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Original Article

Identification and validation of prognostic factors in patients with COVID-19: A retrospective study based on artificial intelligence algorithms ☆

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ABSTRACT

Background: Novel coronavirus disease 2019 (COVID-19) is an ongoing global pandemic with high mortality. Although several studies have reported different risk factors for mortality in patients based on traditional analytics, few studies have used artificial intelligence (AI) algorithms. This study investigated prognostic factors for COVID-19 patients using AI methods.

Methods: COVID-19 patients who were admitted in Wuhan Infectious Diseases Hospital from December 29, 2019 to March 2, 2020 were included. The whole cohort was randomly divided into training and testing sets at a 6:4 ratio. Demographic and clinical data were analyzed to identify predictors of mortality using least absolute shrinkage and selection operator (LASSO) regression and LASSO-based artificial neural network (ANN) models. The predictive performance of the models was evaluated using receiver operating characteristic (ROC) curve analysis.

Results: A total of 1145 patients (610 male, 53.3%) were included in the study. Of the 1145 patients, 704 were assigned to the training set and 441 were assigned to the testing set. The median age of the patients was 57 years (range: 47–66 years). Severity of illness, age, platelet count, leukocyte count, prealbumin, C-reactive protein (CRP), total bilirubin, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Sequential Organ Failure Assessment (SOFA) score were identified as independent prognostic factors for mortality. Incorporating these nine factors into the LASSO regression model yielded a correct classification rate of 0.98, with area under the ROC curve (AUC) values of 0.980 and 0.990 in the training and testing cohorts, respectively. Incorporating the same factors into the LASSO-based ANN model yielded a correct classification rate of 0.990, with an AUC of 0.980 in both the training and testing cohorts.

Conclusions: Both the LASSO regression and LASSO-based ANN model accurately predicted the clinical outcome of patients with COVID-19. Severity of illness, age, platelet count, leukocyte count, prealbumin, CRP, total bilirubin, APACHE II score, and SOFA score were identified as prognostic factors for mortality in patients with COVID-19.

Introduction

The novel coronavirus disease 2019 (COVID-19) is an urgent threat to global health. As of December 6, 2020, there were >6.5 million confirmed cases and 1523,583 deaths from COVID-19 worldwide [1]. The pandemic has led to a huge increase in the demand for hospital beds as well as a shortage of medical equipment, while medical staff are at a high risk of infection. Along

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with the implementation of public health measures aimed at containing the disease and delaying its spread, researchers have been working to identify the factors that influence the outcome of patients with COVID-19 [2].

Prediction models that incorporate multiple variables to estimate the outcome of COVID-19 infection could assist medical staff in patient triage. Models ranging from traditional scoring systems to newly developed risk evaluation systems have been proposed in response to the increasing number of COVID-19 patients worldwide [3–6]. Traditional logistic regression models have been used most frequently to identify the prognostic factors for COVID-19 associated mortality [7–9]. However, given the statistical rule that logistic regression models require a minimum of 10–15 outcome events per included variable, several variables have been excluded due to the limited sample size during the process of multivariable model construction, which could result in residual errors of fit and misleading conclusions.

In this study, we applied an artificial intelligence (AI) algorithm—the least absolute shrinkage and selection operator (LASSO)—for variable selection and model construction. The LASSO model allowed us to simultaneously incorporate all variables of interest, and automatically shrunk the coefficients of nonessential variables to zero while retaining the most important ones for outcome prediction. To ensure that the variables selected by the LASSO algorithm were critical for predicting prognosis, we also constructed an artificial neural network (ANN) model using the same variables [10,11]. This study aimed to identify and validate prognostic factors for COVID-19 patients using both a generalized linear model (LASSO regression) and nonlinear model (ANN).

Methods

Study population

This was a single-center retrospective observational study conducted at Wuhan Infectious Diseases Hospital from December 29, 2019 to March 2, 2020. Hospitalized patients (age ≥18 years) with confirmed COVID-19 were included. Patients were excluded if they did not have sufficient data for modeling or died soon after admission. Clinical outcomes were monitored up to March 30, 2020, the final follow-up date. This study was approved by the ethics commission of Wuhan Infectious Diseases Hospital (approval no. KY-2020–03.01).

Data collection

The following information was extracted from the patients' medical records: (1) demographic data including age, sex, smoking, drinking, comorbidities, and epidemiologic history; (2) clinical data including severity of illness, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, signs and symptoms, and laboratory findings at admission; and (3) outcome (28-day mortality).

Definitions

The diagnosis of COVID-19 was made according to the World Health Organization criteria [12]. Briefly, patients with at least two consecutive positive results from high-throughput sequencing or real-time reverse transcriptase PCR analysis of nasal and pharyngeal swab specimens were confirmed as having COVID-19. The time interval between collection of the two specimens was at least 24 h.

Severity of illness was defined according to the Diagnosis and Treatment of COVID-19 Guidelines (6th Edition) published by the National Health Commission of China [13] as follows: mild (patients with mild clinical symptoms but without abnormal radiologic findings); moderate (patients presenting with fever, cough, and other symptoms and with viral pneumonia on imaging); severe (patients exhibiting one of the following symptoms: respiratory distress, respiratory rate ≥30 breaths/min, oxygen saturation on room air at rest ≤93%, and oxygen index <300 mmHg); and critical (patients experiencing respiratory failure with mechanical ventilation, shock, or organ dysfunction who were admitted to the intensive care unit). Patients with severe or critical COVID-19 were considered as having the highest severity of illness for the evaluation.

Modeling

The whole cohort was randomly divided into training and testing sets at a 6:4 ratio. LASSO regression was used to identify predictors of COVID-19 patient outcome. All variables of interest were entered into the LASSO model for variable selection. With increasing lambda (λ), LASSO shrunk all regression coefficients to zero and removed irrelevant variables. To determine the optimal λ value, 10-fold cross validation with the "lambda.1se" criterion was performed, where the value of λ represented the most regularized model in which the error was within one standard error of the minimum. Retained variables with nonzero coefficients were used for model construction. To prevent overfitting, variable selection and model training were first performed with the training set and then validated with the testing set. The performance of the LASSO regression model was assessed by receiver operating characteristic (ROC) curve analysis and the area under the ROC curve (AUC) in both the training and testing sets. The robustness of selected predictors was verified by constructing an ANN model. The relative importance of individual predictors was evaluated by analyzing model weights. The performance of the ANN model was assessed by ROC curve analysis and the AUC value in both the training and testing sets.

Statistical analysis

Continuous variables with a normal distribution are expressed as mean ± standard deviation and were analyzed by One-way analysis of variance (ANOVA); those with a non-normal distribution are expressed as median (interquartile range [IQR]) and were analyzed with the Wilcoxon rank-sum test; and categorical variables are expressed as number (percentage) and were analyzed with the χ^2 test or Fisher's exact test as appropriate. All statistical analyses were performed using R software (version 3.6.2). The "glmnet" package was used for LASSO regression model construction, and the "neuralnet" package was used for ANN model development [11]. A two-sided P value <0.05 was considered statistically significant.

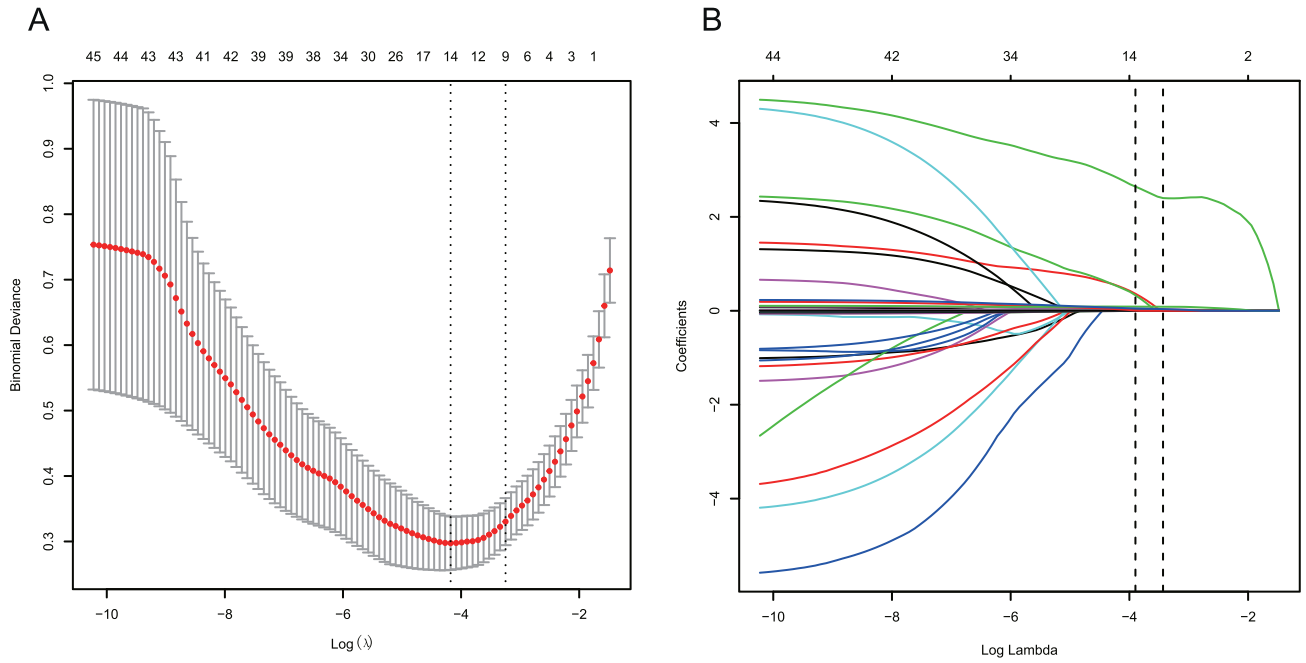

Fig. 1. Risk factor selection using the LASSO regression model. A: Tuning parameter (lambda) selection in the LASSO model used 10-fold cross-validation based on "lambda.1se" criteria for COVID-19 prognosis. B: LASSO coefficient profiles of the 52 prognostic factors for COVID-19.COVID-19: Coronavirus disease 2019; LASSO: Least absolute shrinkage and selection operator.

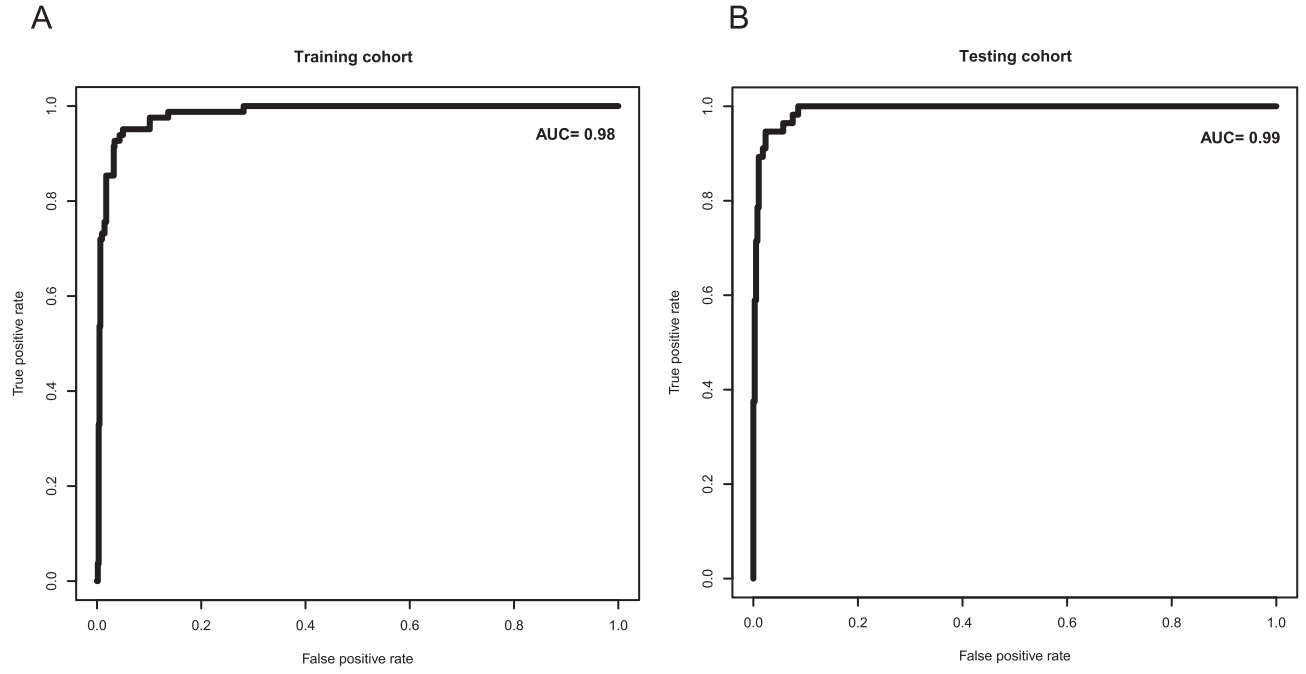

Fig. 2. ROC curve for the LASSO regression model fortrainingand testing cohorts of COVID-19.ROC curve for the training(A) and testing (B) cohorts.COVID-19: Coronavirus disease 2019; LASSO: Least absolute shrinkage and selection operator; ROC: Receiver operating characteristic.

Results

Clinical characteristics

The study population comprised 1145 patients with COVID-19 [Table 1] including 610 males (53.3%). The median age was 57 years (IQR: 47–66 years); median APACHE II score was 11.5 (IQR: 7–18); and median SOFA score was 3 (IQR: 1–5). The in-hospital mortality rate was 12.1% (n = 138). The median duration of hospitalization was 11 days (IQR: 8–15 days). Except for epidemic disease history of influenza A or B and heart rate, all characteristics and outcomes were well

Table 1
Demographic and clinical characteristics and outcomes of study cohort.

Variable	All	Training cohort (n = 704)	Testing cohort (n = 441)	P value
Age(years)	57 (47, 66)	56 (47, 67)	58 (47, 66)	0.430
Sex, male	610 (53.3)	365 (51.8)	245 (55.6)	0.240
Smoking	44 (3.8)	24 (3.4)	20 (4.5)	0.420
Alcohol	47 (4.1)	26 (3.7)	21 (4.8)	0.460
Comorbidities				
Diabetes	140 (12.2)	89 (12.6)	51 (11.6)	0.650
Hypertension	293 (25.6)	182 (25.9)	111 (25.2)	0.850
Cardiovascular disease	39 (3.4)	23 (3.3)	16 (3.6)	0.870
Dementia	34 (3.0)	24 (3.4)	10 (2.3)	0.350
COPD	22 (1.9)	13 (1.8)	9 (2.0)	0.990
CLD	58 (10.7)	28 (10.1)	30 (11.2)	0.797
Diabetes mellitus	86 (15.8)	40 (14.5)	46 (17.2)	0.462
CKD	34 (6.3)	16 (5.8)	18 (6.7)	0.790
Solid tumor	32 (2.8)	19 (2.7)	13 (2.9)	0.950
Immunosuppression	21 (1.8)	9 (1.3)	12 (2.7)	0.120
Tuberculosis	13 (1.1)	7 (1.0)	6 (1.4)	0.780
Hepatitis B	63 (5.5)	42 (6.0)	21 (4.8)	0.460
HIV	8 (0.7)	7 (1.0)	1 (0.2)	0.160
Epidemic disease history				
Influenza A				0.030
Negative	1107 (96.7)	680 (96.6)	427 (96.8)	
Positive	19 (1.7)	8 (1.1)	11 (2.5)	
Unchecked or unknown	19 (1.7)	16 (2.3)	3 (0.7)	
Influenza B				0.040
Negative	1108 (96.8)	680 (96.6)	428 (97.1)	
Positive	18 (1.6)	8 (1.1)	10 (2.3)	
Unchecked or unknown	19 (1.7)	16 (2.3)	3 (0.7)	
Clinical status at the time of admission				
Severity of COVID-19				0.720
Mild	852 (74.4)	528 (75.0)	324 (73.5)	
Moderate	181 (15.8)	111 (15.8)	70 (15.9)	
Severe or critical	112 (9.8)	65 (9.2)	47 (10.7)	
APACHE II score	11.5 (7, 18)	11 (7, 18)	12 (7, 18)	0.467
SOFA score	3 (1, 5)	3 (1, 5)	3 (1, 5)	0.750
Signs and symptoms at admission				
Fever	940 (82.1)	576 (81.8)	364 (82.5)	0.820
Median highest temperature(°C)	38.5 (38, 39)	38.5 (38, 39)	38.5 (38, 39)	0.550
Systolic pressure(mmHg)	122 (112, 135)	122 (114, 135)	122 (110, 136)	0.650
Diastolic pressure(mmHg)	80 (73, 87)	80 (74, 87)	80 (72, 88)	0.690
Heart rate(bpm)	86 (79, 96)	85 (78, 96)	88 (80, 98)	0.020
Respiratory rate(bpm)	22 (20, 25)	21 (20, 25)	22 (20, 25)	0.340
Oxygen therapy	585 (51.1)	345 (49.0)	240 (54.4)	0.080
Laboratory findings				
Leukocytes(10^9/L)	6.3 (4.6, 9.1)	6.2 (4.5, 9.0)	6.6 (4.8, 9.5)	0.120
Neutrophils(10^9/L)	4.4 (2.9, 7.3)	4.4 (2.9, 7.3)	4.5 (3.0, 7.3)	0.250
Lymphocytes(10^9/L)	1.2 (0.7, 1.6)	1.2 (0.8, 1.6)	1.1 (0.7, 1.6)	0.210
Hemoglobin(g/L)	120 (109, 130)	120 (109, 130)	121 (109, 131)	0.400
Platelets(10^9/L)	194 (143.0, 250.0)	197 (141.8, 253.0)	183.5 (146.2, 241.8)	0.270
Prothrombin time(s)	11.5 (10.7, 12.6)	11.5 (10.7, 12.6)	11.5 (10.8, 12.6)	0.880
APTT(s)	27.9 (24.3, 32.6)	27.8 (24.4, 32.3)	28 (24.3, 33.0)	0.790
Thrombin time(s)	17.9 (16.8, 20.8)	17.9 (16.8, 20.7)	17.9 (16.8, 20.8)	0.460
D-Dimer (μg/ml)	0.9 (0.4, 2.5)	0.8 (0.4, 2.5)	0.9 (0.5, 2.6)	0.150
Total bilirubin(μmol/L)	12.9 (10.1, 17.7)	12.8 (9.9, 17.2)	13.2 (10.3, 18.2)	0.180
ALT (U/L)	42 (25, 66)	40 (24, 67)	43 (26, 65)	0.260
AST(U/L)	35 (26, 51)	34 (25, 52)	36 (27, 50)	0.270
Albumin (g/L)	31.4 (28.1, 34.7)	31.5 (28.2, 35.0)	31 (28.0, 34.3)	0.160
Serum prealbumin (g/L)	127 (82.0, 188.0)	132 (85.2, 188.8)	120 (77.0, 187.0)	0.130
Blood urea nitrogen (mmol/L)	5.2 (4.1, 6.8)	5.1 (4.0, 6.9)	5.3 (4.3, 6.6)	0.180
Serum creatinine (μmol/L)	72.7 (59.9, 88.7)	72 (59.6, 88.5)	73.6 (60.6, 88.8)	0.460
CK(U/L)	78 (51.0, 149.0)	79 (50.0, 148.0)	77.5 (51.0, 151.2)	0.990
CK-MB(U/L)	14 (10, 18)	14 (10, 18)	13 (10, 18)	0.190
CRP (mg/L)	30.7 (6.0, 90.2)	26.5 (4.7, 89.4)	35.5 (7.6, 92.4)	0.050
Cardiac troponin I	0.8 (0.0, 5.0)	0.6 (0.0, 4.7)	1 (0.0, 5.5)	0.070
Procalcitonin	0 (0.0, 0.1)	0 (0.0, 0.1)	0 (0.0, 0.1)	0.540
Outcomes				
Length of hospitalization (days)	11 (8, 15)	11 (7, 15)	11 (8, 15)	0.660
ICU duration (days)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.550
LOS of 28 day	11 (8, 15)	11 (7, 15)	11 (8, 15)	0.660
In-hospital mortality	138 (12.1)	82 (11.6)	56 (12.7)	0.660

Data are shown as median (IQR) or n (%).
ALT: Alanine aminotransferase; APACHE II: Acute Physiology and Chronic Health Evaluation II; APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; CK: Creatine kinase; CKD: Chronic kidney disease; CK-MB: Creatine kinase MB form; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of survival;SOFA: Sequential Organ Failure Assessment.

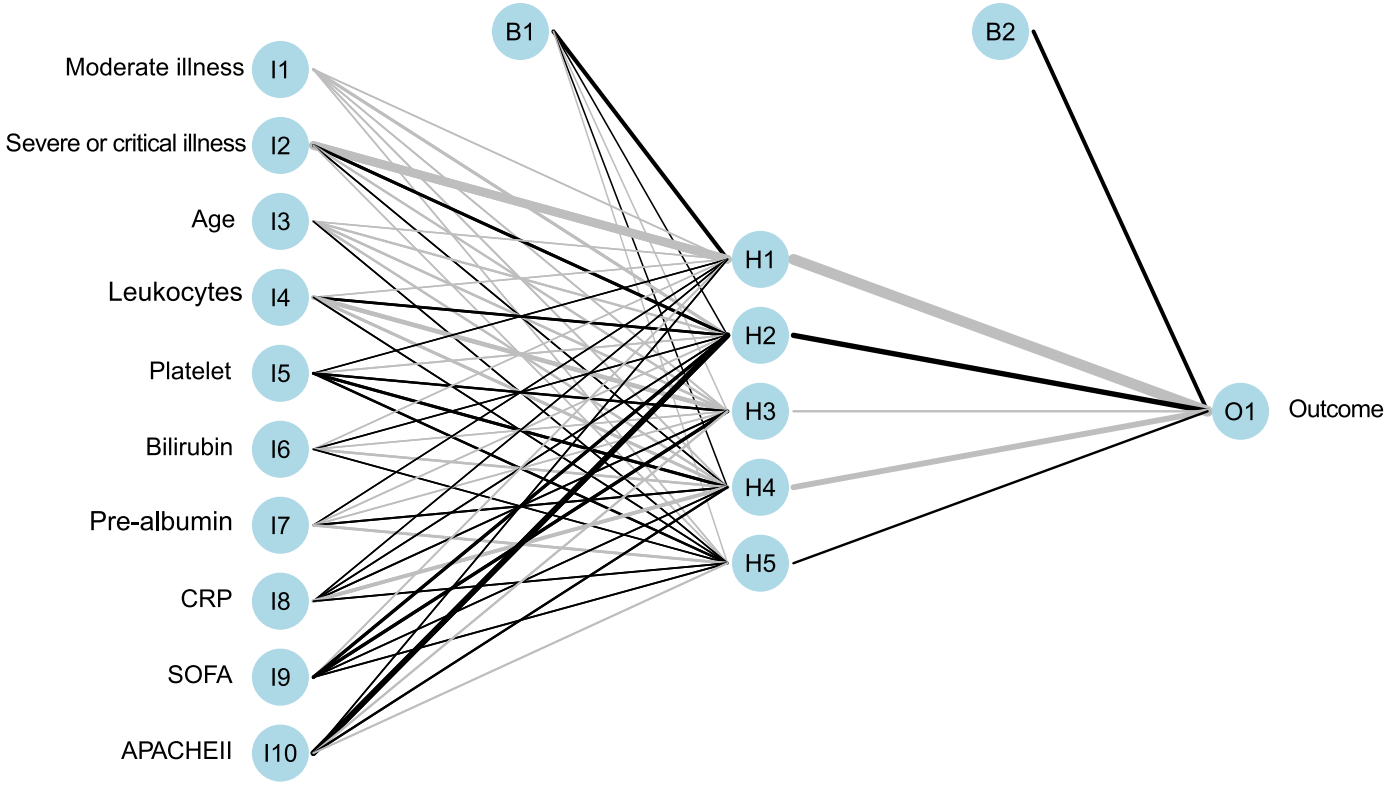

Fig. 3. Artificial neural network interpretation diagram.

balanced between the training and testing cohorts (P>0.05; Table 1).

LASSO regression model

Using the LASSO regression model with the "lambda.1se" criterion, 43 of 52 variables were excluded, leaving the following nine prognostic variables with nonzero coefficients for modeling [Fig. 1]: severity of illness, leukocytes, APACHE II score, platelet count, SOFA score, prealbumin, C-reactive protein (CRP), age, and total bilirubin. The LASSO model had a correct classification rate of 0.980, with an AUC of 0.980 with the training set and 0.990 with the testing set [Fig. 2].

ANN model

The structure of the ANN model is illustrated in Fig. 3; the black and gray lines indicate positive and negative weights, respectively, and the relative magnitude of each weight is represented by line thickness. The first layer comprised all the input variables (I1–I10), each of which was connected to the nodes of the hidden layers (H1–H5). The output layer (O1) received information from hidden layer nodes. Bias nodes (B1 and B2) served as a function similar to that of the intercept in a linear model. The relative importance of each predictor is shown in Fig. 4. The results suggested that severe or critical illness was the most important predictor of mortality, followed by leukocytes and APACHE II score. The ANN model achieved a correct classification rate of 0.980, with an AUC of 0.980 in both the training and testing sets [Fig. 5].

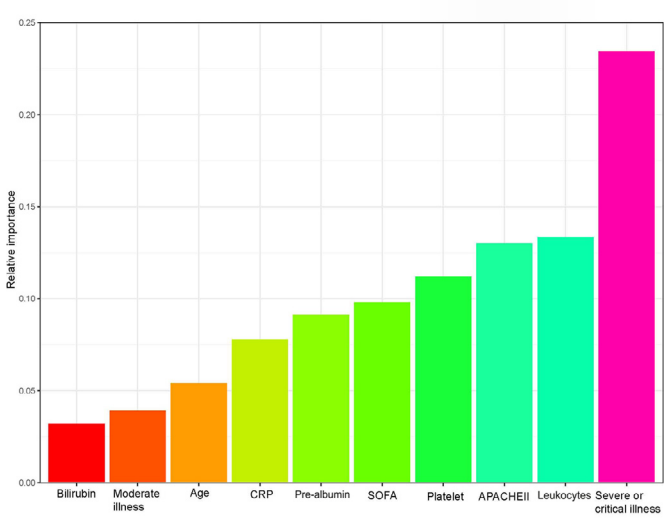

Fig. 4. Relative importance of each predictor for the artificial neural network. APACHE II: Acute Physiology and Chronic Health EvaluationII score; CRP: C-reactive protein; SOFA: Sequential Organ Failure Assessment.

Discussion

The COVID-19 pandemic has put an enormous pressure on public medical systems. Early diagnosis and aggressive treatment of patients at high risk of progression are critical to reduce mortality. This retrospective study analyzes the clinical characteristics and outcome of 1145 patients with COVID-19, and identifies nine predictors of mortality using a LASSO regression model that are then validated using an ANN model. In both

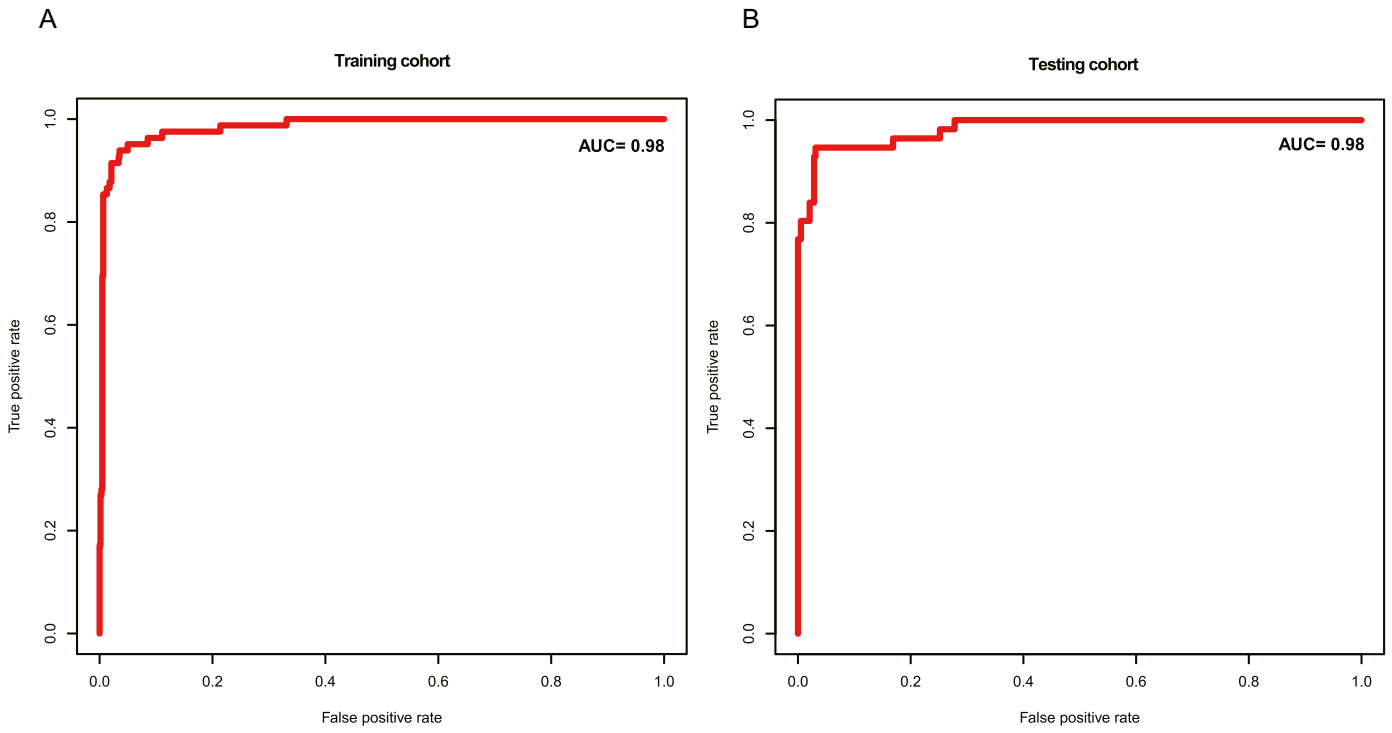

Fig. 5. ROC curve for the artificial neural network for the trainingand testing cohorts of COVID-19.ROC curve for the training (A) and testing (B) cohorts.COVID-19: Coronavirus disease 2019; ROC: Receiver operating characteristic.

the training and testing sets, the models incorporating the nine predictors achieve a high correct classification rate (0.980) and show an excellent discriminatory ability (AUC 0.980–0.990).

Patients with severe or critical COVID-19 have poor prognosis [13,14]. In our study, we confirm using an ANN model that severe or critical illness is the most important predictor of mortality. Other predictors are APACHE II and SOFA scores, which are widely used to assess the severity of illness [15]. In a Cohort study that included 52 critically ill patients with COVID-19, nonsurvivors have a higher APACHE II score than survivors (18 [IQR 16–20] *vs.* 14 [IQR 12–17]) [16]. The prognostic accuracy of APACHE II or SOFA score alone in predicting in-hospital mortality in COVID-19 patients is high, with AUCs of 0.937 and 0.926, respectively [17].

Laboratory findings are important indicators of disease severity in COVID-19 patients. The coefficient for elevated leukocyte count has the second highest weight among variables in the ANN model. The recruitment of inflammatory leukocytes contributes to tissue damage [18]and cytokine release is a key driver of acute respiratory distress syndrome, which is present in a high proportion of COVID-19 patients (31.0%–41.8%) and increases the risk of death [4,19]. Several studies have demonstrated a link between low platelet count and the severity of COVID-19 [20–22]. The low platelet count may reflect a coagulation disorder in severe cases of COVID-19, which can lead to microthrombosis in the lung and other organs. Prealbumin [23], CRP [24,25], and total bilirubin [26] have also previously been identified as independent prognostic factors for in-hospital mortality in COVID-19 patients. Some studies have reported that lymphopenia was associated with severe illness and had prognostic value for COVID-19 patients [27–29]. However, lymphopenia is not a predictor of mortality in our study. One possible explanation is that illness severity—which was identified as a prognostic factor using the LASSO model—encompasses lymphopenia and thus precludes its inclusion in the final predictive model. Additionally, old age was shown to be a risk factor for death in patients with COVID-19 [25,30,31], which was supported by our results.

The strength of our study is that we applied rigorous methods in developing and validating our predictive model. We first divided the whole cohort into training and testing sets to avoid overfitting during model development, and we used both generalized linear (LASSO algorithm) and nonlinear (ANN) models to evaluate the performance of the selected variables in mortality prediction. However, there were also several limitations in our study. First, we included only patients from a single center in China, which could limit the generalizability of the findings. Therefore, validation using datasets from other countries is encouraged. Second, because of the retrospective nature of our study, some important laboratory data were unavailable (eg, lactic acid, cardiac troponin, and radiologic findings) and were not included in the models, which may have biased the results. Finally, we did not consider changes in laboratory data during the process of model development; assessing laboratory parameters at different time points before death may increase the predictive accuracy of our model.

In conclusion, LASSO regression and LASSO-based ANN models are powerful tools for predicting the prognosis of patients with COVID-19. The severity of illness, age, platelet count, leukocyte count, prealbumin, CRP, total bilirubin, APACHE II score, and SOFA score are found to be prognostic factors for mortality. These results can help medical staff to identify critically ill patients who are at the highest risk of progression and who may benefit from aggressive treatments.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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