Heliyon 10 (2024) e28627

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Development and validation of a predicting nomogram for in-hospital mortality of COVID-19 Omicron variant: A cohort study of 1324 cases in Beijing Anzhen Hospital

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ARTICLE INFO

Keywords:
Coronavirus disease 2019 (COVID-19)
Omicron SARS-CoV-2
In-hospital mortality
Nomogram prediction

ABSTRACT

Coronavirus disease 2019 (COVID-19) is continuously posing high global public health concerns due to its high morbidity and mortality. This study aimed to construct a convenient risk model for predicting in-hospital mortality of COVID-19 Omicron variant. A total of 1324 hospitalized patients with Omicron variant were enrolled from Beijing Anzhen Hospital. During hospitalization, the Omicron variant mortality rate was found to be 24.4%. Using the datasets of clinical demographics and laboratory tests, three machine learning algorithms, including best subset selection, stepwise selection, and least absolute shrinkage and selection operator regression analyses were employed to identify the potential predictors of in-hospital mortality. The results found that a panel of twenty-four clinical variables (including age, hyperlipemia, stroke, tumor, and several cardiovascular markers) identified by stepwise selection model exhibited significant performances in predicting the in-hospital mortality of COVID-19. The resultant nomogram showed good discrimination, highlighted by the areas under the curve values of 0.88 for 10 days, 0.81 for 20 days, and 0.82 for 30 days, respectively. Furthermore, decision curve analysis showed a significant reliability and precision for the established stepwise selection model. Collectively, this study developed an accurate and convenience risk model for predicting the in-hospital mortality of COVID-19 Omicron.

1. Introduction

COVID-19 is a new acute respiratory infection caused by the novel coronavirus SARS-CoV-2. Since December 2019, COVID-19 has ravaged the world for over three years, infecting over 750 million people and causing over 6.8 million deaths globally. Meanwhile, the main pathogen, SARS-CoV-2, has been constantly evolving and mutating, giving rise to various variant strains with changes in virulence and transmissibility, such as Alpha, Beta, Gamma, Delta, and Omicron. On November 24, 2021, a variant of the novel coronavirus (Omicron, B.1.1.529) was first reported to the World Health Organization (WHO) in South Africa [3]. On November 26, 2021, WHO named it the Omicron variant. The Omicron variant includes multiple subtypes, such as B.1.1.529, BA.1, BA.2, and BA.3.

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https://doi.org/10.1016/j.heliyon.2024.e28627
Received 6 December 2023; Received in revised form 14 March 2024; Accepted 21 March 2024
Available online 26 March 2024

On December 14, 2021, one imported case of Omicron variant infection was reported in Tianjin, China [6]. Omicron strain has remarkable characteristics such as high transmissibility, fast transmission speed, and immune escape, and has become the main variant strain in the current global epidemic, posing a serious threat to people's lives and health.

Patients infected with the COVID-19 Omicron variant may present with varying clinical manifestations, including fever, sore throat, cough, sputum, dyspnea, and headache. A few patients may have gastrointestinal symptoms such as vomiting and diarrhea as the initial symptoms. Most patients have a mild illness with a good prognosis. However, a small proportion may develop severe illness by prone to acute respiratory distress syndrome and multiple organ dysfunction syndrome, which can increase the risk of death [9]. Therefore, early identification of patients who are at risk of progressing to severe illness or death is crucial for the clinical diagnosis and treatment of COVID-19. Studies have shown that factors such as advanced age, the presence of related diseases, disorders blood indices on admission and other factors may be associated with poor prognosis in patients with COVID-19.

Consideration should be given to the fact that radiological abnormalities may not be observed during the initial presentation in approximately 20% of cases. Therefore, clinical characteristics and routine clinical laboratory tests may provide important prognostic factors quickly [1]. A nomogram is a user-friendly graphic representation of a scoring model that accurately calculates the probability of an outcome using multiple scale axes [2]. Incorporating routine laboratory tests, a nomogram might be a more effective and affordable approach for predicting the risk of mortality [3]. This study aimed to describe the clinical features of Omicron SARS-CoV-2 and establish nomograms based on the latest wave of the COVID-19 in China, incorporating common clinical demographics, characteristics, and laboratory parameters, to early warn the risk of fatal outcomes in patients with Omicron SARS-CoV-2.

2. Methods

2.1. Study cohort

In this study, a total of 1324 patients who confirmed COVID-19 were consecutively collected between December 8th, 2022 and January 31st, 2023 at Beijing Anzhen Hospital, Capital Medical University. The diagnosis of COVID-19 was based on the interim guidance of the World Health Organization and confirmed by real-time reverse transcriptase PCR testing for SARS-CoV-2 RNA [4]. This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Anzhen Hospital of the Capital University of Medical Sciences (Ethics No. 2023038X). Verbal and written consent was obtained from all subjects.

2.2. Data collection

The participants were randomly divided into a derivation cohort and a validation cohort in a 7:3 ratio (Figure S1). The derivation cohort included 927 subjects, of which 725 survived and 202 deceased. The validation cohort included 397 subjects, of which 323 survived and 74 deceased. The collected data included demographic information such as age, gender, body mass index (BMI) and medical history, as well as laboratory test results such as blood routine, blood biochemistry, and arterial blood gas. All laboratory indices were collected at the first time of hospitalization and analyzed using an automated biochemical analyzer to ensure accurate and consistent results.

2.3. Variables selection

Best subset selection analysis, stepwise selection analysis, and least absolute shrinkage and selection operator (LASSO) regression analysis was used to identify factors associated with COVID-19 patient mortality (the workflow diagram of the three machine learning algorithms was depicted in Figure S1). For the best subset selection analysis, we conducted 4 selection models: Max R squared, Max Adjusted R squared, Min BIC, and Min Mallows Cp, to select the variables. The Lambda values were selected using a 10-fold cross-validation process, with a significance level for inclusion criteria set at 0.05.

2.4. Models development

The final model for predicting COVID-19 mortality was determined in the primary cohort using the variables selected by best subset selection analysis, stepwise selection analysis, or LASSO regression analysis. The model was evaluated using the Akaike information criterion (AIC), receiver operating characteristic (ROC) curves, and the Harrell concordance index (C-index). Based on the final models, nomograms were developed to visualize the predicted probability of mortality in COVID-19 patients. The code for the nomogram constructions have been provided in the Supplementary file 1.

2.5. Performance of the nomograms

The performance of the models was tested using the validation cohort. The discrimination ability of the models was measured using the C index. Calibration, which evaluated the degree of agreement between predicted and observed outcomes, was tested using a calibration plot with 1000 bootstrap resamples. The calibration plot compared the predicted probability of mortality from the nomograms with the actual mortality rate of COVID-19 patients.

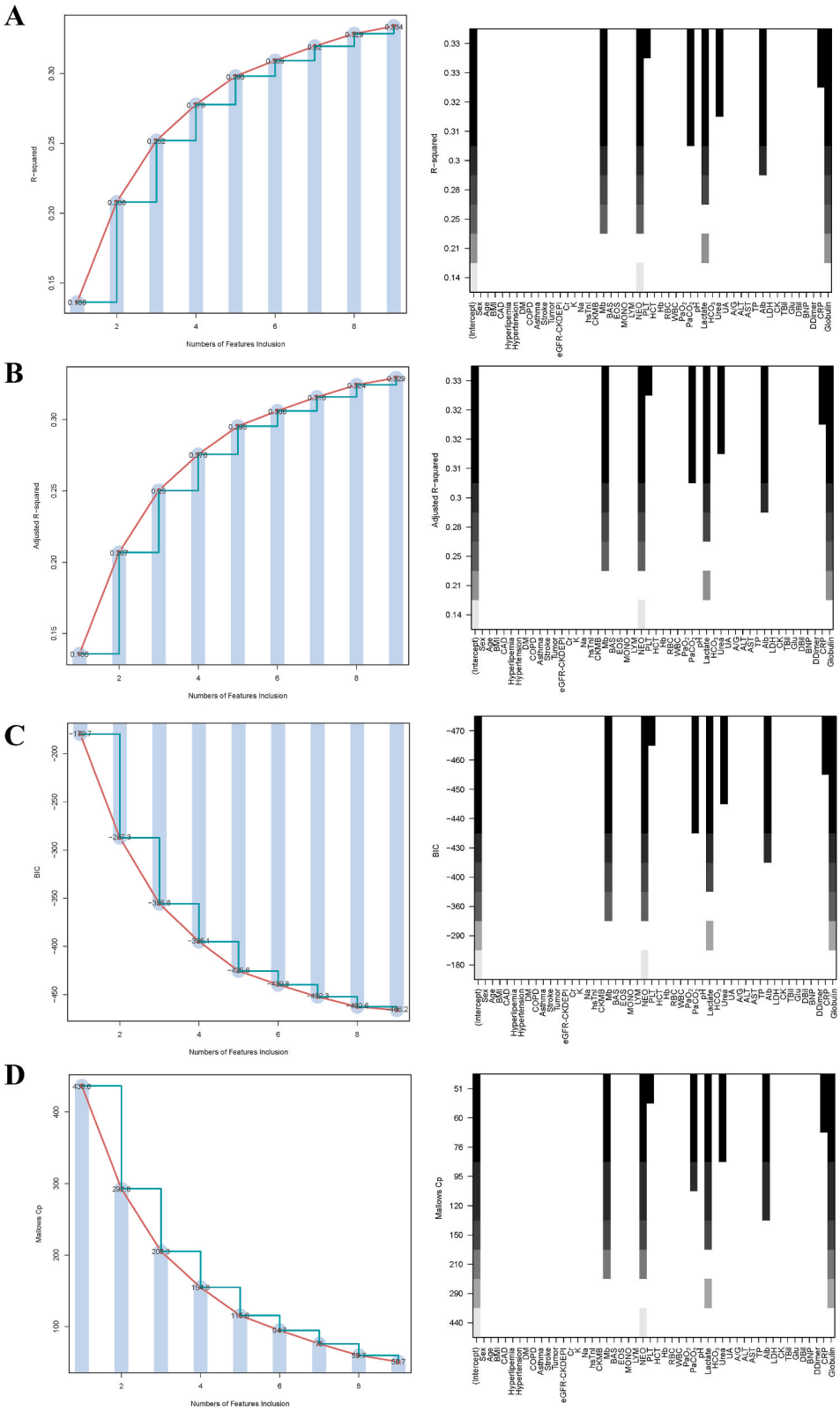

Fig. 1. Important feature and the optimal number selection using best subset selection analysis. (A) Max R squared. (B) T Max Adjusted R squared. (C) Min BIC. (D) Min Mallows Cp.

2.6. Clinical usage

The decision curve analysis (DCA) was performed to assess the clinical usefulness of the nomograms in terms of its ability to predict mortality in patients with COVID-19. DCA has been described in detail in previous reports [5]. Statistical significance was defined as a *P*-value <0.05. The net reclassification index (NRI) and integrated discrimination improvement (IDI) are two alternatives to area under curve (AUC) to assess improvement in risk prediction and measure the usefulness of two models [23,24]. The NRI and IDI were used to evaluate the clinical benefits and utility of the nomogram compared with different models. NRI was calculated using the category-free (or continuous) approach11 with 1000 bootstrap replications to estimate the 95% CI.

2.7. Statistical analysis

Data are presented as mean ± standard deviation (SD) or median (inter-quartile range) for continuous variables, while categorical variables were presented as numbers with percentages. The *t*-test or Mann-Whitney *U* test was used to assess differences in baseline characteristics between groups for continuous variables, while the Chi-square test or Fisher's exact test was used for categorical variables based on their sample size.

Statistical analyses were performed using IBM SPSS v23.0 (SPSS Inc., Chicago, IL, USA), and a two-sided *P*-value <0.05 was considered statistically significant. The nomogram was developed and the calibration curve analysis was carried out using R software v4.2.0 (http://www.R-project.org, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Population clinical characteristics of the derivation and validation set

Table S1 presented a summary of the clinical characteristics of the derivation set (n = 927) and the validation set (n = 397). The mortality rate of COVID-19 Omicron of all enrolled patients was 24.4%. The clinical demographics, including mortality, age, gender, BMI, comorbidities, and laboratory indexes did not show significant differences between the derivation and validation cohorts (all $P > 0.05$). Compared to the surviving patients, the deceased patients were more likely to be male, older, and lower BMI with stroke (all $P < 0.05$). Additionally, they were more frequently found to have a decreased lymphocyte (LYM), eosinophils (EOS), basophilic granulocyte (BAS), platelet (PLT), estimated glomerular filtration rate (eGFR)-CKDEPI, albumin-globulin ratio (A/G), total protein (TP), albumin (Alb), PaO_2, HCO_3, and prothrombin activity (PTA)(all $P < 0.05$). In our analysis of laboratory parameters, we observed notable differences between deceased and surviving patients. Deceased individuals exhibited significantly elevated levels of various inflammatory, metabolic, and cardiovascular markers, such as white blood cells (WBC), neutrophils (NEO), creatinine (Cr), urea, uric acid (UA), aspartate aminotransferase (AST), glucose (Glu), lactate dehydrogenase (LDH), high-sensitivity troponin I (hsTnI), myoglobin (CK-MB), brain natriuretic peptide (BNP), lactate, prothrombin time (PT), and C-reactive protein (CRP).

3.2. In-hospital mortality of COVID-19 Omicron variant-associated clinical factors selection using different machine learning algorithms

We used three machine learning algorithms to identify important clinical variables associated with COVID-19 in-hospital mortality (Figure S1). In the best subset selection analysis, we conducted four selection models to select the mortality-related variables. Interestingly, we found that the variables required to achieve similar results were same based on the established models using different methods (Table S2). Using the best subset selection analysis-based different selection models (Fig. 1A–D), nine variables identified as

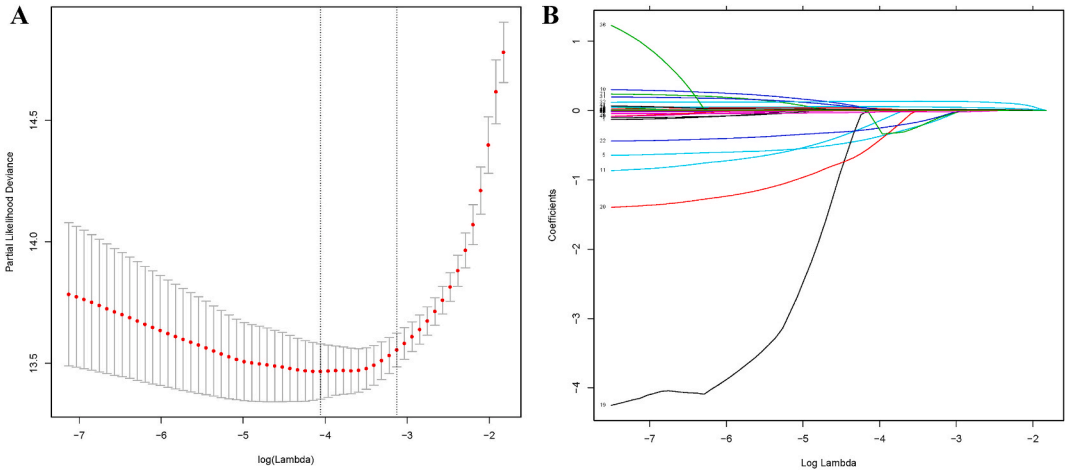

Fig. 2. LASSO regression analysis. (A) 10-fold cross-validation curve. (B) Path coefficients diagram.

related to mortality of COVID-19 are as follows, including myoglobin (Mb), NEO, platelet (PLT), $PaCO_2$, lactate, urea, albumin (Alb), CRP, and globulin. In the stepwise selection analysis, a total of twenty-four potential indicators were identified as related to mortality of COVID-19, mainly including a panel of cardiovascular markers (such as hsTnI, CK-MB, lactate, UA, LDH, BNP, and CRP), MONO, NEO, PLT, WBC, PaO2, pH, ALT, TP, Alb, age, hyperlipemia, stroke, and tumor. The coefficient of each variable was shown in Table S3. In the LASSO regression analysis, after 10-fold cross-validation (the established validation curve was depicted in Fig. 2A), 29 potential indicators with non-zero coefficients were identified as related to mortality of COVID-19 (Fig. 2B), including age, tumor, eGFR-CKDEPI, K, hsTnI, CK-MB, Mb, EOS, LYM, NEO, PLT, PaO_2, $PaCO_2$, pH, lactate, urea, UA, A/G, ALT, Alb, hyperlipemia, globulin, LDH, CK, Glu, BNP, D-Dimer, CRP, and stroke. The changes in the LASSO coefficients were shown in Table S4.

3.3. Construction and validation of a nomogram scoring system by best subset selection model

The results of the subset selection analysis led to the inclusion of 9 variables as predictors for establishing a nomogram (Fig. 3A). Each predictor corresponded to a score, and the total score was used to predict the risk factors for mortality of COVID-19 in the 10 days, 20 days, and 30 days.

The validation cohort consisted of 397 patients. To assess the model's calibration, calibration curves were drawn (Fig. 4A–C, 10 days, 20 days, and 30 days). Discrimination of the model was measured by analyzing the ROC curve, which showed areas under the curve (AUC) of 0.85 for 10 days, 0.78 for 20 days, and 0.77 for 30 days, respectively (Fig. 4D and Table S5). Furthermore, decision curve analysis (DCA) curves demonstrated that the nomogram had higher clinical nets (Figure S2A-C).

3.4. Construction and validation of nomogram scoring systems based on the stepwise selection and LASSO regression models

Using the twenty-four predicative variables identified by the stepwise selection analysis, a nomogram was constructed (Fig. 3B). To assess the model's calibration, calibration curves were drawn (Fig. 4E for 10 days, Fig. 4F for 20 days, and Fig. 4G for 30 days).

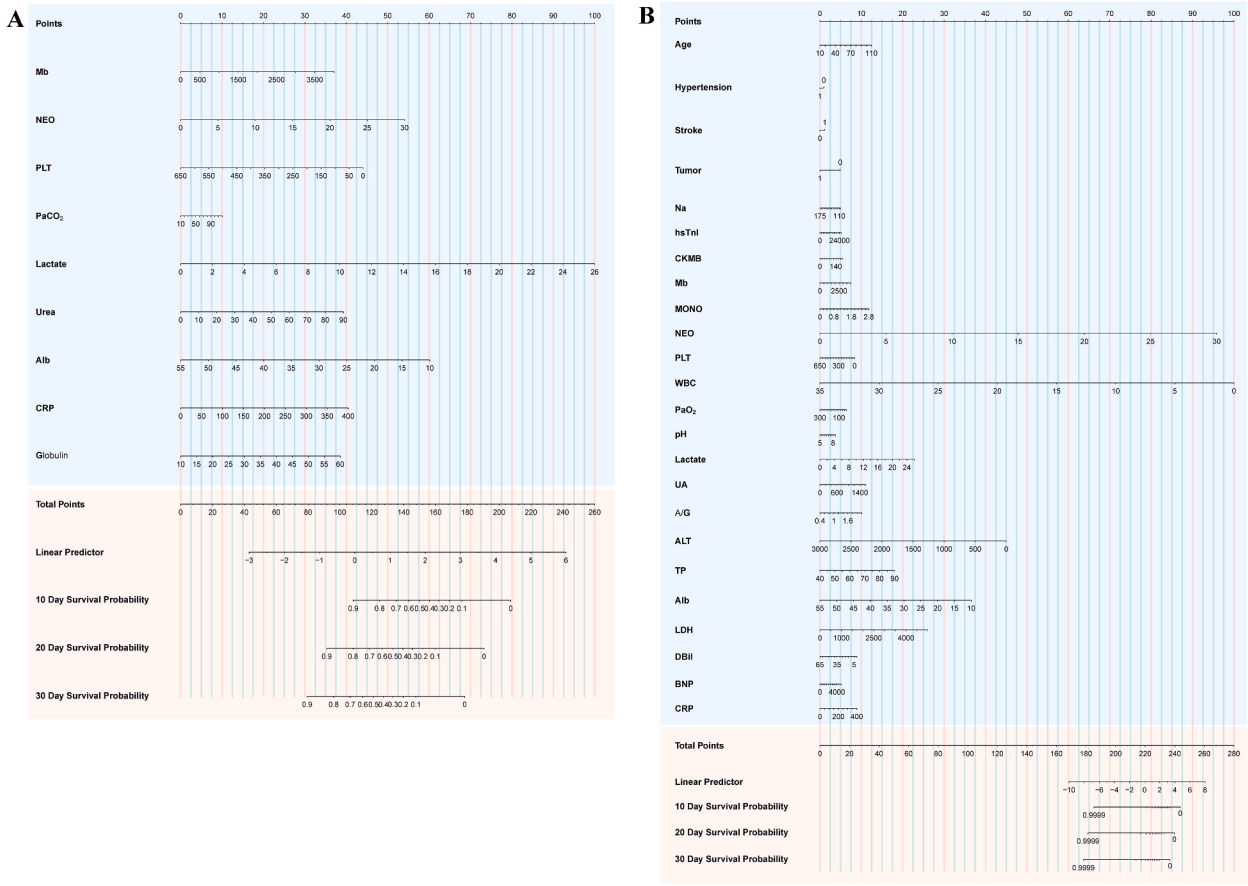

Fig. 3. Construction and validation of the nomogram scoring systems. (A) The nomogram scoring system built by best subset selection. (B) The nomogram scoring system based on stepwise selection model. The value of each of variable was given a score on the point scale axis. Sum up the number of points for all risk factors then draw a line descending from the axis labeled "Total Points" until it intercepts each of the survival axes to determine 10 day, 20 day, and 30 day survival probabilities.

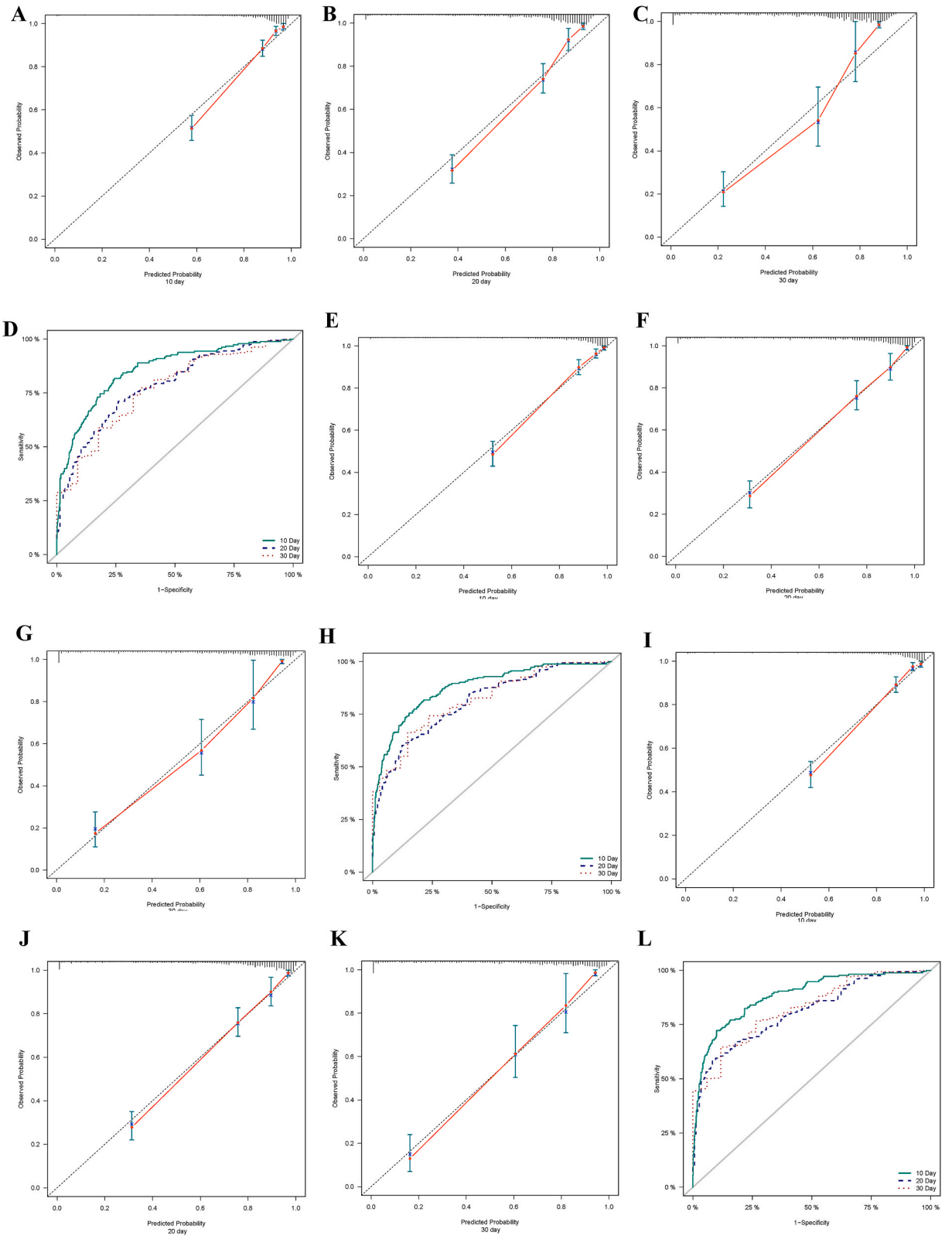

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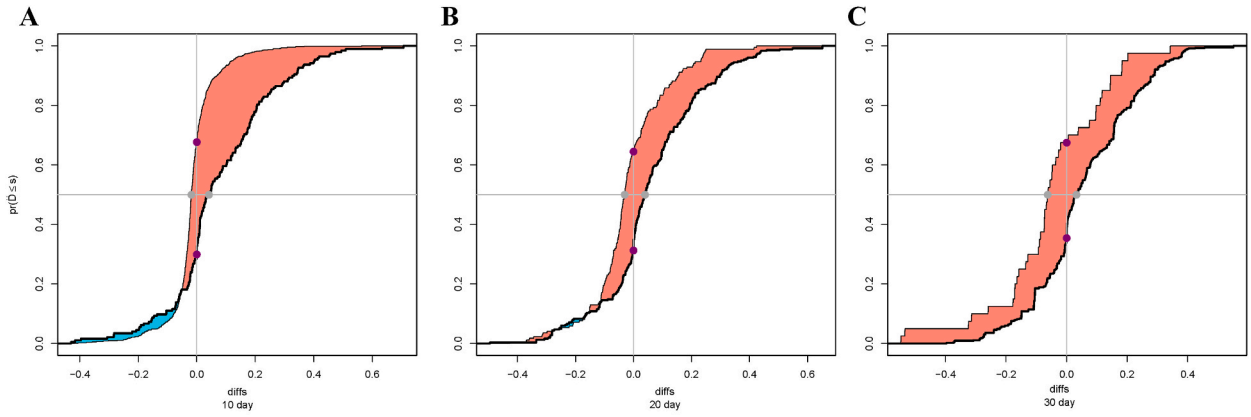
Fig. 4. Calibration curves and discrimination ability assessments of different models. (A–C) Calibration curves based on the best subset selection model at 10days, 20 days, and 30 days. (D) ROC curves based on the best subset selection model. (E–G) Calibration curves based on the stepwise selection model at 10days, 20 days, and 30 days. (H) ROC curves based on the stepwise selection model. (I–K) Calibration curves based on the LASSO regression selection model at 10days, 20 days, and 30 days. (L) ROC curves based on the LASSO regression selection model.

Discrimination of the model was measured by analyzing the ROC curve, which showed areas under the curve (AUC) of 0.88 for 10 days, 0.81 for 20 days, and 0.82 for 30 days, respectively (Fig. 4H and Table S6). Furthermore, DCA curves demonstrated that the nomogram had higher clinical nets (Figure S2D-F). Then, we also used the LASSO regression analysis-selected twenty-nine predictive variables for establishing a nomogram (Figure S3). Each predictor corresponded to a score, and the total score was used to predict the risk factors for mortality of COVID-19 in the 10 days, 20 days, and 30 days. The calibration curves of different days were drawn in Fig. 4I- K. Discrimination of the model was measured by analyzing the ROC curve, which showed areas under the curve (AUC) of 0.88 for 10 days, 0.81 for 20 days, and 0.82 for 30 days, respectively (Fig. 4L and Table S7). Moreover, DCA curves demonstrated that the nomogram had higher clinical nets (Figure S2 H-I).

3.5. The stepwise selection model showed the best performance in predicting the in-hospital mortality of COVID-19 Omicron variant

As described above, the nomograms derived from LASSO regression and stepwise selection model showed similar predictive performances in day 10, 20, and 30. Due to the larger number of LASSO-selected marker panel (variable number = 29), we used the stepwise selection model-selected marker panel (variable number = 24) to further compare the predictive performances with the best subset selection model (variable numbers = 9). The continuous NRI and IDI plots were used to compare the accuracy between the stepwise selection model and the best subset selection model, the resultant plots at different days were summarized in Fig. 5A–C. The NRI values for the 10- and 20-day were 0.377 (95% CI: 0.277–0.454, $P < 0.05$) and 0.332 (95% CI: 0.192–0.432, $P < 0.05$). The IDI values for 10- and 20-day were 0.093 (95% CI: 0.061–0.145, $P < 0.05$) and 0.081 (95% CI: 0.049–0.129, $P < 0.05$) (Fig. 5D). However,



D

Index	Estimate	95% CI	P value
NRI (vs. the best subset selection models)			
10 Day	0.377	0.277-0.454	< 0.05
20 Day	0.332	0.192-0.432	< 0.05
30 Day	0.32	-3.335	0.149
IDI (vs. the best subset selection models)			
10 Day	0.093	0.061-0.145	< 0.05
20 Day	0.081	0.049-0.129	< 0.05
30 Day	0.114	-0.739	0.109

Fig. 5. Comparison between stepwise selection model and the best subset selection model. (A–C) NRI and IDI plots at 10days, 20 days, and 30 days. (D) NRI and IDI values and statistical significances.

the continuous NRI and IDI values had no differences in 30-day ($P > 0.05$). Collectively, the stepwise selection model exhibited the best performances in predicting the in-hospital mortality of COVID-19 Omicron variant.

4. Discussion

COVID-19 is an acute infectious disease caused by the novel coronavirus (SARS-CoV-2) that spreads rapidly and poses significant challenges to human health and healthcare systems [6]. The Omicron variant, the current major strain of the virus, has been associated with a mortality rate of 4.3% in previous studies. Over the past three years, the coronavirus has undergone rapid mutations, leading to the emergence of the highly infectious Omicron strain, which is now prevalent in many parts of the world. Although its virulence has decreased, the infectiousness has significantly increased [7]. In China, the Omicron strain has become the dominant variant of the 2019-nCoV infection [8]. This study retrospectively collected data from designated hospitals.

The study focused on severe cases of novel coronavirus pneumonia at Beijing Anzhen Hospital, covering the period from December 8th, 2022, to January 31st, 2023. Out of the collected cases, 1324 patients met the severe diagnostic criteria for admission as established by the National Health and Wellness Commission in the "Diagnostic Protocol for Novel Coronavirus Pneumonia (Trial Version 7)." The diagnostic criteria were based on SpO_2 and CT imaging [9]. The mortality rate observed in our study was 20.85%. Through multivariate analysis, we identified key predictors and developed a well-calibrated and discriminative nomogram. The nomogram was further validated through bootstrap resampling and an internal validation cohort, providing additional evidence of its usefulness. This nomogram has the potential to assist physicians in predicting the mortality risk of COVID-19 patients and guiding appropriate interventions.

In comparison to previous studies, the majority of COVID-19 patients included in our study were infected after the relaxation of epidemic policies in China. Their disease progression was more severe and rapid, making early identification and intervention challenging. We analyzed clinical demographics, characteristics, and laboratory tests to investigate the risk of fatal outcomes in COVID-19 patients, particularly during this severe epidemic. In particular, during this severe COVID-19 epidemic, many non-respiratory physicians are involved in the critical battle against the pandemic, and a simpler method that does not require respiratory doctors and radiologists to evaluate multiple lung lobes is practical. Therefore, we focused on variables related to clinical features and laboratory tests in order to create a rapid and user-friendly nomogram. Our multivariate analysis helped identify significant predictors.

Numerous clinical indicators have shown promise in predicting mortality in critically COVID-19 patients [10–12]. In our study, we developed and internally validated predictive models specifically for patients affected by the Omicron. We employed LASSO regression and multivariate logistic regression analysis to identify significant factors associated with in-hospital mortality in critically COVID-19 patients. The resulting prognostic model incorporated demographic, clinical, and laboratory parameters, including age, procalcitonin (PCT), glucose, D-dimer, C reactive protein (CRP), troponin, blood urea nitrogen (BUN), length of stay (LOS), mean arterial pressure (MAP), aspartate aminotransferase (AST), temperature, O_2Sats, and platelets. These parameters were used to construct prognostic line graphs that demonstrated good discrimination and calibration in predicting the probability of death in the 10 days, 20 days, and 30 days in COVID-19 patients. In our study, the comprehensive analysis identified the top 5 affective factors associated with an increased risk of serious disease and mortality in COVID-19 patients with the Omicron variant. These key indicators include WBC, NEO, ALT, ALB, and LDH. The significance of these factors in predicting adverse outcomes highlights their potential as crucial variables in assessing disease severity. By prioritizing these factors, clinicians may have valuable insights into the patient's prognosis and can tailor interventions accordingly.

As an example to better explain the nomogram model, a real data from a patient who are 59 years old, with no hyperglycemia, stroke and tumor, Na of 142.3 mmol/L, hsTnI of 19.1 pg/ml, CK-MB of 0.8 U/L, MONO of 0.35×10^9/L, NEO of 2.83×10^9/L, PLT of 207×10^9/L, WBC of 5.38×10^9/L, PaO_2 of 73.8 mmHg, pH of 6.0, lactate of 3 mmol/L, UA of 461.8 mmol/L, A/G of 1.84 mmol/L, ALT of 15 U/L, TP of 68.7 g/L, Alb of 44.5 g/L, LDH of 122 U/L, DBil of 6.29 μmol/L, BNP of 61 pg/ml, and CRP of 3.37 mg/L, the probability of risk factors for survived of COVID-19 in the 10 days, 20 days, and 30 days were estimated to be 99.2%, 98.2% and 96.7%. Various evaluation metrics, such as NRI, IDI, and AUC values calibration plots, supported the model's performance and clinical utility.

Age was identified as a significant predictor, with the death group having a higher average age compared to the survivor group. While advanced age has been associated with adverse outcomes in previous models, some studies indicate that age-related comorbidities may have a more significant impact on mortality than age itself [13]. Our study also found associations between COVID-19 mortality and clinical parameters such as hypertension, stroke, and tumors. Previous research has demonstrated worse outcomes in COVID-19 patients with pre-existing hypertension [13,14]. Patients with hypertension, stroke, and tumors experience clinically unfavorable conditions that place them at higher risk for poor prognosis. Consequently, these patients should be given high priority for improved health and survival outcomes.

Regarding laboratory parameters in the nomogram, we included PCT, glucose, D-dimer, CRP, troponin, BUN, LOS, MAP, AST, temperature, O_2Sats, and platelets. Comorbid diabetes has been associated with an increased risk of disease severity or death in Chinese COVID-19 patients, as concluded by a recent meta-analysis. Another study highlighted high direct bilirubin levels as an important factor for diagnosing COVID-19 and predicting mortality in adult inpatients [15]. However, a study with a larger sample size found that inflammation-related factors, including neutrophils, C-reactive protein, IL-19, and D-dimer, were strongly associated with the risk of COVID-19 mortality [16]. Additionally, elevated levels of NT-proBNP, a biomarker of heart failure, were significantly linked to adverse outcomes in COVID-19 patients [11]. NT-proBNP is released by cardiomyocytes in response to high intraventricular pressure caused by ventricular wall stretching [17].

5. Conclusions

It is important to note several limitations of our study. Firstly, being a retrospective study, potential selection bias may exist in the patient selection process. Secondly, our study primarily focuses on the Omicron variant, which was the predominant strain in China at the time of the study. Therefore, the applicability of our nomogram to other COVID-19 strains may be restricted. Lastly, our nomogram model was only internally validated. Future studies should incorporate more extensive analyses and external validation to confirm the accuracy and applicability of this nomogram. In conclusion, our study introduces a practical nomogram based on routine clinical tests to predict mortality in critically ill patients with SARS-CoV-2. The stepwise selection model analysis identified a panel of Omicron variant mortality-associated clinical demographics and clinical laboratory features. Based on these identified predictors, the derived nomogram exhibited good discrimination, high reliability, and significant precision in predicting the in-hospital mortality of COVID-19 Omicron variant. This early warning model has the potential to help clinicians identify patients at high risk of severe disease. Further research is necessary to validate the prognostic capability of this nomogram.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Anzhen Hospital of the Capital University of Medical Sciences (Ethics No. 2023038X).

Funding

This work was supported by National Natural Science Fund of China (No. 82200441, 81970291, 82170344, 82100295) and the Major State Basic Research Development Program of China (973 Program, No. 2015CB554404).

Data availability statement

Data reported in this paper will be shared by the lead contact upon request. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

CRediT authorship contribution statement

Yuchen Shi: Writing – original draft, Investigation, Conceptualization. **Ying Ma:** Writing – review & editing, Validation. **Ze Zheng:** Resources. **Yanwen Qin:** Validation. **Zhiyong Du:** Writing – original draft, Validation, Project administration, Funding acquisition. **Jinghua Liu:** Validation, Project administration, Funding acquisition.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28627.

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