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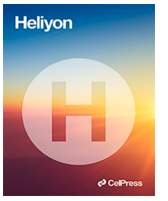

Research article

Development and validation of a nomogram for predicting in-hospital survival rates of patients with COVID-19

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ABSTRACT

Objective: Our aim was to develop and validate a nomogram for predicting the in-hospital 14-day (14 d) and 28-day (28 d) survival rates of patients with coronavirus disease 2019 (COVID-19).
Methods: Clinical data of patients with COVID-19 admitted to the Renmin Hospital of Wuhan University from December 2022 to February 2023 and the north campus of Shanghai Ninth People's Hospital from April 2022 to June 2022 were collected. A total of 408 patients from Renmin Hospital of Wuhan University were selected as the training cohort, and 151 patients from Shanghai Ninth People's Hospital were selected as the verification cohort. Independent variables were screened using Cox regression analysis, and a nomogram was constructed using R software. The prediction accuracy of the nomogram was evaluated using the receiver operating characteristic (ROC) curve, C-index, and calibration curve. Decision curve analysis was used to evaluate the clinical application value of the model. The nomogram was externally validated using a validation cohort.
Result: In total, 559 patients with severe/critical COVID-19 were included in this study, of whom 179 (32.02 %) died. Multivariate Cox regression analysis showed that age >80 years [hazard ratio (*HR*) = 1.539, 95 % confidence interval (*CI*): 1.027–2.306, $P = 0.037$], history of diabetes (*HR* = 1.741, *95 % CI*: 1.253–2.420, $P = 0.001$), high APACHE II score (*HR* = 1.083, *95 % CI*: 1.042–1.126, $P < 0.001$), sepsis (*HR* = 2.387, *95 % CI*: 1.707–3.338, $P < 0.001$), high neutrophil-to-lymphocyte ratio (NLR) (*HR* = 1.010, *95 % CI*: 1.003–1.017, $P = 0.007$), and high D-dimer level (*HR* = 1.005, *95 % CI*: 1.001–1.009, $P = 0.028$) were independent risk factors for 14 d and 28 d survival rates, whereas COVID-19 vaccination (*HR* = 0.625, *95 % CI*: 0.440–0.886, $P = 0.008$) was a protective factor affecting prognosis. ROC curve analysis showed that the area under the curve (AUC) of the 14 d and 28 d hospital survival rates in the training cohort was 0.765 (*95 % CI*: 0.641–0.923) and 0.814 (*95 % CI*: 0.702–0.938), respectively, and the AUC of the 14 d and

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28 d hospital survival rates in the verification cohort was 0.898 (*95 % CI*: 0.765–0.962) and 0.875 (*95 % CI*: 0.741–0.945), respectively. The calibration curves of 14 d and 28 d hospital survival showed that the predicted probability of the model agreed well with the actual probability. Decision curve analysis (DCA) showed that the nomogram has high clinical application value.
Conclusion: In-hospital survival rates of patients with COVID-19 were predicted using a nomogram, which will help clinicians in make appropriate clinical decisions.

1. Introduction

The coronavirus disease 2019 (COVID-19) epidemic has created a huge burden on the healthcare systems of many countries. To guide the allocation of limited medical resources and identify and intervene in high-risk patients at an early stage, an effective prognostic assessment system is needed [1–3]. Many studies on COVID-19 prognostic prediction models have been published at home and abroad [4–9], but most of the studies use internal verification, with few external verification cohorts. Furthermore, few outcomes are reported in most studies, indicating a high risk of overfitting and thus a limited value for clinical application.

In this study, we summarised the medical records of patients with severe/critical COVID-19 diagnosed at the North Campus of Shanghai Ninth People's Hospital from April to June 2022 and at Renmin Hospital of Wuhan University from December 2022 to February 2023. As the median time to death due to COVID-19 was reported to be 18.5 days (18.5 d) [10], we believe that 14 d and 28 d may be appropriate time points for evaluation of death events. The purpose of our study was to explore the risk factors for in-hospital mortality at 14 d and 28 d, construct a nomogram to predict the survival probability of patients with COVID-19 at 14 d and 28 d, and evaluate the predictive performance and clinical value of the model.

2. Materials and methods

2.1. Research type

This study was a dual-centre, retrospective, observational cohort study.

2.2. Study objective

Data were collected from patients with severe/critical COVID-19 diagnosed at the Renmin Hospital of Wuhan University from December 2022 to February 2023 and the north campus of Shanghai Ninth People's Hospital from April 2022 to June 2022. Patients were ≥18 years old with complete case data. Patients admitted to the Renmin Hospital of Wuhan University were selected as the training cohort (n = 408) and those admitted to the North Hospital of Shanghai Ninth People's Hospital as the validation cohort (n =

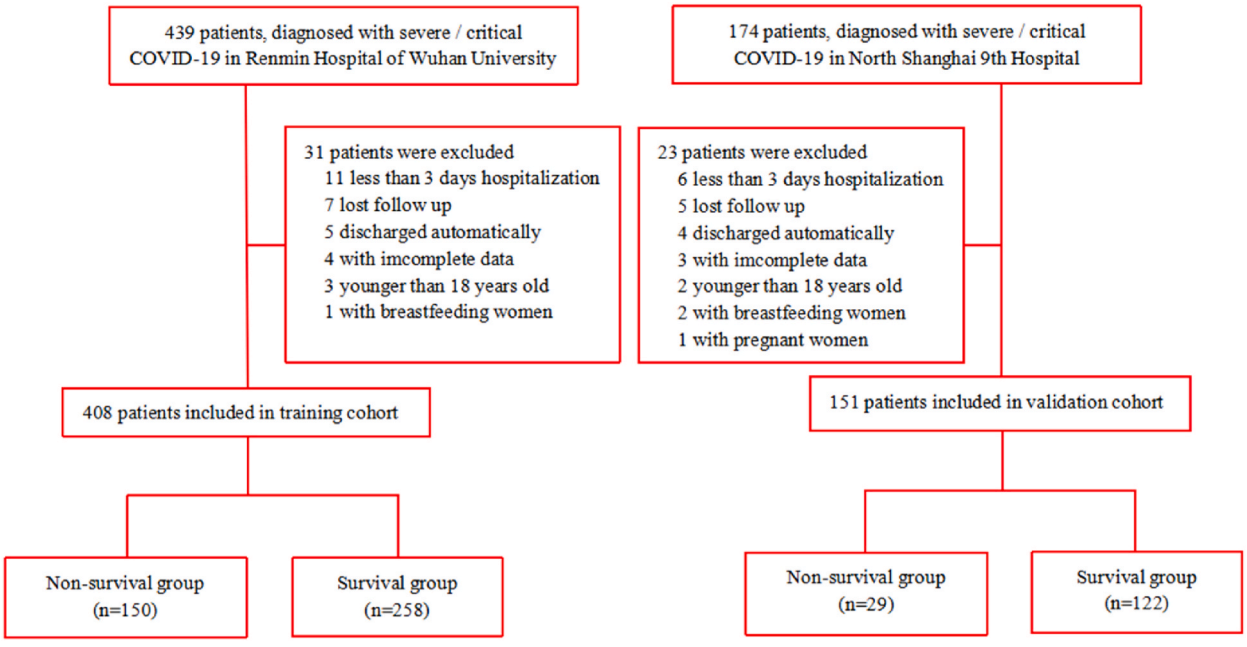

Fig. 1. The flowchart of participant recruitment for the study.

151). With in-hospital death or 28 d outcomes as the study endpoint, the final follow-up date for patients in Wuhan was March 28, 2023 and that for patients in Shanghai was July 2, 2022. None of the authors had access to information that could identify individual participants during or after data collection. The detailed process of participant recruitment for this study was illustrated in Fig. 1.

2.3. Inclusion criteria

All enrolled patients were diagnosed according to the ninth version of COVID-19 guidelines [11]. The patients with severe COVID-19 meeting the following conditions were included: (1) shortness of breath and respiratory rate ≥30 breaths/min; (2) oxygen saturation according to a finger monitor of ≤93 % when breathing air in a resting state; (3) partial pressure of arterial oxygen (PaO_2)/fraction of inspiration O_2 (FiO_2) ≤ 300 mmHg; (4) progressive worsening of clinical symptoms and lung imaging showing significant progression of >50 % of the lesion within 24–48 h. The patients with critical COVID-19 meeting the following conditions were included: (1) respiratory failure and the need for mechanical ventilation; (2) shock occurs; (3) other organ failure requiring intensive care unit (ICU) monitoring and treatment.

2.4. Exclusion criteria

The patients with the following condition were excluded: (1) aged <18 years; (2) pregnant or lactating; (3) hospitalised for ≤3 days; (4) no longer undergoing active treatment and unable carry out conventional comprehensive treatment; (5) patients with incomplete data and those lost to follow-up.

2.5. Observation indicators

2.5.1. Basic data

General patient information was retrieved from the hospital information system, including sex, age, course of disease, clinical symptoms, medical history, complications, invasive treatment, physical examination results, and auxiliary examination, and the classification of was determined according to the guidelines [11]. Complications were defined as follows: shock, the occurrence of a mean arterial pressure of <65 mmHg accompanied by tachycardia during hospitalisation; sepsis, a confirmed or suspected infection with a sequential organ failure assessment (SOFA) score increase of ≥2 points compared to baseline; acute myocardial injury, a cardiac troponin I (cTnI) level above the 99th percentile of the upper reference limit. Acute renal failure was diagnosed based on any one of the following criteria: an increase in serum creatinine of ≥26.5 μmol/L within 48 h, an increase in serum creatinine to more than 1.5 times the baseline value within 7 days, or a reduction in urine output (<0.5 ml kg^{-1} h^{-1}) lasting for more than 6 h. Deep venous thrombosis of the lower limbs was diagnosed based on ultrasound findings indicating thrombosis during hospitalisation.

2.5.2. Laboratory examination

The laboratory test results of patients within 72 h after the diagnosis of severe/critical COVID-19, including routine blood tests, biochemistry, blood coagulation function, myocardial enzymography, and arterial blood gas analysis, were collected and used to calculate the acute physiology and chronic health evaluation II (APACHE II) score. If there were multiple results for the same laboratory indicator within 72 h after the diagnosis of severe/critical COVID-19, the worst results would be selected for subsequent analysis.

2.6. Starting and end points

The diagnosis of severe/critical COVID-19 was considered as the starting point, death or follow-up deadline was considered as the end point, and the follow-up time was recorded.

2.7. Statistical analysis

SPSS 27.0 and R software 4.3.1 were used for statistical analyses and graphing. As none of the measurement data followed a normal distribution, they are expressed as median (interquartile range), and the Mann-Whitney *U* test was used for comparisons between groups. Count data are expressed as number (%), and groups were compared using the chi-square test or chi-square test with continuous correction or Fisher's exact probability test. Multiple imputation methods were used to handle missing values. The "rms" package of R software was used to construct the nomogram, and the predictive ability of the model for prognosis was evaluated using the receiver operating characteristic (ROC) curve. Internal validation was performed using the bootstrap method with 1000 replications and comparing differences in differentiation and C-index between groups. The prediction models were further evaluated using a calibration curve and decision curve analysis (DCA). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline data analysis

The screening process for the study population is shown in Fig. 1. A total of 559 patients with severe/critical COVID-19 were

included. Mortality rates in the training and verification cohorts were 36.76 % and 19.21 %, respectively. The baseline data for the two groups are shown in Table 1.

3.2. Analysis of laboratory indicators

The 26 laboratory indicators (routine blood tests, blood biochemistry, myocardial enzymography, blood coagulation function, and arterial blood gas analysis) within 72 h after the diagnosis of severe/critical COVID-19 were compared between the training and validation cohorts (Table 2).

3.3. Cox regression analysis

Cox regression analysis was used to analyse the risk factors affecting prognosis. Variables in the univariate Cox regression with $P <$

Table 1
Comparison of baseline characteristics between patients in training and validation cohorts.

Variables	Training cohort (n = 408)				Validation cohort (n = 151)			
	Non-survival group (n = 150)	Survival group (n = 258)	Z/χ^2 value	*P*-value	Non-survival group (n = 29)	Survival group (n = 122)	Z/χ^2 value	*P*-value
Male/Female (cases)	108/42	175/83	0.776	0.378	15/14	64/58	0.005	0.943
COVID-19 severe/critical (cases)	46/104	156/102	33.693	<0.001	3/26	88/44	30.691	<0.001
Age [n (%)]								
18–50 years	11 (7.3 %)	34 (13.2 %)	3.302	0.069	1 (3.4 %)	15 (12.3 %)	1.115	0.291[a]
51–60 years	17 (11.3 %)	48 (18.6 %)	3.744	0.053	2 (6.9 %)	13 (10.7 %)	0.069	0.793[a]
60–70 years	34 (22.7 %)	80 (31.0 %)	3.278	0.070	4 (13.8 %)	18 (14.8 %)	0.017	0.895[a]
70–80 years	54 (36.0 %)	74 (28.7 %)	2.359	0.125	10 (34.5 %)	49 (40.2 %)	0.318	0.673
>80 years	34 (22.7 %)	22 (13.9 %)	3.954	0.047	12 (41.4 %)	27 (22.1 %)	4.531	0.033
Clinical manifestations [n (%)]								
Fever	78 (52.0 %)	119 (46.1 %)	1.312	0.252	15 (51.7 %)	54 (44.3 %)	0.526	0.468
Cough/sputum	76 (50.7 %)	116 (45.0 %)	1.239	0.266	19 (65.5 %)	65 (52.8 %)	1.524	0.217
Panting (breathing rate ≥30/min)	64 (42.7 %)	80 (31.0 %)	5.646	0.017	11 (37.9 %)	34 (27.9 %)	1.134	0.287
Systemic acidosis	14 (9.3 %)	34 (13.2 %)	1.351	0.245	5 (17.2 %)	30 (24.6 %)	0.711	0.399
Chest tightness	28 (18.7 %)	45 (17.4 %)	0.097	0.756	4 (13.8 %)	28 (23.0 %)	1.177	0.278
Diarrhea	8 (5.3 %)	15 (5.8 %)	0.041	0.839	7 (24.1 %)	16 (13.1 %)	1.434	0.231[a]
Consciousness disorder	24 (15.0 %)	49 (19.0 %)	1.092	0.296	10 (34.5 %)	31 (25.4 %)	0.975	0.323
Others	16 (10.7 %)	41 (15.9 %)	2.154	0.142	4 (13.8 %)	5 (4.1 %)	2.390	0.122[a]
Comorbidities [n (%)]								
Chronic lung disease	25 (16.7 %)	31 (12.0 %)	1.733	0.188	16 (41.0 %)	60 (49.2 %)	0.789	0.375
Hypertension	81 (54 %)	129 (50.0 %)	0.608	0.436	13 (44.8 %)	55 (45.1 %)	0.001	0.980
Diabetes	72 (48.0 %)	76 (29.5 %)	14.108	<0.001	12 (41.4 %)	30 (24.6 %)	3.289	0.070
Cardiovascular disease	35 (21.9 %)	63 (24.4 %)	0.356	0.551	13 (44.8 %)	40 (32.8 %)	1.491	0.222
Cerebrovascular disease	23 (15.3 %)	37 (14.3 %)	0.074	0.785	13 (44.8 %)	36 (29.5 %)	2.509	0.113
Digestive diseases	7 (4.7 %)	18 (7.0 %)	0.880	0.348	3 (10.3 %)	13 (9.8 %)	0.000	1.000[a]
Chronic kidney disease	18 (12.0 %)	26 (10.1 %)	0.364	0.546	7 (24.1 %)	17 (12.9 %)	1.571	0.210[a]
Autoimmune system diseases	6 (4.0 %)	11 (4.2 %)	0.015	0.904	2 (6.9 %)	3 (2.5 %)	0.388	0.533[a]
Malignancy	11 (7.3 %)	26 (10.1 %)	0.866	0.352	2 (6.9 %)	4 (3.3 %)	0.135	0.713[a]
Others	17 (11.3 %)	36 (14.0 %)	0.576	0.448	2 (6.9 %)	5 (4.1 %)	0.023	0.878[a]
Invasive treatments [n (%)]								
Mechanical ventilation	121 (80.7 %)	71 (27.5 %)	107.542	<0.001	25 (86.2 %)	33 (27.0 %)	34.661	<0.001
CRRT	56 (37.3 %)	58 (21.8 %)	11.626	0.001	10 (34.5 %)	17 (13.9 %)	6.738	0.009
ECMO	9 (6.0 %)	1 (0.4 %)	10.259	0.001[a]	2 (6.9 %)	0 (0.0 %)	–	0.036[b]
Complications [n (%)]								
Shock	51 (34.0 %)	38 (14.8 %)	20.278	<0.001	10 (34.5 %)	12 (10.5 %)	10.192	0.001
Sepsis	77 (51.3 %)	30 (11.6 %)	77.290	<0.001	8 (27.6 %)	4 (3.3 %)	15.747	<0.001[a]
Acute myocardial injury	80 (53.3 %)	120 (46.5 %)	1.766	0.184	12 (41.4 %)	66 (54.1 %)	1.518	0.218
Acute renal failure	48 (32.0 %)	52 (20.2 %)	7.193	0.007	13 (44.8 %)	20 (16.4 %)	11.092	0.001
Deep venous thrombosis	32 (21.3 %)	26 (10.1 %)	9.854	0.002	5 (17.2 %)	12 (9.8 %)	0.652	0.420[a]
Others	10 (6.7 %)	17 (6.6 %)	0.001	0.976	2 (6.9 %)	6 (4.9 %)	0.000	1.000[a]
Vaccination history [n (%)]	53 (35.3 %)	126 (48.6 %)	6.843	0.009	3 (10.3 %)	39 (32.0 %)	5.456	0.02
APACHE II score [points, M (Q_L, Q_U)]	18.0 (15.8, 21.0)	15.0 (12.0, 17.0)	−7.445	<0.001	20.0 (17.0, 25.5)	15.0 (11.0, 18.0)	−5.361	<0.001

COVID-19 is corona virus disease 2019; CRRT is continuous renal replacement therapy; ECMO is extracorporeal membrane oxygenation; APACHE II is acute physiology and chronic health evaluation II.

[a] Is the chi-square value of continuous correction.

[b] Is the Fisher test.

0.2 were included in the multiple Cox regression analysis, and the indicators with statistically significant differences were screened using the backward stepwise method. The results of multivariate Cox regression showed that age >80 years, history of diabetes, high APACHE II score, sepsis, high neutrophil-to-lymphocyte ratio (NLR), and high D-dimer level were risk factors for 14 d and 28 d in-hospital survival, while receiving the COVID-19 vaccine was the only protective factor (all $P < 0.05$) (Table 3).

3.4. Adjusting for common confounding factors

Based on clinical experience and the literature, a multifactorial Cox regression analysis was used to adjust for common confounding factors such as sex, chronic lung disease, cardiovascular disease, and combinations of these three indicators (Table 4). After adjustment, age >80 years, history of diabetes, high APACHE II score, concomitant sepsis, high NLR, and high D-dimer levels were independent risk factors affecting prognosis. COVID-19 vaccination was identified as an independent protective factor, with all differences being statistically significant ($P < 0.05$).

3.5. Construction of nomogram

Multivariate Cox regression analysis included seven independent variables, including age, history of diabetes, APACHE II score, sepsis, NLR, D-dimer, and COVID-19 vaccination, to construct a nomogram. The nomogram was obtained by visual processing using the R language software (Fig. 2). According to the above seven easily available clinical indicators, clinicians can evaluate the in-hospital survival rates of patients with COVID-19 by individualized quantification. The C-index of the 14 d and 28 d in-hospital survival rates in the training cohort were 0.765 (*95 % CI*: 0.641–0.923) and 0.814 (*95 % CI*: 0.702–0.938), respectively. The higher the C-index, the better the model differentiation, indicating a higher prediction accuracy and judgment ability.

Table 2
Comparison of the laboratory indicators for severe/critical COVID-19 patients in training and validation cohorts.

Variables [M(Q_L, Q_U)]	Training cohort (n = 408)				Validation cohort (n = 151)			
	Non-survival group (n = 150)	Survival group (n = 258)	*Z*-value	*P*-value	Non-survival group (n = 29)	Survival group (n = 122)	*Z*-value	*P*-value
WBC(× 10^9/L)	12.4 (7.7, 15.5)	8.8 (5.6, 13.5)	−3.921	<0.001	11.0 (7.9, 14.3)	6.8 (4.5, 11.3)	−2.518	0.012
N (× 10^9/L)	12.5 (7.9, 22.5)	7.2 (4.2, 12.4)	−6.400	<0.001	7.3 (4.3, 10.5)	4.8 (2.8, 9.5)	−1.623	0.105
L (× 10^9/L)	0.6 (0.3, 1.3)	0.7 (0.4, 1.1)	−0.0995	0.320	0.6 (0.4, 0.9)	0.8 (0.5, 1.4)	−2.175	0.030
NLR	10.8 (6.2, 20.9)	10.3 (4.8, 23.6)	−5.533	<0.001	14.1 (5.0, 20.8)	5.7 (2.3, 15.9)	−2.480	0.013
PLT (× 10^9/L)	160.0 (115.0, 220.3)	192.0 (130.5, 248.0)	−2.428	0.015	115.0 (76.0, 175.5)	172.0 (104.0, 228.5)	−2.894	0.004
NPR	0.08 (0.04, 0.16)	0.04 (0.02, 0.07)	−7.249	<0.001	0.07 (0.03, 0.13)	0.03 (0.02, 0.05)	−2.936	0.003
PCT (μg/L)	1.2 (0.3, 7.4)	0.2 (0.1, 1.0)	−7.597	<0.001	1.6 (0.3, 3.0)	0.1 (0.1, 0.9)	−3.747	<0.001
CRP (mg/L)	105.4 (45.7, 164.9)	31.2 (11.8, 98.0)	−6.616	<0.001	87.5 (21.4, 171.0)	29.4 (7.7, 113.5)	−1.939	0.052
SAA (mg/L)	262.0 (100.5, 300.0)	153.4 (35.0, 300.0)	−3.221	0.001	140.9 (51.2, 214.4)	104.0 (22.6, 225.0)	−1.124	0.261
IL-6 (pg/ml)	68.9 (33.2, 127.9)	22.6 (11.6, 65.4)	−6.876	<0.001	44.2 (29.7, 63.6)	22.6 (13.1, 64.4)	−2.736	0.006
ALT (U/L)	28.0 (18.0, 62.3)	24.0 (15.0, 42.0)	−2.653	0.008	18.5 (13.0, 35.3)	18.0 (15.0, 32.0)	−0.097	0.923
AST (U/L)	44.5 (27.8, 85.0)	30.0 (21.0, 49.0)	−4.868	<0.001	33.0 (23.0, 51.3)	32.0 (21.5, 49.5)	−0.858	0.391
TBIL (μmol/L)	14.9 (9.7, 22.4)	12.2 (8.0, 15.4)	−3.644	<0.001	12.5 (11.4, 16.6)	11.8 (9.4, 16.3)	−0.905	0.366
DBIL (μmol/L)	7.3 (4.6, 10.5)	4.8 (3.2, 6.7)	−5.609	<0.001	5.3 (3.1, 6.9)	2.9 (2.2, 4.5)	−3.068	0.002
ALB (g/L)	30.0 (27.0, 34.0)	33.5 (30.3, 37.9)	−5.651	<0.001	30.2 (29.0, 34.0)	39.0 (35.0, 42.0)	−2.849	0.004
Urea (mmol/L)	12.2 (8.7, 20.5)	8.5 (5.9, 12.7)	−5.783	<0.001	12.1 (7.6, 20.5)	8.8 (6.1, 14.0)	−2.710	0.007
Cr (μmol/L)	96.0 (68.8, 162.0)	80.0 (59.0, 121.0)	−2.916	0.004	106.0 (83.8, 138.0)	85.0 (65.0, 111.0)	−2.665	0.008
eGFR (ml/min)	69.0 (28.4, 88.3)	79.9 (46.84, 97.0)	−3.125	0.002	54.5 (38.8, 81.0)	74.0 (53.0, 90.0)	−2.339	0.019
CK(U/L)	51.0 (22.0, 127.0)	41.0 (4.1, 108.5)	−1.402	0.161	80.0 (48.0, 364.3)	76.5 (43.5, 178.0)	−0.362	0.717
LDH(U/L)	419.0 (331.1, 550.3)	305.0 (221.5, 373.0)	−8.008	<0.001	558.0 (459.0, 667.5)	305.0 (230.1, 438.5)	−5.542	<0.001
Lac(mmol/L)	2.1 (1.5, 3.9)	1.7 (1.2, 2.4)	−4.274	<0.001	2.5 (2.0, 3.8)	1.7 (1.2, 2.2)	−4.451	<0.001
BNP(ng/L)	2803.0 (732.6, 7295.8)	748.1 (254.3, 2387.0)	−5.464	<0.001	536.5 (216.5, 1148.3)	158.0 (51.5, 473.5)	−4.616	<0.001
cTnI (gl/L)	0.20 (0.04, 1.11)	0.04 (0.01, 0.17)	−6.038	<0.001	0.10 (0.03, 0.17)	0.03 (0.01, 0.09)	−3.530	<0.001
PT(s)	13.7 (12.5, 15.6)	12.4 (11.5, 13.4)	−6.482	<0.001	12.7 (12.3, 13.3)	12.0 (11.4, 12.8)	−3.519	<0.001
APTT(s)	36.2 (30.0, 44.2)	28.9 (27.1, 32.0)	−4.196	<0.001	32.6 (27.1, 35.3)	30.6 (27.9, 35.2)	−0.555	0.579
D-dimer (mg/L)	12.8 (3.7, 36.7)	1.5 (0.7, 4.4)	−7.548	<0.001	4.2 (1.4, 6.8)	1.2 (0.5, 4.5)	−3.501	<0.001

WBC is complete blood count; N is neutrophil; L is lymphocyte; NLR is neutrophil-to-lymphocyte ratio; PLT is platelet; NPR is neutrophil to platelet ratio; PCT is procalcitonin; CRP is C-reaction protein; SAA is serum amyloid A; IL-6 is interleukin-6; ALT is alanine amino transferase; AST is aspartate amino transferase; TBIL is total bilirubin; DBIL is direct bilirubin; ALB is albumin; Urea is Carbamide; Cr is creatinine; eGFR is estimated glomerular filtration rate; CK is creatine kinase; LDH is lactate dehydrogenase; Lac is lactic acid; BNP is brain natriuretic peptide; cTnI is cardiac troponin I; PT is prothrombin time; APTT is activated partial thromboplatin time.

Table 3
Cox regression analysis of risk factors affecting the prognosis of COVID-19 patients.

Variables	Univariate		Multivariate	
	HR (*95%CI*)	*P*-value	HR (*95%CI*)	*P*-value
18–50 years	0.556 (0.301–1.028)	0.061	–	–
70–80 years	1.423 (1.019–1.988)	0.038	–	–
>80 years	1.940 (1.323–2.843)	0.001	1.539 (1.027–2.306)	0.037
Fever	1.456 (1.052–2.016)	0.053	–	–
Panting	1.459 (1.055–2.016)	0.082	–	–
Systemic acidosis	1.910 (1.101–3.313)	0.061	–	–
Consciousness disorder	0.485 (0.280–0.841)	0.078	–	–
History of diabetes	1.859 (1.349–2.562)	<0.001	1.741 (1.253–2.420)	0.001
Vaccination history	0.638 (0.456–0.892)	0.009	0.625 (0.440–0.886)	0.008
APACHE II score	1.141 (1.103–1.180)	<0.001	1.083 (1.042–1.126)	<0.001
Comorbid spesis	4.272 (3.090–5.905)	<0.001	2.387 (1.707–3.338)	<0.001
WBC($\times 10^9$/L)	1.013 (1.006–1.020)	0.092	–	–
N ($\times 10^9$/L)	1.004 (1.002–1.005)	0.105	–	–
L ($\times 10^9$/L)	1.066 (1.039–1.094)	0.021	–	–
NLR	1.001 (1.000–1.001)	<0.001	1.010 (1.003–1.017)	0.007
NPR	1.383 (1.151–1.661)	0.001	–	–
CRP (mg/L)	1.013 (1.007–1.020)	0.098	–	–
SAA (mg/L)	1.007 (1.005–1.009)	0.028	–	–
ALB (g/L)	1.007 (0.998–1.016)	0.140	–	–
LDH(U/L)	0.992 (0.987–0.996)	0.078	–	–
PT(s)	1.013 (0.996–1.031)	0.143	–	–
APTT(s)	1.019 (1.011–1.028)	0.102	–	–
D-dimer (mg/L)	1.017 (1.009–1.026)	<0.001	1.005 (1.001–1.009)	0.028
Lac(mmol/L)	1.0112 (1.064–1.161)	<0.001	–	–

APACHE II is acute physiology and chronic health evaluation II; WBC is complete blood count; N is neutrophil; L is lymphocyte; NLR is neutrophil-to-lymphocyte ratio; NPR is neutrophil to platelet ratio; CRP is C-reaction protein; SAA is serum amyloid A; ALB is albumin; LDH is lactate dehydrogenase; PT is prothrombin time; APTT is activated partial thromboplatin time; Lac is lactic acid.

Table 4
Cox regression analysis of independent risk factors of COVID-19 affecting prognosis.

Variables		Adjusting for sex	Adjusting for chronic lung disease	Adjusting for cardiovascular disease	Adjusting for sex + chronic lung disease + cardiovascular disease
	Pre-adjusted HR (*95%CI*)	Adjusted HR (*95%CI*)	Adjusted HR (*95%CI*)	Adjusted HR (*95%CI*)	Adjusted HR (*95%CI*)
Age >80 years	1.539 (1.027–2.306)	1.321 (1.108–2.156)	1.424 (1.273–2.204)	1.371 (1.019–2.162)	1.489 (1.107–2.206)
History of diabetes	1.741 (1.253–2.420)	1.621 (1.132–2.317)	1.527 (1.021–2.368)	1.544 (1.204–2.378)	1.284 (1.091–2.452)
Vaccination history	0.625 (0.440–0.886)	0.507 (0.387–0.946)	0.613 (0.451–0.873)	0.525 (0.383–0.856)	0.613 (0.483–0.805)
APACHE II score	1.083 (1.042–1.126)	1.071 (1.025–1.215)	1.026 (1.011–1.098)	1.052 (1.021–1.075)	1.076 (1.036–1.094)
Comorbid sepsis	2.387 (1.707–3.338)	2.207 (1.584–3.017)	2.071 (1.261–3.261)	2.146 (1.621–3.087)	2.291 (1.667–3.280)
NLR	1.010 (1.003–1.017)	1.002 (1.000–1.025)	1.004 (1.043–1.219)	1.003 (1.001–1.014)	1.008 (1.000–1.030)
D-dimer (mg/L)	1.005 (1.001–1.009)	1.003 (1.000–1.012)	1.001 (1.001–1.013)	1.002 (1.001–1.010)	1.004 (1.000–1.011)

APACHE II is acute physiology and chronic health evaluation II; NLR is neutrophil-to-lymphocyte ratio.

3.6. Internal and external verification of the nomogram

The training cohort was internally validated by bootstrapping to obtain the same C-index; that is, the predicted results of the model were consistent with the actual results. The AUC of the 14 d in-hospital survival rates of the training cohort was 0.765 (*95 % CI*: 0.641–0.923), with a sensitivity of 76.3 % and a specificity of 85.7 %; the AUC of the 28 d in-hospital survival rate of the training cohort was 0.814 (*95 % CI*: 0.702–0.938), with a sensitivity of 78.4 % and a specificity of 89.2 % (Fig. 3A). The AUC of the 14 d in-hospital survival rate of the verification cohort was 0.898 (95 % CI: 0.765–0.962), with a sensitivity of 77.6 % and a specificity of 88.1 %. The AUC of the 28 d in-hospital survival rate of the verification cohort was 0.875 (95 % CI: 0.741–0.945), with a sensitivity of 73.7 % and a specificity of 86.1 % (Fig. 3B), indicating that the model had good pretest performance.

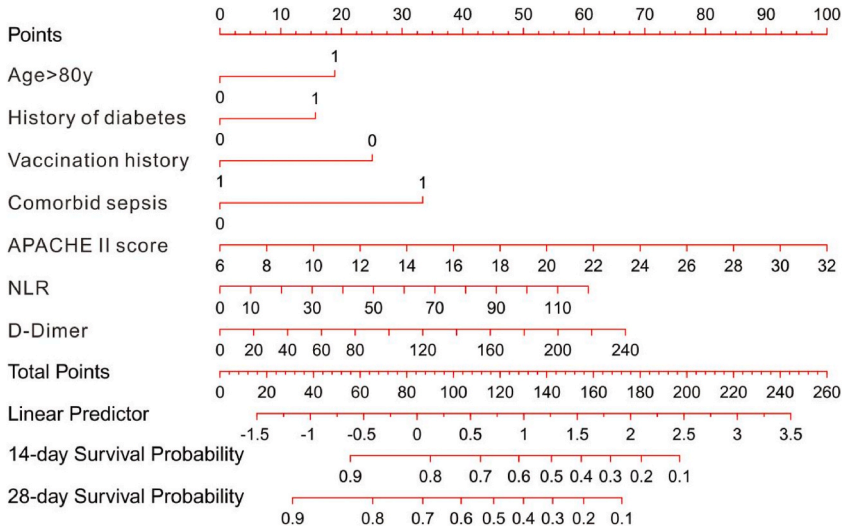

Fig. 2. Construction of nomogram to predict COVID-19 patients' 14 d and 28 d survival rate.

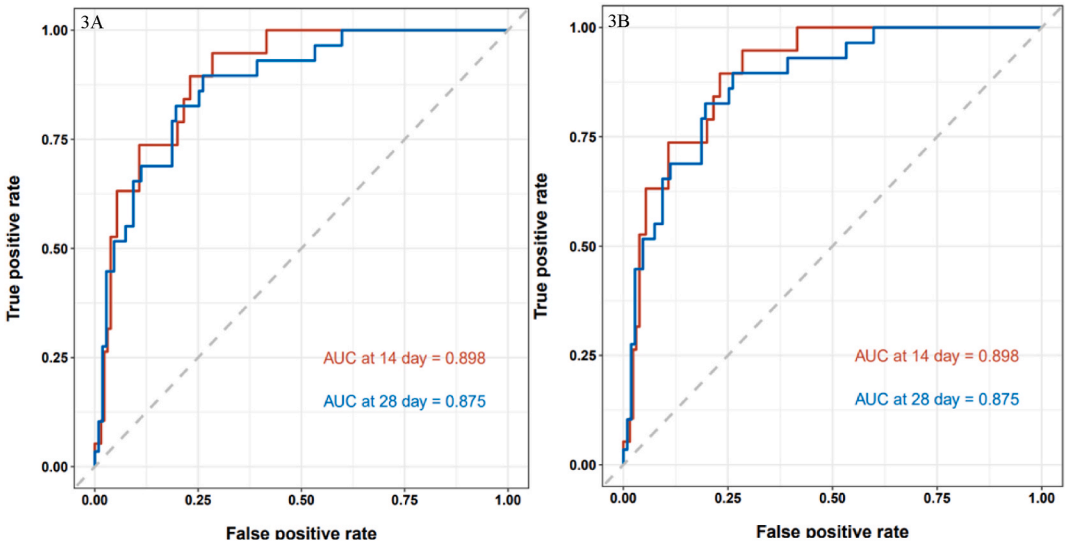

Fig. 3. Nomogram predict the 14 d and 28 d survival rate of COVID-19 patients by ROC curve (3A for training cohort; 3B for validation cohort).

3.7. Calibration curves

The calibration curve visualized the results of the *Hosmer-Lemeshow* test, primarily serving to evaluate the calibration accuracy of the nomogram. If the predicted probabilities on the calibration curve closely resembled the observed probabilities, and the *P*-value of the *Hosmer-Lemeshow* test was greater than 0.05, it indicated a high calibration accuracy of the nomogram. In our study, it clearly demonstrated a high degree of concordance between the four black diagonal lines (reference lines) and the red line (calibration curve) in Fig. 4. Additionally, the *P*-values obtained from the *Hosmer-Lemeshow* test were all greater than 0.05. These results suggested that the 14 d model (Fig. 4A_1), 28 d model (Fig. 4A_2) of the training cohort and the 14 d model (Fig. 4B_1), 28 d model (Fig. 4B_2) of the validation cohort exhibited high calibration accuracy.

3.8. Decision curve analysis (DCA)

DCA determined the clinical application value of the nomogram by calculating the net benefit (NB) under each risk threshold (RT) of death risk. The abscissa of the DCA was the RT, and the ordinate was the NB. When the model reached a certain value, the probability of death for COVID-19 patients was recorded as P_i. When P_i reached a certain threshold (recorded as P_t), it was defined as positive. The RT was set at (0, 1). The NB and the valuable range of predictive probabilities were judged by offsetting the falsely

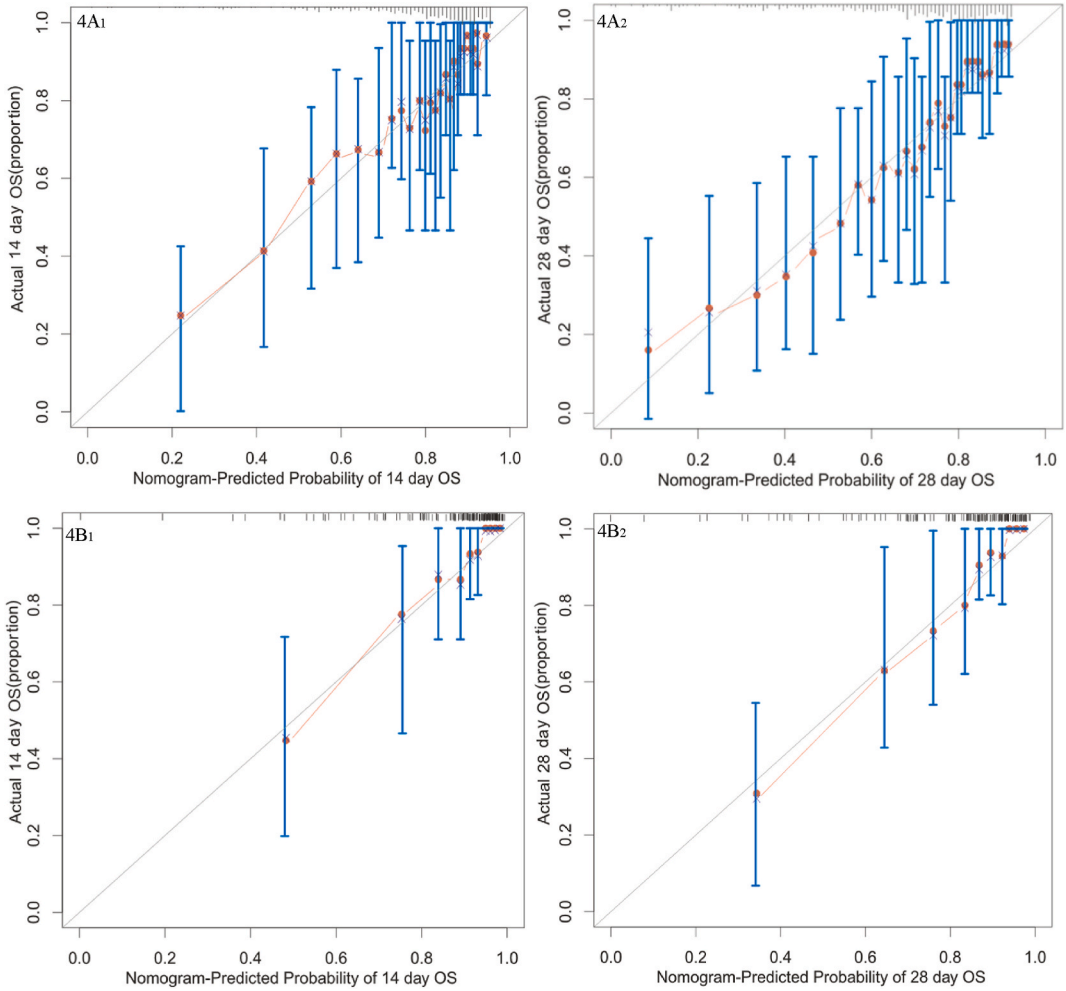

Fig. 4. Nomogram predict the 14 d and 28 d survival rate of COVID-19 patients by calibration curve ($4A_{1\text{-}2}$for training cohort; $4B_{1\text{-}2}$ for validation cohort).

positive population falsely judged by the model. In our study, the model had no clinical value when none or all of the severe/critical COVID-19 patients died. The RT of the 14 d model in the training cohort ranged from 0.25 to 0.99, with the highest NB of 0.21, while for the 28 d model, the RT ranged from 0.37 to 0.99, with the highest NB of 0.30 (Fig. 5A). In the validation cohort, the threshold probability of the 14 d model fell between 0.08 and 0.99, with the highest NB of 0.10, while for the 28 d model, it ranged from 0.20 to 0.99, with the highest NB of 0.13 (Fig. 5B). Within the range of RT from 0.08 to 0.99, the clinical NB of intervention based on the model's predicted probability was higher than that of no intervention (None) or intervention for severe/critical COVID-19 patients (All), suggesting that the model had a high practical value.

4. Discussion

COVID-19 is a serious respiratory infectious disease, and the 28 d mortality of severely ill patients has been as high as 61.5 % in the past 3 years since the emergence of the pandemic [12], especially under the condition of limited medical resources, which has caused a serious burden on the social economy and medical care. Early identification of critical cases and effective intervention measures can improve patient prognosis [13]. Compared with previously published predictive model-related studies [5,7,9,14], this study focuses on the 14 d and 28 d in-hospital survival rates of severe patients with COVID-19 and constructs a simple and practical nomogram based on common and easily available clinical indicators for hierarchical management of patients, which can allocate medical resources effectively. Based on previous research [15], this study improved predictive performance and clinical practical value through continuous optimisation of the model.

Previous studies have shown that advanced age is an important predictor of death in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [16,17], and our study found that advanced age was associated with poor prognosis in patients with severe COVID-19. In previous studies on SARS coronavirus (SARS-CoV) infected rhesus monkeys, it was

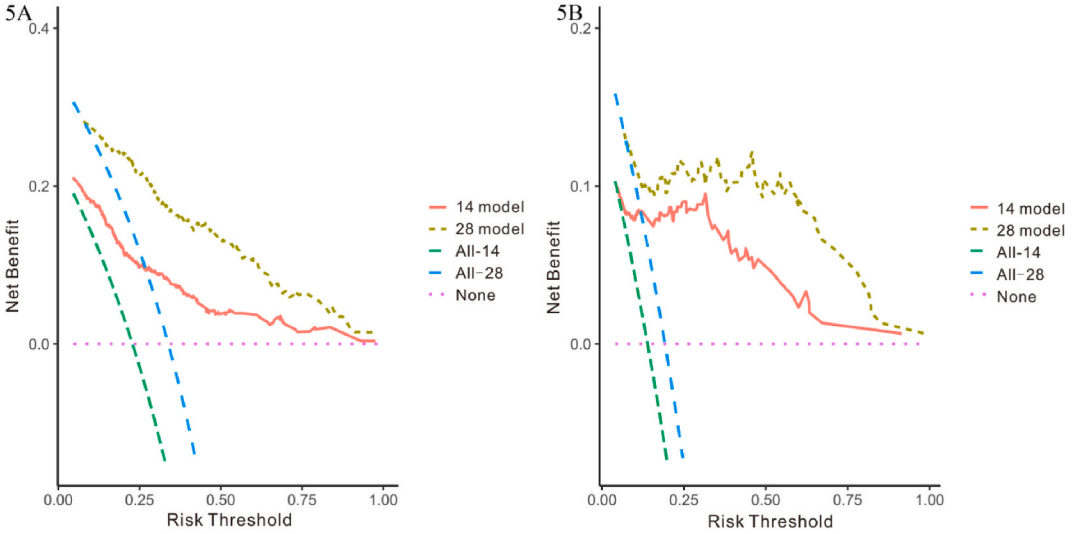

Fig. 5. Nomogram predict 14 d and 28 d survival rate of COVID-19 patients by DCA (5A for training cohort; 5B for validation cohort).

found that aged macaques had a stronger host response to viral infection than young adult macaques and that the differential expression of genes associated with increased inflammation may lead to a poor prognosis [18], which is consistent with the results of Zhou et al. [19]. The present study found that a history of diabetes is an independent risk factor affecting the prognosis of COVID-19, which may be related to the fact that insulin resistance promotes overexpression of the angiotensin-converting enzyme (ACE_2) receptor, consistent with the conclusions reported by Moon et al. [13] and Peralta Amaro et al. [20]. The APACHE II score is an acute physiological index that takes into account age and chronic health status and reflects the state and severity of multiple organ dysfunction. Many prognostic studies on COVID-19 have shown that the higher the APACHE II score, the worse the prognosis [14,21,22], which is consistent with the conclusion of our study. Many COVID-19 studies also used the SOFA score to evaluate the severity and prognosis of the disease [19,21,23], but we found difference in the SOFA score between the two cohorts, which may be related to the timing of calculating the SOFA score after the initial hospital admission rather than after ICU admission. Although bacterial infections are the main cause of sepsis, viral infections can also lead to septic syndromes. Sepsis is a common complication of severe COVID-19 [16] and may be related to cytokine storms, lymphopenia, and systemic multiple organ involvement caused by SARS-CoV-2 [24]. Recently, NLR has been identified as a potential biological marker that reflects immune and inflammatory responses in vivo [25]. Previous studies have confirmed that an increase in NLR is positively correlated with the death of patients with severe COVID-19 [1,8,26], which is consistent with the results of the present study, and may be due to the dysregulation of inflammatory cytokine expression, abnormal increase in pathological neutrophils, and upregulation of genes related to the lymphocyte death pathway caused by the SARS-CoV-2 infection mechanism [27]. D-dimer is the product of a combination of fibrin formation, activation of coagulation factor XIII, and plasmin, which can indicate secondary abnormalities in fibrinolytic activity and can be used as a molecular marker to evaluate hyperfibrinolysis and hypercoagulability in vivo [3,28]. Our study found that up to 88.53 % of the patients who died had elevated D-dimer levels, and the D-dimer level at admission was >5 μg/L, which was associated with in-hospital mortality. This may be related to thrombosis and multiple organ damage caused by the excessive activation of the coagulation system during the systemic inflammatory response caused by SARS-CoV-2 [29]. The effectiveness of COVID-19 vaccination has been confirmed in different epidemiological studies [30,31], and our study also confirmed that patients with severe COVID-19 who received the vaccine had higher in-hospital survival rates and better prognoses.

The data in this study were all from patients with severe and critical COVID-19; therefore, the model is suitable for severely ill adult patients. We performed risk stratification for the results predicted by the model as well as close monitoring and early intervention and made positive and effective treatment decisions for patients with a high risk of death, which may improve the prognosis of such patients. For patients with a low risk of death, we should improve the allocation of critical care resources as soon as possible and allocate manpower and resources reasonably.

However, this study had several limitations. First, this was a dual-centre observational study based in mainland China. Due to regional differences, it may not be representative of patients with COVID-19 in other regions or countries. Therefore, multicentre, prospective, large-sample studies are required for external verification. Second, this was a retrospective study. The data obtained from the electronic medical record system were not complete, and although we used multiple imputation methods to supplement some of the missing data, our results were susceptible to the influence of outliers. Third, we did not collect data on lymphocyte subtypes, organ damage markers, and other indicators and therefore could not analyse their impact on prognosis. Fourth, the laboratory data changed with disease progression, and we did not include the dynamic changes of each variable in the model for analysis.

5. Conclusion

The nomogram established in this study showed good predictive ability and discrimination, which was not only verified internally but also externally combined with Shanghai data. It demonstrated high stability, reliability, and repeatability and can help clinicians make appropriate clinical decisions.

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Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committees of the Renmin Hospital of Wuhan University (No. WDRY:2020-K026) and Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine (No. SH9H-2022-T156-1).

Data availability statement

The datasets used during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Wen-Hui Bai: Writing – original draft, Conceptualization. **Jing-Jing Yang:** Methodology, Investigation, Data curation. **Zhou Liu:** Software, Formal analysis. **Wan-Shan Ning:** Supervision, Funding acquisition. **Yong Mao:** Data curation. **Chen-Liang Zhou:** Visualization, Supervision, Resources. **Li Cheng:** Writing – review & editing, Visualization, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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