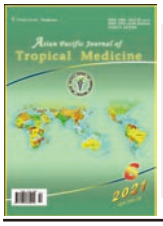

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A nomogram for predicting acute respiratory distress syndrome in COVID-19 patients

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ABSTRACT

Objective: To predict the in-hospital incidence of acute respiratory distress syndrome (ARDS) in COVID-19 patients by developing a predictive nomogram.

Methods: Patients with COVID-19 admitted to Changsha Public Health Centre between 30 January 2020, and 22 February 2020 were enrolled in this study. Clinical characteristics and laboratory variables were analyzed and compared between patients with or without ARDS. Clinical characteristics and laboratory variables that were risk factors of ARDS were screened by the least absolute shrinkage and selection operator binary logistic regression. Based on risk factors, a prediction model was established by logistic regression and the final nomogram prognostic model was performed. The calibration curve was applied to evaluate the consistency between the nomogram and the ideal observation.

Results: A total of 113 patients, including 99 non-ARDS patients and 14 ARDS patients were included in this study. Eight variables including hypertension, chronic obstructive pulmonary disease, cough, lactate dehydrogenase, creatine kinase, white blood count, body temperature, and heart rate were included in the model. The area under receiver operating characteristic curve, specificity, sensitivity, and accuracy of the full model were 0.969, 1.000, 0.857, and 0.875, respectively. The calibration curve also showed good agreement between the predicted and observed values in the model.

Conclusions: The nomogram can be used to predict the in-hospital incidence of ARDS in COVID-19 patients.

KEYWORDS: Nomogram; Acute respiratory distress syndrome; COVID-19

1. Introduction

Evidence indicated that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as the pathogen of COVID-19, was a new type of coronavirus[1]. It could result in multiple system infections in humans, especially in the respiratory system, and in some cases, it may lead to acute respiratory distress syndrome (ARDS), even multiple organ failure and death with the progression of the disease[2].

ARDS is one of the most common complications of COVID-19, and it is more likely to lead to poor clinical outcomes[3]. An observation study showed that 75% of 36 patients with COVID-19 were transferred to the intensive care unit (ICU) due to the development of ARDS[4]. Another report by Huang[5] *et al*. reported a proportion of 85%. Early identification and prediction of the incidence of ARDS are extremely important. However, the accurate model for predicting the risk of developing ARDS in patients with COVID-19 is limited. Nomogram, as a statistical model constructed based on different clinical and laboratory variables, has been widely applied to predict clinical outcomes in different diseases[6,7].

Therefore, in this study, we analyzed the clinical characteristics in COVID-19 patients with ARDS and explored an easily applicable nomogram to provide further guidance on medical treatment.

2. Subjects and methods

2.1. Patients and study design

This was a retrospective single-center study conducted between 30 January 2020 and 22 February 2020. We analyzed data of patients

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with COVID-19 admitted to Changsha Public Health Centre, which was the only designated tertiary hospital for COVID-19 patients in Changsha. All the patients were diagnosed with SARS-CoV-2 infection based on the World Health Organization interim guidance[8]. Inclusion criteria were set as follows: age ⩾18 and confirmed diagnosis of COVID-19. Patients missing >5% individual data and age <18 were excluded. This study was approved by the institutional ethics board of the Second Xiangya Hospital, Central South University (Changsha, China, No. LYF2020044).

2.2. Study variables

All candidate predictors were collected based on relevant literature reported[2–5] and associated clinical evidences. We collected the patient demographic information (age and gender); history of travel within the past two weeks, body temperature, systolic blood pressure, diastolic blood pressure, heart rate, and duration (days) from illness onset to hospital admission; underling diseases [hypertension, cardiovascular disease, diabetes, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and chronic liver disease], laboratory tests [erythrocyte sedimentation rate, C-reactive protein, procalcitonin, liver and renal function, blood chemistry, coagulation test, complete blood count, lactate dehydrogenase (LDH) and creatine kinase (CK)], and symptoms of onset illness.

2.3. Outcomes

ARDS was diagnosed by a decrease in the PaO_2/FiO_2 index below 300 mmHg according to the Berlin definition[9]. Arterial blood gas analysis was performed for patients who had a dyspnea during hospitalization. In-hospital incidence of ARDS was calculated.

2.4. Variables selection and model establishment

In the study, there were several variables, while the number of patients was relatively low. To avoid overfitting of the model, the least absolute shrinkage and selection operator (LASSO) algorithm was used to further screen the predictive variables among previously selected variables. Ten-fold cross-validation was utilized for the tuning parameter (lambda) selection in the LASSO model. A prediction model was established by logistic regression and the final nomogram prognostic model was performed. Moreover, calibration curves were plotted to improve the perfect nomogram's prediction.

2.5. Statistical analysis

All variables of the patients were presented as means±standard deviations or medians (interquartile ranges, IQR) for continuous variables, and categories variables were presented as frequencies and percentages. The groups for normally and skewed distributed continuous variables used one-way ANOVA and Kruskal-Wallis tests, respectively, and categorical variables used the *chi*-squared test. The LASSO binary logistic regression analysis was performed by the *R* package "glmet". The nomogram and decision curve were established by the "rms" package and packages *R*. The receiver operating characteristic curves were plotted and the area under receiver operating characteristic curve was accessed. We used 500 bootstraps resamples to compute the area under receiver operating characteristic curve with a 95% *CI*. Then we displayed the sensitivity, specificity, and accuracy of the stepwise model by bootstrap. The statistical analyses were performed with statistical packages *R* (http://www.R-project.org) and Empower-Stats. A *P*-value <0.05 was considered statistically significant.

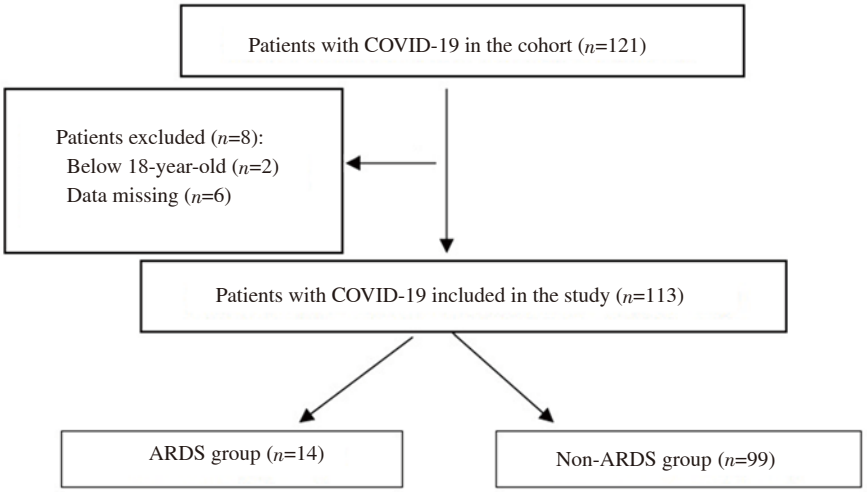

Figure 1. Flowchart for patients' enrollment and study design.

3. Results

3.1. Base clinical characteristics

Initially, a total of 121 COVID-19 patients were involved. However, 16 patients were excluded based on certain criteria discussed previously, a total of 113 patients including 14 patients in the ARDS group and 99 patients in the non-ARDS group were involved in this study (Figure 1). In this cohort study, the baseline characteristics of the patients were shown in Table 1. The patients who developed ARDS were older, had higher body temperature and faster heart rates, and they were also more likely to have hypertension and symptoms of fever and dyspnea (all $P<0.05$). Laboratory tests were performed at the patients' first admission to the hospital. The level of C-reactive protein, LDH, CK, and aspartate aminotransferase were significantly higher in ARDS patients than those without ARDS (all $P<0.05$). Prothrombin time was significantly longer, and the levels of albumin, white blood count (WBC), lymphocyte, and monocyte were significantly lower in ARDS patients (all $P<0.05$).

3.2. Feature extraction and selection

The LASSO algorithm was used to extract predictive variables. The best match variables were selected from the value of lambda that gives minimum mean cross-validated error. In the end, only 8 variables were extracted from the 50 variables (Figure 2A and 2B), including hypertension, COPD, cough, LDH, CK, WBC, body temperature, and heart rate.

3.3. Nomogram construction and validation

To better predict the ratio of developing ARDS, we created a nomogram which could represent different patients' prediction based on their characteristics (Figure 3A). Eight variables including hypertension, COPD, cough, LDH, CK, WBC, body temperature, and heart rate were regarded as highly clinically appropriate to accumulatively determine ARDS occurrences. High body temperature, fast heart rate, cough as well as comorbidities including COPD and hypertension were risk factors for developing ARDS. Risk of developing ARDS was also increased with elevating levels of LDH and CK, while decreased level of WBC.

In the nomogram, the total points were obtained by adding the point of each variable, which were corresponding to the incidence of ARDS.

The calibration curve of the nomogram demonstrated a good fit (Figure 3B and Figure 3C). The calibration curve also showed good consistency between the predicted and observed values in the model. The predictive capability of the full model was shown in Figure 3C. The area under receiver operating characteristic curve, specificity, sensitivity, and accuracy of the full model were 0.969, 1.000, 0.857 and 0.875, respectively. The decision curve showed that the nomogram had superior standardized net benefit and was good at predicting the possibility of the patients to develop ARDS (Figure 3D).

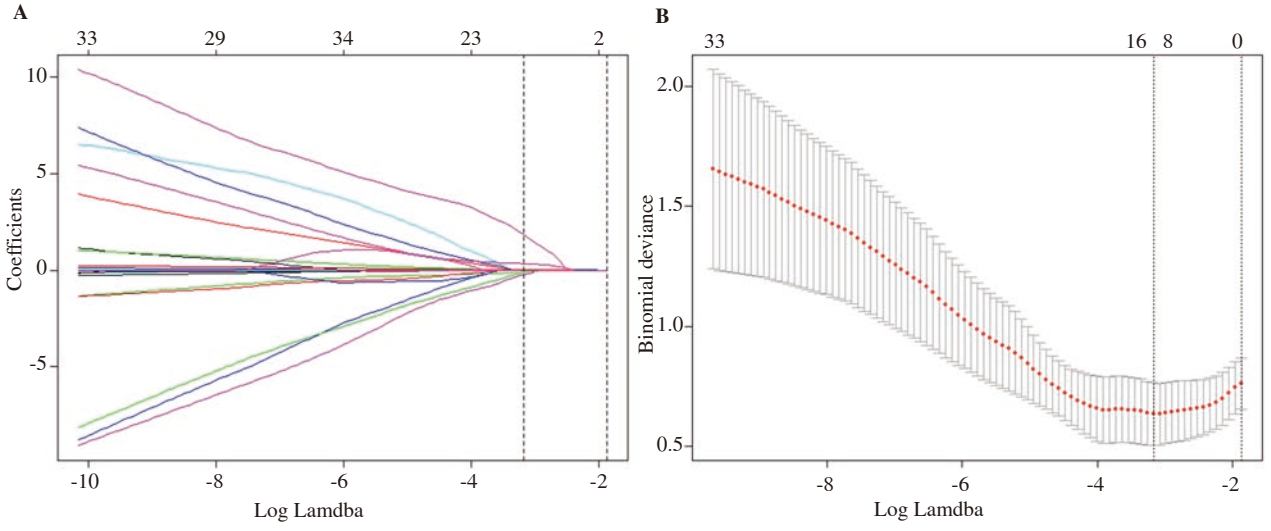

Figure 2. The least absolute shrinkage and selection operator algorithm and 10-fold cross validation were used to extract the optimal subset of all variables. (A) Optimal variables selection according to the area under the curve value. When the value in (λ) increased to -3.174 8, the area under the curve value reached the peak corresponding to the optimal number of predictive variables. (B) The least absolute shrinkage and selection operator coefficient profiles of the 50 variables. The vertical line was drawn at the value selected by 10-fold cross validation, where the optimal λ resulted in 8 nonzero coefficients.

Table 1. The demographic and baseline characteristics of the study patients.

Characteristics	Non-ARDS (*n*=99)	ARDS (*n*=14)	$\chi^2/T/W$	*P*-value
Age, mean±SD (years)	44.90±17.30	55.30±14.60	-2.44	0.030
Gender, *N* (%)				
Female	48 (48.48)	3 (21.43)	3.63	0.084
Male	51 (51.52)	11 (78.57)		
Hubei exposure, *N* (%)	65 (65.66)	10 (71.43)	0.18	0.770
Temperature, mean±SD (℃)	37.00±0.60	37.60±0.80	-2.94	0.004
Systolic pressure, mean±SD (mmHg)	125.20±13.00	122.30±12.00	0.85	0.378
Diastolic pressure, mean±SD (mmHg)	79.20±9.30	76.50±8.00	1.14	0.412
Heart rate, mean±SD (per minute)	87.70±12.70	101.30±11.20	-4.18	<0.001
Days from illness onset to first hospital admission, IQR (Q1-Q3) (d)	4.00 (3.00-7.00)	4.50 (3.00-6.75)	-0.08	0.829
Any comorbidity, *N* (%)				
Hypertension	12 (12.12)	5 (35.71)	5.34	0.036
Cardiovascular disease	2 (2.02)	1 (7.14)	1.25	0.330
Diabetes	5 (5.05)	1 (7.14)	0.11	0.557
Cerebrovascular disease	1 (1.01)	0 (0.00)	0.14	1.000
Chronic obstructive pulmonary disease	0 (0.00)	1 (7.14)	1.30	0.125
Chronic liver disease	1 (1.01)	1 (7.14)	2.65	0.233
Laboratory testing				
White blood cell count, mean±SD ($\times 10^9$/L)	4.90±1.50	4.10±1.90	2.10	0.022
Neutrophil count, IQR (Q1-Q3) ($\times 10^9$/L)	2.91 (2.21-3.57)	2.87 (2.09-3.18)	-0.15	0.616
Lymphocyte count, IQR (Q1-Q3) ($\times 10^9$/L)	1.25 (0.91-1.79)	0.70 (0.43-0.92)	2.82	<0.001
Monocyte count, IQR (Q1-Q3) ($\times 10^9$/L)	0.38 (0.28-0.45)	0.14 (0.09-0.33)	2.34	0.002
Hemoglobin, g/L	129.90±20.30	135.40±14.60	-1.26	0.403
Platelet count, IQR (Q1-Q3) ($\times 10^9$/L)	169.00 (144.50-229.50)	149.00 (135.50-162.75)	1.51	0.082
C-reactive protein, IQR (Q1-Q3) (mg/L)	11.00 (3.83-32.80)	33.00 (21.92-74.80)	-2.94	<0.001
Procalcitonin, IQR (Q1-Q3) (ng/mL)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	-0.96	0.610
Erythrocyte sedimentation rate, IQR (Q1-Q3) (mm/h)	38.00 (15.75-70.00)	51.50 (45.50-66.00)	-1.03	0.250
Alanine aminotransferase, IQR (Q1-Q3) (U/L)	20.00 (14.35-27.00)	21.35 (19.21-31.75)	-1.31	0.132
Aspartate aminotransferase, IQR (Q1-Q3) (U/L)	24.70 (19.94-30.00)	39.50 (25.50-51.72)	-2.40	0.014
Albumin, IQR (Q1-Q3) (g/L)	39.00 (36.00-42.00)	34.00 (31.89-35.64)	2.12	<0.001
Total bilirubin, mean±SD (mmol/L)	12.20±5.40	12.80±5.10	-0.38	0.647
Direct bilirubin, IQR (Q1-Q3) (mmol/L)	3.88 (2.64-5.45)	4.25 (3.77-6.03)	-1.08	0.188
Lactate dehydrogenase, mean±SD (U/L)	177.40±59.20	278.20±89.40	-4.10	<0.001
Creatinine, mean±SD (μmol/L)	55.90±24.30	53.40±13.40	0.57	0.913
Blood urea nitrogen, IQR (Q1-Q3) (mmol/L)	4.33 (3.15-5.16)	5.00 (4.20-6.22)	-0.66	0.052
Uric acid, mean±SD (μmol/L)	272.60±105.90	246.40±77.20	1.13	0.423
Prothrombin time, mean±SD (s)	11.80±0.90	12.50±0.70	-3.66	0.003
Activated partial thromboplastin time, mean±SD (s)	33.20±4.20	32.40±3.20	0.86	0.553
D-dimer, IQR (Q1-Q3) (μg/mL)	0.19 (0.12-0.39)	0.38 (0.13-0.49)	-1.06	0.296
Creatine kinase, IQR (Q1-Q3) (U/L)	75.00 (48.00-105.50)	127.50 (63.17-495.00)	-2.18	0.019
Creatine kinase-MB, IQR (Q1-Q3) (U/L)	10.00 (6.80-13.00)	11.10 (7.30-14.78)	-0.60	0.510
Signs and symptoms, *N* (%)				
Fever	63 (63.63)	14 (100.0)	7.47	0.004
Fatigue	32 (32.32)	5 (35.71)	0.06	0.770
Cough	51 (51.51)	10 (71.43)	1.96	0.252
Anorexia	3 (3.03)	0 (0.00)	0.44	0.509
Myalgia	9 (9.09)	2 (14.29)	0.38	0.625
Dyspnea	7 (7.07)	6 (42.86)	15.43	0.001
Expectoration	31 (31.31)	2 (14.29)	1.72	0.228
Sore throat	12 (12.12)	0 (0.00)	1.90	0.356
Diarrhea	3 (3.03)	0 (0.00)	0.44	0.510
Nausea	1 (1.01)	0 (0.00)	0.14	0.706
Dizziness	4 (4.04)	2 (14.29)	2.56	0.160
Headache	5 (5.05)	2 (14.29)	1.80	0.208

ARDS: acute respiratory distress syndrome. *Chi*-square test for percentage, *t*-test for mean±SD, and rank sum test for median (IQR).

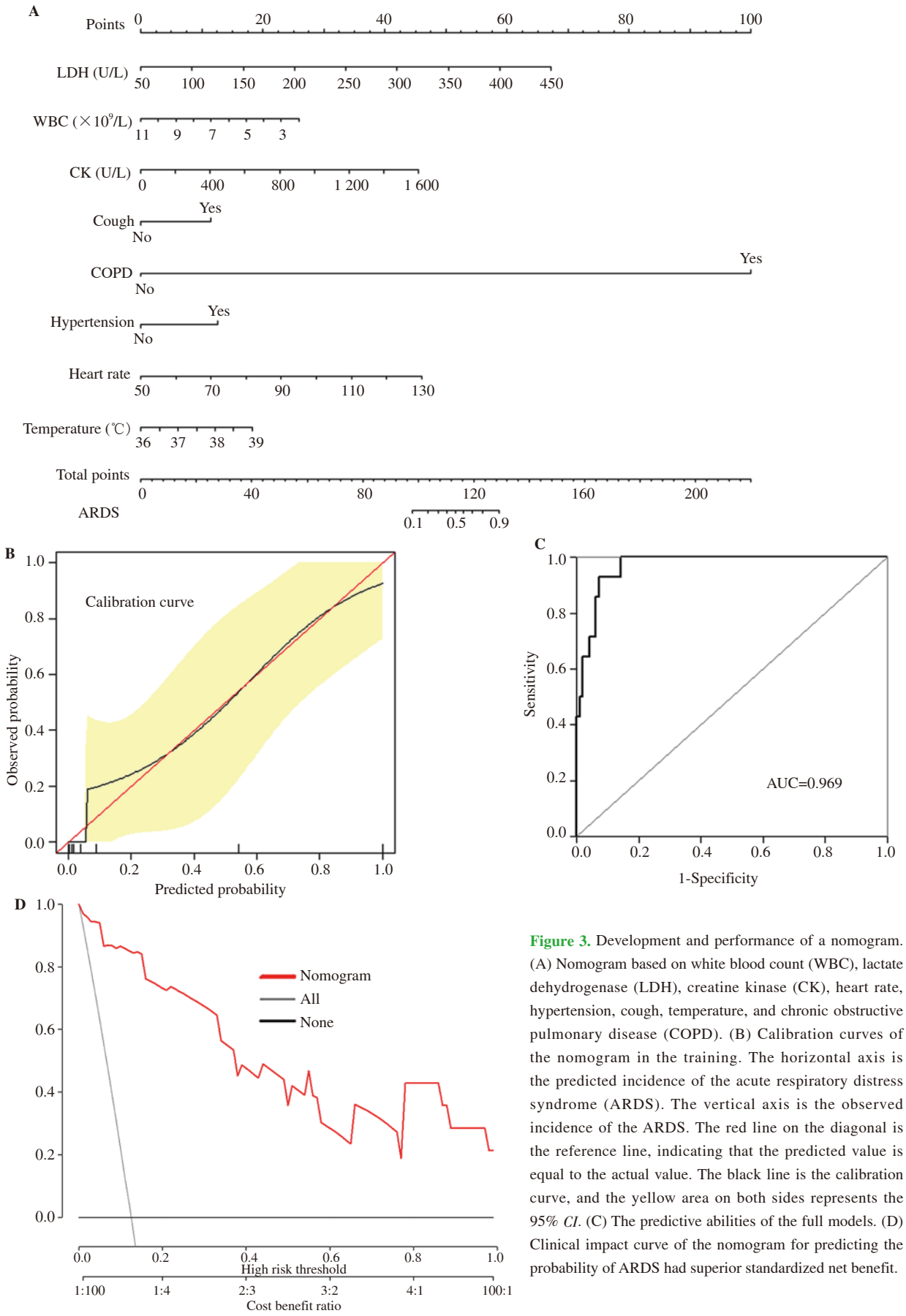

Figure 3. Development and performance of a nomogram. (A) Nomogram based on white blood count (WBC), lactate dehydrogenase (LDH), creatine kinase (CK), heart rate, hypertension, cough, temperature, and chronic obstructive pulmonary disease (COPD). (B) Calibration curves of the nomogram in the training. The horizontal axis is the predicted incidence of the acute respiratory distress syndrome (ARDS). The vertical axis is the observed incidence of the ARDS. The red line on the diagonal is the reference line, indicating that the predicted value is equal to the actual value. The black line is the calibration curve, and the yellow area on both sides represents the 95% *CI*. (C) The predictive abilities of the full models. (D) Clinical impact curve of the nomogram for predicting the probability of ARDS had superior standardized net benefit.

4. Discussion

Severe acute respiratory syndrome coronavirus 2, the virus which is responsible for coronavirus disease, uses an angiotensin-2-converting enzyme as a cell receptor in humans. Available data suggests that around 40% of patients with COVID-19 developed ARDS[10]. Early evaluating and predicting the in-hospital incidence of ARDS in patients can help to improve their clinical prognosis. In this study, we established a model based on 8 variables from the data of 113 patients with COVID-19, including COPD, hypertension, cough, heart rate, body temperature, WBC, LDH and CK, and the model performed well in predicting incidence of ARDS.

In this model, high body temperature, fast heart rate, and cough were risk factors (Figure 3A), which were all common clinical characteristics of pneumonia presented in previous studies[11–15]. Moreover, higher body temperature and elevated heart rate in pneumonia were associated with severe inflammation response and hypoxia, which also showed a significant higher prevalence in ARDS patients[15,16]. In this study, we speculated that elevated heart rates occurred in ARDS group due to systemic inflammatory reaction and intense sympathetic activation. Researches showed that WBC was an indicator of the systemic inflammatory response, and could be a potential marker for evaluating the severity and prognosis in various disorders[17,18]. However, our results suggested that WBC decreased with the increasing incidence of ARDS in COVID-19 patients (Figure 3A). The reason may be explained by the different types of pathogen infections. Previous studies verified that SARS-CoV-2 could invade the respiratory system, impair cells and tissues, induce immune reaction which results in changes of peripheral white blood cells, leading to decreased leukocytes and lymphocytes[19–21]. In addition, researches demonstrated that patients with comorbidity were more likely to have poor clinical outcomes[22]. COPD was one of the maximum features in our model (Figure 3A). Experimental and clinical studies verified that COPD patients were more susceptible to pathogen infection, resulting in impaired lung function and the incidence of ARDS[23].

In our study, the relative maximum features were LDH and CK. The levels of LDH and CK significantly increased in patients with ARDS. LDH and CK were not only markers of inflammation but also indicators of prognosis in critical illness[24,25]. Liu *et al*.[26] reported that patients with acute lung injury also had elevated levels of enzymes including LDH and CK due to inflammation and oxidative stress. Esteves *et al*.[27] found that LDH was a diagnostic biomarker of pneumocystis pneumonia in patients, which was in agreement with our results. Recent studies also reported that, with the increasing level of viral load detected from respiratory tracts, lung functions were getting worse in COVD-19 patients[26]. Finally, the eight variables discussed above were selected as predictive indexes by LASSO regression.

To the best of our knowledge, this is one of the first studies to develop a nomogram for predicting the in-hospital incidence of ARDS in COVID-19 patients, which would help physicians calculate the probability of ARDS and adjust a patient's individualized medical treatments accordingly. Furthermore, patients who are more likely to develop ARDS during hospitalization could be monitored closely and moved to ICU promptly. Individualized managements including ventilation support can be applied earlier too. Considering that the incidence of ARDS in the cohort was about 12.38% (14/113), this study provides a useful tool for predicting ARDS in COVID-19.

However, there are limitations. (1) The sample size is relatively small and the nomogram needs to be validated by a larger population. (2) All the patients included were Chinese, so caution must be considered while applying the proposed nomogram to patients of other ethnicities. (3) This study was retrospective and there might be patient selection biases though we tried our best to minimize the bias by analyzing all the possible factors including underling comorbidities, signs, symptoms and laboratory test results. The model needs to be validated for future studies with larger sample sizes that can be conducted in multi-centers. Further studies should focus on finding effective treatments like drugs and interventions for patients with early-stage of ARDS.

In the study, the proposed nomogram can be used to predict the in-hospital incidence of ARDS in COVID-19 patients which would help physicians make individualized treatment plans.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

Conception and design by N.D., Y.Z., G.Y., X.C.; Administrative support by X.C.; Provision of study materials or patients by N.D.; Collection and assembly of data: N.D.; Data analysis and interpretation: Y.Z., G.Y., X.C.; Manuscript writing: N.D., Y.Z.; Final approval of manuscript by all the authors.

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