging data, thereby curbing the mortality of COVID-19.

Methods

Study design and patient population

This retrospective study included 202 confirmed COVID-19 patients (≥18 years of age) admitted to the Fifth Affiliated Hospital of Sun Yat-sen University and Shiyan Taihe Hospital between January 17 and April 30, 2020. A confirmed case of COVID-19 was defined as; positive SARS-CoV-2 virus nucleic acids on the nasal and pharyngeal swab specimens by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay.

COVID-19 was diagnosed and classified clinically according to the new coronavirus pneumonia diagnosis and treatment plan (trial version 7) [5] drafted by the National Health Committee of the People's Republic of China. Clinical classification of COVID-19 was; (1) mild, with mild symptoms and no obvious signs of pneumonia on imaging, (2) moderate, with fever, respiratory-tract symptoms and obvious signs on imaging indicating pneumonia, (3) severe, with one of the following; (a) respiratory rate ≥30 beats per min (bpm), (b) mean oxygen saturation in the resting state ≤ 93%, (c) ratio of arterial oxygen partial pressure (PaO_2) to the fraction of inspiration (FiO_2) ≤300 mmHg (1 mmHg = 0.133 kPa), or (d) pulmonary imaging showing an increase in manifestations of >50% within 24~48 h, (4) critical, with one of the following, (a) respiratory failure requiring mechanical ventilation, (b) shock, or (c) intensive-care unit (ICU) admission due to multiple-organ failure. The non-severe group comprised mild and moderate cases, whereas the severe group comprised the severe and critical cases. The inclusion criteria were: 1) Admission within 7 days from the onset of symptoms, 2) completed laboratory or medical examinations and questionnaires, 3) presence of the first lung CT examination. All the participants were followed until the end of the disease course; cure or death. This retrospective observational study was approved by the Research Ethics Committee of The Fifth Affiliated Hospital of Sun Yat-sen University (Approval Series No. K153-1). The need for informed consent was waived due to the retrospective study design.

Clinical data

Clinical data, including basic demographics, symptoms, vital signs, clinical classification, and complications, were extracted from electronic medical records. Laboratory evaluations included total blood cell count, coagulation function, liver and kidney function, electrolyte levels, lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzyme MB (CK-MB), alpha-hydroxybutyrate dehydrogenase (α-HBDH), C-reactive protein (CRP), blood gas analysis and D-dimer if the patient was breathing room air. Categorical

variables were presented as frequency and percentages, whereas continuous variables as mean (±SD, standard deviation) and median (interquartile range (IQR) values.

CT scanning protocol

Each patient was placed in the supine position on the CT machine (uCT760 or Umi780, United Imaging, Shanghai, China; Precison32, Campo imaging, Shenyang, China) and scanned during the inspiratory phase. Images were reconstructed with a slice thickness of 1 mm and an interval of 1mm.

Lung CT images were screened by three imaging physicians who were blind to the RT-PCR results and clinical information. The CT images were independently read by two radiologists with more than 5 years' experience in the diagnosis of chest CT scans. In case of dispute, they discussed and reached a consensus that was reviewed by a senior imaging physician with more than 10 years of experience.

Feature Selection and Model Establishment

Patients were randomly assigned to the training dataset (n = 163, with 43 in the severe group) or the validation dataset (n = 39, with 10 in the severe group) at a ratio of 8:2. Univariate analysis was applied to select candidate features with significant differences ($p < 0.05$) between non-severe and severe groups. Best subset selection via an exhaustive algorithm was then performed to establish the predictive model.

The features were selected using the leaps and rms package in R (version 3.6.2) which were used to fit the logistic regression model and nomogram, respectively. A decision curve analysis was performed by calculating the net benefits for a range of threshold probabilities in the whole cohort to assess the clinical efficiency of the nomogram. The prediction performance of the logistic regression model was evaluated based on sensitivity, specificity, and area under the receiver operator characteristic (ROC) curve (AUC).

Results

1.High ratio of severe to critical COVID-19 patients

The study excluded 92 patients with an interval >7 days between the first lung CT examination/admission and onset of symptoms because it aimed to establish a nomogram prediction model in the early stage of COVID-19. Ultimately, 202 patients were included in the study; 149 non-severe and 53 severe cases (Figure. 1).

2.Original clinical characteristics of COVID-19 patients

Fifty-four clinical indexes were recorded and analyzed (Table 1, 2). The average age was 44 years, with a higher fraction of older patients in the severe than the non-severe group (P=0.000). The most common symptoms were fever (63.4%), cough (44.1%), fatigue (14.9%), and myalgia (14.4%). Most patients (68.8%) had abnormal chest CT findings. There was a higher number of lung lobes involved in the severe COVID-19 cases than in non-severe cases ($P < 0.05$). The most common imaging sign in COVID-19 patients was ground-glass opacity (GGO; Figure 2).

3. Selection of significant predictive factors and establishment of a clinical-nomogram model to predict the risk of progression to severe COVID-19.

The PaO_2 and $PaCO_2$ variables were excluded because the grouping of severe and non-severe cases involved these indexes; 52 variables were entered into the feature selection part.

The following 17 significant variables were obtained using univariate analysis P <0.05 (Table 3): Gender, age, underlying disease, hypertension, diabetes, BMI (Body Mass Index), temperature (TEMP), LYM, LDH/LYM, PLT, CRP (C-reactive protein), D-dimer, TP, ALB, α-HBDH, involved lobe, and the involved lung segment. An optimal subset of 8 factors was attained with subset selection method based on adjusted R^2, including gender (coefficient =-0.12), age (0.0030), BMI (0.017), CRP (0.0030), D-dimer (0.00037), TP (-0.014), ALB (-0.018) and involved-lobe (0.084). The model was established and analyzed according to the eight clinical indicators (Figure 3). The AUC in the training cohort was 0.91 (95% CI, 0.87-0.96) and 0.87 (95% CI, 0.76-0.99) in the validation cohort (Figure 4). The decision curve analysis (DCA) showed the nomogram had an overall net benefit of differentiating severe from the non-severe group for the majority of the reasonable threshold probabilities (Fig. 5).

Discussion

This study found that older males with more involved lung lobes, higher CRP, D-dimer and BMI, and lower TP and ALB on admission may have higher odds of severe COVID-19. A clinical nomogram model, comprising 8 factors, to predict the risk of progression to severe disease was developed and validated. The performance of this nomogram model was satisfactory with AUC 0.91 in the training dataset and 0.87 in the validation dataset. The nomogram model can be used by clinicians to estimate a patient's risk of developing severe illness and provide reliable evidence for early intervention to reduce mortality.

Nomogram analysis can generate an accurate individualized risk assessment through an intuitive and visual graphical model, compared with other predictive statistical methods [6, 7]. Several studies have reported risk factors for severe COVID-19 such as demographics, symptoms, laboratory, and imaging findings. Gong *et al* [8] found that old age, C-reactive protein, and lower albumin are associated with severe COVID-19. Huang *et al* [9] found that BMI ≥ 28 kg/m^2 was an independent risk factor in predicting severe illness in patients with COVID-19. Pulmonary imaging has been widely used to predict the severity of pulmonary diseases and patient survival rates [5, 10]. Abnormalities in the chest radiography were included in the COVID risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. High-resolution CT (HRCT) of the chest is critical for early detection, disease severity evaluation, and follow-up of COVID-19 patients [11]; therefore a predictor containing pulmonary imaging would be more credible. Gong *et al* [8] developed a nomogram that showed similar AUC in the training and validation dataset (0.91/0.85 vs 0.91/0.87) as this study, however, it did not include pulmonary imaging data. The nomogram in this study showed good differentiation performance indicated by AUC values in the training and validation datasets.

There were some limitations to the study: 1.) A relatively small sample. 2.) The data for nomogram establishment and validation are entirely from China, which limits the generalizability of the nomogram model. Further studies on different populations, outside China, with larger patient cohorts, are required.

Conclusions

An efficient and reliable clinical nomogram model for determining the progression of COVID-19 to the severe disease form was established. It was based on 8 factors that were comprehensive, relatively inexpensive, and easy to obtain from clinical data. This prediction model will help in making early assessments, regulating treatment, and containing the disease progression to severe COVID-19.

Abbreviations

COVID-19 Coronavirus disease 2019

SARS-CoV-2 Acute respiratory syndrome coronavirus 2

AUC Area under the curve

BMI Body Mass Index

CRP C-reactive protein

TP Total protein

ALB Albumin

RT-PCR Real-time reverse-transcriptase polymerase chain reaction

Bpm Beats per min

PaO_2 Arterial oxygen partial pressure

$PaCO_2$ Arterial partial pressure of carbon dioxide

FiO_2 Fraction of inspiration

ICU Intensive-care unit

CT Computerized tomography

LDH Lactate dehydrogenase

CK Creatine kinase

CK-MB Creatine kinase isoenzyme MB

α-HBDH Alpha-hydroxybutyrate dehydrogenase

SD Standard deviation

IQR Interquartile range

- ROC Receiver operator characteristic
- GGO Ground-glass opacity
- TEMP Temperature
- LYM Lymphocyte
- LDH/LYM Lactate dehydrogenase to Lymphocyte Ratio
- PLT Platelet
- DCA Decision curve analysis
- HRCT High-resolution CT

Declarations

Ethics approval and consent to participate

The study was approved by and carried out under the guidelines of the Ethical Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (Approval Series No. K153-1). All the study subjects provided their informed consent for the collection of samples and subsequent analysis.

Consent to publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this manuscript.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

Experimental conception and design, Changli Tu, Guojie Wang, Jing Liu, Hong Shan. Collection of samples, Changli Tu, Guojie Wang, Cuiyan Tan, Meizhu Chen, Hu Peng, Yingjian Liang, Yiying Huang, Zhenguo Wang, Jian Wu, Kongqiu Wang, Qinhuan Huang, Jin Huang, Xiaobin Zheng, Xiaorong Zhou, Xinran Liu,Ning Cui,Qizhen Cao,Qiang Han,Lin Xu,Zijun Xiang.

Performing the experiment, Changli Tu, Guojie Wang, Cuiyan Tan. Data analysis, Changli Tu, Guojie Wang, Ying Wang, Qiuyue Chen, Yayuan Geng, Na Guo, Xiaorong Zhou.

Contribution of reagents, materials and/or analysis tools, Yayuan Geng, Na Guo. Writing the paper, Changli Tu, Guojie Wang.

Critical review and approval, Jing Liu, Hong Shan.

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Tables

Table1 Demographics and Clinical Characteristics Among COVID-19 Patients

	All patients (n=202)	**Severe type (n=53)**	**Non-severe type(n=149)**
Characteristic			
Age, Median (IQR), y	44.0(32.0,59.0)	60.0(40.5,68.0)	40.0(31.0,54.0)
Gender			
Male, No./No.(%)	90/202(44.6)	28/53(52.8)	62/149(41.6)
Female, No./No.(%)	112/202(55.4)	25/53(47.2)	87/149(58.4)
BMI, Median (IQR),Kg/m^2	22.5(20.5,24.7)	22.3(20.3,24.4)	22.8(20.8,25.2)
Symptoms and signs, No./No.(%)			
Fever	128/202(63.4)	35/53(66.0)	93/149(62.4)
Cough	89/202(44.1)	23/53(43.4)	66/149(44.3)
Fatigue	30/202(14.9)	10/53(18.9)	20/149(13.4)
Myalgia	29/202(14.4)	8/53(15.1)	21/149(14.1)
Headache	18/202(8.9)	13/149(8.7)	5/53(9.4)
Diarrhea	12/202(5.9)	4/53(7.5)	8/149(5.4)
Shortness of breath	10/202(5.0)	4/53(7.5)	6/149(4.0)
Temperature, Median (IQR),℃	37.2(36.6,37.9)	37.7(36.7,38.0)	37.0(36.6,37.8)
Respiratory rate, Median (IQR),breaths/min	20(18,20)	20(16.5,20)	20(18,20)
Heart rate, Median (IQR),beats /min	89(79,100)	86(77,100)	89(80,100)
Blood pressure, Median (IQR),mmHg			
Systolic	126(119.140)	130(119,145)	125(118,140)
Diastolic	82(76,90)	85(76,90)	82(76,90)
Underlying disease, No./No.(%)	61/202(30.2)	28/53(52.8)	33/149(22.1
Hypertension	36/202(17.8)	18/53(34.0)	18/149(12.1)
Diabetes	16/202(7.9)	11/53(20.8)	5/149(3.3)
Coronary heart disease	10/202(5.0)	2/53(3.8)	8/149(5.4)
Tumor	9/202(4.5)	2/53(3.8)	7/149(4.7)
Other disease	20/202(9.9)	16/53(30.2)	4/149(2.7)

Table 2 Laboratory and Image Findings Among COVID-19 Patients

	All patients（n=202）	Severe type(n=53)	Non-severe type(n=149)
Laboratory findings, Median (IQR)			
White blood cell count,×10^9/L	5.13(4.07,7.17)	4.53(3.48,6.57)	5.40(4.17,7.38)
Neutrophil cell count,×109/L	3.22(2.31,4.80)	3.08(2.12,4.36)	3.23(2.32,4.91)
Lymphocyte count,×10^9/L	1.32(0.99,1.72)	1.08(0.71,1.54)	1.37(1.07,1.84)
Neutrophil to Lymphocyte Ratio,%	2.31(1.74,3.83)	2.67(1.86,4.23)	2.24(1.60,3.50)
Monocyte count,×109/L	0.44(0.32,0.59)	0.41(0.26.0.67)	0.46(0.00,0.58)
Hemoglobin, Mean(SD),g/L	139.1(21.8)	131.9(27.3)	141.7(19.0)
Platelet count, ×109/L	185.5(152.0,228.0)	154.0(126.0,193.5)	199.0(165.0,238.5)
C-reactive protein, mg/L	9.75(1.70,26.82)	26.60(9.13,48.70)	6.95(1.11,18.54)
Prothrombin time, S	12.4(11.6,13.1)	12.7(12.1,13.2)	12.2(11.6,12.9)
Activated partial thromboplastin time, S	31.4(29.2,33.9)	32.6(29.6,34.3)	31.0(29.1,33.4)
Fibrinogen, g/L	3.76(2.98,4.81)	3.91(3.26,4.69)	3.67(2.88,4.88)
D-dimer,ng/ml	1.19(0.14,104.0)	109.0(0.93,167.0)	0.43(0.09,56.5)
Alanine transaminase,U/L	18.0(11.9,29.0)	21.3(13.7,29.3)	17.0(11.0,27.7)
Aspartate transaminase,U/L	21.3(17.0,28.0)	27.0(20.7,33.6)	20.0(16.1,26.0)
Total bilirubin(TP), μmol/L	9.45(7.35,13.43)	9.40(7.67,13.65)	9.50(7.20,13.40)
Direct bilirubin, μmol/L	3.70(3.00,5.03)	4.28(3.00,5.42)	3.60(2.95,4.76)
Indirect bilirubin,μmol/L	6.00(4.09,8.53)	5.97(4.04,8.30)	6.04(4.21,8.65)
Total protein, Mean(SD),g/L	70.9(5.3)	68.3(5.8)	71.9(4.9)
Albumin(ALB),Mean(SD),g/L	41.6(4.9)	38.0(3.3)	42.9(4.7)
Globulin, g/L	29.3(26.4,32.0)	30.4(26.4,33.3)	28.9(26.3,31.7)
Lactic dehydrogenase,U/L	193.5(158.0,251.0)	212.0(179.5,272.0)	185.0(153.5,237.0)
α-hydroxybutyrate dehydrogenase,U/L	135.0(114.0,162.3)	161.0(135.0,201.5)	129.0(109.5,154.0)
Creatine kinase,U/L	77.5(54.0,114.0)	77.0(59.0,121.5)	78.0(52.0,112.5)
Creatine kinase-MB, U/L	11.4(9.1,15.0)	13.7(10.5,16.6)	11.0(9.0,14.0)
Urea nitrogen, mmol/L	3.80(2.98.4.58)	4.10(3.50,5.50)	3.46(2.90.4.40)
Creatine, μmol/L	72.9(59.2,85.1)	71.8(56.6,90.8)	73.5(60.0,84.4)
Sodium,mmol/L	139.1(137.0,141.2)	137.6(136.0,139.7)	140.0(137.6,142.0)

Chlorine,mmol/L	101.0(99.0,103.0)	100.0(96.8,103.0)	101.2(99.4,103.1)
Potassium,mmol/L	3.86(3.59,4.12)	3.82(3.51,4.12)	3.86(3.64,4.13)
PaO2,Mean(SD),mmHg	97.5(15.1)	86.3(11.9)	101.6(14.1)
PaCO2Mean(SD),mmHg	39.2(3.6)	37.1(4.0)	40.0(3.1)
CT characteristic			
Abnormal CT,No./No.(%)	139/202(68.8)	48/53(90.6)	91/149(61.1)
Involved lung lobe, Median (IQR)	2(0,4)	5(2,5)	1(0,3)

Table3 Variables to the establishment of a clinical-nomogram model to predict the progression of COVID-19 to severe disease

Variations	F value	*p*-value
Gender	4.59	3.00E-02
Age	29.84	1.75E-07
Underlying-disease	14.88	1.70E-04
Hypertension	8.87	3.30E-03
Diabetes	8.58	3.90E-03
BMI	8.07	5.10E-03
Temperature	7.24	7.90E-03
LYM	11.73	7.80E-04
LDH/LYM	8.11	4.90E-03
PLT	19.09	2.23E-05
CRP	17.22	5.38E-05
D-dimer	17.34	5.08E-05
TP	20.1	1.39E-05
ALB	57.87	2.21E-12
a-HBDH	7.26	7.80E-03
Involved-lobe	68.01	5.46E-14
Involved-segment	69.73	2.96E-14

Table4 Performance of nomogram for early prediction of severe COVID-19

	Severe COVID-19 vs Non-severe COVID-19		
	AUC (95% CI)	Sensitivity (%)	Specificity (%)
Training cohort(n=163)	0.91(0.87,0.96)	84	86
Validation cohort(n=39)	0.87(0.76,0.99)	66	80

Figures

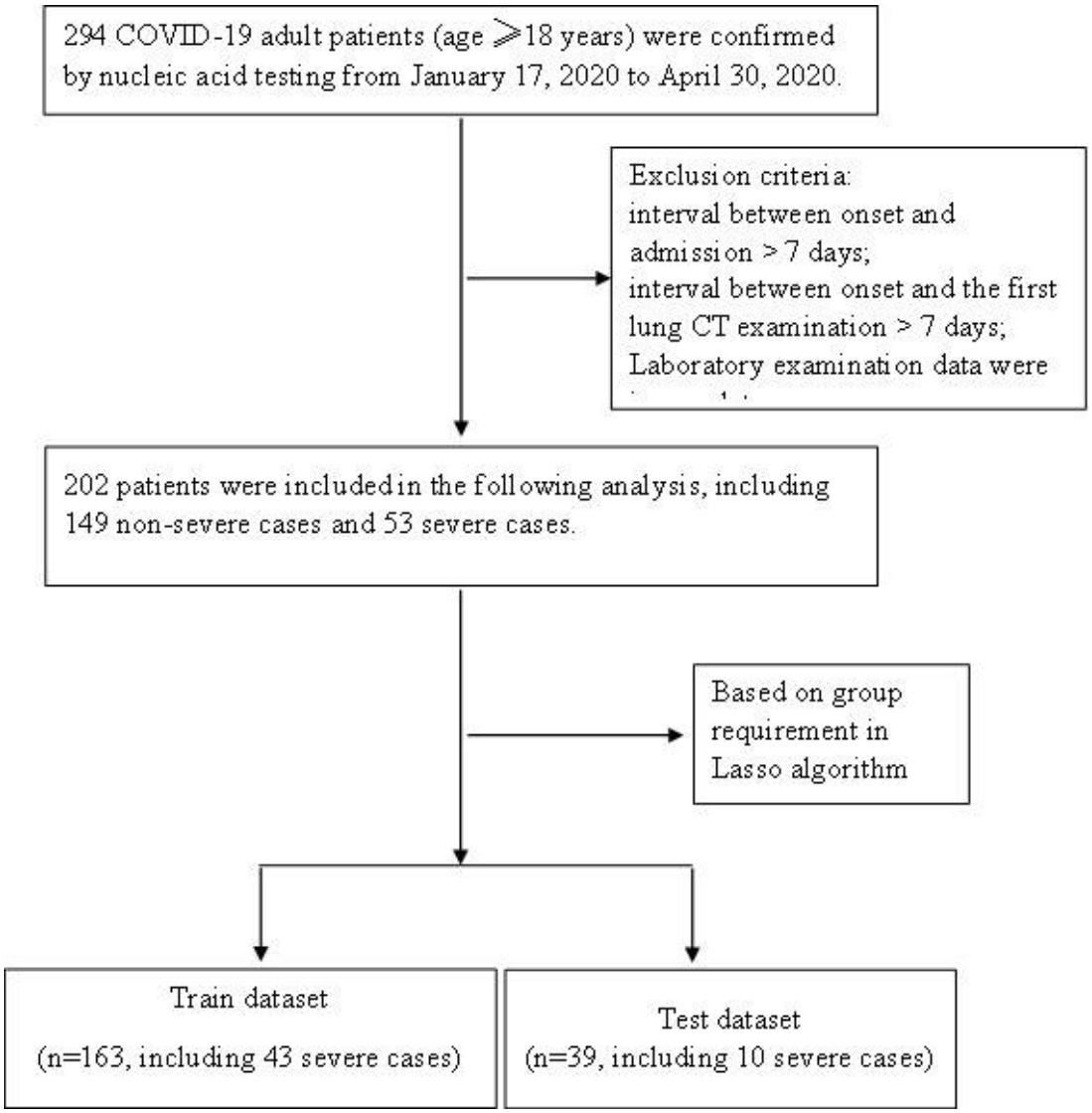

Figure 1

Flow chart for screening for COVID-19.

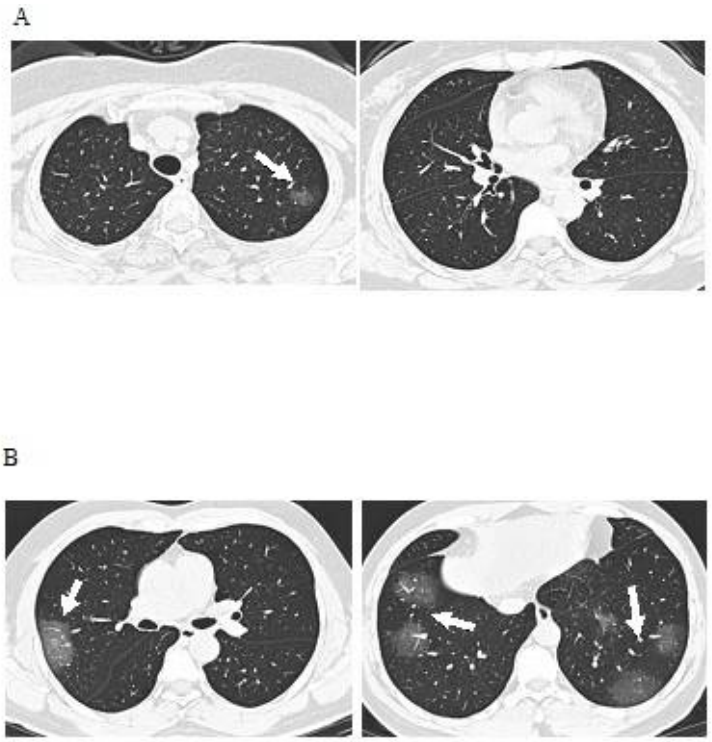

Figure 2

Typical chest images of COVID-19 patients. A. A 35-year-old male patient with mild COVID-19, was admitted to the hospital 3 days after developing a fever. Axial thin-section CT images show ground-glass opacity (GGO) in the left upper lobe. B. A 44-year-old male patient with severe COVID-19, presenting with fever and cough, was admitted to the hospital 1 day later. Axial thin-section CT images show multiple GGO in bilateral-lung.

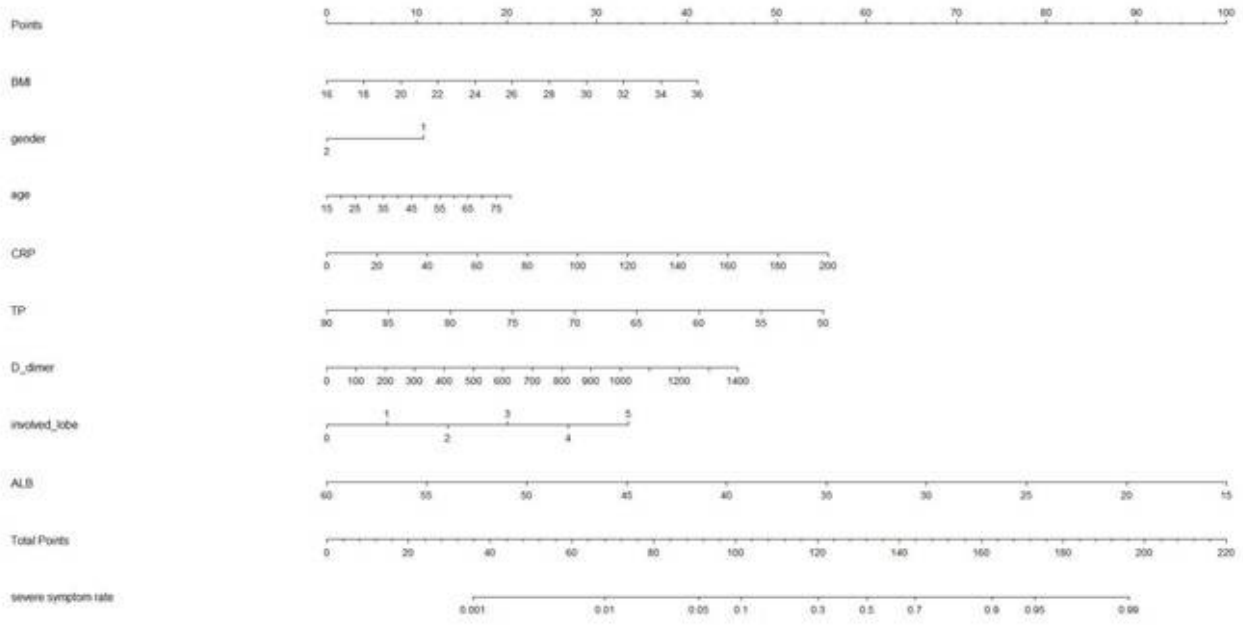

Figure 3

Nomogram predicting the probability of severe disease in patients with COVID-19. The nomogram, combining BMI, gender, age, CRP, TP, D-dimer, involved-lobe, and ALB, developed in the training set.

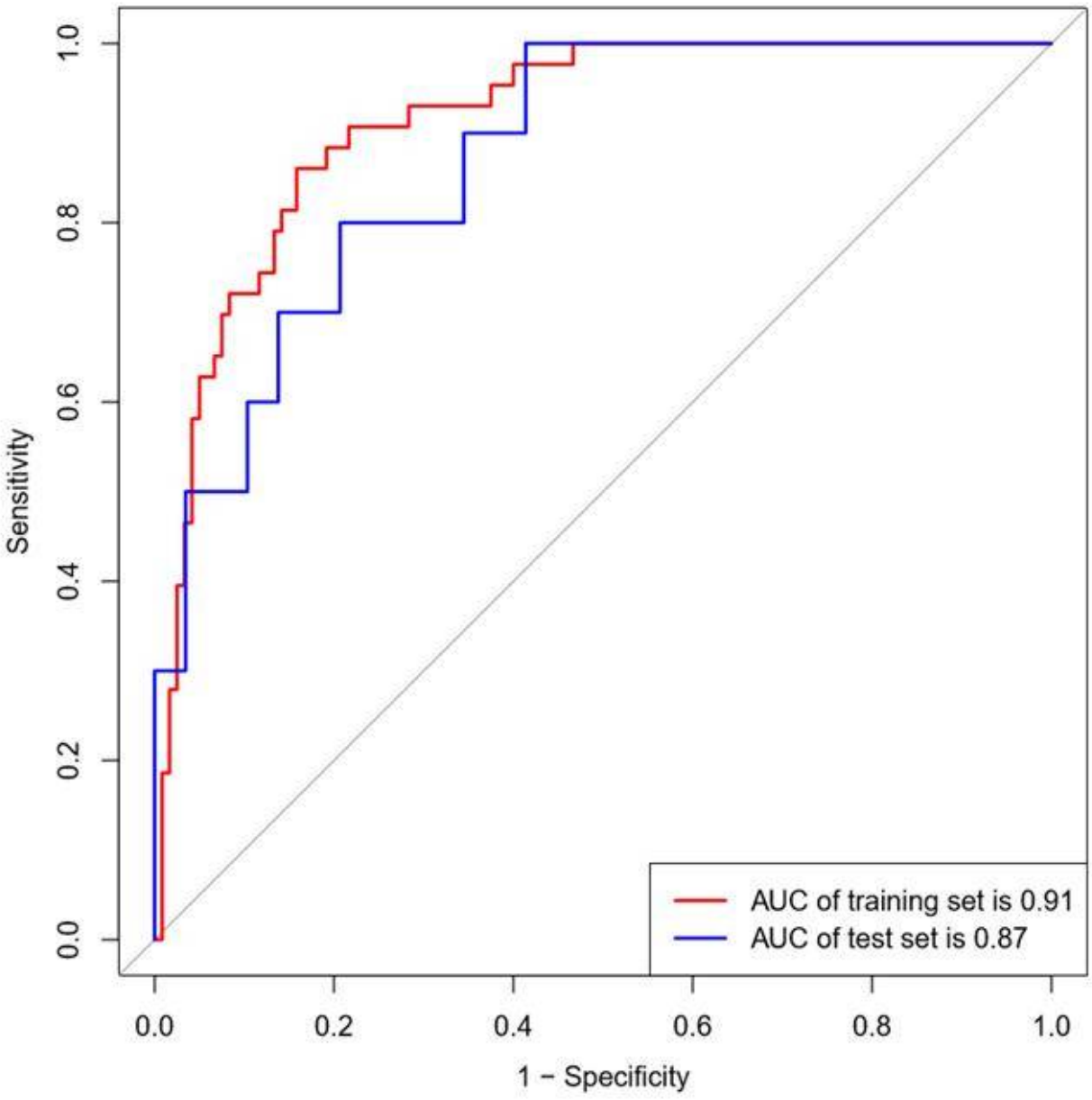

Figure 4

The ROC curves of the nomogram. The ROC curves of the nomogram in the training and validation sets, respectively.

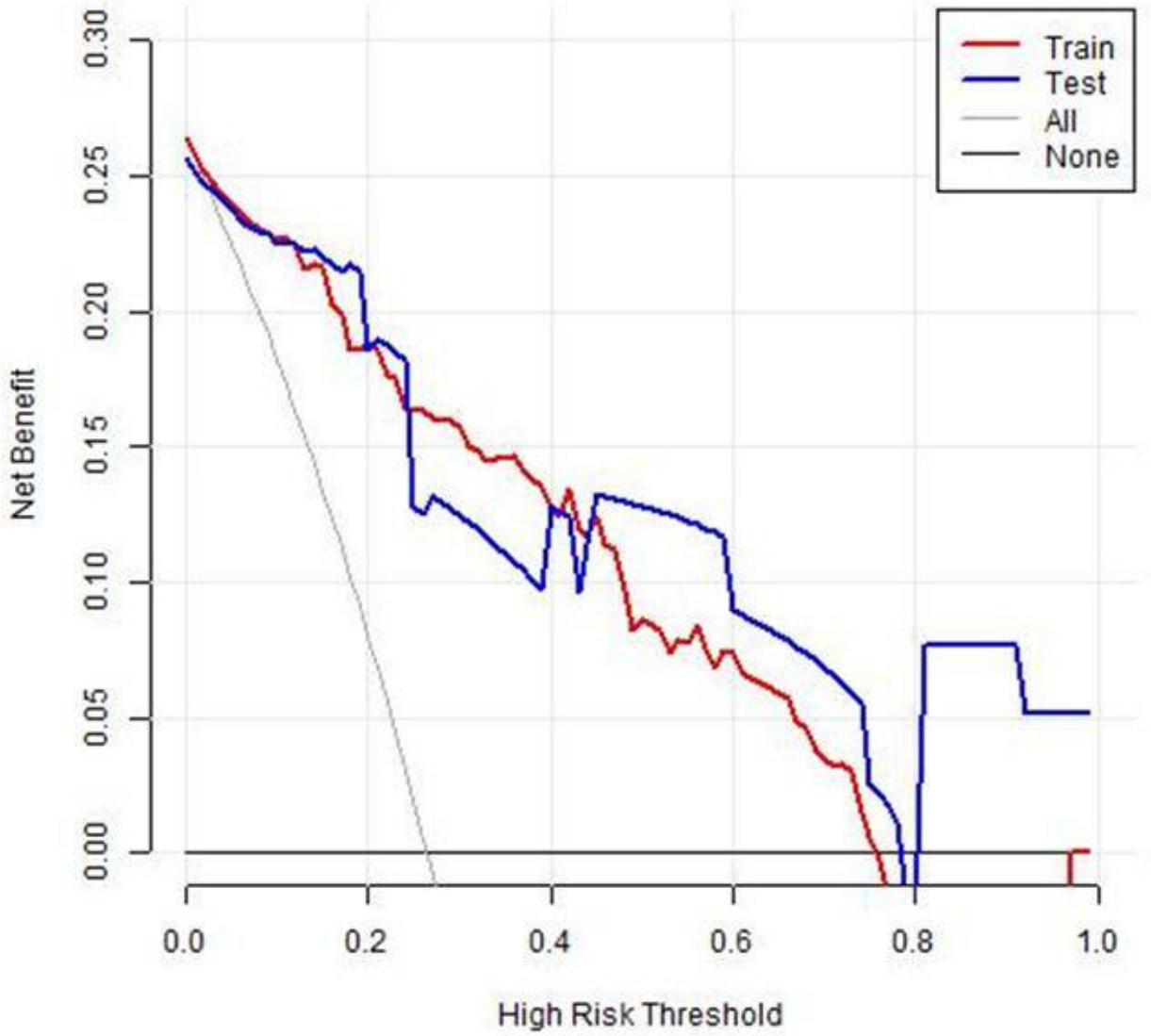

Figure 5

Decision curve analysis for the nomogram. The y-axis indicates the net benefit; the x-axis indicates threshold probability. The blue and red lines represent the net benefit of the nomogram in the training and validation sets, respectively. This nomogram outperformed simple diagnoses such as those categorising patients as severe (gray line) or non-severe (blackline) across the full range of threshold probabilities at which a patient would be diagnosed as severe.