Infection and Drug Resistance

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ORIGINAL RESEARCH

# Establishment and Validation of Models for the Risk of Multi-Drug Resistant Bacteria Infection and Prognosis in Elderly Patients with Pulmonary Infection: A Multicenter Retrospective Study

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**Purpose:** The aim of this study was to establish risk prediction and prognosis models for multidrug-resistant bacterial infections (MDRB) in elderly patients with pulmonary infections in a multicenter setting.

**Patients and Methods:** This study is a retrospective cohort analysis in Anhui province of China. Data dimension reduction and feature selection were performed using the lasso regression model. Multifactorial regression analysis to identify risk factors associated with MDRB infection and prognosis. The relevant risks of each patient in the prognostic training cohort were scored based on prognostic independent risk factors. Subsequently, patients were classified into high-risk and low-risk groups, and survival differences were compared between them. Finally, models were established based on independent risk factors for infection, risk groups, and independent prognostic factors, and were presented on nomograms. The predictive accuracy of the model was assessed using corresponding external validation set data.

**Results:** The study cohort comprised 994 elderly patients with pulmonary infection. Multivariate analysis revealed that endotracheal intubation, previous antibiotic use beyond 2 weeks, and concurrent respiratory failure or cerebrovascular disease were independent risk factors associated with the incidence of MDRB infection. Cox regression analysis identified respiratory failure, malnutrition, an APACHE II score of at least 20, and higher blood creatinine levels as independent prognostic risk factors. The models were validated using an external validation dataset from multiple centers, which demonstrated good diagnostic ability and a good fit with a fair benefit.

**Conclusion:** In conclusion, our study provides an appropriate and generalisable assessment of risk factors affecting infection and prognosis in patients with MDRB, contributing to improved early identification of patients at higher risk of infection and death, and appropriately guiding clinical management.

**Keywords:** multi-drug resistant bacteria, risk factors, prediction model

## Introduction

The use of antibiotics has greatly promoted the recovery of elderly patients with pulmonary infection, but it also poses great challenges. With the continuous use and upgrading of antibiotics, multi-drug resistant bacteria infection has become

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an important global population health problem and a serious clinical treatment problem.[1–3] Elderly patients are particularly vulnerable to pulmonary infections due to age-related declines in tissue and organ function, decreased respiratory mucosal clearance ability, and compromised immunity, and other factors. Inappropriate antibiotic use following pulmonary infection and frequent invasive procedures may further increase the risk of multidrug-resistant bacterial infection in patients.[4] At present, the most common multidrug-resistant bacteria worldwide include *multidrug-resistant Acinetobacter baumannii, multidrug-resistant Pseudomonas aeruginosa, multidrug-resistant Klebsiella pneumoniae, multidrug-resistant Escherichia coli* and so on.[5–7] The occurrence of multidrug-resistant bacterial infections in patients can result in prolonged hospital stays, increased hospitalization costs, and higher mortality rates.[8] A recent study estimated that there were 49.5 million deaths worldwide in 2019 related to bacterial drug resistance, with 12.7 million attributed to bacterial drug resistance.[9] In the United States alone, drug-resistant bacterial or fungal infections affect at least 2.8 million people annually, resulting in over 35,000 deaths per year. Numerous studies have confirmed that patients infected with MDRB have significantly worse outcomes, such as higher mortality rates and longer hospital stays, compared to patients who are not infected or infected with susceptible strains.[10–12] Due to the complexity and difficulty of treating drug-resistant bacterial infections, greater attention should be directed towards epidemiologic risk profiling of such infections.

In current medical literature, there is a growing interest in identifying risk factors associated with the development and prognosis of multidrug-resistant bacterial infections. A foreign meta-analysis revealed that previous antibiotic treatment, inappropriate antibiotic treatment, chronic lung disease, chronic liver disease, brain disease, prior MDRB and *Pseudomonas aeruginosa* infection/colonization, recent hospitalization, prolonged hospitalization, endotracheal intubation and mechanical ventilation, enteral feeding, nursing home residency, and higher disease severity scores were independent risk factors for MDRB. Our investigation also suggests that the causes of treatment failure in drug-resistant bacterial infections may be multifactorial, including bacterial adaptation, severity of underlying disease, delayed treatment, and, in some cases, lack of effective treatment.[10] Multiple studies have shown that improving the control of drug-resistant bacteria and implementing various comprehensive intervention measures can significantly reduce the infection rate of MDRB.[13,14] Despite significant research efforts, we are still facing challenges in predicting individuals who are more susceptible to MDRB infection. Therefore, it is essential to construct a robust prediction model by incorporating multiple established risk factors for MDRB infection.

To address this knowledge gap and contribute to future research, we conducted a cross-sectional survey of patients with pulmonary infection recruited from five hospitals in Anhui Province of China, aiming to identify potential risk factors associated with MDRB infection and its prognosis. To enhance the clinical applicability of our findings, we plan to develop a risk prediction and prognosis nomogram model based on the most significant attributes, which can serve as a valuable reference for the clinical prevention and treatment of MDRB infection.

# Materials and Methods

## Study Population

Antibiotic sensitivity patterns are often different among different geographical regions, populations and hospital types/units, so five representative hospitals were selected. The study included 994 patients with pulmonary infections who were sampled from these hospitals between January 2017 and June 2022, which included 207 at Hefei Binhu Hospital, 68 at the First Affiliated Hospital of the University of Science and Technology of China, 459 at the Third Affiliated Hospital of Anhui Medical University, 175 at Anqing Municipal Hospital, and 85 at Fuyang Hospital Affiliated of Anhui Medical University. The inclusion criteria were as follows: (1) Age>60, regardless of gender; (2) All cases met the diagnostic criteria for community-acquired pneumonia or hospital acquired pneumonia; (3) Sputum samples are qualified (Sputum smears showed <10 epithelial cells, >25 leukocytes or a leukocyte/epithelial cell ratio >1:2.5 per low magnification field), and the types of pathogenic bacteria and the drug resistance of various antibiotics were clear; (4) Cases of MDRB were screened out according to the results of drug sensitivity of pathogenic bacteria; (5) complete clinical data were available; (6) repeated cases or isolates from the same patient were excluded. The exclusion criterion was a lifetime of less than 24 hours.

In this retrospective study, we collected clinical and laboratory data through the electronic medical record of the hospital information system. The following variables were included: age, gender, long-term bed rest, length of hospital stay beyond 2 weeks, smoking, history of drug allergy, surgical history, combined with underlying diseases, endotracheal intubation, sputum aspiration, gastric tube placement, catheter indwelling, deep vein catheterization, type of antibacterial drugs (more than 2 types), previous antibiotic use beyond 2 weeks, white blood cell count, neutrophil count, neutrophil ratio, neutrophil to lymphocyte ratio, red blood cell count, hemoglobin, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and albumin. The combined with underlying diseases variable included chronic obstructive pulmonary disease, respiratory failure, pulmonary heart disease, coronary heart disease, arrhythmia, heart failure, diabetes, hypertension, gastrointestinal bleeding, peptic ulcer, cerebrovascular disease, infection in other parts, shock, primary tumor in other parts, arteriosclerosis, severe pneumonia, malnutrition, and dementia. The type of antibacterial drugs variable included antibiotics and chemically synthesized antimicrobials. Antibiotics mainly included β-lactams antibiotics, aminoglycosides, tetracyclines, chloramphenicol, macrolides, Lincosamides, glycopeptides, anti-fungal antibiotics, and anti-tumor antibiotics. Chemically synthesized antimicrobials mainly included sulfonamides, quinolones, trimethoprim, nitrofurans, nitroimidazoles, and oxazolones.

Microbial pathogens were identified following the national clinical inspection process with strict adherence. The collected sputum samples were inoculated on the surface of solid medium using the four-zone line method, and then incubated in a carbon dioxide incubator(35°C, 5%), For single colony, the French Merieux mass spectrometer was used. Antimicrobial susceptibility testing was performed using the K-B agar diffusion method. The drug sensitivity results were assessed according to the 2017 standards of the American Society for Clinical Laboratory Standardization (CLSI). If the drug sensitivity standards were modified in different years, the standards issued in the respective year were employed as the basis of evaluation. Multidrug-resistant bacteria (MDRB) were defined as *Staphylococcus aureus* resistant to oxacillin or/and cefoxitin for MRSA; *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Escherichia coli* resistant to imipenem or/and meropenem were determined as CRAB, CRPA, CRKP, and CREC, respectively. *Enterococcus faecalis* or *Enterococcus faecium* resistant to vancomycin was determined as VRE.

## Study Design

As shown in Figure 1, A total of 994 elderly patients with positive sputum culture results were collected from several hospitals in Anhui province between January 2017 and June 2022 to form the study cohort. The dates from Hefei Binhu Hospital and the First Affiliated Hospital of The University of Science and Technology of China were selected as the multi-source external validation cohort, while the remaining dates from The Third Affiliated Hospital of Anhui Medical University, Anqing Municipal Hospital, and Fuyang Hospital affiliated of Anhui Medical University were used as the training cohort in an approximate ratio of 3:7. Patients in the training cohort were separated into the MDRB infection group and the non-MDRB infection group based on the isolation of sputum culture. Logistic regression analysis was conducted to identify the risk factors for the incidence of MDRB. Patients in the MDRB group were further separated into survivors and nonsurvivors based on their 14-days survival status. Cox regression analysis was used to identify significant prognostic factors. The prognostic independent risk factors were used to score the relevant risks of each patient in the prognostic training cohort. Patients were then classified into a low-risk group (< median) or a high-risk group (≥ median) based on the median of the risk score. The risk scores of patients with MDRB were calculated using the following formula:

$$\begin{aligned}\text{Risk score} = {} & \text{Exp}_{\text{respiratory failure}} \times \beta_{\text{respiratory failure}} + \text{Exp}_{\text{Malnutrition}} \times \beta_{\text{Malnutrition}} + \cdots \\ & + \text{Exp}_{\text{APACHE II score>=20}} \times \beta_{\text{APACHE II score>=20}}\end{aligned}$$

Kaplan-Meier (K-M) survival curves were utilized to compare the overall survival (OS) between the high-risk and low-risk groups. Subsequently, risk and prognostic models were constructed based on Logistic regression, Cox regression, and risk groups. The performance of the nomogram was assessed using calibration and discrimination in the external validation cohort. Moreover, Decision curve analysis (DCA) was performed to evaluate the clinical utility of the model.

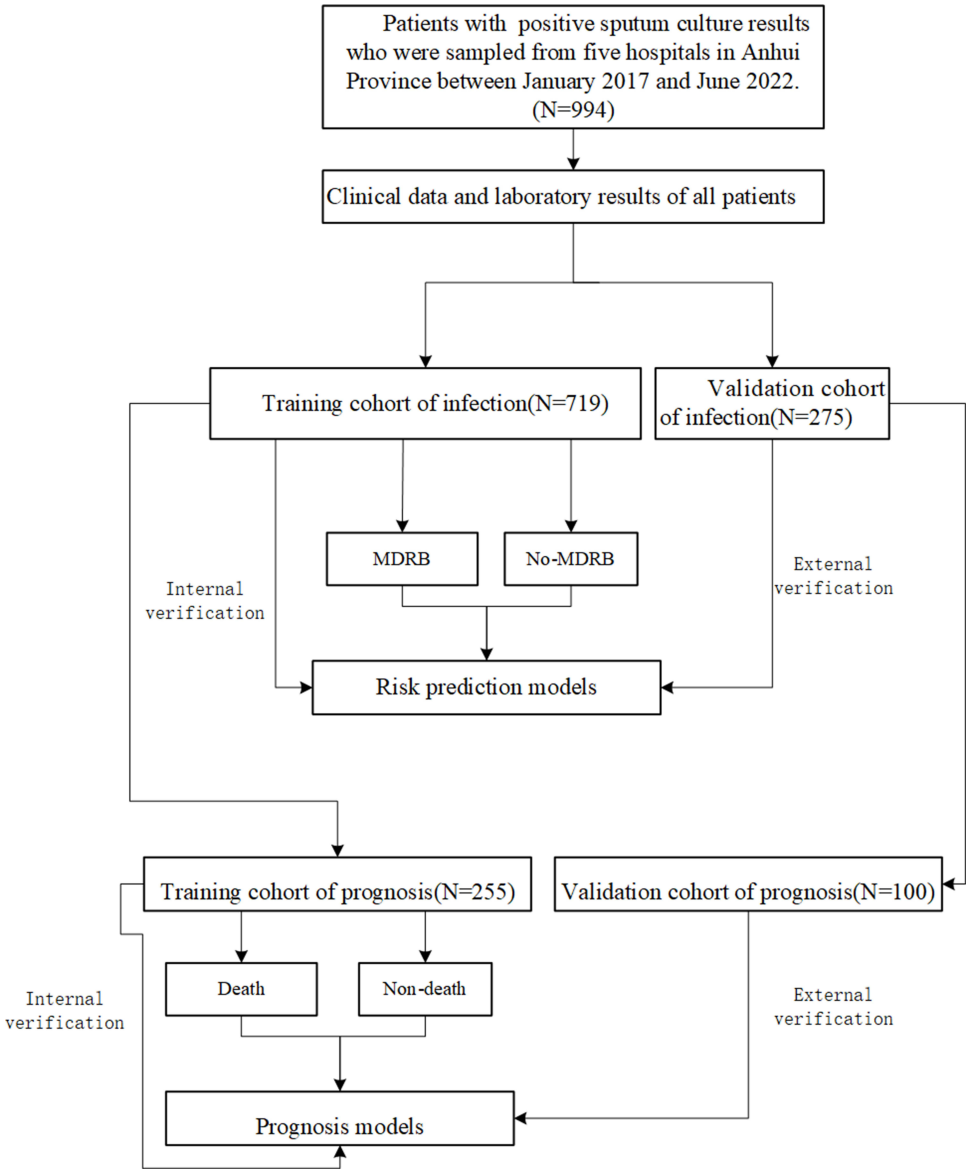


**Figure 1** Flow chart of the enrolled patients.

## Statistical Analysis

When comparing training cohort and validation cohort data, the Kolmogorov–Smirnov test was performed to assess the distribution equality of continuous parameters. Continuous variables with normal distribution were expressed as the mean ± standard deviation (SD), and continuous nonnormal distributed variables were expressed as the median (interquartile range, IQR). Independent *t*-test and Mann–Whitney *U*-test were used to analyze differences in continuous variables between groups, while chi-square test and the Fisher's exact test were used for categorical variables.

The selection of predictive features of the nomogram used the least absolute shrinkage and selection operator (Lasso) regression model.[13] A multivariate logistic regression analysis was performed on the selected variables, and a nomogram was constructed based on the results of the multivariate logistic regression analysis ($P < 0.05$). In the prognosis model, the variables screened by lasso regression were included in the cox multivariate regression model for analysis. Kaplan-Meier method was used to draw survival curves, and the differences in high risk group and low risk group were compared by Log rank test. The Prognostic nomogram was constructed based on the result of multivariable analyses in the training cohort. We applied a bootstrapped resample with 1000 iterations to verify the accuracy of the nomogram. Receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) were used to determine the discrimination ability of the nomogram. The calibration was performed by

plotting the calibration curve to analyze the association between the observed incidence and the predicted probability. We evaluated the clinical usefulness and net benefit of the new predictive models by using DCA.[15] All statistical tests were performed using R statistical software version 4.2.1 and SPSS 27.0. Statistical significance was assumed at $P < 0.05$.

# Results

## Demographic Baseline Characteristics

A total of 994 patients were included in this study. The training cohort for infection consisted of 719 patients, while the validation cohort for infection consisted of 275 patients. The training cohort for prognosis included 255 MDRB-infected patients, and the validation cohort for prognosis included 100 MDRB-infected patients.

The demographics and characteristics of patients in the different cohorts are presented in Table 1 and Table 2, respectively. Notably, there were no significant differences in the distribution of predictive variables between the training and validation cohorts for both infection and prognosis.

**Table 1** Baseline Demographics and Characteristics of All Patients in Training Cohort of Infection and Validation Cohort of Infection

| Variables | | Training Cohort(%) (n=719) | Validation Cohort(%) (n=275) | F/M/ $\chi$ 2 | P |
|---|---|---|---|---|---|
| Sex | Female | 209 (29.1) | 73(26.5) | 0.623 | 0.430 |
| | Male | 510 (70.9) | 202 (73.5) | | |
| Smoking | No | 568 (79.0) | 225 (81.8) | 0.980 | 0.322 |
| | Yes | 151 (21.0) | 50 (18.2) | | |
| History of drug allergy | No | 633 (88.0) | 248 (90.2) | 0.907 | 0.341 |
| | Yes | 86 (12.0) | 27 (9.8) | | |
| Surgical history | No | 482 (67.0) | 190 (69.1) | 0.383 | 0.536 |
| | Yes | 237 (33.0) | 85 (30.9) | | |
| Long-term bedridden | No | 550 (76.5) | 204 (74.2) | 0.581 | 0.446 |
| | Yes | 169 (23.5) | 71 (25.8) | | |
| Underlying diseases | | | | | |
| COPD | No | 523 (72.7) | 192 (69.8) | 0.841 | 0.359 |
| | Yes | 196 (27.3) | 83 (30.2) | | |
| Respiratory failure | No | 544 (75.7) | 208 (75.6) | <0.001 | 0.996 |
| | Yes | 175 (24.3) | 67 (24.4) | | |
| Cor pulmonale | No | 661 (91.9) | 249 (90.5) | 0.495 | 0.482 |
| | Yes | 58 (8.1) | 26 (9.5) | | |
| Coronary heart disease | No | 508 (70.7) | 198 (72.0) | 0.175 | 0.676 |
| | Yes | 211 (29.3) | 77(28.0) | | |
| Heart failure | No | 634 (88.2) | 242 (88.0) | 0.006 | 0.938 |
| | Yes | 85 (11.8) | 33 (12.0) | | |

(*Continued*)

**Table 1** (Continued).

| Variables | | Training Cohort(%) (n=719) | Validation Cohort(%) (n=275) | F/M/ $\chi$ 2 | P |
|---|---|---|---|---|---|
| Diabetes | No | 579 (80.5) | 232 (84.4) | 1.948 | 0.163 |
| | Yes | 140 (19.5) | 43 (15.6) | | |
| Hypertension | No | 330 (45.9) | 142 (51.6) | 2.628 | 0.105 |
| | Yes | 389 (54.1) | 133 (48.4) | | |
| Gastrointestinal bleeding or ulceration | No | 640 (89.0) | 243 (88.4) | 0.084 | 0.771 |
| | Yes | 79 (11.0) | 32 (11.6) | | |
| Cerebrovascular disease | No | 359 (49.9) | 133 (48.4) | 0.195 | 0.659 |
| | Yes | 360 (50.1) | 142 (51.6) | | |
| Infection of other sites | No | 621 (86.4) | 238 (86.5) | 0.005 | 0.942 |
| | Yes | 98 (13.6) | 37 (13.5) | | |
| Shock | No | 669 (93.0) | 246 (89.5) | 3.507 | 0.061 |
| | Yes | 50 (7.0) | 29 (10.5) | | |
| Primary Tumor in other sites | No | 624 (86.8) | 237 (86.2) | 0.063 | 0.802 |
| | Yes | 95 (13.2) | 38 (13.8) | | |
| Atherosclerosis | No | 612 (85.1) | 229 (83.3) | 0.520 | 0.471 |
| | Yes | 107 (14.9) | 46 (16.7) | | |
| APACHE IIscore≥20 | No | 595 (82.8) | 226 (82.2) | 0.045 | 0.832 |
| | Yes | 124 (17.2) | 49 (17.8) | | |
| Treatment related factors | | | | | |
| Length of hospital stay (Beyond 2 weeks) | No | 251 (34.9) | 101 (36.7) | 0.287 | 0.592 |
| | Yes | 468 (65.1) | 174 (63.3) | | |
| Type of antibacterial drugs (more than 2 types) | No | 462 (64.3) | 176 (64.0) | 0.006 | 0.940 |
| | Yes | 257 (35.7) | 99 (36.0) | | |
| Previous antibiotic Use (Beyond 2 weeks) | No | 442 (61.5) | 164 (59.6) | 0.282 | 0.595 |
| | Yes | 277 (38.5) | 111(40.4) | | |
| Sputum aspiration | No | 352 (49.0) | 136 (49.5) | 0.020 | 0.888 |
| | Yes | 367 (51.0) | 139 (50.5) | | |
| Invasive manipulation | | | | | |
| Endotracheal intubation | No | 555 (77.2) | 206 (74.9) | 0.006 | 0.448 |
| | Yes | 164 (22.8) | 69 (25.1) | | |
| Gastric tube placement | No | 394 (54.8) | 158 (57.5) | 0.568 | 0.451 |
| | Yes | 325 (45.2) | 117 (42.5) | | |

(*Continued*)

**Table 1** (Continued).

| Variables | | Training Cohort(%) (n=719) | Validation Cohort(%) (n=275) | F/M/ $\chi$ 2 | P |
|---|---|---|---|---|---|
| Catheter indwelling | No | 421 (58.6) | 168 (61.1) | 0.530 | 0.466 |
| | Yes | 298 (41.4) | 107 (38.9) | | |
| Deep vein catheterization | No | 623 (86.6) | 243 (88.4) | 0.522 | 0.470 |
| | Yes | 96 (13.4) | 32 (11.6) | | |
| Geriatric Syndrome | | | | | |
| Dementia | No | 671 (93.3) | 256 (93.1) | 0.017 | 0.896 |
| | Yes | 48 (6.7) | 19 (6.9) | | |
| Malnutrition | No | 656 (91.2) | 248 (90.2) | 0.269 | 0.604 |
| | Yes | 63 (8.8) | 27 (9.8) | | |
| Laboratory test index | | | | | |
| White blood cell count($10^9$) | | 9.51(6.45, 12.56) | 8.90(6.50, 12.18) | 96,865.50 | 0.622 |
| Neutral ratio | | 82.00(72.00, 88.90) | 82.50(71.70, 88.60) | 98,808.50 | 0.989 |
| Neutrophil count($10^9$) | | 7.90(4.87, 10.83) | 7.39(4.90, 10.50) | 96,669.00 | 0.588 |
| NLR | | 7.52(4.15, 14.83) | 8.29(4.11, 13.00) | 97,888.00 | 0.810 |
| Red blood cell count($10^9$) | | 3.82(3.35, 4.34) | 3.78(3.26, 4.28) | 93,636.50 | 0.197 |
| Hemoglobin(mg/L) | | 113.15(98.00, 130.00) | 116.00(97.00, 129.00) | 97,324.500 | 0.704 |
| Platelet count($\times 10^9$/L) | | 179.00(129.00, 229.00) | 185.00(143.00, 232.00) | 92,631.00 | 0.124 |
| ALT(u/l) | | 18.30(11.10, 30.00) | 18.00(12.00, 28.00) | 97,780.00 | 0.789 |
| AST(u/l) | | 26.00(18.00, 38.40) | 24.00(17.00, 35.00) | 92,868.50 | 0.139 |
| Cre(umol/l) | | 77.00(58.50, 110.30) | 77.00(54.00, 104.00) | 94,746.00 | 0.309 |
| Alb(mmol/l) | | 33.30(29.30, 37.54) | 32.80(30.20, 37.00) | 96,368.50 | 0.538 |

**Abbreviations**: NLR, neutrophil to lymph ratio; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cre, creatinine; Alb, albumin.

## Risk Factors Contributing to the Incidence of MDRB and Infection Model Was Established

After applying the LASSO regression model, we were able to identify 6 potential predictors of multidrug-resistant bacterial (MDRB) infections in elderly patients with pulmonary infections: respiratory failure, endotracheal intubation, use of more than two types of antibacterial drugs, previous antibiotic use beyond 2 weeks, cerebrovascular disease, and albumin levels (Figure 2A and B). We then conducted a multivariate logistic regression analysis of these 6 potential predictors and found that endotracheal intubation, previous antibiotic use beyond 2 weeks, and combined respiratory failure or cerebrovascular disease were independently associated with MDRB infections (Table 3). We used these factors to construct a risk prediction nomogram for MDRB infections in elderly patients with pulmonary infections (Figure 3A).

The area under the curve (AUC) for the infection risk prediction nomogram was 0.738 in the training cohort and 0.731 in the validation cohort (Figure 3B). The calibration plot of the risk of MDRB infection in elderly patients with pulmonary infections revealed good agreement between the observed and predicted values, with a P value of 0.919 in the training cohort and 0.152 in the validation cohort (Figure 3C). The decision curve analysis (DCA) of the nomograms for the risk of MDRB infection showed that the nomogram provided a moderate net benefit in predicting the risk of MDRB infection (Figure 3D).

**Table 2** Baseline Demographics and Characteristics of All Patients in Training Set of Prognosis and Validation Set of Prognosis

| Variables | | Training Cohort(%) (n=255) | Validation Cohort(%) (n=100) | F/M/ $\chi$ 2 | P |
|---|---|---|---|---|---|
| Sex | Female | 65 (25.5) | 24 (24.0) | 0.085 | 0.771 |
| | Male | 190 (74.5) | 76 (76.0) | | |
| Smoking | No | 199 (78.0) | 85 (85.0) | 2.175 | 0.140 |
| | Yes | 56 (22.0) | 15 (15.0) | | |
| History of drug allergy | No | 221 (86.7) | 86 (86.0) | 0.027 | 0.869 |
| | Yes | 34 (13.3) | 14 (14.0) | | |
| Surgical history | No | 160 (62.7) | 55 (55.0) | 1.804 | 0.179 |
| | Yes | 95 (37.3) | 45 (45.0) | | |
| Long-term bedridden | No | 182 (71.4) | 70 (70.0) | 0.066 | 0.800 |
| | Yes | 73 (28.6) | 30 (30.0) | | |
| Underlying diseases | | | | | |
| COPD | No | 188 (73.7) | 76 (76.0) | 0.195 | 0.659 |
| | Yes | 67 (26.3) | 24 (24.0) | | |
| Respiratory failure | No | 153 (60.0) | 62 (62.0) | 0.120 | 0.729 |
| | Yes | 102 (40.0) | 38 (38.0) | | |
| Corpulmonale | No | 237 (92.9) | 94(94.0) | 0.128 | 0.721 |
| | Yes | 18 (7.1) | 6 (6.0) | | |
| Coronary heart disease | No | 186 (72.9) | 76 (76.0) | 0.348 | 0.556 |
| | Yes | 69 (27.1) | 24(24.0) | | |
| Heart failure | No | 221 (86.7) | 81 (81.0) | 1.816 | 0.178 |
| | Yes | 34 (13.3) | 19 (19.0) | | |
| Diabetes | No | 207 (81.2) | 87 (87.0) | 1.712 | 0.191 |
| | Yes | 48 (18.8) | 13 (13.0) | | |
| Hypertension | No | 116 (45.5) | 51 (51.0) | 0.875 | 0.350 |
| | Yes | 139 (54.5) | 49 (49.0) | | |
| Gastrointestinal bleeding or ulceration | No | 222 (87.1) | 88(88.0) | 0.057 | 0.811 |
| | Yes | 33 (12.9) | 12(12.0) | | |
| Cerebrovascular disease | No | 104 (40.8) | 36 (36.0) | 0.688 | 0.407 |
| | Yes | 151 (59.2) | 64 (64.0) | | |
| Infection of other sites | No | 214 (83.9) | 80 (80.0) | 0.776 | 0.378 |
| | Yes | 41 (16.1) | 20 (20.0) | | |

(*Continued*)

**Table 2** (Continued).

| Variables | | Training Cohort(%) (n=255) | Validation Cohort(%) (n=100) | F/M/ $\chi$ 2 | P |
|---|---|---|---|---|---|
| Shock | No | 232 (91.0) | 87 (87.0) | 1.249 | 0.264 |
| | Yes | 23 (9.0) | 13 (13.0) | | |
| Primary tumor in other sites | No | 218 (85.5) | 88 (88.0) | 0.380 | 0.537 |
| | Yes | 37 (14.5) | 12 (12.0) | | |
| Atherosclerosis | No | 217 (85.1) | 85 (85.0) | <0.001 | 0.981 |
| | Yes | 38 (14.9) | 15 (15.0) | | |
| APACHE II score≥20 | No | 200 (78.4) | 79 (79.0) | 0.014 | 0.907 |
| | Yes | 55 (21.6) | 21 (21.0) | | |
| Treatment related factors | | | | | |
| Type of antibacterial drugs (more than 2 types) | No | 129 (50.6) | 51 (51.0) | 0.005 | 0.944 |
| | Yes | 126 (49.4) | 49(49.0) | | |
| Previous antibiotic use (Beyond 2 weeks) | No | 123 (48.2) | 44 (44.0) | 0.517 | 0.472 |
| | Yes | 132 (51.8) | 56 (56.0) | | |
| Sputum aspiration | No | 95 (37.3) | 39 (39.0) | 0.093 | 0.760 |
| | Yes | 160 (62.7) | 61(61.0) | | |
| Invasive manipulation | | | | | |
| Endotracheal intubation | No | 156 (61.2) | 56 (56.0) | 0.800 | 0.371 |
| | Yes | 99 (38.8) | 44 (44.0) | | |
| Gastric tube placement | No | 105 (41.2) | 38(38.0) | 0.301 | 0.583 |
| | Yes | 150 (58.8) | 62 (62.0) | | |
| Catheter indwelling | No | 116 (45.5) | 47 (47.0) | 0.066 | 0.797 |
| | Yes | 139 (54.5) | 53 (53.0) | | |
| Deep vein catheterization | No | 208 (81.6) | 84 (84.0) | 0.291 | 0.590 |
| | Yes | 47 (18.4) | 16 (16.0) | | |
| Geriatric Syndrome | | | | | |
| Dementia | No | 235 (92.2) | 90 (90.0) | 0.432 | 0.511 |
| | Yes | 20 (7.8) | 10 (10.0) | | |
| Malnutrition | No | 225 (88.2) | 89 (89.0) | 0.041 | 0.839 |
| | Yes | 30 (11.8) | 11 (11.0) | | |
| Laboratory test index | | | | | |
| White blood cell count($10^9$) | | 10.21(6.68, 12.97) | 9.16(7.21, 11.83) | 12,022.50 | 0.403 |
| Neutral ratio | | 82.80(73.90, 89.60) | 84.80(75.93, 90.20) | 11,873.50 | 0.314 |

(*Continued*)

**Table 2** (Continued).

| Variables | | Training Cohort(%) (n=255) | Validation Cohort(%) (n=100) | F/M/ χ 2 | P |
|---|---|---|---|---|---|
| Neutrophil count($10^9$) | | 8.22(4.92, 11.35) | 7.50(5.43, 10.37) | 12,383.50 | 0.673 |
| NLR | | 7.84(4.51, 16.52) | 8.61(4.77, 17.82) | 12,235.50 | 0.554 |
| Red blood cell count(×$10^9$) | | 3.79±0.74 | 3.65±0.76 | 1.595 | 0.112 |
| Hemoglobin(mg/L) | | 111.45±22.42 | 109.57±21.64 | 0.730 | 0.466 |
| Platelet count(×$10^9$/L) | | 176.0(129.0, 227.0) | 181.00(131.00, 232.25) | 12,330.50 | 0.630 |
| ALT(u/l) | | 19.0(11.10, 32.48) | 18.00(11.25, 28.00) | 11,965.50 | 0.367 |
| AST(u/l) | | 26.60(18.70, 39.40) | 24.00(18.00, 35.00) | 11,422.00 | 0.127 |
| Cre(umol/l) | | 76.30(54.60, 110.50) | 88.50(54.00, 137.68) | 11,795.00 | 0.272 |
| Alb(mmol/l) | | 31.69(28.10, 35.80) | 31.60(29.53, 36.00) | 12,192.00 | 0.521 |

## Risk Factors for Mortality in Patients with MDRB and Prognostic Model Was Established

We conducted a LASSO regression analysis to screen 39 variables in the training cohort, and identified 7 potential predictors that were significantly associated with poor prognosis in elderly patients with MDRB. These included respiratory failure, malnutrition, APACHE II score ≥20, long-term bedridden, heart failure, shock, and Creatinine (Figure 4A and B). Further multivariate Cox regression analysis showed that respiratory failure, malnutrition, APACHE II score ≥20, and Creatinine were independent prognostic factors for elderly patients with MDRB in the training cohort (Table 4 and Figure 5A).

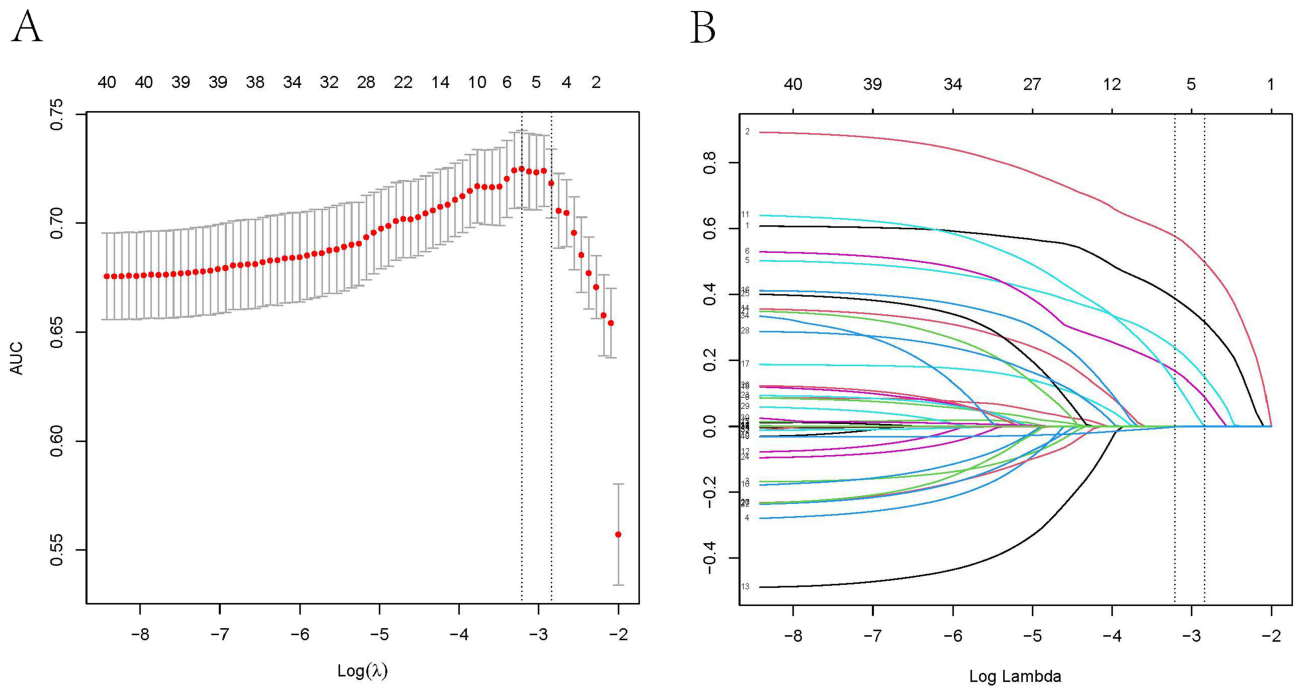


**Figure 2** The 40 variables in the training cohort of infection were screened by LASSO regression. (**A**) The optimal Lambda parameter was selected used by 10-fold cross validation.The Lambda value was taken as the optimal value of the model when the cross validation error was minimum, and the number of variables corresponding to the non-zero regression coefficient was counted at this time; (**B**) LASSO coefficients for infection-related factors in the training cohort.

**Table 3** Multivariate Logistic Regression Analysis of MDRB Infection in Elderly Patients with Pulmonary Infection

| Variables | SE | Wald $\chi$ 2 | P value | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | | Lower |
| Respiratory failure | 0.237 | 5.767 | 0.016 | 1.768 | 1.110 | 2.814 |
| Endotracheal intubation | 0.241 | 8.936 | 0.003 | 2.058 | 1.282 | 3.304 |
| Previous antibiotic use≥two weeks | 0.191 | 5.141 | 0.023 | 1.541 | 1.060 | 2.238 |
| Cerebrovascular disease | 0.013 | 9.241 | 0.002 | 1.670 | 1.200 | 2.325 |

Kaplan-Meier analysis revealed significant differences in survival between the high-risk group and low-risk group (P<0.001) (Figure 5B). The risk score of patients was inversely proportional to survival in older patients with MDRB. The AUC of the risk score was 0.834, indicating that the risk score was a good predictor for the prognosis of MDRB (Figure 5C). We also selected the best cutoff value of mortality risk and observed more deaths in the high-risk group (Figure 5D and E). The prognostic model was constructed using the independent factors and risk groups, which was presented as a nomogram in Figure 6. Both internal and external validation showed good performance of the nomogram, with AUC values of 0.826 in the training cohort and 0.805 in the validation cohort (Figure 7A). The DCA of the nomograms for the prognosis illustrated in Figure 7B showed that the nomogram provided a moderate net benefit in predicting the risk of prognosis with MDRB infected. The calibration plot of the risk of prognosis with MDRB infected also revealed good agreement between the observed and predicted values (Figure 7C and D).

## Discussion

Multidrug-resistant bacterial infections are a significant cause of hospital-acquired infections. Unfortunately, the development of drug resistance outpaces the development of new antibacterial drugs.[1] Consequently, selecting the appropriate empirical antibiotics has become increasingly challenging as more individuals are at risk of developing multidrug-resistant bacterial infections.[16] Barrasa Villar et al have confirmed that MDRB infection is an independent risk factor leading to population mortality.[17] Therefore, identifying the risk factors associated with multidrug-resistant bacterial infections is crucial for effective prevention and control of drug-resistant bacteria. Regional epidemiological assessments can greatly assist in the precise coordination of prevention and control measures for drug-resistant bacteria.[18,19] Accordingly, we conducted this study to determine the independent risk factors for infection and mortality associated with multidrug-resistant bacteria in Anhui Province.

In this study, the high incidence rate of MDRB infection among hospitalized elderly patients with pulmonary infection (35.71%; 355/994) highlights the vulnerability of this patient population to this type of infection. The clinical value of identifying risk factors for MDRB infection is to guide empirical therapy before the availability of culture results. Our study identified several independent risk factors for MDRB infection, including endotracheal intubation, previous antibiotic use (>2 weeks), and the presence of respiratory failure or cerebrovascular disease. The risk factors for MDRB infection detected in our study were similar to those observed in previous studies. For instance, It was indicated that endotracheal intubation was significantly related with MDRB infections in a 10-year multicenter study of China,[18] and several investigations have demonstrated that invasive procedures and prior antibiotic use are independent risk factors for MDRB infections.[20,21] Endotracheal intubation increases the risk of infection by providing a pathway for bacteria to enter the respiratory tract. Prolonged mechanical ventilation time can lead to the formation of biofilm on the inner wall of the artificial airway, promoting bacterial drug resistance.[22] Moreover, longer ventilation times increase the likelihood of drug-resistant bacterial colonization and transmission, which are key factors in the development of MDRB.[18] Long-term antibiotic use can reduce the permeability of the bacterial cell membrane, alter the antibiotic structure, and/or produce inactivating enzymes, leading to the development of MDRB.[23] Additionally, long-term use of antibiotics can disrupt the balance of bacterial flora, allowing non-pathogenic, drug-resistant bacteria to colonize the

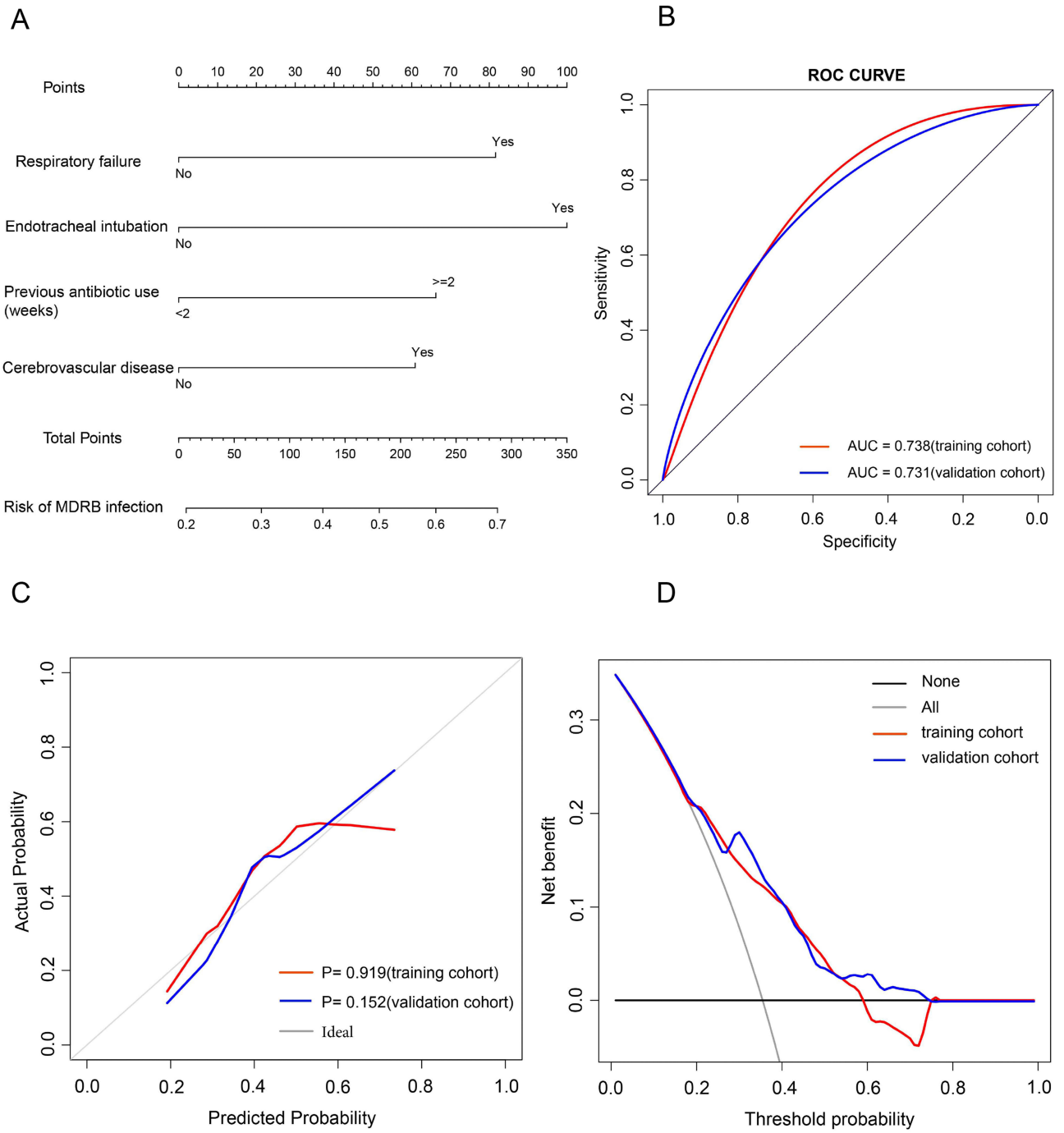


**Figure 3** (**A**) The Nomogram of risk model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection: Draw a vertical line from the corresponding axis for each risk factor until it reaches the axis labeled "Point". Sum up and draw a line down the axis labeled "Total Score" until it intersects the last axis to calculate the probability.In our nomogram: Respiratory failure (81.6 points), Endotracheal intubation (100 points), Previous antibiotic use≥two weeks (66.2 points), and Cerebrovascular disease(60.9 points). (**B**) The ROC curve of risk model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection; (**C**) The calibration curve of risk model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection; (**D**) The decision curve of risk model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection.

airway and cause infections.Respiratory failure, one of the identified risk factors, may reduce the ability of the respiratory mucosa to clear phlegm and lead to the accumulation of secretions in the lung, providing an environment for the proliferation of drug-resistant bacteria. Patients with acute cerebrovascular disease, another risk factor, may have weakened swallowing and cough reflexes, require nasogastric feeding, and have reduced digestive function, increasing the risk of gastric reflux and aspiration of drug-resistant strains into the lungs. Our study constructed a nomogram model

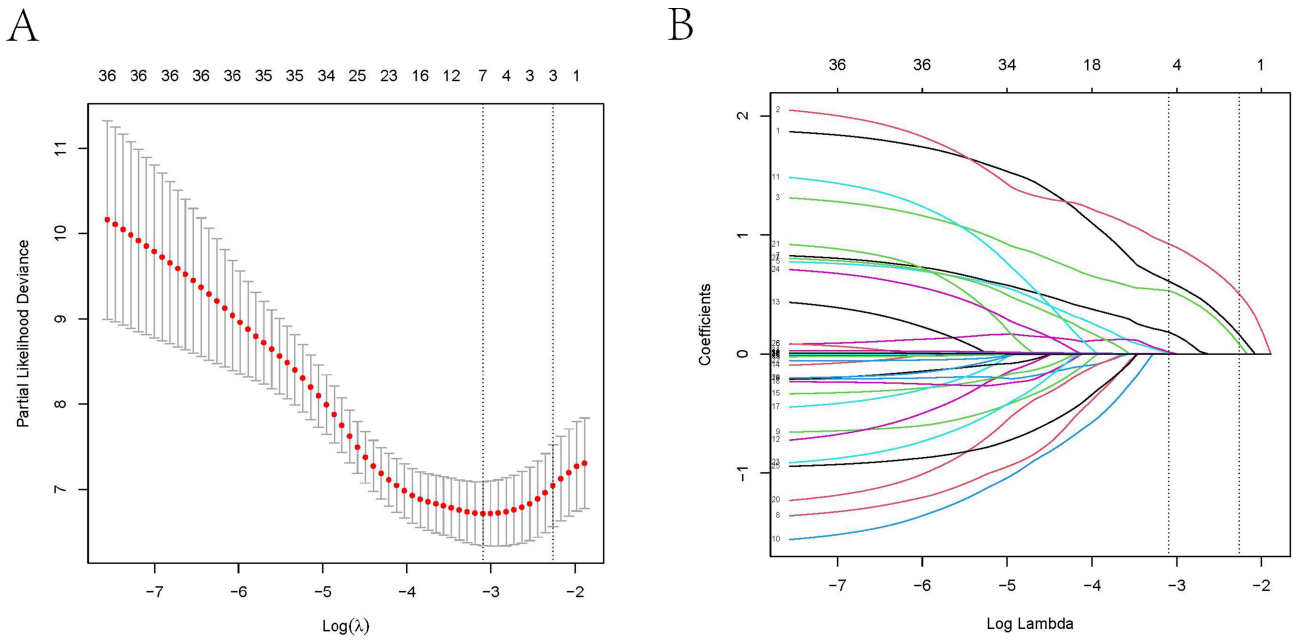


**Figure 4** The 39 variables in the training cohort of prognosis were screened by LASSO regression. (**A**) The optimal Lambda parameter was selected used by 10-fold cross validation.The Lambda value was taken as the optimal value of the model when the cross validation error was minimum, and the number of variables corresponding to the non-zero regression coefficient was counted at this time; (**B**) LASSO coefficients for factors associated with survival in the training cohort.

that enables clinical staff to screen high-risk patients, intervene early, and optimize the use of antibacterial drugs while strengthening measures such as hand hygiene management and environmental cleaning and disinfection. These interventions can help reduce the production and spread of MDRB in the hospital setting.[24,25]

The infection of multi-drug resistant bacteria is severe and the prognosis is poor.The prognosis of patients with multidrug-resistant bacteria infection can be affected by a variety of factors, including patients' own constitution, combined underlying diseases, medical measures taken and so on. It is necessary to analyze these factors and give targeted preventive measures to improve the prognosis of patients with multidrug-resistant bacteria infection.By studying the prognosis of elderly patients with multidrug-resistant pulmonary infection in several hospitals in Anhui province, we determined that respiratory failure, malnutrition, APACHE II score ≥20 and increased serum creatinine were independent risk factors for death in patients with MDRB.Malnutrition is very common in elderly patients which can be defined as a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease.[26]

Previous studies found the rate of death in patients with malnutrition-related multidrug-resistant bacterial infections was higher than those with normal nutrition.[27] In patients with respiratory failure, gas exchange is impaired and the ratio of blood flow to ventilation is unbalanced, which can induce hypoxemia. In addition, the patient's ability to autonomously clear sputum is reduced, secretion is blocked, and drug-resistant bacteria multiply in the lung, which is more

**Table 4** Multivariate Cox Regression Analysis of MDRB Prognosis in Elderly Patients with Pulmonary Infection

| Variables | HR(95% CI) | P value |
|---|---|---|
| Respiratory failure | 3.080(1.490–6.368) | 0.002 |
| Malnutrition | 3.465(1.897–6.326) | <0.001 |
| APACHE II score≥20 | 2.038(1.074–3.867) | 0.029 |
| Creatinine | 1.003(1.001–1.005) | 0.010 |

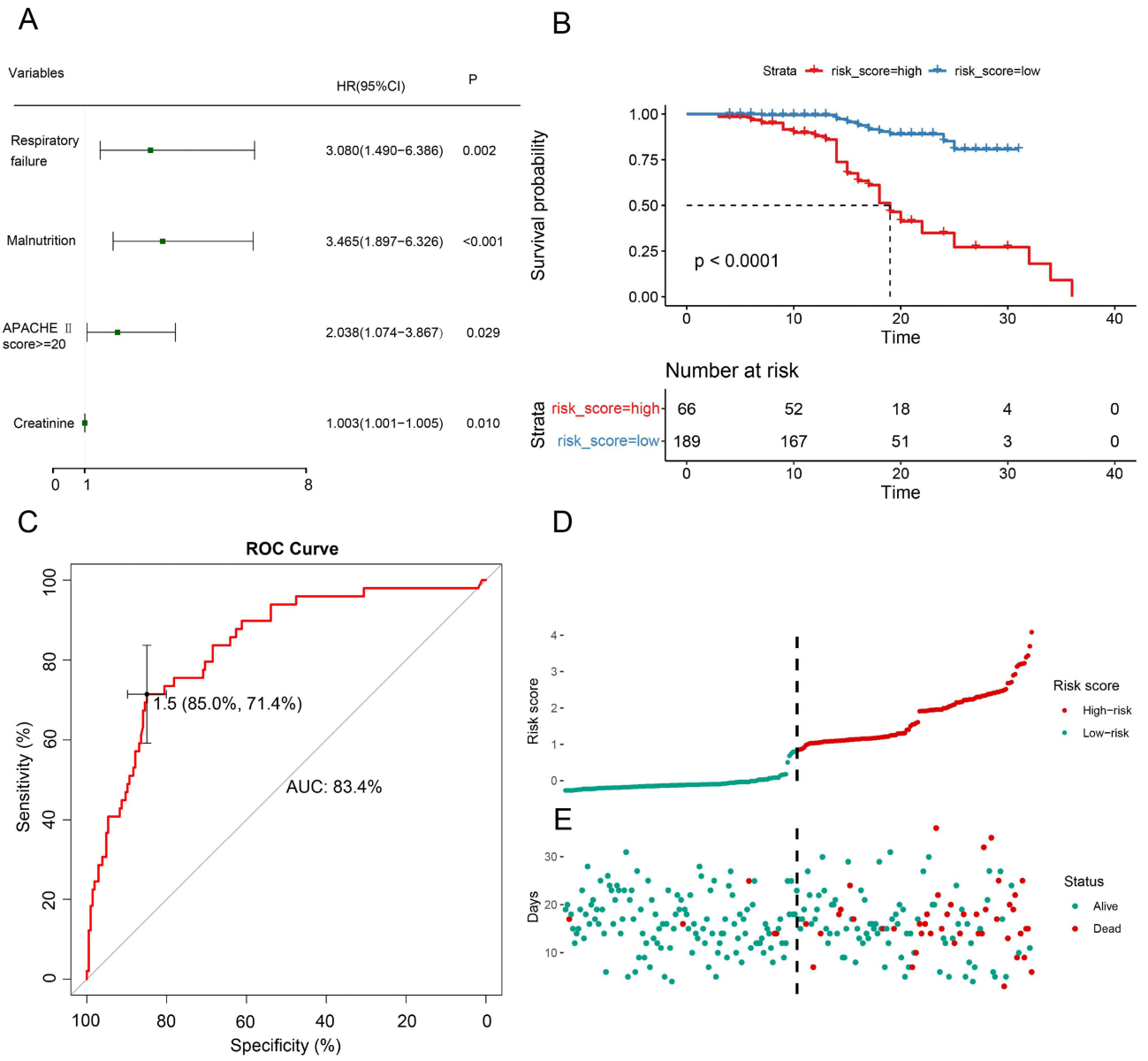


**Figure 5** (**A**) Forest plots showing the multivariate analysis results of prognosis. (**B**) Comparison of overall survival in high and low risk groups. (**C**) The AUC of the risk score. (**D**) Risk score of each patient in high-risk and low-risk group. (**E**) The relationship between survival status and risk score of patients.

likely to lead to dyspnea and the decline of gas exchange ability, and thus the prognosis is worse. With respect to "creatinine" as an independent risk factor, our model shows that higher serum creatinine levels may lead to higher mortality in elderly patients infected with multidrug-resistant bacteria, although the HR of creatinine is only slightly greater than 1. However, the relationship between creatinine and prognosis of infection with multidrug-resistant bacteria has not been directly clarified in the previously published literature.Serum creatinine is a widely used clinical biomarker of glomerular filtration rate and global renal function. Creatinine clearance based on serum creatinine is often used to estimate glomerular filtration rate.[28] Therefore, we hypothesized that serum creatinine is associated with the prognosis of multidrug-resistant bacteria in elderly pulmonary infections, and it may be that decreased glomerular filtration rate affects the pharmacokinetics. It further restricts the use of some antibiotics and other therapeutic drugs, thus leading to the death of patients who cannot receive effective treatment. Whether creatinine will have a direct impact on the reproduction and invasion of drug-resistant bacteria, the specific mechanism of action is worth further exploration.APACHE II score is a critical evaluation system based on patients' acute physiological state and organ function. It is closely related to

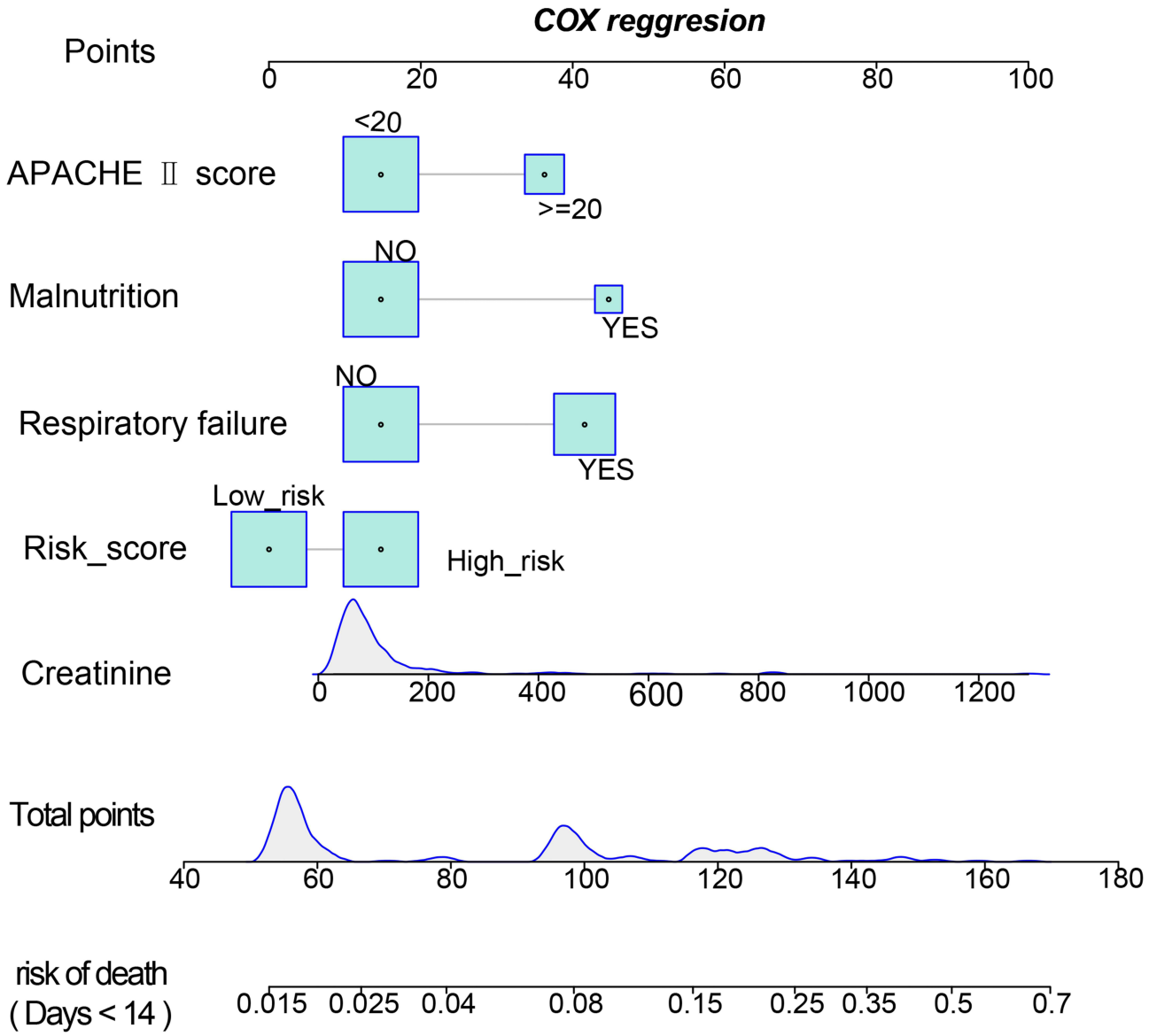


**Figure 6** The Nomogram of prognosis model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection.

patients' condition and prognosis. Generally, the higher the score, the greater the risk of poor prognosis.[29] In patients with MDRB infections, Casadeval et al[30] discovered a significant relationship between mortality and APACHE score greater than 20, and Huiping Huang et al[31] also mentioned high APACHE II score as a risk factor for infections with drug-resistant bacteria, which is also consistent with the findings of our study. As the factors were accessible and objective, the infection and dead risk could be evaluated more fleetly and reliably using a nomogram tool than traditional methods. If a high risk was hinted at, the clinicians could intervene more soon. Therefore, we hope this tool could help the clinicians avoid inappropriate treatment and control clinical indicators which were influential in mortality earlier.

Nomogram is effective complementary tool to help clinicians make clinical decisions, and there are many models on drug-resistant bacteria and lung infections worldwide, such as Hui Zhang et al[32] built a model to predict the risk of death in patients with Acinetobacter baumannii infection; Wei et al[5] constructed a risk prediction model for drug-resistant bacterial infections in respiratory inpatients during the COVID-19 epidemic, and Gonzalez et al[16] constructed and validated a model for predicting the risk of multidrug-resistant microbial infections in the emergency medicine population in the Spanish region. It's no doubt that these predictive models bring great benefits to medicine, but our model has

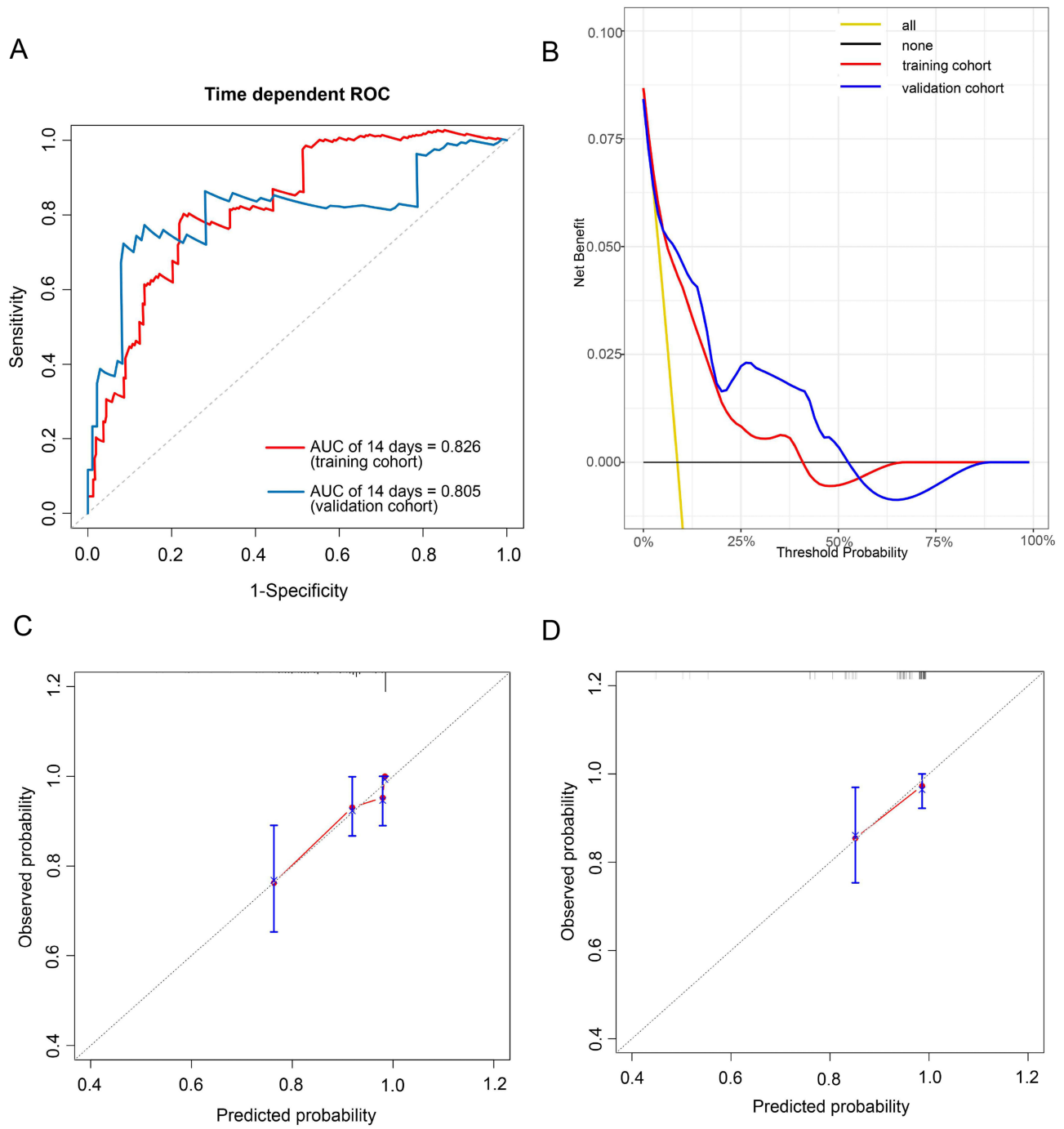


**Figure 7** (**A**) The ROC curve of prognosis model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection; (**B**) The decision curve of prognostic model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection; (**C**) The calibration curve of prognostic model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection(training cohort); (**D**) The calibration curve of prognostic model for multi-drug resistant bacteria infection in elderly patients with pulmonary infection(validation cohort).

some significant advantages over these models. First, an independent exogenous validation cohort was used to increase the reliability and clinical applicability of the model in our study; Second, The study utilized multi-center data from Anhui province, which avoided the overfitting phenomenon that may occur when constructing a model with a single dataset. However, some limitations should be considered, including the exclusion of potential factors such as the use of hormone, specific antibiotic application and other missing information about the studied factors in the cases for the retrospective study. Next, the study population being limited to several hospitals in Anhui province, which may limit the

generalizability of the nomogram. Nonetheless, this rigorous nomogram construction, including predictor selection, internal and external validation, provides a reliable and accurate risk stratification tool for infection and death in elderly patients with multidrug-resistant pulmonary infections. In the future, the sample size and population are needed to further expand to construct more accurate and wider applicable models.

## Conclusion

In conclusion, several important risk factors were identified for the morbidity and mortality of MDRB in elderly patients with pulmonary infections, which are very common for elderly patients with pulmonary infections in clinical practice, especially prolonged use of antibiotics, cerebrovascular disease, and nutritional deficiencies. Nomogram model provides a comprehensive and generalizable assessment of the key risk factors that affect infection and subsequent patient outcomes, and can help to improve early identification of patients with higher risk of infections and mortality, as well as to guide appropriate clinical management.

## Informed Consent Statement

This study was approved by the ethical committee of the First People's Hospital of Hefei and was conducted in accordance with the declaration of Helsinki. Individual informed consent was waived because this study used data previously collected during the course of routine diagnosis and did not pose any additional risks to the patients.

## 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.

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## Disclosure

The authors declare no conflicts of interest in this work.

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