Journal of Inflammation Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Development of a Prognostic Nomogram for Nonneutropenic Invasive Pulmonary Aspergillosis Based on Machine Learning

Weiwei Du, Wentao Ji, Tian Luo, Yinying Zhang, Weihong Guo, Jianping Liang, Yanhua Lv

Department of Respiratory and Critical Care Medicine, Zhongshan City People's Hospital, Zhongshan, Guangdong Province, People's Republic of China

Correspondence: Yanhua Lv, Department of Respiratory and Critical Care Medicine, Zhongshan City People's Hospital, No. 2 Sunwen East Road, Zhongshan, 528400, Guangdong Province, People's Republic of China, Tel/Fax +86-760-89880256, Email lyh009001@163.com

Background: The incidence of invasive pulmonary aspergillosis (IPA) is progressively rising in the nonneutropenic population, but studies investigating relevant prognostic factors remain scarce.

Methods: Participants who were hospitalized at Zhongshan City People's Hospital from January 2018 to May 2023 and diagnosed with nonneutropenic deficient IPA were included in this study. The least absolute shrinkage and selection operator (LASSO) regression and multivariate Cox regression methods were used to select variables for constructing the predictive model. The performance of the predictive model was evaluated using the concordance index (C-index), calibration curve, time-dependent receiver operating characteristic (T-ROC) curve, area under the curve (AUC), and decision curve analysis (DCA). Finally, prognostic risk stratification was performed for nonneutropenic IPA patients, transforming the nomogram into a risk-stratified prognostic model.

Results: A total of 210 participants were included in this study, divided into training and validation cohorts at a ratio of 7.5:2.5. Lasso regression identified seven potential predictive factors, including age, comorbid bacterial pneumonia, pleural effusion, neutrophil to lymphocyte ratio (NLR), lactate dehydrogenase (LDH), invasive mechanical ventilation and ICU treatment. Multivariate Cox regression analysis showed age (HR=1.02), comorbid bacterial pneumonia (HR=3.36), NLR (HR=1.02), LDH (HR=1.001), and invasive mechanical ventilation (HR=4.86) as independent predictive factors and constructed nomogram. The calibration curves show that the nomogram performs well in terms of consistency between predictions and actual observations. The T-ROC curves and DCA of the nomogram model show that the recognition ability of the nomogram model was outstanding. Participants could be classified into high and low-risk groups based on the final score of this nomogram, demonstrating the excellent risk stratification performance of our model.

Conclusion: The nomogram model developed in this study is an effective tool for predicting mortality risk in nonneutropenic IPA patients, aiding clinicians in identifying high-risk patients and optimizing early treatment strategies.

Keywords: invasive pulmonary aspergillosis, pulmonary fungal infections, overall survival, risk stratification, nomogram, model

Introduction

Invasive pulmonary aspergillosis (IPA) is an acute infectious disease resulting from the inhalation of aspergillus spores, primarily affecting individuals with compromised immune function and prolonged neutrophil depletion.[1] Recently, there has been a growing number of reports on IPA in nonneutropenic populations, including individuals with chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome, and compromised mucociliary clearance following influenza infection.[2,3] While advancements in diagnostic methods and treatment strategies have improved the clinical prognosis of IPA,[4] a mortality rate ranging from 40% to 90% still persists.[5] Moreover, in comparison to neutropenic patients, nonneutropenic individuals exhibit varying degrees of immune competence, leading to diverse clinical presentations that may be overlooked by clinicians and result in higher mortality rates.[6] In addition to emerging diagnostic and therapeutic approaches, the identification of prognostically relevant risk factors is crucial for recognizing

Received: 16 October 2024
Accepted: 17 November 2024
Published: 26 November 2024

high-risk patients and making appropriate clinical decisions, ultimately improving clinical outcomes. Although some studies have investigated prognostic factors influencing IPA outcomes,[4,7,8] only a limited number with small sample sizes have explored prognostic factors in nonneutropenic IPA,[9] and there is a lack of corresponding predictive models. Therefore, through a retrospective analysis of clinical data, this study aims to construct a predictive model visualized as a nomogram. This nomogram will provide a foundation for identifying high-risk individuals and making informed clinical decisions, addressing the current gap in predictive modeling for nonneutropenic IPA.

Materials and Methods

Study Subjects

This study is a single-center retrospective investigation. Clinical data were collected from January 2018 to May 2023 for 210 study participants diagnosed with nonneutropenic IPA and hospitalized in the Department of Respiratory and Critical Care Medicine of the Zhongshan City People's Hospital (Guangdong Province). All cases were randomly divided into a training set and an internal validation set at a ratio of 7.5:2.5, including 157 cases in the training set and 53 cases in the internal validation set. The primary endpoint was all-cause mortality, with the secondary endpoint being follow-up from diagnosis to 180 days. Overall survival (OS) was calculated based on the time from when the patient was recognized as having the disease to death or the last follow-up visit. This study was approved by Approval of Zhongshan City People's Hospital clinical research and animal experiment Ethic Committee (No. 2022–040) on January 04, 2023. Written informed consent was waived by the IRB due to the retrospective nature of this study. All data used in the analysis was anonymized and de-identified.

Inclusion and Exclusion Criteria

The diagnostic criteria for IPA according to the European Organisation for Research and Treatment of Cancer and Mycosis Research Group Education and Research Consortium (EORTC/MSGERC) guidelines,[10] only proven IPA and probable IPA described in the EORTC/MSGERC criteria were included: The diagnosis of IPA is as follows:

Proven IPA: histopathological or cytological examination of tissue samples obtained by needle aspiration or biopsy, demonstrating histopathological evidence of Aspergillus hyphae. Probable IPA: requires at least one host factor, radiological features, and mycological evidence. Specifically: (a) host factors consistent with the presence of risk factors for IPA, including but not limited to prolonged use of corticosteroids and immunosuppressive agents, acute respiratory distress syndrome and COPD; (b) radiological features include dense, well-defined lesions with or without halo signs, crescent signs, cavities, or wedge-shaped, segmental, or lobar consolidations; (c) mycological evidence included a single galactomannan (GM) test ≥1.0, serum/plasma GM ≥0.7, BALF GM ≥0.8, Aspergillus PCR, or culture result (from qualified samples such as sputum, bronchoalveolar lavage fluid, bronchial brushing, or aspirate).

In addition, the definition of neutropenia is an absolute peripheral blood neutrophil count of$<0.5\times10^9$/L. Therefore, IPA patients who meet the inclusion criteria must have a peripheral blood neutrophil count of $> 0.5\times10^9$/L.

Exclusion criteria included: 1) According to the definition of EORTC/MSGERC criteria, patients with suspected IPA were excluded; 2) excluding cases of chronic aspergillosis, pulmonary aspergilloma, and allergic bronchopulmonary aspergillosis; 3) absolute neutrophil count in peripheral blood$<0.5\times10^9$/L.

Diagnosis Criteria and Definitions

Other Diagnostic Criteria: the diagnosis of combined bacterial pneumonia is established based on the results of pathogenic bacteria culture, primarily focusing on bacteriology. This diagnosis is based on the 2016 Clinical Practice Guidelines provided by the Infectious Diseases Society of America and the Thoracic Society, specifically the guidelines for managing hospital-acquired pneumonia and ventilator-associated pneumonia in adults.[11]

Data Collection

By reviewing relevant literature on prognostic factors in IPA,[1,7–9,12,13] we selected several variables as screening variables for the prediction model in this study. The dataset encompassed demographic characteristics (sex, age, smoking

history and disease history) and laboratory profiles included counts of C-reactive protein, interleukin-6, procalcitonin, hemoglobin, platelet, serum creatinine, albumin, white blood cell (WBC), neutrophil to lymphocyte ratio (NLR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH). In addition, comorbidities, treatment and follow-up data during hospitalisation were recorded. Except for follow-up data, all other data were collected from the initial 24h of hospitalization at Zhongshan City People's Hospital.

Statistical Analysis

Statistical analysis was performed using R software version 4.1.3 and BM SPSS Version 29. Continuous data were tested for normality. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), and compared between groups by *t*-test. Continuous variables with non-normal distribution were expressed as median (interquartile range, IQR), and compared between groups by WilCoxon rank sum test. Categorical data were represented by the number of cases (%), and Chi-square or Fisher's exact test was used for comparison between groups. Independent variables that are significant in the Lasso analysis would be included in the multivariate model. Multivariate Cox regression analysis was used to analyze independent variables associated with all-cause mortality. Based on the results of the multivariate regression analysis, nomogram constructed using the R software 'rms' package were used to predict OS at 28, 90 and 180 days. The discriminative power of this model was evaluated and compared using metrics such as the concordance index (C-index) and area under the curve (AUC) of the time dependent receiver operating characteristic (T-ROC) curve. The calibration curve was used to visually compare the actual and predicted probabilities of nonneutropenic IPA, while 1000 bootstraps resamples were utilized for internal validation. Additionally, calibration curves and decision curve analysis (DCA) were used to evaluate the model's performance and clinical utility. A risk classification system was established by computing the cumulative score for each patient in the training set using nomogram. The optimal cut-off point for the nomogram scores was determined from the surv_cutpoint() function in the "survminer" package in R software, thereby stratifying participants into high-risk and low-risk groups. Kaplan-Meier survival analysis was used to perform subgroup analysis of OS stratified by different risk groups and Log rank test was used to test the difference between subgroups. P-value <0.05 was considered statistically significant, and all tests of significance were two-tailed.

Results

Patient Characteristics

A Total of 210 Participants Who Met the Inclusion Criteria Were Included in the Study. The included cases were stratified into a training set (n=157) and a validation set (n=53) through a randomized method at a ratio of 7.5:2.5. The training cohort consisted of 103 (65.6%) male and 54 (34.4%) female participants, with a median age of 57.26 years (SD = 15.56); the remaining 41 (77.4%) male and 12 (22.6%) female with a median age of 53.83 years (SD = 15.54) formed the validation cohort. A total of 65 (41.4%) deaths were recorded in the training cohort and 19 (35.8%) deaths in the validation cohort, the proportion of the death group was similar between the training and validation sets (41.4% vs 35.8%; P = 0.581). The clinical characteristics between these two sets were meticulously compared using appropriate statistical methods, considering the data's nature. The comparative analysis showed no significant differences between the two cohorts in terms of sex, age, history of underlying diseases, C-reactive protein, interleukin-6, procalcitonin, hemoglobin, platelets, serum creatinine, albumin, white blood cell count, neutrophil-to-lymphocyte ratio, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase (P > 0.05). Therefore, it is reasonable to use them as the training and validation sets for the model due to the lack of significant differences (Table 1).

Lasso and Multivariate Cox Regression

The study evaluated a total of 28 parameters for mortality. The measures were tested using Spearman correlation analysis and visualised as heatmap before data analysis (Figure 1). Considering the high correlation between C-reactive protein (CRP), interleukin-6 (IL-6), white blood cell count (WBC), lactate dehydrogenase (LDH), and neutrophil to lymphocyte ratio (NLR). To choose the most representative predictor variables, dimensionally reduced Lasso regression was used on

Table 1 Baseline Data for Patients with Nonneutropenic Invasive Pulmonary Aspergillosis

Parameters	Overall (n = 210)	Internal Validation Cohort (n = 53)	Training Cohort (n = 157)	*P*
Baseline				
Sex, n(%)				0.155
Female	66 (31.4)	12 (22.6)	54 (34.4)	
Male	144 (68.6)	41 (77.4)	103 (65.6)	
Age, year	56.40 ± 15.59	53.83 ± 15.54	57.26 ± 15.56	0.168
Smoking, n(%)	56 (26.7)	13 (24.5)	43 (27.4)	0.82
Disease history				
Solid tumour, n(%)	20 (9.5)	7 (13.2)	13 (8.3)	0.432
COPD, n(%)	32 (15.2)	7 (13.2)	25 (15.9)	0.799
Diabetes, n(%)	54 (25.7)	16 (30.2)	38 (24.2)	0.496
Tuberculosis, n(%)	38 (18.1)	7 (13.2)	31 (19.7)	0.388
Bullae, n(%)	34 (16.2)	9 (17.0)	25 (15.9)	1
Cirrhosis, n(%)	5 (2.4)	3 (5.7)	2 (1.3)	0.103
Kidney insufficiency, n(%)	16 (7.6)	2 (3.8)	14 (8.9)	0.368
Comorbidity, n(%)				
Bacterial infection	107 (51.0)	24 (45.3)	83 (52.9)	0.426
Pleural effusion	54 (25.7)	11 (20.8)	43 (27.4)	0.439
Laboratory results				
C-reactive protein, mg/L	45.30 (5.64, 145.63)	36.60 (3.80, 148.49)	48.65 (6.41, 145.30)	0.646
Interleukin-6, pg/mL	35.18 (5.45, 168.48)	46.80 (5.40, 246.80)	32.14 (5.50, 133.10)	0.258
Procalcitonin, ng/mL	0.20 (0.05, 0.78)	0.20 (0.04, 0.71)	0.21 (0.05, 0.78)	0.406
WBC, 10^9/L	10.22 (6.94, 15.91)	11.18 (7.26, 19.13)	9.89 (6.88, 15.60)	0.357
NLR, %	7.28 (3.21, 17.25)	8.63 (2.81, 18.83)	7.17 (3.26, 16.01)	0.577
Hemoglobin, g/L	114.50 ± 25.52	114.23 ± 23.87	114.59 ± 26.12	0.925
Platelet, 10^9/L	249.00 (177.75, 326.25)	248.00 (157.50, 348.50)	249 0.00 (181.50, 308.00)	0.57
ALT, U/L	18.00 (12.00, 42.00)	20.00 (13.50, 46.00)	17.00 (11.00, 37.00)	0.216
AST, U/L	22.00 (15.20, 44.25)	25.00 (15.00, 48.50)	21.00 (14.10, 41.00)	0.533
Serum creatinine, umol/L	67.00 (56.00, 99.00)	67.00 (55.50, 87.50)	67.00 (56.00, 107.5)	0.661
LDH, U/L	220.00 (168.75, 374.25)	211.00 (177.50, 381.50)	222.00 (164.00, 376.5)	0.877
Albumin, g/L	36.15 (31.30, 39.53)	36.30 (29.05, 40.25)	36.10 (32.20, 39.15)	0.83
Treatment, n(%)				
ICU treatment	79 (37.6)	17 (32.1)	62 (39.5)	0.424
Invasive mechanical ventilation	70 (33.3)	17 (32.1)	53 (33.8)	0.955

(*Continued*)

Table 1 (Continued).

Parameters	Overall (n = 210)	Internal Validation Cohort (n = 53)	Training Cohort (n = 157)	*P*
Glucocorticoid	78 (37.1)	18 (34.0)	60 (38.2)	0.697
Antibiotic	123 (58.6)	28 (52.8)	95 (60.5)	0.412
Follow-up				
Overall survival, day	90.00 (25.75, 180.00)	129.00 (23.00, 180.00)	70.00 (25.5, 180.00)	0.796
Survival, n(%)				0.581
No	84 (40.0)	19 (35.8)	65 (41.4)	
Yes	126 (60.0)	34 (64.2)	92 (58.6)	

Abbreviations: SD, Standard Deviation; IQR, Inter Quartile Range; COPD, Chronic obstructive pulmonary disease; WBC, White blood cell; NLR, Neutrophil to lymphocyte ratio; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase.

the training set's variables. The ideal value for the model was determined by taking the lambda value that had the smallest cross-validation error (Figure 2). The results of Lasso regression analysis showed that seven independent variables were predictive variables for death in participants with nonneutropenic IPA, including age, comorbid bacterial pneumonia, pleural effusion, NLR, LDH, invasive mechanical ventilation, and receipt of ICU treatment. The above seven

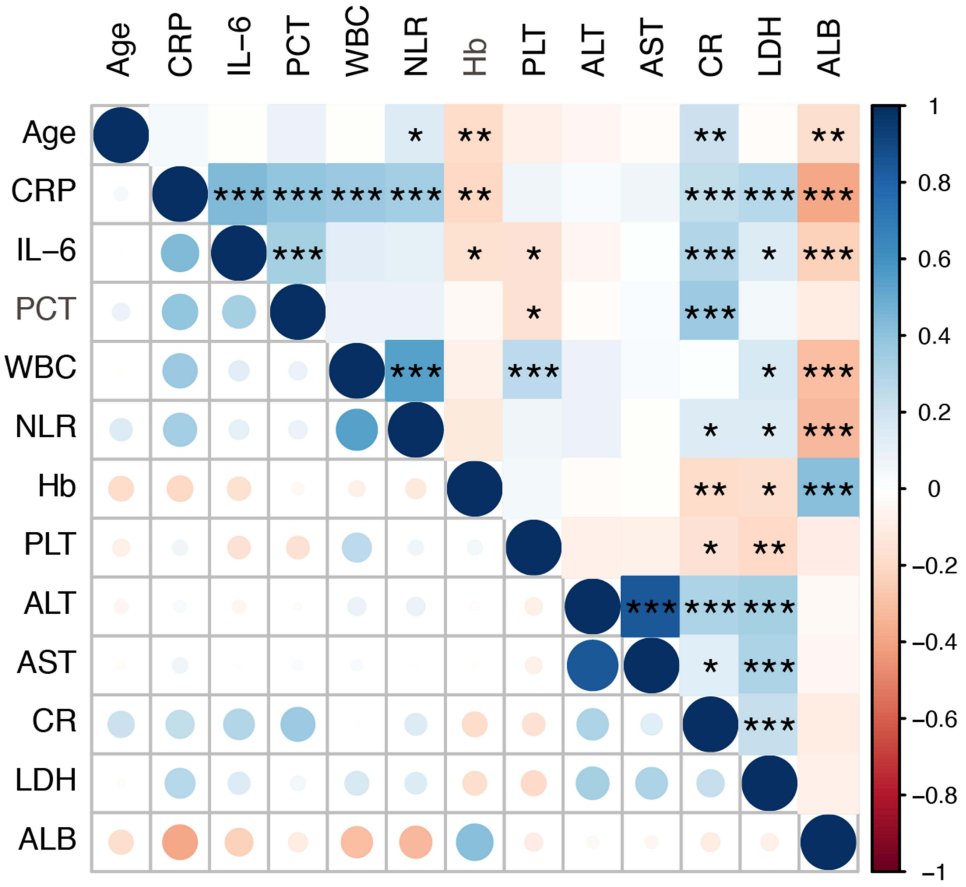

Figure 1 Heat map of correlation.
Notes: The correlation of quantitative data was analysed using Spearman correlation, where the depth of colour and size of the points were proportional to the correlation coefficient. ***p<0.001; **p<0.01; *p<0.05.
Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; WBC, white blood cell count; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Hb, Hemoglobin; PLT, Platelet; PCT, Procalcitonin; CR, Serum creatinine; ALB, Albumin.

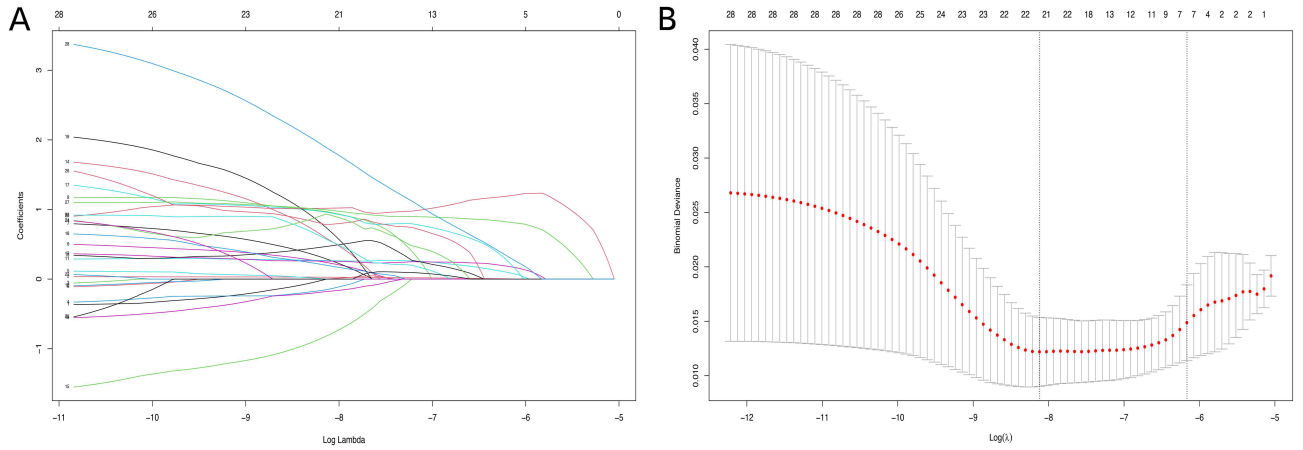

Figure 2 Selection of predictors using Lasso regression analysis.
Notes: (**A**) Coefficient profiles created based on log(lambda) series, (**B**) Tuning parameter (lambda) selection for bias in Lasso regression based on the minimum criterion (left dashed line) and the 1-SE criterion (right dashed line). In this study, predictors were selected based on the 1-SE criterion (right dashed line), in which seven non-zero coefficients were chosen.

variables were further included in multifactorial Cox regression analysis, which revealed that age (HR=1.019, 95% CI:1.003–1.035, P=0.021), comorbid bacterial pneumonia (HR=3.357, 95% CI:1.585–7.109, P=0.002), NLR (HR=1.017, 95% CI:1.004–1.031, P=0.010), LDH (HR=1.001, 95% CI:1.000–1.001, P=0.005) and invasive mechanical ventilation (HR=4.863, 95% CI:1.389–17.033, P=0.013) were independent risk factors affecting prognosis (Table 2).

Establishment of Nomogram Model

Based on Lasso and multifactorial Cox regression analyses, five independent risk factors associated with the prognosis of nonneutropenic IPA were finalized, including age, comorbid bacterial pneumonia, NLR, LDH, and invasive mechanical ventilation. Thus, we developed a risk prediction nomogram model incorporating the above five variables (Figure 3). The constructed nomogram predicted the probability of OS at 28, 90 and 180 days in participants with nonneutropenic IPA. The C-index values for OS nomogram predicting nonneutropenic IPA were 0.902 (95% CI 0.870–0.934), 0.859 (95% CI 0.814–0.903), and 0.853 (95% CI 0.781–0.924) for all data, training set, and internal validation set, respectively, showing that the nomogram has excellent predictive effect.

Table 2 Multivariate COX Regression Analysis of Prognosis in Nonneutropenic Invasive Pulmonary Aspergillosis

Parameters	*HR (95% CI)*	*P*
Age	1.019 (1.003–1.035)	0.021
Bacterial infection	3.357 (1.585–7.109)	0.002
Pleural effusion	1.197 (0.733–1.956)	0.472
NLR	1.017 (1.004–1.031)	0.010
LDH	1.001 (1.000–1.001)	0.005
Invasive mechanical ventilation	4.863 (1.389–17.033)	0.013
ICU	0.850 (0.219–3.308)	0.815

Abbreviations: HR, hazard ratio; CI, confidence interval; NLR, Neutrophil to lymphocyte ratio; LDH, Lactate dehydrogenase.

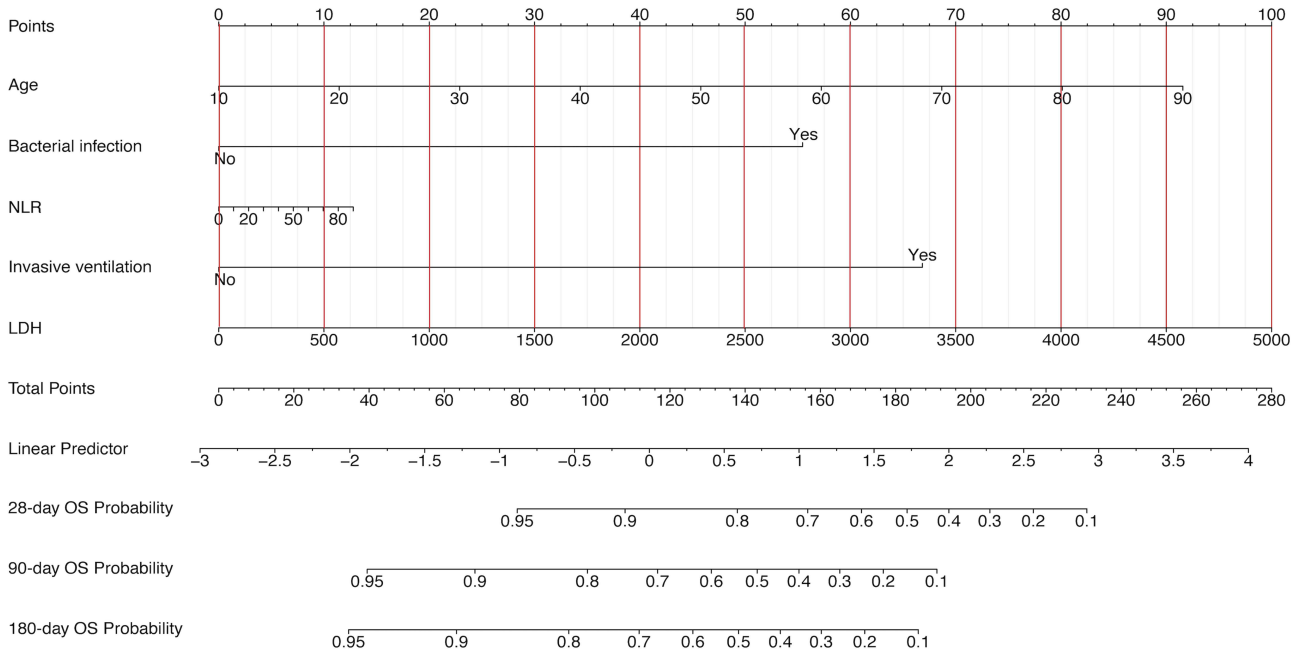

Figure 3 Nomogram predicting prognostic risk in nonneutropenic deficient invasive pulmonary aspergillosis.
Notes: Nomogram model to predict 28-day, 90-day, and 180-day overall survival of nonneutropenic deficient invasive pulmonary aspergillosis. The specific algorithm for the nomogram is as follows: firstly, a score is assigned to each risk factor for non-neutropenic IPA patients, corresponding to points calculated at the top. The total score is then calculated by summing the scores obtained for all risk factors. Ultimately, the total score corresponds to the predicted probability of survival for the patient at 28, 90, and 180 days.
Abbreviations: OS, overall survival; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio.

Internal Validation of the Model

In this study, the T-ROC curves in the training set demonstrated excellent discriminative ability and the AUC of 28, 90, and 180 days OS were 0.879 (95% CI, 0.817–0.939), 0.948 (95% CI, 0.910–0.986), and 0.948 (95% CI, 0.906–0.989), respectively (Figure 4A). Furthermore, AUC of 28, 90, and 180 days in the internal validation OS were 0.900 (95% CI, 0.837–0.963), 0.932 (95% CI, 0.892–0.972), and 0.939 (95% CI, 0.894–0.983), respectively (Figure 4B). The C-index of the model in the training set was 0.859 (95% CI, 0.814–0.903), and in the internal validation set, it was 0.853 (95% CI,

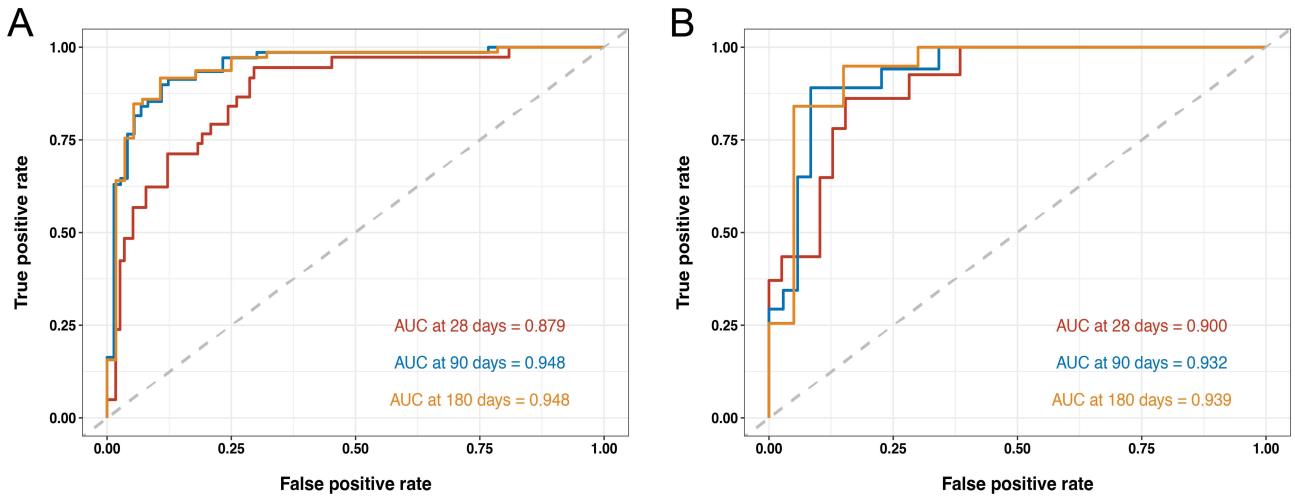

Figure 4 T-ROC curves of the model in the training and validation sets.
Notes: (**A**) T-ROC curve of the model in the training set, (**B**) T-ROC curve of the model in the validation set.
Abbreviations: T-ROC, time dependent receiver operating characteristic; AUC, area under the curve.

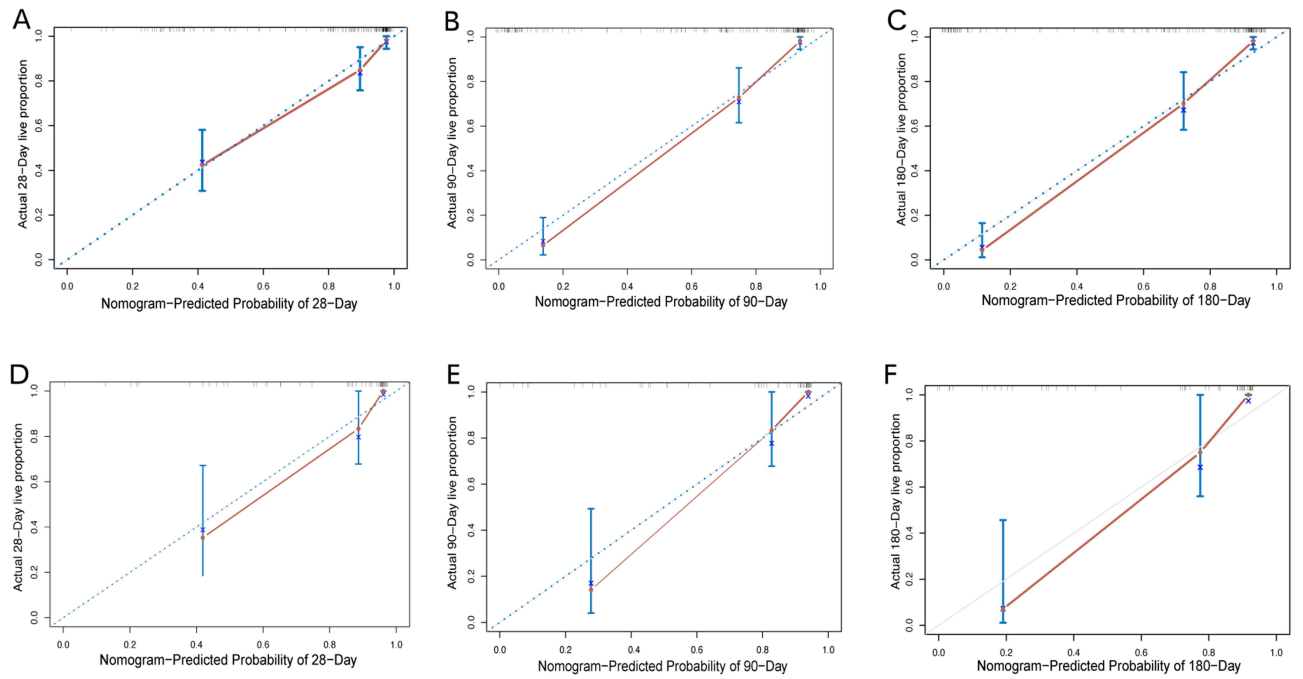

Figure 5 Calibration curve of the prediction model.
Notes: (**A**) Training set calibration curve for predicting 28-day OS of nonneutropenic IPA, (**B**) Training set calibration curve for predicting 90-day OS of nonneutropenic IPA, (**C**) Training set calibration curve for predicting 180-day OS of nonneutropenic IPA, (**D**) Internal validation set calibration curve for predicting 28-day OS of nonneutropenic IPA, (**E**) Internal validation set calibration curve for predicting 90-day OS of nonneutropenic IPA, (**F**) Internal validation set calibration curve for predicting 180-day OS of nonneutropenic IPA.
Abbreviation: OS, overall survival.

0.781–0.924), showing a favorable predictive ability of the nomogram. In addition, the calibration curves based on 1000 times of bootstrapping showed excellent consistency between predicted and observed values in the training and internal validation sets (Figure 5).

Clinical Decision Curve Analysis

To evaluate the clinical benefits of the nomogram model, DCA was performed to demonstrate how nonneutropenic IPA participants can gain higher net benefits in the constructed predictive model. The horizontal axis of the DCA represents the probability threshold, while the vertical axis represents the net benefit. The results indicate that the predictive model developed in this study, when the threshold probability ranges from 1% to 73%, has DCA above both the "all-treat" and "none-treat" strategies in both the training and validation sets, demonstrating higher net benefit and clinical utility. (Figure 6) showed the decision curves for the nomogram model at 28, 90 and 180 days for the training and validation sets.

Risk Stratification Using the Nomogram

Every patient is computed and graded based on the nonneutropenic IPA final nomogram model. The training set (n = 157) generated by the R software's "survminer" package was our basis for determining the cut-off value of OS scores. The visualization of the distribution of participants into high and low-risk categories is presented in (Figure 7D). Using a Log rank test, the survival times of various risk groups were compared. All data (n=210) were stratified into two groups with different survival probabilities based on a cutoff value of 116.21: the low-risk group (≤116.21), which consisted of 86 participants from the training set (n=157) and 36 participants from the internal validation set (n=53), and the high-risk group (>116.21), which consisted of 71 participants from the training set (n=157) and 17 participants from the internal validation set (n=53). When using a threshold score of 116.21 for the model, the determined high-risk individuals in the all dataset, training set, and validation set were 88 (41.9%), 71 (45.2%), and 17 (32.1%), respectively. The actual numbers of deaths in the all dataset, training set, and validation set were 84 (40%), 65 (41.4%), and 19 (35.8%),

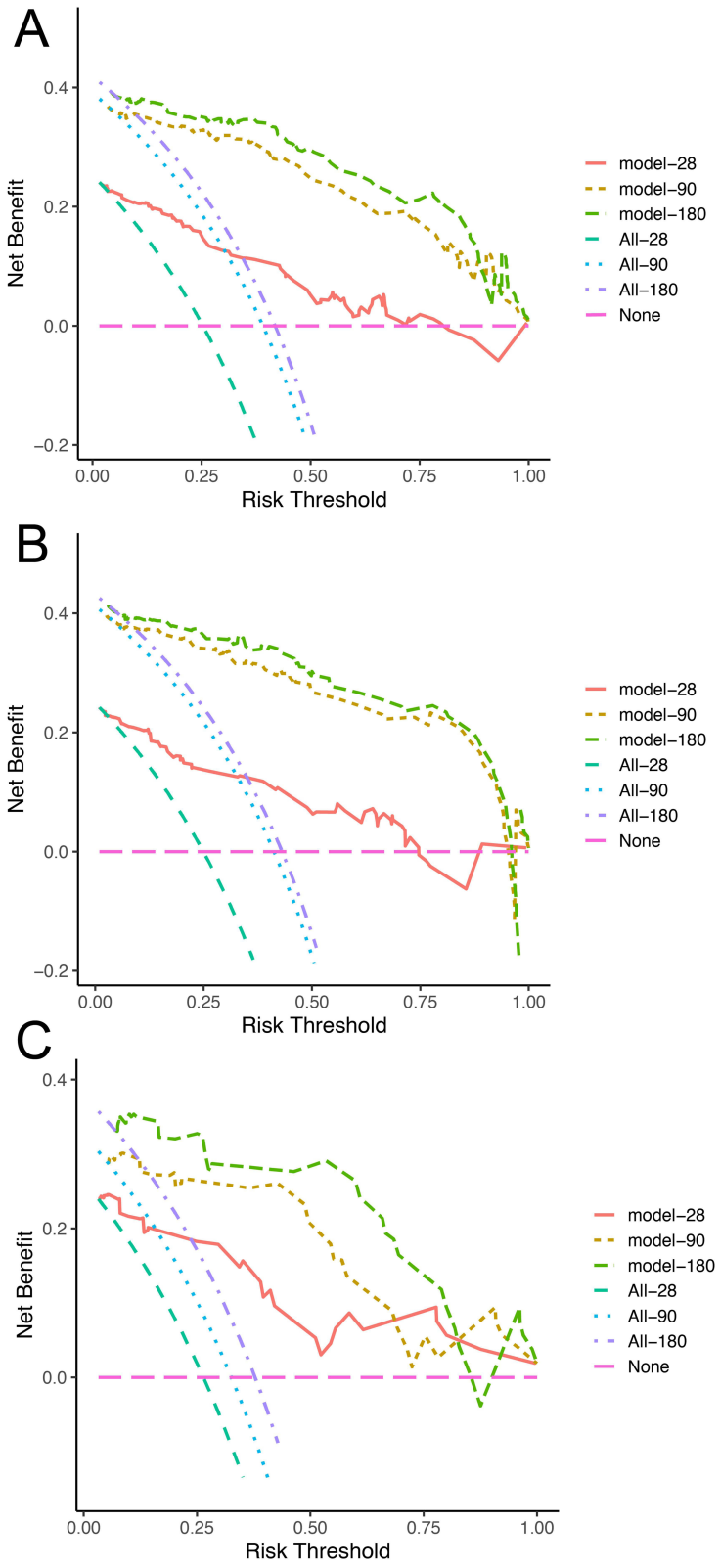

Figure 6 Decision curve analysis of the predictive model.
Notes: (**A**) Decision curve analysis (DCA) of all data predicting survival at 28, 90, and 180 days for nonneutropenic IPA, (**B**) Decision curve analysis (DCA) of the training set predicting survival at 28, 90, and 180 days for nonneutropenic IPA, (**C**) Decision curve analysis (DCA) of the internal validation set predicting survival at 28, 90, and 180 days for nonneutropenic IPA.

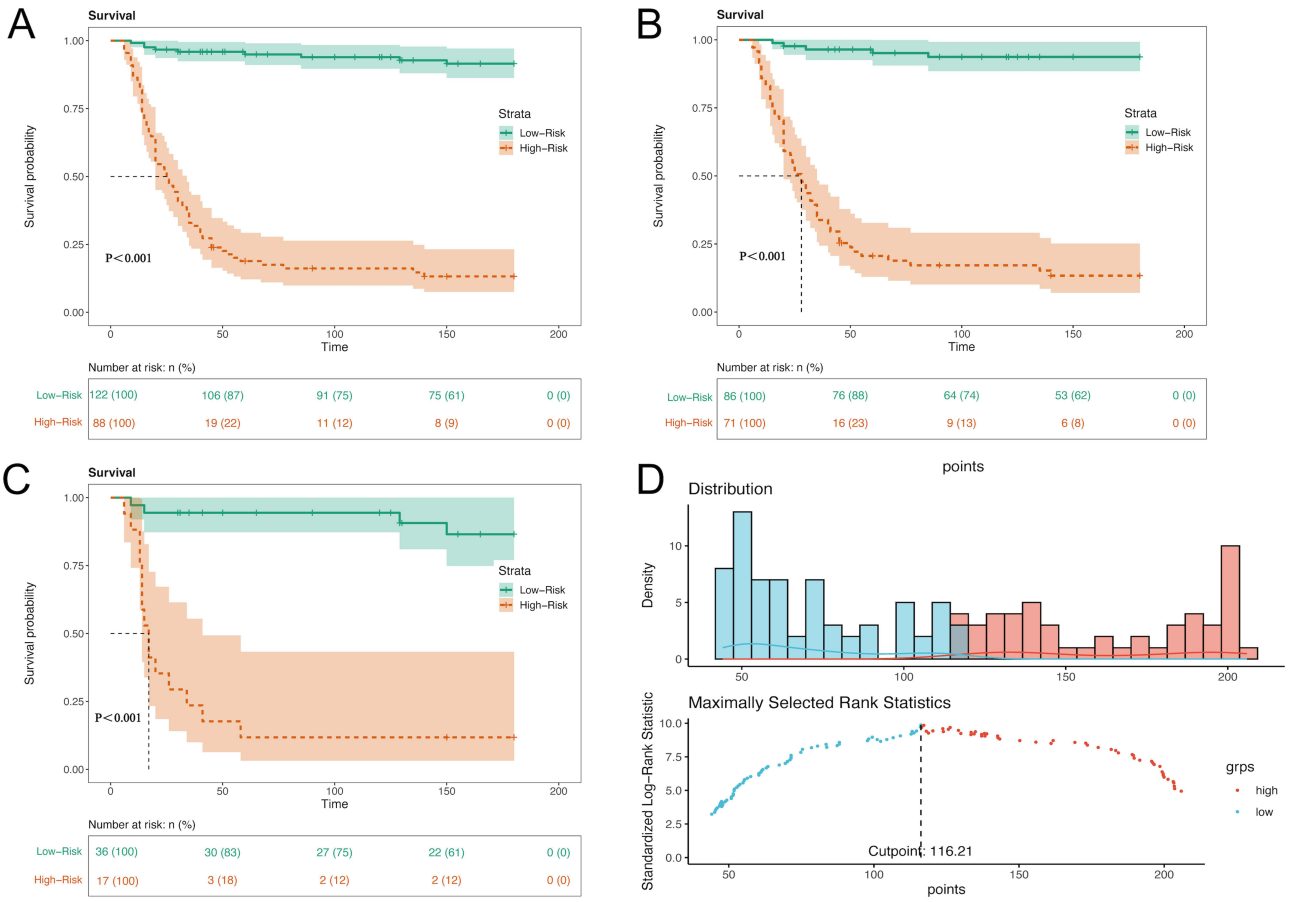

Figure 7 Kaplan-Meier survival curves for different scores in patients with nonneutropenic IPA.
Notes: (**A**) All datasets, (**B**) Training set, (**C**) Internal validation set, (**D**) Plot of truncated values visualised in the training set based on overall survival scores of nomogram patients.

respectively, indicating the reliability of our threshold determination. The Kaplan-Meier curves stratified by risk scores for all data, training set and validation set were shown (Figure 7A–C), and all P-values were less than 0.001. The prognosis differences between the two risk stratification groups were statistically significant, indicating the excellent risk stratification capacity of our nomogram model.

Discussion

IPA is characterized as an acute and progressive infectious disease, often manifesting in immunocompromised patients, with a notably high mortality rate.[14] Neutropenia has classically been identified as a typical risk factor for IPA. However, recent data suggest a growing prevalence of IPA in patients without neutropenia, attributed to the increasing incidence of age-related diseases, widespread use of glucocorticoids, and broad-spectrum antibiotics.[15] Notably, less than one-third of patients diagnosed with IPA exhibit neutropenia[1]. Presently, most studies on nonneutropenic IPA have suffered from limited sample sizes, primarily focusing on clinical characteristics and diagnostic efficacy.[12,16–18] For instance, research has identified risk factors for the onset of nonneutropenic IPA, including sepsis, COPD, diverse antibiotic treatments, and hepatic and/or renal dysfunction.[19] Prognostic factors for nonneutropenic IPA have received scant attention in the literature. Earlier, Dai et al conducted a retrospective study on prognostic factors in nonneutropenic IPA patients,[9] but the inclusion of a relatively small number of cases underscores the significance of our study, which incorporates a larger cohort of nonneutropenic IPA patients, thereby enhancing the reliability of our conclusions. Given the current absence of specific biomarkers for accurately predicting the prognosis of such IPA patients, our study aims to explore the factors influencing the prognosis of nonneutropenic IPA patients and establish a relevant prognostic model.

In this study, a total of 210 participants were included, and the main research results are as follows: Firstly, 40% of participants died during the follow-up period, a rate consistent with previous reports.[4,6,20] In addition, we identified age, comorbid bacterial pneumonia, elevated NLR and LDH levels, and the need for invasive mechanical ventilation as independent prognostic factors.

By reviewing pertinent literature, potential factors influencing the prognosis were identified. Considering the relatively limited total sample size and the multitude of independent variables, correlation analysis revealed collinearity among several clinical variables. To address this issue, particularly in scenarios involving high-dimensional data, Lasso regression was chosen for its stability in variable selection and ability to handle multicollinearity.[21,22] Ultimately, a prognostic nomogram was constructed, incorporating age, concomitant bacterial pneumonia, NLR, LDH levels, and invasive mechanical ventilation. This nomogram was designed to predict the probabilities of survival at 28, 90, and 180 days. To comprehensively evaluate the model's performance, internal validation was conducted. The results of internal validation demonstrated the model's favorable calibration, discrimination, and clinical utility. Furthermore, a population analysis was performed, categorizing participants into high-risk and low-risk groups. The nomogram model was refined into a risk-stratified prognostic tool, enhancing its overall performance.

This study identified age, comorbid bacterial pneumonia, elevated NLR and LDH levels, and invasive mechanical ventilation as independent prognostic factors. Advanced age is associated with compromised immune function, posing a dual risk as both a factor for disease onset and increased mortality rates. This connection may be linked to diminished immune capacity and organ function, rendering individuals more susceptible to severe pneumonia and subsequently elevating the risk of mortality.[23] NLR variations reflect the balance between neutrophil and lymphocyte counts, serving as an indicator of systemic inflammatory response.[24] Post-infection, anti-inflammatory factors released into the bloodstream can induce immune suppression, leading to significant lymphocyte apoptosis and an imbalance in the neutrophil to lymphocyte ratio. Numerous studies have established an elevated NLR as an independent prognostic factor in conditions like malignant tumors, ischemic strokes, acute cardiovascular events, and acute infectious diseases.[25] In patients with IPA, inhaled fungal spores activate resident cells, recruiting inflammatory cells and triggering cytokine and chemokine secretion,[26] IPA infection can result in excessive pulmonary inflammation,[27] and as patients experience severe inflammation, NLR may increase with the occurrence and severity of systemic inflammatory diseases. Previous research indicated a significant increase in NLR in IPA patients with normal immune function.[28] However, the clinical prognostic value of NLR in IPA remains unclear. Results from this study demonstrate a significant correlation between NLR and disease severity, as well as clinical outcomes in nonneutropenic IPA patients. Therefore, NLR can serve as a potential biomarker for the prognosis of nonneutropenic IPA, deserving further clinical investigation. Additionally, LDH was identified as an independent predictor of mortality. LDH, a widely distributed enzyme, is highly sensitive to tissue damage. Under normal conditions, serum LDH levels are relatively low, while tissue LDH levels can be over 500 times higher. Diseases causing cellular damage release LDH into the blood, resulting in a rapid increase in serum levels. Previous studies have identified LDH as a prognostic indicator correlated with disease severity and outcomes in IPA patients,[8,9,29] aligning with the results of this study. Earlier research indicates that IPA patients with comorbid bacterial or influenza infections exhibit more severe inflammatory responses and respiratory failure. Concurrent infections significantly increase the risk of mortality, associated with severe pulmonary damage, infection, respiratory failure, and compromised immune function.[13,27] Nonneutropenic IPA patients requiring invasive mechanical ventilation typically indicate more severe respiratory failure, signifying a more critical disease condition and thus a higher risk of mortality. Studies have suggested that pleural effusion increases the overall mortality rate in IPA patients,[30,31] This could be attributed to pleural effusion serving as an indicator of increased fungal burden, late-stage lung invasion, or potential deterioration of immune function, leading to more severe inflammatory responses and worsened disease conditions.[7] However, in the multifactorial analysis conducted in this study, pleural effusion did not show statistical significance, potentially due to the sample size. In summary, the findings of this study are generally consistent with those reported in the literature.

However, this study has certain limitations that should be acknowledged. Firstly, the model's validation is derived from a single institution, and further confirmation through collaborative data from other healthcare institutions is required. Secondly, some indicators reported in the literature, such as lymphocyte subgroups and serum galactomannan

levels, were not included in our study due to the lack of data. Lastly, laboratory test results may evolve with the progression of the disease, and due to the retrospective nature of the study, it was not feasible to incorporate the dynamic changes of various indicators into the analysis. Despite these limitations, all predictive indicators included in this study are routine clinical tests that are fast, cost-effective, and, to the best of our knowledge, our nomogram model developed here is the first of its kind to predict the prognosis risk for nonneutropenic IPA patients. In the future, we aim to collaborate with other research institutions to conduct multi-sample data validation and refine the nomogram model. Ultimately, this will contribute to predicting and enhancing the prognosis of patients with nonneutropenic IPA.

Conclusion

In conclusion, our study successfully developed and validated the first nomogram model for predicting the survival probability of patients with nonneutropenic IPA. Our nomogram demonstrated excellent predictive capabilities, accurately distinguishing between different risk groups and guiding clinicians in formulating early combined antifungal treatment strategies based on individual patient risks.

Data Sharing Statement

Datasets used and/or analyzed in the present study were availed by the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by Approval of Zhongshan City People's Hospital clinical research and animal experiment Ethic Committee (No. 2022-040) on January 04, 2023. Written informed consent was waived by the IRB due to the retrospective nature of this study. All data used in the analysis was anonymized and de-identified.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was supported by the grant from the National Natural Science Foundation of China (no. 82200038).

Disclosure

The authors report no conflicts of interest in this work. This paper has been uploaded to SSRN as a preprint: https://dx.doi.org/10.2139/ssrn.4774668.

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