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Article

A SHAP-Based Interpretable Model for MDRO-Infection Risk in Chronically Multimorbid Middle-Aged and Elderly ICU Adults

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Abstract

Aims/Background: Multidrug-resistant organism (MDRO) infection poses a significant clinical challenge, resulting in poor outcomes for middle-aged and older intensive care unit (ICU) patients with chronic multimorbidity. While conventional prediction models can identify high-risk patients, they often lack transparency in clinical decision-making. To bridge this gap, we aimed to develop a prediction model that incorporates Shapley Additive Explanations (SHAP)–based explainability analysis. This approach aims to achieve accurate risk prediction while quantitatively assessing the contribution of each risk factor, thereby providing clear guidance for clinical intervention. **Methods**: We employed a hospital-based consecutive sampling strategy to enroll 314 middle-aged and older patients with chronic multimorbidity admitted to the intensive care units of three Grade A tertiary hospitals and one secondary hospital in Bengbu, Anhui, from May 2024 to May 2025. Based on standard diagnostic criteria for MDROs, patients were categorized into an MDRO infection group and a non-MDRO infection group. Twenty candidate variables potentially associated with MDRO infection were extracted from electronic medical record systems. Univariate analysis, Least Absolute Shrinkage and Selection Operator (LASSO) regression, and multivariable logistic regression were utilized to identify high-risk factors for MDRO infection. The model's discriminative ability and calibration were evaluated using receiver operating characteristic (ROC) analysis and the Hosmer–Lemeshow goodness-of-fit test. Internal validation was performed through bootstrap resampling (1000 iterations). We compared logistic regression, Naive Bayes, support vector machine (SVM), decision tree, linear discriminant analysis (LDA), and quadratic discriminant analysis (QDA) models, selecting the optimal model for SHAP analysis. **Results**: (1) Univariate analysis revealed significant differences between the two groups in age, length of hospital stay, admission diagnosis, history of antibiotic use, blood transfusion history, catheter category and number, mechanical ventilation, tracheostomy, white blood cell count, C-reactive protein, and other indices. (2) Variables identified as significant in univariate analysis were further analyzed using LASSO regression, which pinpointed eight predictors with non-zero coefficients; these were included in multivariable logistic regression for refined selection. (3) ROC analysis and the Hosmer–Lemeshow test indicated strong model performance, with an area under the curve (AUC) of 0.906 (95% confidence interval [CI]: 0.896–0.912), sensitivity of 77.92%, and specificity of 88.46%. Bootstrap internal validation confirmed that the model retained satisfactory discriminative ability. (4) Among the models compared, logistic regression demonstrated high predictive accuracy along with superior interpretability and stability, making it the chosen model for detailed analysis. A nomogram was developed based on seven key predictors: age, length of hospital stay, admission diagnosis, history of antibiotic use, tracheostomy, C-reactive protein, and white blood cell count. (5) SHAP analysis revealed that history of antibiotic use, length of hospital stay, and age were the most significant factors for MDRO infection among ICU patients with chronic multimorbidity, with antibiotic exposure identified as the strongest contributor. **Conclusion**: The prediction model developed in this study demonstrates strong predictive performance for in-hospital MDRO infection in ICU patients with chronic multimorbidity. It serves as a preliminary tool for identifying high-risk patients and may facilitate early risk stratification and targeted prevention strategies.

Keywords: drug resistance; bacteria; machine learning; model; risk factors

1. Introduction

Multidrug-resistant organisms (MDROs) are bacteria that simultaneously resist three or more classes of antimicrobial agents. They are particularly prevalent in intensive care units (ICUs), where the widespread early use of broad-spectrum antibiotics has contributed to MDRO infections becoming a common issue for critically ill patients [1]. The World Health Organization highlights that common resistant pathogens, such as carbapenem-resistant *Acinetobacter baumannii*, utilize ICUs as major sites for infection and transmission [2]. Data from multiple countries indicate that ICU MDRO infection rates exceed 50% in most regions, with associated mortality rates reaching as high as 40% [3]. Thus, early identification and timely intervention for

MDRO infections are essential for improving patient outcomes and preventing nosocomial spread.

As the population ages, the number of middle-aged and older ICU patients with multiple chronic conditions has risen markedly [4]. This demographic is more vulnerable to MDRO infections due to factors such as impaired immune function, frequent invasive procedures, and prolonged exposure to antimicrobial agents. Consequently, their risk of death is approximately 1.5-fold [5,6], making them a critical target group for prevention and control efforts. A previous study has shown that chronic multimorbidity is an independent risk factor for MDRO infections, demonstrating a "dose–response" relationship: the more comorbidities a patient has, the greater the infection risk [7]. Each additional day of broad-spectrum antibiotic use further increases the risk of MDRO infection [8]. This scenario leads to longer hospitalizations, escalating costs [9,10,11], extended ICU stays, increased reliance on mechanical ventilation, and higher mortality [12]. Moreover, the microbiome and medication exposure histories of middle-aged and older patients with chronic multimorbidity—such as those with chronic kidney disease—can undergo long-term alterations, which may influence the transition from colonization to infection and alter the infection spectrum [13]. However, there are few prediction models specifically developed for this population, and analyses of contributing factors remain limited.

Despite the implementation of routine screening and empirical treatment in clinical practice, current identification and prediction methods have significant limitations. Traditional approaches, which rely on clinical experience or single indicators and culture results, often suffer from delays and lack specificity, making it challenging to accurately assess individual risks in a timely manner. Moreover, prediction models specifically tailored to the subgroup of "middle-aged/older adults with multimorbidity" are still relatively scarce [14]. Recently, machine learning methods that leverage large-scale electronic medical records and multimodal information have demonstrated improved discriminative ability and transfer potential for infection prediction [15]. However, their clinical application is limited by the "black-box" nature of these models, where key variables' effects and the basis for individualized decisions remain unclear. Shapley Additive Explanations (SHAP) offers a unified explainability framework that can quantitatively reveal the marginal contributions of each feature to prediction outcomes at both global and individual levels, helping to bridge the gap between model complexity and clinical interpretability [16,17].

This study aims to integrate multidimensional information—including clinical characteristics, treatments, and medication exposure—among middle-aged and older ICU patients with chronic multimorbidity to construct and validate an explainable prediction model for MDRO infection. To enhance predictive performance, SHAP will be employed to identify key risk factors and quantify their contributions to individual predictions, thus generating actionable risk stratification and intervention trigger points. Additionally, we will explore the associations between model-based risk strata and clinical outcomes (e.g., ICU length of stay, mechanical ventilation, and mortality), providing evidence to support individualized infection prevention strategies and enhance clinical decision-making.

2. Methods

2.1 Participants

This study was a multicenter retrospective observational study using a hospital-based consecutive sampling approach. Data were collected from four hospitals in Bengbu City, northern Anhui Province, China, including three Grade A tertiary hospitals (Bengbu First People's Hospital, The Third People's Hospital, and The Second Affiliated Hospital of Bengbu Medical University) and one secondary hospital (The Fifth People's Hospital of Bengbu). The secondary hospital was included because it is a major comprehensive medical institution in the local area and admits a large number of patients who meet the inclusion criteria, thereby ensuring that the sample is representative of regional healthcare resources.

All middle-aged and older patients with chronic multimorbidity who were admitted to the intensive care units of these hospitals between May 2024 and May 2025 and met the specified inclusion and exclusion criteria were consecutively enrolled. Eligible cases were systematically identified through the electronic medical record databases during the study period. A total of 314 patients were enrolled, comprising 177 males and 137 females.

For sample size estimation, a commonly accepted rule for the development of prediction models for binary outcomes stipulates the need for at least 10 outcome events per predictor variable (10 EPV) [18]. Following Least Absolute Shrinkage and Selection Operator (LASSO) regression, eight predictors were preliminarily retained, indicating a requirement for at least 80 outcome events. With 314 patients included and 129 outcome events recorded, the study met the EPV requirement. Consequently, the results are considered reliable and clinically representative.

The inclusion criteria were as follows: (1) age >45 years; (2) confirmed comorbidity of two or more chronic diseases; and (3) complete medical records.

The exclusion criteria included: (1) end-stage disease or multiple organ failure; and (2) acute infection or MDRO infection present at the time of admission.

2.2 Data Collection

First, we conducted an extensive literature review, considering the latest clinical advances [19,20,21,22], to identify 20 high-risk factors potentially associated with MDRO infection among middle-aged and older ICU pa-

tients with chronic multimorbidity. We then accessed inpatient information from electronic medical record systems. Two researchers independently collected and cross-checked all necessary clinical data. Based on microbiological culture results obtained throughout the entire ICU stay, we retrospectively assessed each patient's infection status. Following the diagnostic criteria for MDROs [23], we classified the 314 patients into two groups: the MDRO infection group (n = 129) and the non-infection group (n = 185).

The variables we collected included demographic and health-related information such as sex, age, body mass index, history of surgery, and history of malignancy. In addition, we recorded infection-related factors, including history of antibiotic use, blood transfusion, mechanical ventilation, and catheter categories and counts.

2.3 Main Outcome Indicators

2.3.1 Baseline Admission Data

The baseline admission data encompassed age (years), sex (0 = male, 1 = female), body mass index (BMI), history of surgery (0 = no, 1 = yes), admission diagnosis (0 = non-pneumonia, 1 = pneumonia), length of hospital stay (days), history of malignancy (0 = no, 1 = yes), history of blood transfusion (0 = no, 1 = yes), and history of antibiotic use (0 = none, 1 = one antibiotic, 2 = two or more antibiotics).

2.3.2 Infection Status

During ICU hospitalization, we cultured blood, sputum, and urine samples according to standard clinical laboratory procedures. MDRO infection was diagnosed when resistant bacteria were isolated, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus aureus*, and *Escherichia coli*, among others [2]. Patients were classified as having MDRO infection (0 = no infection, 1 = infection).

2.3.3 Catheter Status

In this study, we categorized catheter types and counts based on clinical function and risk related to invasiveness, referencing the tripartite classification commonly used for rapid clinical assessment in Chinese ICUs [24]. Type I catheters included chest drains, T-tubes, tracheostomy tubes, endotracheal (oral/nasal) tubes, ventricular drainage tubes, and arterial/venous catheters. Type II catheters comprised double-lumen tubes, negative-pressure drainage tubes, central venous catheters, triple-lumen tubes, and ostomy tubes. Type III catheters included urinary catheters, infusion lines, nasogastric tubes, and oxygen tubing. We recorded catheter counts using their original values.

2.3.4 Mechanical Ventilation Status

This study examined the impact of various invasive ventilation modalities as medical intervention factors on the risk of MDRO infection. During data collection, we noted whether each patient received mechanical ventilation and the specific modality used (endotracheal intubation or tracheostomy). The variable was defined as follows: (1) No invasive mechanical ventilation: the patient did not receive any invasive ventilatory support. (2) Endotracheal intubation: the patient received invasive mechanical ventilation via oral or nasal endotracheal intubation. (3) Tracheostomy: the patient received invasive mechanical ventilation through a tracheostomy cannula.

2.3.5 Laboratory Indices

Laboratory indices [25] included white blood cell count (4–10 $\times$ 10^9/L), neutrophil count (1.8–6.3 $\times$ 10^9/L), lymphocyte count (0.8–4 $\times$ 10^9/L), haemoglobin levels (male: 120–160 g/L; female: 110–150 g/L), and C-reactive protein ($<$2.87 mg/L). For statistical analysis, we converted all laboratory parameters into ordinal categorical variables according to their clinical reference ranges. Specifically, each index was classified into three categories: "below the normal range", "within the normal range", and "above the normal range" [26].

2.4 Statistical Analysis

Statistical analyses were conducted using SPSS 26.0 (IBM Corp., Armonk, NY, USA), Python 3.12.7 (Python Software Foundation, Wilmington, DE, USA), and R 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided with a significance level of α = 0.05. Continuous variables were initially assessed for normality using the Shapiro–Wilk test. Normally distributed variables were presented as mean $\pm$ standard deviation and compared using independent-samples *t* tests. In contrast, non-normally distributed variables were expressed as median (P25, P75) and analyzed using rank-sum tests. Categorical variables were reported as n (%) and compared using the chi-square test or Fisher's exact test, as appropriate. To evaluate MDRO infection during ICU stay as the outcome, univariate analyses were performed to identify candidate variables ($p < 0.05$). These variables were then incorporated into LASSO regression. The key features selected by LASSO were included in a forward stepwise multivariable logistic regression, and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported along with model fit testing. Using the same feature set, Naive Bayes, support vector machine, decision tree, linear discriminant analysis (LDA), and quadratic discriminant analysis (QDA) models were constructed using the full original dataset. The predictive performance of each model was internally validated using bootstrap resampling with 1000 iterations. The area under the receiver operating characteristic curve (AUC) and its 95% confidence interval (CI) were estimated, and DeLong's test was used to compare the discrimination performance among models. Additionally, sensitivity, specificity, accuracy, F1 score, and precision–recall area under the curve (PR-AUC) were reported.

Table 1. Univariate analysis of multidrug-resistant organism (MDRO) infection in middle-aged and older intensive care unit (ICU) patients with chronic multimorbidity.

Variables	MDRO		Statistics	*p*
	NO (n = 185)	YES (n = 129)		
Sex			0.000[a]	1.000
Male	104 (56.22%)	73 (56.59%)		
Female	81 (43.78%)	56 (43.41%)		
BMI (kg/m^2)			3.218[a]	0.200
<18.5	24 (12.97%)	21 (16.28%)		
18.5~25	106 (57.30%)	81 (62.79%)		
>25	55 (29.73%)	27 (20.93%)		
Surgical history			0.908[a]	0.341
NO	113 (61.08%)	71 (55.04%)		
YES	72 (38.92%)	58 (44.96%)		
Admission diagnosis			43.695[a]	<0.001
Non-pneumonia	175 (94.59%)	84 (65.12%)		
Pneumonia	10 (5.41%)	45 (34.88%)		
History of malignancy			0.116[a]	0.733
NO	179 (96.76%)	123 (95.35%)		
YES	6 (3.24%)	6 (4.65%)		
History of blood transfusion			18.905[a]	<0.001
NO	152 (82.16%)	78 (60.47%)		
YES	33 (17.84%)	51 (39.53%)		
History of antibiotic use			111.850[a]	<0.001
No antibiotics	46 (24.86%)	4 (3.10%)		
A single antibiotic	114 (61.62%)	33 (25.58%)		
Two or more antibiotics	25 (13.51%)	92 (71.32%)		
Mechanical ventilation			44.383[a]	<0.001
NO	92 (49.73%)	24 (18.60%)		
Endotracheal intubation	86 (46.49%)	77 (59.69%)		
Tracheostomy	7 (3.78%)	28 (21.71%)		
Tracheostomy			28.264[a]	<0.001
NO	173 (93.51%)	91 (70.54%)		
YES	12 (6.49%)	38 (29.46%)		
Endotracheal intubation			1.224[a]	0.269
NO	99 (53.51%)	60 (46.51%)		
YES	86 (46.49%)	69 (53.49%)		
Class I catheter count			25.054[a]	<0.001
NO	23 (12.43%)	1 (0.78%)		
A single	66 (35.68%)	32 (24.81%)		
Two catheters	77 (41.62%)	68 (52.71%)		
Three or more	19 (10.27%)	28 (21.71%)		
Class II catheter count			20.813[a]	<0.001
NO	28 (15.14%)	10 (7.75%)		
A single	80 (43.24%)	32 (24.81%)		
Two catheters	55 (29.73%)	58 (44.96%)		
Three or more	22 (11.89%)	29 (22.48%)		
Class III catheter count			26.029[a]	<0.001
NO	99 (53.51%)	31 (24.03%)		
One or more	86 (46.49%)	98 (75.97%)		
White blood cell count			24.43[a]	<0.001
Within the normal range	104 (56.22%)	40 (31.01%)		
Below the normal range	23 (12.43%)	13 (10.08%)		
Above the normal range	58 (31.35%)	76 (58.91%)		

Table 1. Continued.

Variables	MDRO		Statistics	*p*
	NO (n = 185)	YES (n = 129)		
Neutrophil count			11.597[a]	0.003
Within the normal range	80 (43.24%)	35 (27.13%)		
Below the normal range	26 (14.05%)	14 (10.85%)		
Above the normal range	79 (42.70%)	80 (62.02%)		
Lymphocyte count			3.126[a]	0.210
Within the normal range	78 (42.16%)	42 (32.56%)		
Below the normal range	76 (41.08%)	64 (49.61%)		
Above the normal range	31 (16.76%)	23 (17.83%)		
Hemoglobin			5.827[a]	0.054
Within the normal range	76 (41.08%)	37 (28.68%)		
Below the normal range	90 (48.65%)	80 (62.02%)		
Above the normal range	19 (10.27%)	12 (9.30%)		
C-reactive protein			33.765[a]	<0.001
Within the normal range	84 (45.41%)	28 (21.71%)		
Below the normal range	43 (23.24%)	18 (13.95%)		
Above the normal range	58 (31.35%)	83 (64.34%)		
Age (years)	67.00 (58.00, 77.00)	79.00 (71.00, 84.00)	6496.5[b]	<0.001
Length of hospital stay (days)	6.00 (3.00, 12.00)	14.00 (9.00, 21.00)	5801.0[b]	<0.001

a: χ^2 test. b: Mann-Whitney U test. BMI, body mass index.

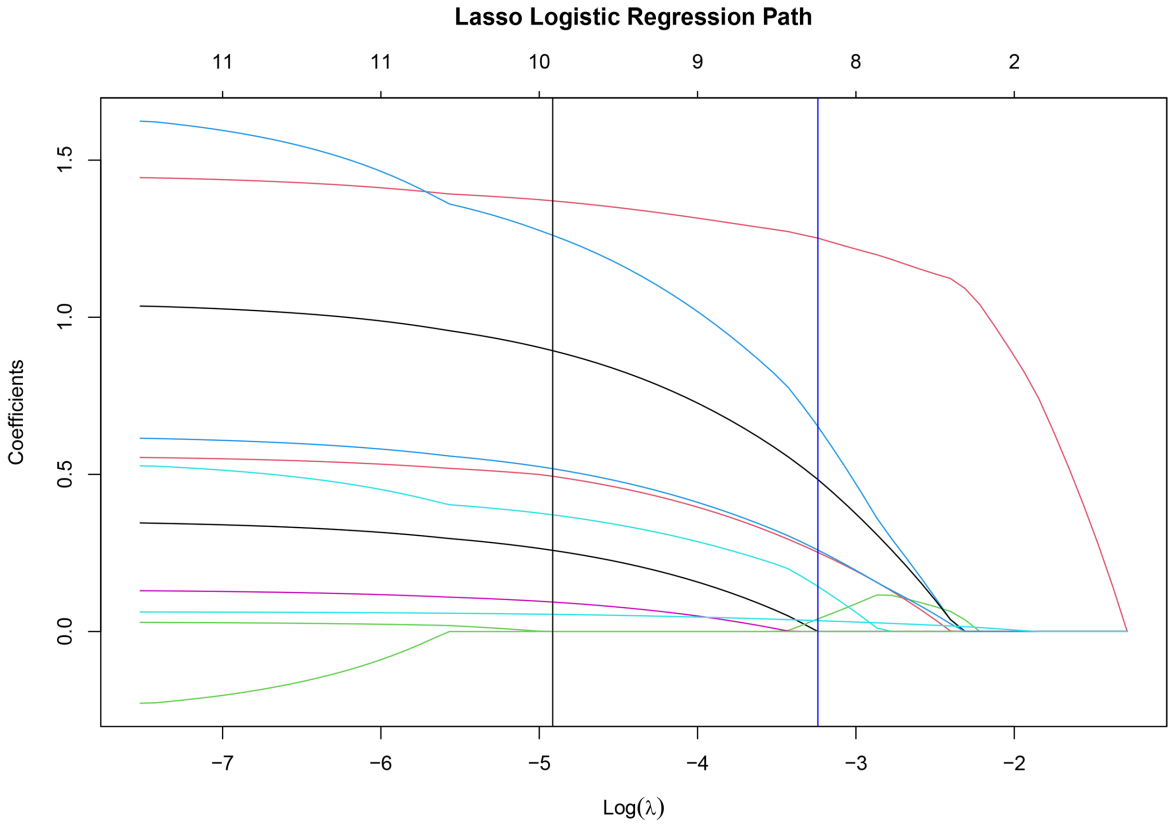

Fig. 1. Coefficient profile plot for feature selection in Least Absolute Shrinkage and Selection Operator (LASSO) regression.

Calibration was evaluated through calibration curves, the Brier score, and the Hosmer–Lemeshow test, while clinical utility was assessed using decision curve analysis (DCA). The robustness of the findings was examined through bootstrap resampling and sensitivity analyses under various imbalance-handling strategies. Finally, for the

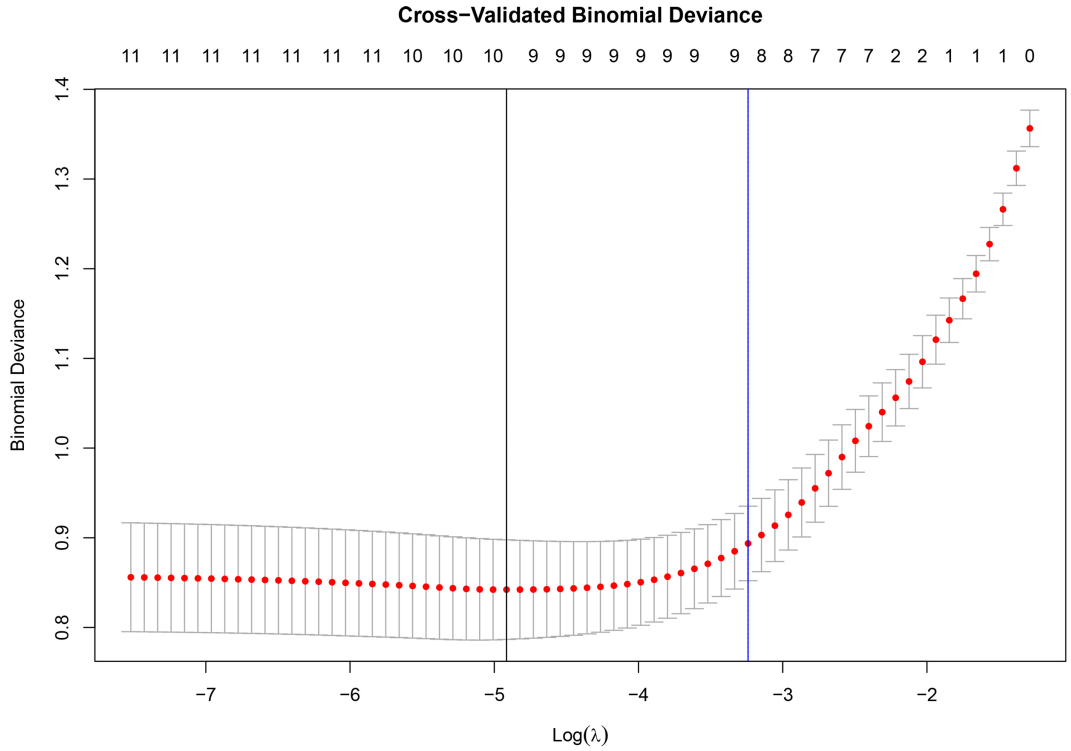

Fig. 2. LASSO penalty (cross-validation) plot.

best-performing model, SHAP values (version 0.48.0) were calculated at both global and individual levels to quantify the contribution and direction of each predictor.

3. Results

3.1 Univariate Analysis

Univariate analysis revealed significant differences between the MDRO infection group and the non-infection group in several factors, including age (years), length of hospital stay (days), admission diagnosis, history of antibiotic use, history of blood transfusion, catheter and counts, mechanical ventilation, tracheostomy, white blood cell count, neutrophil count, and C-reactive protein ($p < 0.05$). However, no significant differences were found between the two groups regarding sex, BMI, history of surgery, history of malignancy, lymphocyte count, endotracheal intubation, or haemoglobin ($p > 0.05$). Further details are provided in Table 1.

3.2 LASSO Regression Analysis

Variables that were significant in the univariate analysis ($p < 0.05$) were included in the LASSO regression for further selection. Using an optimal penalty parameter of $\lambda = 0.036$, we identified eight predictors with non-zero coefficients: age (years), length of hospital stay (days), admission diagnosis, history of antibiotic use, mechanical ventilation, tracheostomy, C-reactive protein, and white blood cell count (see Figs. 1,2).

3.3 Multivariable Regression Analysis

These eight variables were further incorporated into a forward stepwise multivariable logistic regression model for refinement. The coding of the categorical variables is shown in Table 2. Since Mechanical Ventilation was not statistically significant, we excluded it, resulting in the inclusion of seven variables in the forward stepwise multivariate logistic regression. The results of this analysis are presented in Table 3. Age, length of hospital stay, pneumonia as the admission diagnosis, use of two or more antibiotics, tracheostomy, elevated white blood cell count, and elevated C-reactive protein were significant independent predictors of MDRO infection. In contrast, single antibiotic use, decreased white blood cell count, and decreased C-reactive protein were not statistically significant.

3.4 Evaluation and Internal Validation of the Prediction Model

The model's discriminative ability and calibration were evaluated using receiver operating characteristic (ROC) curve analysis and the Hosmer–Lemeshow (H–L) test. The original model achieved an AUC value of 0.911 (Fig. 3). After applying 1000-iteration bootstrap resampling, the optimism-corrected mean AUC was found to be 0.906 (95% CI: 0.896–0.912), with a sensitivity of 77.92% and a specificity of 88.46%. These results indicate good discrimination and stable, satisfactory performance (Fig. 4).

The H–L test results showed $\chi^2 = 4.2234$ and $p = 0.8364$ (>0.05), suggesting good calibration. To further

Table 2. Variable coding/assignment.

Variable	Coding
Age (years)	Entered as original value
Length of hospital stay (days)	Entered as original value
Admission diagnosis	Non-pneumonia = 0, Pneumonia = 1
History of antibiotic use	None = 0, One antibiotic = 1, Two or more antibiotics = 2
Mechanical ventilation	None = 0, Endotracheal intubation = 1, Tracheostomy = 2
Tracheostomy	No = 0, Yes = 1
C-reactive protein	Within the normal range = 0, Below the normal range = 1, Above the normal range = 2
White blood cell count	Within the normal range = 0, Below the normal range = 1, Above the normal range = 2

Table 3. Multivariable logistic regression analysis of MDRO infection in middle-aged and older ICU patients with chronic multimorbidity.

Predictors	Standardized coefficient (β)	SE	OR	95% CI	p
Constant	–2.907	0.656	0.055	[0.015, 0.197]	<0.001
Age (years)	0.780	0.195	2.181	[1.489, 3.196]	<0.001
Length of hospital stay (days)	1.195	0.303	3.305	[1.823, 5.990]	<0.001
Admission diagnosis (Reference group: Non-pneumonia)					
Pneumonia	1.049	0.486	2.855	[1.102, 7.393]	0.031
History of antibiotic use (Reference group: No antibiotics)					
A single antibiotic	0.534	0.631	1.705	[0.493, 5.868]	0.397
Two or more antibiotics	1.974	0.667	7.196	[1.948, 26.576]	0.003
Tracheostomy (Reference group: No)					
Yes	1.378	0.528	3.965	[1.410, 11.154]	0.009
White blood cell count (Reference group: Within the normal range)					
Below the normal range	–0.091	0.567	0.913	[0.301, 2.774]	0.873
Above the normal range	1.258	0.387	3.520	[1.648, 7.517]	0.001
C-reactive protein (Reference group: Within the normal range)					
Below the normal range	0.093	0.507	1.097	[0.406, 2.964]	0.855
Above the normal range	1.188	0.393	3.279	[1.517, 7.088]	0.003

SE, Standard Error; CI, confidence interval; OR, odds ratio. Age and length of hospital stay were standardized before being entered into the logistic regression model.

assess the accuracy of the nomogram, a calibration curve was plotted, demonstrating that the predicted probabilities were in good agreement with the ideal model (Fig. 5). Additionally, decision curve analysis (DCA) visually confirmed the clinical usefulness of the risk prediction model. The model achieved a maximal net benefit across threshold probabilities ranging from 5% to 85%, consistently providing a higher net benefit than the "treat-all" or "treat-none" strategies, thereby demonstrating good clinical applicability (Fig. 6).

3.5 Comparison of Multiple Machine-Learning Models

Comparative experiments were conducted to evaluate the performance of logistic regression, Naive Bayes, support vector machine (SVM), decision tree, linear discriminant analysis (LDA), and quadratic discriminant analysis (QDA). The results, summarized in Table 4, indicate that logistic regression was ultimately selected for further analysis due to its high predictive accuracy, as well as its superior interpretability and stability (Fig. 7).

3.6 Nomogram Construction

Following the model comparison, logistic regression was recommended for the development of the visual nomogram. Seven key predictors were identified: age, length of hospital stay, admission diagnosis, history of antibiotic use, tracheostomy, C-reactive protein, and white blood cell count. Based on these indicators, a nomogram was constructed, as shown in Fig. 8.

3.7 SHAP Analysis

To further explore the key determinants of MDRO infection among middle-aged and older ICU patients with chronic multimorbidity, logistic regression was ultimately selected for SHAP-based feature analysis after comparing multiple machine-learning models. The findings are presented in Fig. 9, which details the importance ranking of each feature.

Key factors associated with MDRO infection in this population include history of antibiotic use, length of hospital stay, and age, with history of antibiotic use contributing

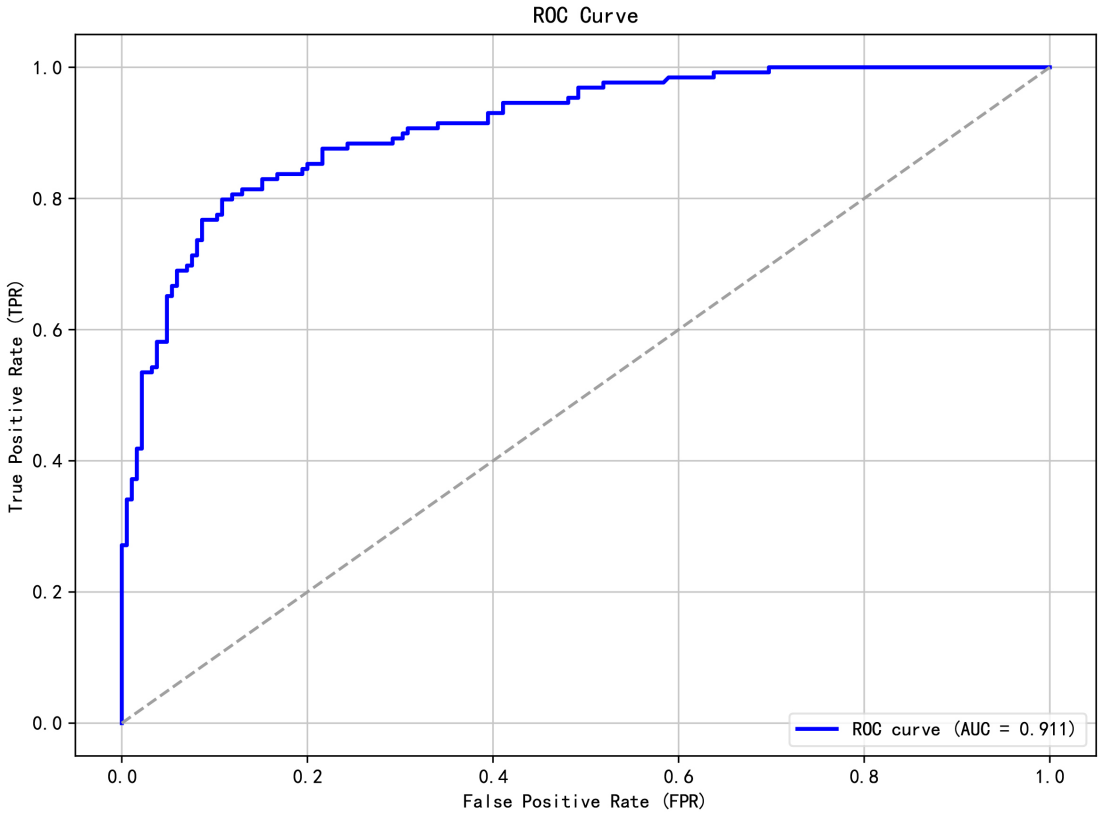

Fig. 3. Receiver operating characteristic (ROC) curve of the nomogram model. AUC, area under the curve.

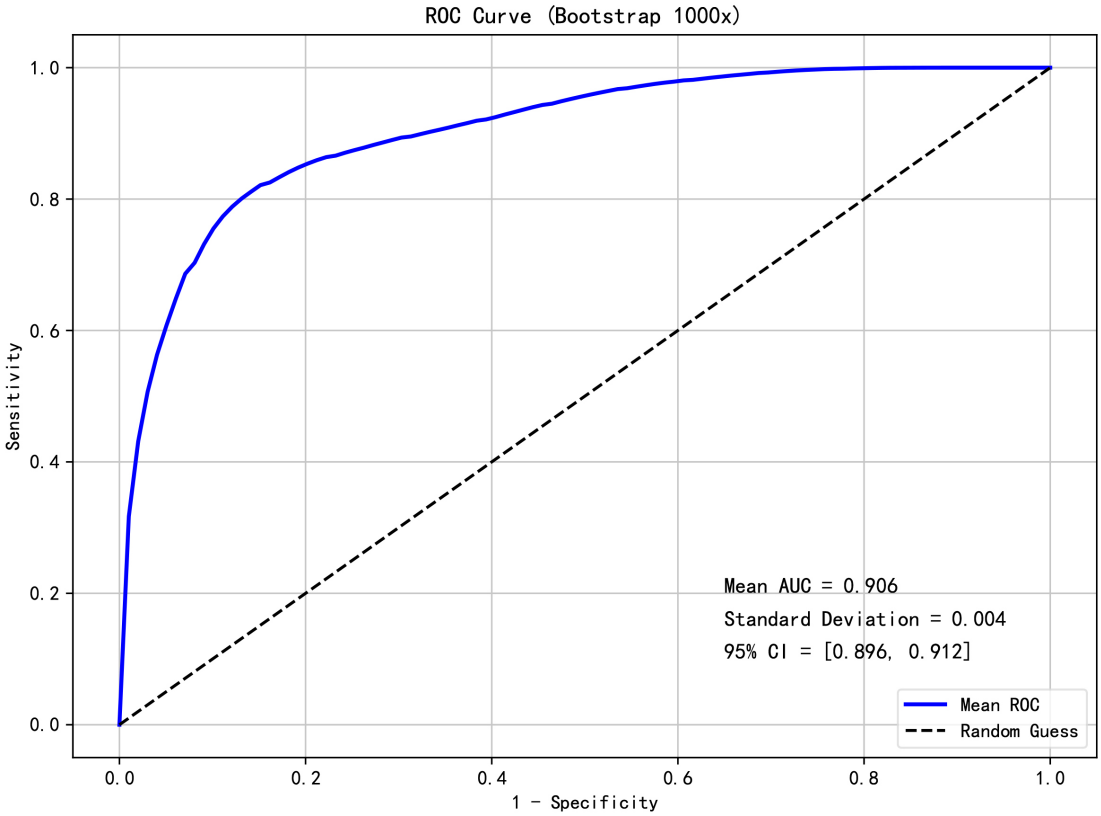

Fig. 4. ROC curve of the nomogram model after bootstrap internal validation (1000 resamples). CI, confidence interval.

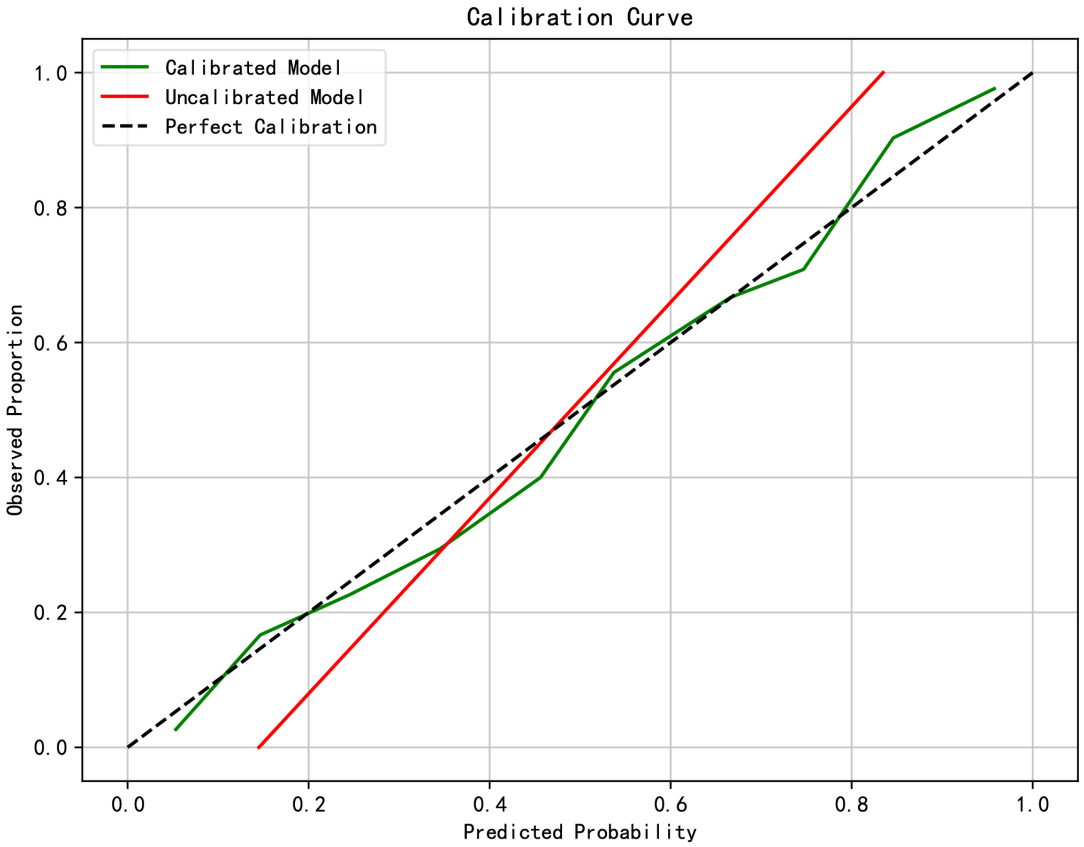

Fig. 5. Calibration curve of the nomogram model for predicting MDRO infection. Red curve represents a smoothed calibration trend.

the most significantly. For the partitioned dataset, SHAP values were computed using the SHAP package in Python, as depicted in Fig. 10. In this figure, each dot represents an individual sample from the dataset. The x-axis position (i.e., the SHAP value) indicates the contribution of a specific feature to the model output for that sample, indicating its effect on the relative risk of MDRO infection. Thus, samples with higher SHAP values are predicted to have a greater risk of MDRO infection compared to those with lower SHAP values. Features are organized along the y-axis according to their overall importance, measured by the mean absolute SHAP value; features positioned higher on the axis are deemed more important.

4. Discussion

4.1 Current Status and Harm

The incidence of MDRO-related nosocomial infections has been increasing annually [27]. In ICUs, the reported occurrence of MDRO infections is approximately 30.0%, significantly higher than that in general wards [28]. Middle-aged and older patients with chronic multimorbidity are now recognized as a high-risk population for MDRO infections, exhibiting both elevated infection rates and high mortality. In our study, the incidence of MDRO infection among middle-aged and older ICU patients with chronic multimorbidity was 41.08%, surpassing the rate observed in the overall ICU population. Once infected, these patients not only endure prolonged hospitalization but also face increased mortality risk. Previous studies indicate that the mortality rate for middle-aged and older ICU patients with chronic multimorbidity who develop MDRO infections can reach. Additionally, the number of comorbidities is positively associated with mortality risk—the more comorbidities a patient has, the higher the risk of death [29].

4.2 Risk Factors

MDRO infections are influenced by multiple factors. In this study, we analyzed the risk factors for MDRO infection among middle-aged and older ICU patients with chronic multimorbidity and developed a nomogram prediction model. Through several rounds of selection, we identified seven key predictors of MDRO infection: age, length of hospital stay, admission diagnosis, history of antibiotic use, tracheostomy, C-reactive protein, and white blood cell count.

4.2.1 Age

Our findings indicate that older age is associated with a higher risk of MDRO infection among middle-

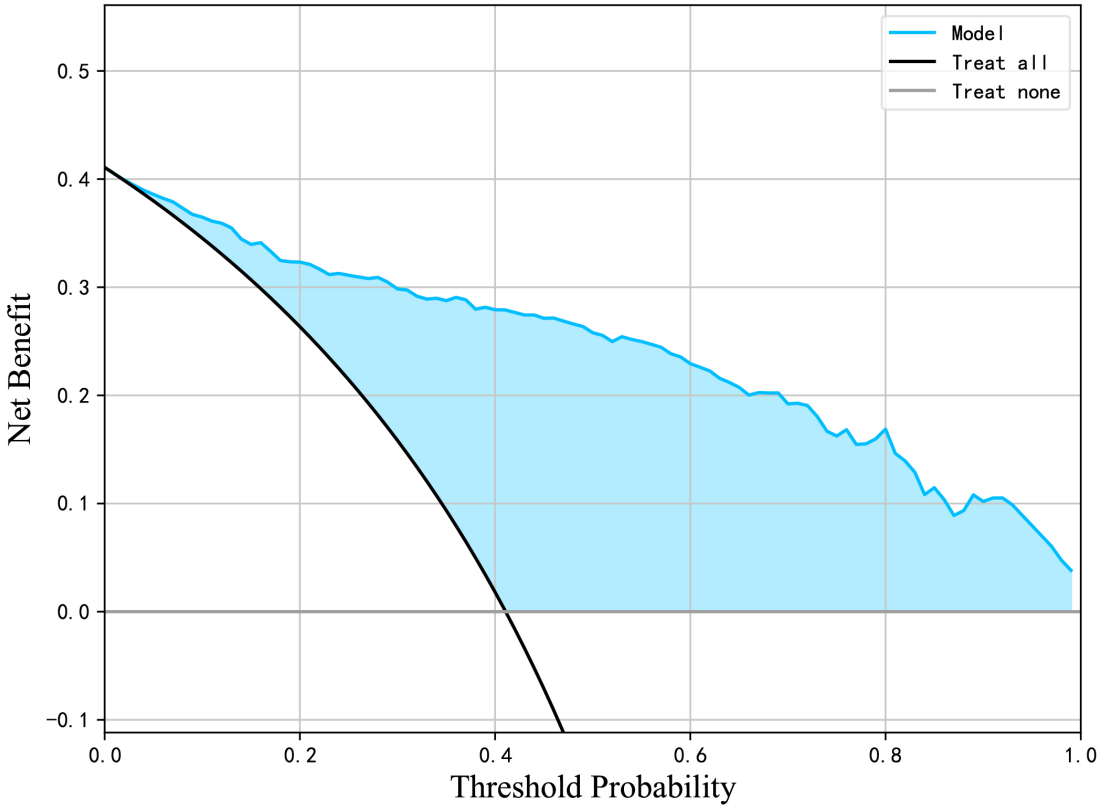

Fig. 6. Decision curve analysis of the prediction performance of the nomogram model for multidrug-resistant organism (MDRO) infection.

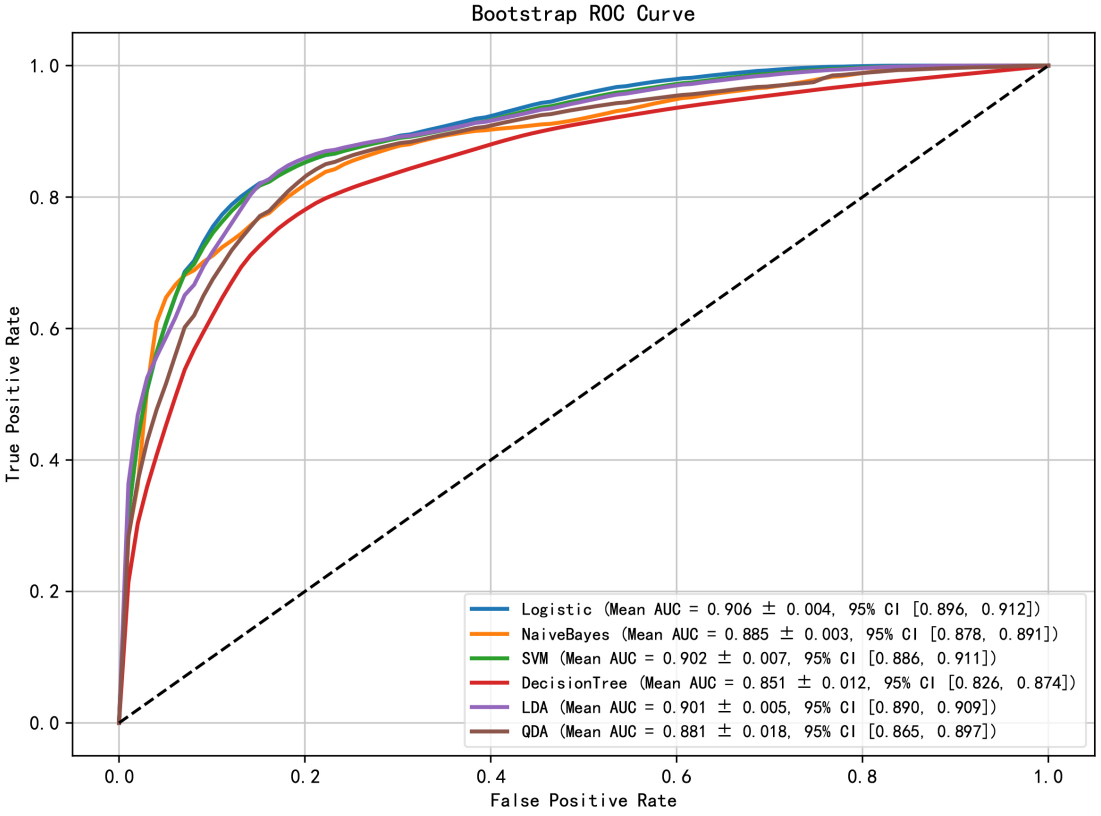

Fig. 7. Comparison of receiver operating characteristic (ROC) curves across multiple models for predicting MDRO infection.

Table 4. Comparative analysis of multiple machine-learning models.

Model name	Mean AUC	F1	Specificity	Sensitivity	Youden index	*p*-value
Logistic	0.906 (95% CI: 0.896–0.912)	0.801	0.885	0.779	0.664	
Decision tree	0.851 (95% CI: 0.826–0.874)	0.747	0.853	0.724	0.577	0.011
LDA	0.901 (95% CI: 0.890–0.909)	0.785	0.882	0.755	0.637	0.258
Naive Bayes	0.885 (95% CI: 0.878–0.891)	0.769	0.889	0.725	0.614	<0.001
QDA	0.881 (95% CI: 0.865–0.897)	0.780	0.818	0.805	0.623	0.051
SVM	0.902 (95% CI: 0.886–0.911)	0.797	0.878	0.778	0.656	0.643

p-value: DeLong's test. AUC, area under the curve; LDA, linear discriminant analysis; QDA, quadratic discriminant analysis; SVM, support vector machine.

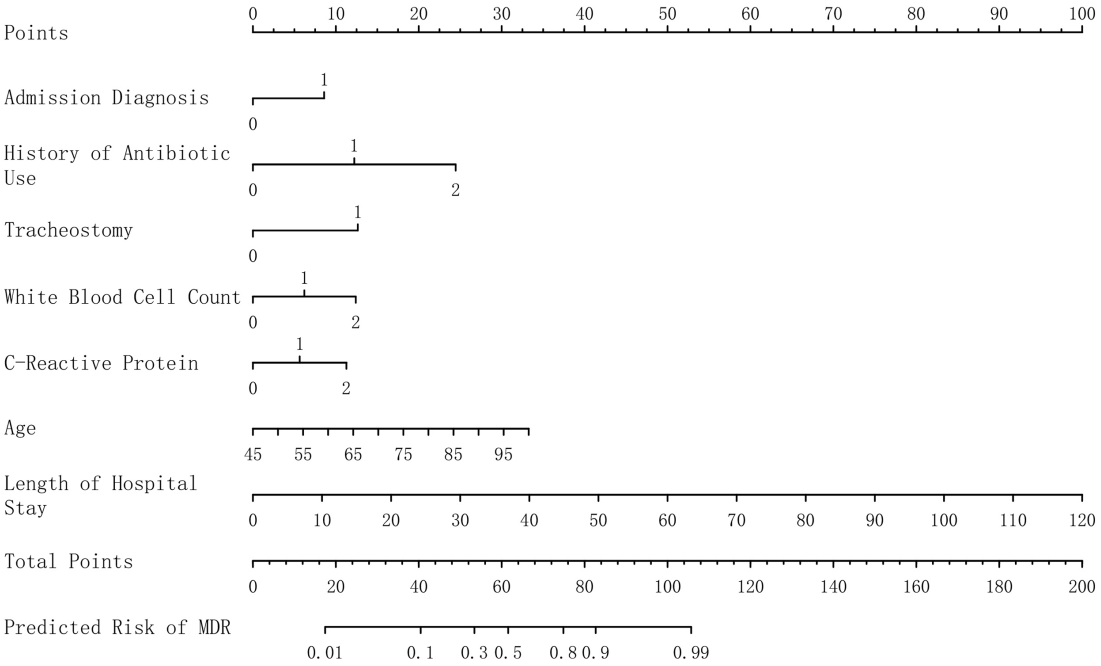

Fig. 8. Nomogram for predicting multidrug-resistant organism (MDRO) infection in middle-aged and older patients with chronic multimorbidity. MDR, multidrug-resistant.

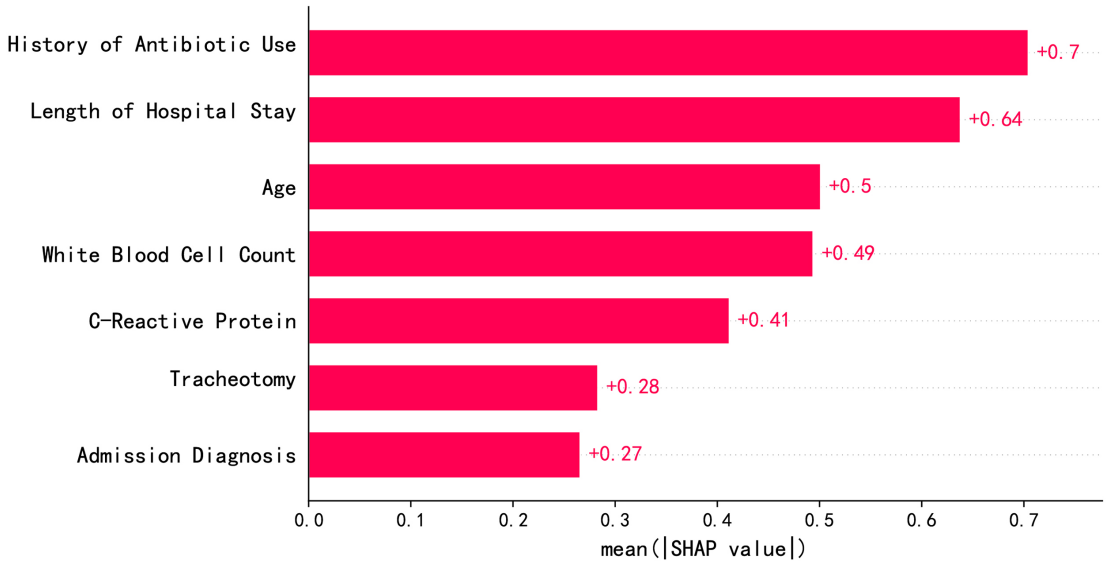

Fig. 9. Shapley Additive Explanations (SHAP) feature-importance bar plot for the Logistic regression model in the training set.

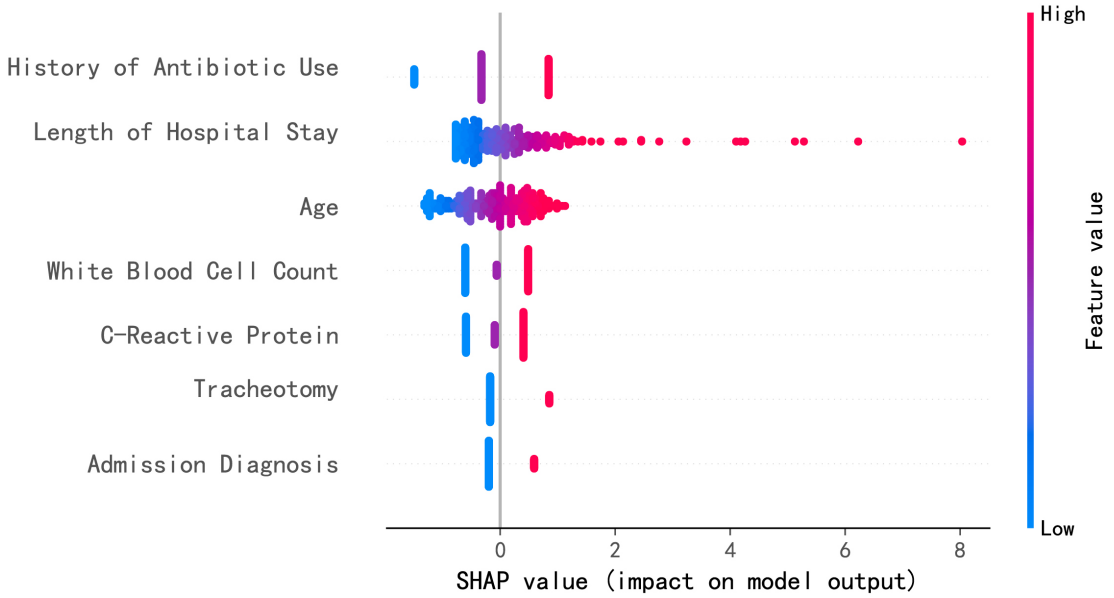

Fig. 10. SHAP beeswarm plot for the logistic regression model in the training set.

aged and older ICU patients with chronic multimorbidity, which aligns with the research by Moreira SB et al. [29]. Evidence suggests that immunosenescence, which occurs with aging, leads to declines in both innate and adaptive immune functions, significantly increasing the likelihood of MDRO colonization and infection [30]. Furthermore, middle-aged and older patients often require repeated hospitalizations or long-term invasive treatments due to cumulative comorbidities—such as urinary catheters and central venous catheters—thereby increasing their exposure to MDROs.

4.2.2 Length of Hospital Stay

Cui Z et al. [31] reported that, due to the cumulative effects of medical exposure make patients with prolonged hospital stays more likely to undergo invasive procedures (e.g., mechanical ventilation and central venous catheterization). These devices can disrupt physiological barriers and promote biofilm formation, creating potential reservoirs for MDRO growth. Prolonged hospital stays often involve extended use of broad-spectrum antibiotics, which suppress susceptible bacteria and allow resistant strains to overgrow. Longer stays also increase opportunities for cross-transmission, raising the frequency of contact with resistant pathogens in the healthcare environment. Multiple studies have demonstrated a positive association between MDRO infection rates and length of hospital stay [32,33], which is consistent with our findings.

4.2.3 Admission Diagnosis

Because the severity of underlying conditions varies, the risk of MDRO infection among middle-aged and older ICU patients with chronic multimorbidity also differs based on admission diagnoses. Patients admitted for pneumonia represent a high-risk group for MDRO infection. Previous data indicate that pneumonia-related admissions are often accompanied by more profound immunosuppression and disruption of mucosal barriers [34]. Meanwhile, this study also found that the MDRO infection rate in these patients was significantly higher than that in patients admitted for non-infectious diseases. Moreover, treatment intensity varies by diagnosis; patients with respiratory failure or those admitted after surgery typically require more frequent invasive procedures, directly increasing opportunities for MDRO colonization [35].

4.2.4 History of Antibiotic Use

Patients with chronic respiratory diseases or urinary tract infections often experience repeated antibiotic exposure before admission, resulting in sustained selective pressure for resistant organisms [36]. Long-term antibiotic exposure can increase the expression of bacterial resistance genes and promote the spread of resistance through horizontal gene transfer [37]. Moreover, prolonged antibiotic use alters the immune microenvironment, weakening mucosal immunity (e.g., reduced immunoglobulin A [IgA] secretion) [38]. In patients with chronic diseases, this "double-hit" effect significantly increases the risk of invasive MDRO infection. These mechanisms collectively explain why antibiotic exposure is one of the most important determinants of MDRO infection in this population. In this study, we categorized the history of antibiotic use using a three-level scheme; however, for practical bedside practicality, future validation studies may simplify this variable into a binary form ("no antibiotic use" vs. "any antibiotic use") to assess whether such simplification can enhance model usability without materially compromising performance.

4.2.5 Tracheostomy

Our results indicated that the rate of lower respiratory tract MDRO colonization in patients with tracheostomy reached 76%, which is 2.2 times higher than in the non-tracheostomy group. Tracheostomy bypasses upper airway defenses, including filtration, humidification, and mucociliary clearance, disrupting anatomical barriers and exposing the lower airway directly to pathogens. This facilitates pathogen access to the alveoli and biofilm formation, increasing the risk of pneumonia [39]. Furthermore, frequent airway suctioning not only damages the airway mucosa but also increases the risk of aspiration, thereby providing an invasion pathway for multidrug-resistant organisms (MDROs) [40]. Studies have further reported that among tracheostomized patients receiving prolonged mechanical ventilation, older adults experience significantly higher complication and mortality rates than younger patients [41,42], highlighting the need for targeted prevention in this subgroup.

4.2.6 C-Reactive Protein

This study confirmed that C-reactive protein (CRP) levels are associated with the risk of MDRO infections, indicating that CRP may serve as an early warning biomarker for identifying patients at high risk, particularly in ICU or long-stay populations [43]. CRP is an acute-phase protein produced by the liver during inflammatory responses; it activates immune pathways to protect the body from injury or infection. It has been validated as a rapid and reliable biomarker for assessing the severity of infection in vulnerable groups, such as older adults [44,45]. Poggiali E et al. [46] found that serum CRP levels correlate with respiratory function and may help predict respiratory failure, facilitating early etiological testing. However, CRP should be considered an auxiliary indicator of MDRO risk, necessitating further studies for comprehensive evaluation and validation.

4.2.7 White Blood Cell Count

Multivariable regression analyses in this study demonstrated that white blood cell (WBC) count is a determinant of MDRO infection among middle-aged and older ICU patients with chronic multimorbidity, aligning with previous reports [47]. WBCs form a crucial defense against pathogen invasion, and typically, WBC counts increase during infection to combat pathogens [48]. However, in this high-risk population, abnormal WBC counts are more likely to indicate dysregulated, ineffective, or exhausted immunity rather than a robust protective response. Persistent, marked leukocytosis in older multimorbid ICU patients often signals severe and uncontrolled infections, potentially indicating the failure of initial antibiotic therapy and ongoing pathogen stimulation of the immune system, creating a biological environment conducive to MDRO colonization and infection.

The specific characteristics of our study population—middle-aged and older ICU patients with chronic multimorbidity—amplify the predictive value of WBC count. First, older adults experience immunosenescence, characterized by reduced lymphocyte function and impaired neutrophil chemotaxis and phagocytosis [49]. Consequently, their WBC response patterns differ from those of healthy younger individuals, making them more susceptible to blunted or disordered reactions. Second, chronic conditions such as heart failure, Chronic Obstructive Pulmonary Disease (COPD), and hepatic or renal insufficiency can lead to long-standing low-grade inflammation and depletion of immune reserves [50], limiting the capacity for a robust immune response during acute MDRO infections. Additionally, many ICU interventions (e.g., sedatives/analgesics, renal replacement therapy) can affect both the quantity and function of WBCs [51]. Thus, the WBC count observed in our cohort reflects the combined effects of multiple interacting factors, and its abnormalities may more accurately identify individuals with the most fragile immune defenses.

4.3 Effectiveness of the Prediction Model

We conducted a retrospective case-analysis to identify factors associated with MDRO infection in middle-aged and older ICU patients with chronic multimorbidity. This was achieved through univariate analysis, LASSO regression, and multivariable logistic regression. We also compared multiple machine-learning prediction models to identify the optimal model and evaluate various risk factors, enabling effective prediction and identification of high-risk ICU patients with chronic multimorbidity who are susceptible to MDRO infection.

Based on the identified risk factors, we developed a nomogram prediction model and systematically evaluated its performance. The AUCs and sensitivities of the candidate models were highly comparable: Logistic regression, LDA, and SVM all achieved AUCs of approximately 0.91, with similar sensitivities (0.75–0.78), indicating only marginal differences in discrimination. In terms of specificity, both Logistic regression and SVM performed well (both 0.88). Although Naive Bayes showed slightly higher specificity (0.89), it demonstrated a clearly lower sensitivity (0.72) and a lower AUC, suggesting a higher risk of missing high-risk patients. Considering the trade-off among AUC, sensitivity, specificity, and model parsimony and interpretability (as indicated by the lowest Akaike Information Criterion/ Bayesian Information Criterion [AIC/BIC]), we ultimately recommend the simpler and more clinically deployable logistic regression model for MDRO risk screening in the ICU. SHAP analysis indicated that antibiotic exposure had the most significant influence on MDRO infection in this population, consistent with the findings of Yassin A et al. [52]. We further constructed a nomogram for visualized risk assessment, assigning a specific score to

each independent risk factor that can be directly referenced from the score scale. By summing these scores and consulting the total-score scale, clinicians can readily obtain the predicted probability of MDRO infection for middle-aged and older ICU patients with chronic multimorbidity from the risk-probability scale [53,54].

4.4 Limitations

This study has several limitations. First, the sample was drawn solely from three Grade A tertiary hospitals and one secondary hospital in the Bengbu region, with a relatively limited number of cases, which may introduce selection bias. For example, patients with more severe conditions or those who had access to concentrated medical resources may have been preferentially included, potentially affecting the representativeness of the sample. Due to the limited sample size, we were unable to explore a broader set of potential predictors, and some relevant variables may have been omitted, which could influence model accuracy. In the future, it will need to conduct external validation in diverse healthcare settings—such as primary hospitals and medical institutions in other provinces—to confirm the generalizability of this model beyond the tertiary hospital population in Bengbu.

Second, the data analysis focused primarily on static indicators at ICU admission and did not incorporate time-varying clinical information (e.g., longitudinal evolution of laboratory results), which may have resulted in a loss of predictive signal. Additionally, continuous laboratory variables were transformed into three ordinal categories ("below normal", "normal", and "above normal"). While this method retains more information than a binary approach, it still reduces the granularity of the original continuous data and may underestimate the true strength of association with outcomes.

Third, we acknowledge that the use of locally common classification standards (e.g., the tripartite catheter classification), although clinically relevant in our setting, lacks international validation and may introduce measurement bias, limiting the model's generalizability to other healthcare systems. Furthermore, although feature selection was based on clinical experience and involved univariate analysis followed by multivariable adjustment, residual confounding may still exist. This highlights the necessity for external validation in diverse healthcare settings (e.g., primary hospitals and institutions in other provinces) to confirm the model's applicability beyond the tertiary hospital population in Bengbu.

In addition, this model was developed as a retrospective risk-identification tool where predictors and outcomes overlap temporally. Its purpose is to identify patients at high risk of having an existing or imminent MDRO infection during the same hospitalization. This approach differs in logic and application from prospective models, which utilize baseline data to predict future incident infections.

Future studies should expand the sample source by employing larger, multicenter, and prospective designs. This expansion should include hospitals from broader regions and different levels of care to enhance the model's generalizability and predictive performance. Additionally, the model structure should be continuously refined and validated in real-world applications.

5. Conclusion

Among middle-aged and older ICU patients with chronic multimorbidity, several factors influence the occurrence of MDRO infection during hospitalization. These factors include age, length of hospital stay, admission diagnosis, history of antibiotic use, tracheostomy, C-reactive protein levels, and white blood cell count. SHAP analysis further identified the history of antibiotic use as the most significant determinant of MDRO infection in this population. Based on these predictors, we developed a logistic regression model whose performance was comparable to five other candidate models and demonstrated good predictive ability. Therefore, we recommend the traditional and parsimonious logistic regression approach for predicting and managing the risk of MDRO infection during ICU stays in middle-aged and older patients with chronic multimorbidity. This model provides preliminary insights for identifying high-risk individuals. Future multicenter prospective studies are necessary for external validation to assess the model's generalizability and real-world clinical utility.

Key Points

• This study aimed to develop and validate a prediction model that incorporates SHAP-based explainability to accurately identify the risk of MDRO infection in middle-aged and older ICU patients with chronic multimorbidity, with the goal of quantitatively clarifying the contribution of each risk factor and enhancing the decision transparency often lacking in conventional models.

• Through univariate analysis, LASSO regression, and multivariable logistic regression, seven key predictors were identified: age, length of hospital stay, admission diagnosis, history of antibiotic use, tracheostomy, C-reactive protein, and white blood cell count. These predictors were used to construct the logistic regression prediction model.

• After undergoing internal validation, the model exhibited excellent discriminative performance, achieving an AUC of 0.906 (95% CI: 0.896–0.912), with a sensitivity of 77.92% and a specificity of 88.46%.

• In summary, this model demonstrates strong predictive performance for assessing MDRO infection risk in middle-aged and older ICU patients with chronic multimorbidity, providing a valuable tool for the early identification of high-risk patients and supporting informed clinical decision-making.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to privacy concerns, but are available from the corresponding author upon reasonable request.

Author Contributions

RZ and QKL designed the study framework, established the methodology, and developed the experimental protocol to ensure feasibility and rigor. MZ, YXW, and YX were responsible for data collection and organization, and performed the formal statistical analyses and visualization to generate interpretable results. All authors participated in drafting the manuscript and revised it critically to ensure logical coherence and academic completeness. JG and XYZ provided supervision throughout the study, including ethical oversight and resource management, and participated in the analysis and interpretation of data. JXY and JPZ validated the methodology to ensure robustness. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Bengbu First People's Hospital (Approval No.: BBYYLWPJ2025021). This observational study involved no interventions. As anonymized retrospective data were used, the requirement for informed consent was waived by the Ethics Committee of Bengbu First People's Hospital.

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Conflicts of Interest

The authors declare no conflicts of interest.

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