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Risk factors and prediction model for carbapenem-resistant organism infection in sepsis patients

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Abstract

Background It aimed to identify the key risk factors associated with carbapenem-resistant organism (CRO) infections in septic patients, and subsequently develop a nomogram and assess its predictive accuracy.

Methods The study population comprised adult critically ill patients with sepsis, drawn from the MIMIC-IV 2.0 data set. The data were split into a training set and a validation set at a 7:3 ratio. Independent predictors were identified using both univariate and multivariate logistic regression models, followed by the construction of a nomogram. The predictive performance of the model was evaluated using the C-index, receiver operating characteristic (ROC) curve, area under the curve (AUC), calibration curve, and decision curve.

Results We enrolled 8814 patients, with 529 (6%) CRO-infected and 8285 (94%) non-CRO-infected. Using risk factors such as age, gender, laboratory values (WBC_max, Creatinine_max, BUN_max, Hemoglobin_min, Sodium_max), and medical conditions (COPD, hypoimmunity, diabetes), along with medications (meropenem, ceftriaxone), we developed a predictive model for CRO infection in septic patients. The model demonstrated good performance, with AUC values of 0.747 for the training set and 0.725 for the validation set. The calibration curve indicates that predicted outcomes align well with observed outcomes. The clinical decision curve results indicate that the nomogram prediction model has a high net benefit, which is clinically beneficial.

Conclusions The nomogram we have developed for predicting the risk of CRO infection in sepsis patients is reasonably accurate and reliable.

Clinical trial number: Not applicable.

Keywords Sepsis, CRO, Nomogram, MIMIC-IV

Background

Bacterial resistance is a major global public health issue, and carbapenem-resistant microorganisms (CRO) are of particular concern. CRO refers to microorganisms that are resistant to any carbapenem antibiotics, such as imipenem [1], with complex resistance mechanisms often carrying multiple resistant genes or even being pan-resistant, severely hindering clinical anti-infection treatment [2–6]. CRO primarily includes drug-resistant Gram-negative bacteria, such as *Klebsiella pneumoniae* (CRKP) and *Escherichia coli* (CRE) [7, 8]. The WHO has

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listed it as a major resistant pathogen due to its association with high morbidity and mortality rates in hospital settings [9]. In the United States, the annual number of deaths due to CRAB and CRKP exceeds 50,000 [10, 11]. China's CHINET monitoring shows a significant increase in the infection rates of CRKP and CRAB from 2005 to 2023 [12]. Globally, the infection rate of CRO is rising with a high mortality rate, posing a real challenge to its prevention and control. Although both China and the United States face problems created by CRKP and CRAB infections, there are differences in both resistance spectrum and transmission due to their different usage practices of antibiotics [13–15]. Previous research indicates that early identification of factors predisposed to carbapenem susceptibility helps prevent infections and their sequelae [16]. Therefore, active prevention and control of CRO infections is imperative.

Sepsis is characterized as a life-threatening condition marked by organ dysfunction due to an unregulated host response to infection [17]. In sepsis patients, especially in intensive care units (ICUs), CROs have become the primary pathogens. Sepsis is the leading cause of morbidity and mortality during and after ICU hospitalization [18, 19]. Worldwide, sepsis accounts for approximately 30 million cases and 6 million deaths annually, with survivors frequently experiencing physical, cognitive, and psychological impairments. Therefore, early identification and proper management of infectious factors can not only improve the prognosis of sepsis patients [20], but also provide valuable scientific basis and practical guidance for reducing the mortality rate of infected patients.

As a visualization-based predictive model, a nomogram transforms complex regression equations into visual graphs, making the results of the predictive model more readable. Traditional assessment methods are often limited to one or a few factors, which may yield relatively abstract risk assessments, requiring doctors to spend considerable time and effort on interpretation. In addition, these methods may lack precision and fail to provide sufficient targeting in treatment plan formulation. A nomogram can integrate multidimensional information, such as patient age, underlying diseases, history of antibiotic use, and invasive procedures. It presents the risk probability of patients with infections caused by carbapenem-resistant microorganisms in a clear graphical manner, based on the magnitude of each influencing factor. A nomogram can also be used to assist in formulating treatment plans, enhancing the accuracy and effectiveness of decision-making [21]. Several nomograms for predicting the risk factors of CRO infection in ICU patients have been developed [22], and prediction models for sepsis infections have been constructed and validated [23]. However, there is currently no nomogram prediction model available to assess the risk factors and infection susceptibility of CROs in sepsis patients. Previous models designed for ICU patients [22] are not suitable for sepsis patients, as ICU patients often present with complex etiologies, while sepsis triggers a distinct systemic inflammatory response and organ dysfunction due to infection. Consequently, ICU models are inadequate in capturing critical developments of the condition, such as the impact of early stage changes in inflammatory markers on the CRO infection risk. Previous nomogram predictive models for sepsis-related risk factors also show limitations [23]; most models are constructed based on data from a single center or limited geographic areas, without considering regional and medical environmental differences, resulting in poor generalizability. Our goal was to develop and validate a predictive nomogram for CRO infections in sepsis patients, with the aim of identifying individuals at high risk for CRO infection in sepsis.

Methods

Data collection

(1) Data sources

This study is a retrospective cohort analysis. The data employed in this research were obtained from the MIMIC-IV online intensive care medical database, a collaborative effort between Beth Israel Deaconess Medical Center (BIDMC) and the Massachusetts Institute of Technology (MIT). This comprehensive database encompasses information from 2008 to 2019 for 73,181 ICU patients at Beth Israel Deaconess Medical Center in Boston, Massachusetts, including de-identified medical records from the BIDMC intensive care unit (ICU). The data set consolidates a variety of accurate digital data sources, including patient vital signs, laboratory test results, medication usage, nursing documentation, surgical procedure codes, disease diagnosis codes, and more [24].

As patient privacy information has been encrypted in the MIMIC-IV database, this study does not require obtaining individual patient consent. However, to ensure that the study complies with ethical standards, the research team has already completed the necessary ethical approval process. Specifically, all researchers have successfully completed the online ethics examination of the CITI Program (Collaborative Institutional Training Initiative) and received certification numbers (record number: 12313185). This certification serves as the ethical approval basis for accessing and using the MIMIC-IV database.

(2) The study population comprised adult ICU patients diagnosed with sepsis. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), which required patients to exhibit confirmed or suspected infection and have a total SOFA score of 2.
(3) Inclusion and exclusion criteria

Inclusion criteria: Data from the initial ICU admission were utilized for patients with multiple ICU admissions. The following patients were excluded: (a) patients younger than 18 years (the physiological development of individuals under 18 is immature and significantly different from that of adults, and including them may complicate data interpretation and generalization.). (b) Patients who were not admitted to the ICU. (c) Patients who were repeatedly admitted to the ICU. (d) Patients with missing variable data.

Data extraction

(1) Study variables

This study referenced previous research findings and theoretical results, rigorously selecting variables to ensure the scientific validity and practical applicability of the model [25]. Structured Query Language (SQL) was employed to extract demographic information, laboratory indicators, comorbidities, and scores from the MIMIC-IV database. Comorbidities and personal medical history of the patients were determined based on ICD-9 and ICD-10 classifications. The indicators we gathered encompassed fundamental patient information (age, gender, insurance, and race), essential vital signs (respiratory rate and heart rate), laboratory parameters (prothrombin time, partial prothrombin time, white blood cell count, red blood cell distribution width, creatinine, urea nitrogen, blood calcium, hemoglobin, blood sugar, platelet count, and blood sodium levels), comorbidities (Malignant_Cancer, Liver_disease, Chronic_renal_disease, COPD, Hypoimmunity, Cerebrovascular_disease, Diabetes, and Cardiovascular_disease), pre-cultured antibiotic usage (Ampicillin.Sulbactam, Tobramycin Sulfate, Daptomycin, Meropenem, Piperacillin.Tazobactam, Cefepime, Ceftriaxone, Cefotazidime, Cefazolin, Vancomycin, Levofloxacin, and Ciprofloxacin), and pre-cultured invasive procedures (Arterialvalue, Ventilation and Dialysis_catheter), Bronchoscopy, SAPS II, etc.

In cases of repeated hospitalizations, we specifically utilized data from the patients' initial admission. For indicators with multiple measurements, we only included the worst value from the first day in the ICU [22]. When addressing recurring variables, we considered the timing of laboratory tests, procedures, treatments, and microbial culture results. To reduce reverse causality bias, data collected after the outcome event were deemed invalid. To reduce bias caused by sample exclusion, we calculated the percentage of missing values for each continuous variable. For variables with a missing value proportion less than 10%, we used the multiple imputation method based on the R language "mice" package to predict missing values, predicting five outcomes and calculating their average as the final result. For variables with a missing value proportion greater than 10%, we excluded severely missing variables.

The primary outcome of this study was the isolation of a CRO. CROs were defined as bacteria obtained from bodily fluid cultures that demonstrated resistance to carbapenem antibiotics. (Bacteria that are naturally resistant to imipenem, such as Morganella, Proteus and Providencia, are also resistant to carbapenems other than imipenem).

Model construction

The data set was split into a training set and a validation set at a 7:3 ratio. Within the training set, potential predictors were identified using both univariate and multivariate logistic regression analyses. To address the risk of false positives that may arise from multiple comparisons, we employed a method to control the false discovery rate (FDR) to adjust the p values. Statistically significant predictors were then utilized to develop a model for predicting the risk of CRO infection in sepsis patients. Subsequently, the prediction accuracy and discriminatory power of the model were evaluated. In addition, we further conducted a sensitivity analysis using a median imputed data set to further verify the stability of the model's performance. Ultimately, we created a dynamic and visually informative nomogram to predict the risk in septic patients.

Statistical analysis methods

All statistical analyses were performed using R version 4.3.1. Continuous variables with normal distributions were presented as mean ± standard deviation (SD), whereas nonparametric continuous variables were expressed as median and interquartile range. Categorical variables were reported as frequencies and percentages, along with 95% confidence intervals (95% CIs). The threshold for statistical significance was set at $P < 0.05$.

Results

Clinical characteristics of patients

The study included a total of 8814 patients, with 529 (6%) identified as CRO-infected and 8285 (94%) classified

as non-CRO-infected. The mean age of the entire study population was 66.72 years, with 51.8% females and 48.2% males. The mean leukocyte count was 17.87 K/μL, and the mean Sapsii score was 40.18. It is important to note that no statistically significant differences were observed between the training and validation sets (Table S1).

Univariate and multivariate logistic regression analyses of independent predictors of CRO infection

A univariate logistic analysis was performed on all factors to identify independent risk factors associated with CRO infections in sepsis patients. Subsequently, variables that showed significant associations ($P<0.05$) in the univariate analysis were included in a multivariate logistic analysis to determine the independent risk factors for CRO infections in sepsis patients. After p value adjustment, the results we reported still demonstrated high statistical validity. The results (Table S2) revealed the following risk factors for predicting CRO infections in septic patients: age (OR: 0.975, 95% CI 0.967–0.983), gender (female as ref, male OR: 1.622, 95% CI 1.293–2.034), WBC_max (OR: 1.008, 95% CI 1.002–1.014), Creatinine_max (OR: 0.937, 95% CI 0.879–0.999), BUN_max (OR: 1.006, 95% CI 1.001–1.01), Hemoglobin_min (OR: 0.857, 95% CI 0.806–0.912), Sodium_max (OR: 1.021, 95% CI 1.001–1.042), COPD (OR: 1.991, 95% CI 1.492–2.656), hypoimmunity (OR: 1.793, 95% CI 1.107–2.905), diabetes (OR: 1.340, 95% CI 1.053–1.704), Meropenem (unused as ref,used OR: 3.090, 95% CI 1.847–5.169), and CeftriaXONE (unused as ref,used OR: 0.580, 95% CI 0.356–0.945).

Nomogram development and validation

Utilizing the identified risk factors for CRO infection in septic patients, including Age, Gender, WBC_max, Creatinine_max, BUN_max, Hemoglobin_min, Sodium_max, COPD, Hypoimmunity, Diabetes, Meropenem, and CeftriaXONE, we developed a predictive nomogram for assessing the risk in septic patients. As shown in Fig. 1, after locating the corresponding values on each variable axis, the total score was calculated for each variable according to the instructions of the nomogram. Based on the calculated total score, the corresponding position was located on the total score axis to read the risk of carbapenem-resistant microbial infection in sepsis patients. Dynamic visualization tools offer adjustable parameters, such as time sliders, filters, and more. By manipulating these options, the trends of data changes can be observed.

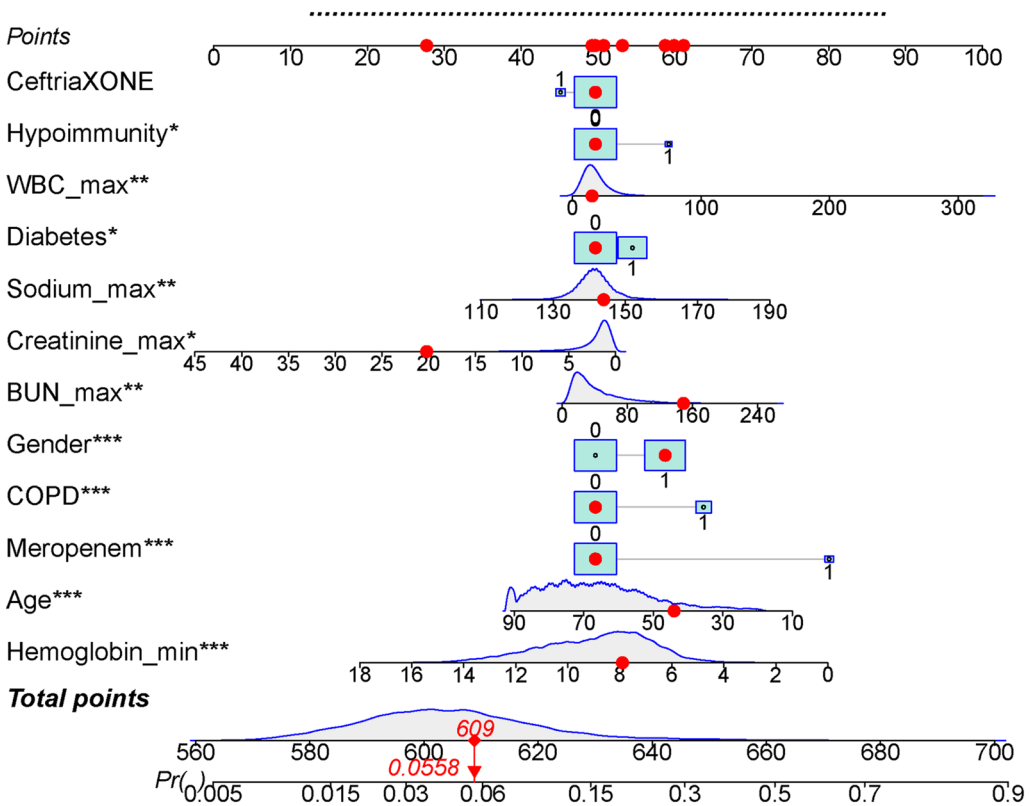

Fig. 1 Nomogram predicting CRO infection risk in sepsis patients

In the training set, the area under the ROC curve (AUC) of the nomogram predicting the risk of carbapenem-resistant microbial infections in sepsis patients was 0.747 (95% CI 0.722–0.773) (Fig. 2A), with a specificity of 0.701, sensitivity of 0.686, accuracy of 0.700, and NPV of 0.971; in the validation set, the AUC was 0.725 (95% CI 0.682–0.767) (Fig. 2B), with a specificity of 0.604, sensitivity of 0.735, accuracy of 0.611, and NPV of 0.975. In addition, in the sensitivity analysis, we used a data set with median imputation, and the resulting AUC/ROC curve (see Appendix Fig. 5) had an AUC value of 0.739, demonstrating that the model still had good discriminative ability in the data set after median imputation. These values indicated that the nomogram possessed a robust predictive capacity. The calibration curve (Fig. 3) displayed a nearly linear trend with a slope close to 1, indicating that the predicted outcomes of the nomogram model closely matched the actual observed outcomes. The clinical decision curve (Fig. 4) further demonstrated that the nomogram provided a relatively high net benefit, highlighting its strong clinical utility.

Finally, we have developed a dynamic nomogram to aid in the thorough validation of the CRO infection risk in sepsis patients [https://zz123.shinyapps.io/Tqmxnyyclxt/].

Discussion

In this study, both univariate and multivariate regression analyses showed that the CRO infection risk in sepsis patients is associated with age, gender, maximum white blood cell count, maximum creatinine, maximum blood urea nitrogen, minimum hemoglobin, maximum sodium, chronic obstructive pulmonary disease, immunodeficiency, diabetes, meropenem use, and

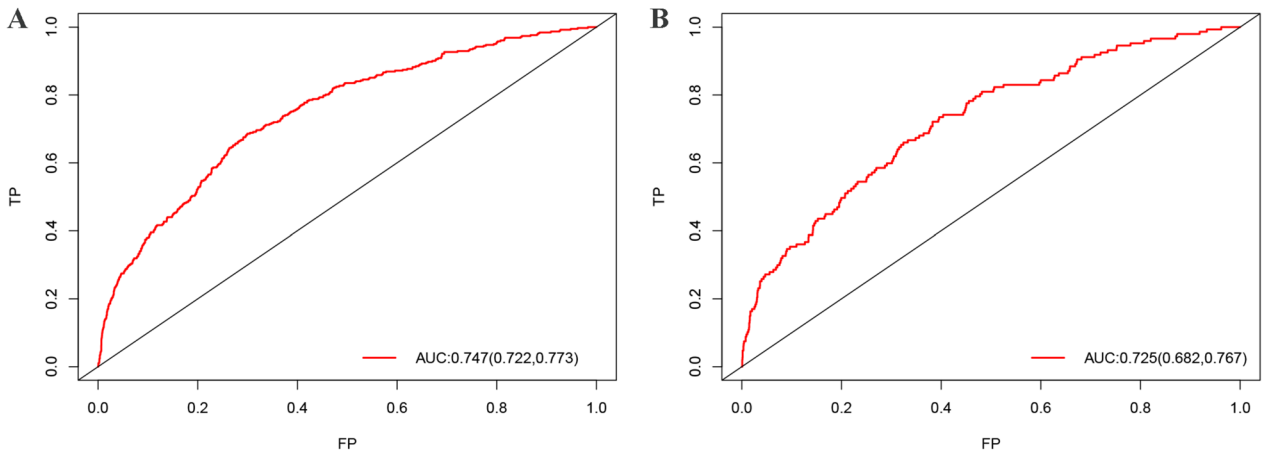

Fig. 2 Receiver operating characteristic curve (ROC curve) for nomograms predicting the risk of sepsis patients acquiring CRO in the training set (**A**) and validation set (**B**), AUC being the area under the curve

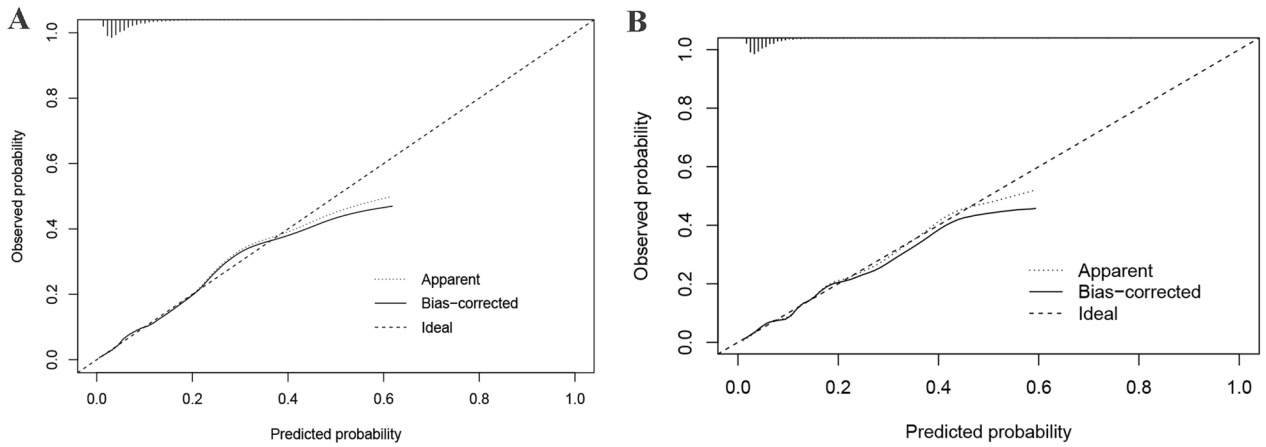

Fig. 3 Calibration curves for predicting the risk of sepsis patients acquiring CRO in the training set (**A**) and validation set (**B**)

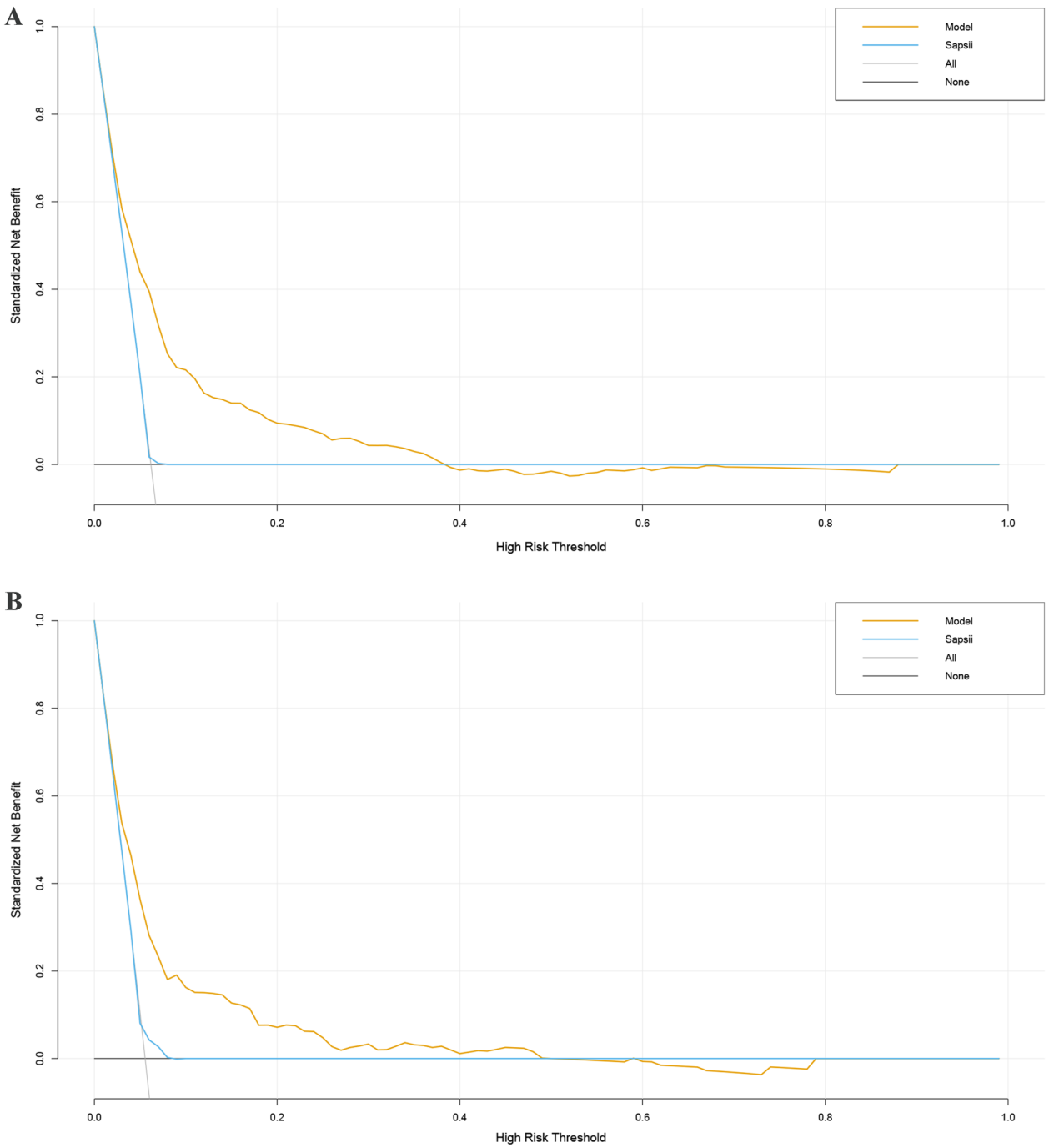

Fig. 4 Clinical decision curves for predicting the risk of sepsis patients acquiring CRO in the training set (**A**) and validation set (**B**)

ceftriaxone use. In addition, we developed a nomogram to visually represent the model based on these 12 factors. The nomogram was internally validated and demonstrated strong predictive accuracy and clinical utility. This is the first risk prediction model for CRO infection risk factors in sepsis patients, providing a simple and accurate tool for risk assessment. This tool assists clinicians in the early identification of CRO infection risk

in sepsis patients, enabling the development of effective prevention and control strategies to reduce the incidence of CRO infections in this patient population.

In this study, the model constructed using univariate and multivariate regression analysis achieved a relatively moderate AUC value (e.g., 0.725 in the validation set). The closer the AUC value is to 1, the stronger the model's ability to distinguish between positive and negative cases. The AUC values for both the training and validation sets were above 0.7, indicating that the model demonstrated moderate to high predictive ability on both data sets. In contrast, the study by Kang et al. [26] achieved only an AUC value of 0.68 in their univariate and multivariate regression models. This may be due to a small sample size and the selection of variables not sufficiently reflecting the characteristics of the subjects, leading to poor generalizability of the model. Liu et al. [27] combined machine learning algorithms with univariate and multivariate regression analysis, obtaining an AUC value of 0.767 for the model. Machine learning algorithms demonstrate advantages in handling complex data relationships, as they can uncover potential information easily overlooked by traditional regression analysis, and also enhance the prediction and control capabilities for CROs [28]. In the future, we could draw on the practices of other studies, such as optimizing variable selection and data processing, as well as making attempts to incorporate machine learning algorithms, to further improve model performance.

Patient age and gender are closely related to CRO infection. The two hospitals, located in Beijing and Yinchuan, respectively, found isolated CROs primarily in middle-aged and elderly patients with severe symptoms, which is consistent with related studies in the United States [29–31]. Hu et al. [32] also confirmed that aging increases the incidence of CROs. In addition, this study found that male gender is a risk factor for CRO infection in sepsis patients, which aligns with the findings of Zhang et al. [22]. The elderly population faces declining physiological functions and decreased immunity, leading to higher infection risks; men and women demonstrate differences in physiological structures, hormone levels, and lifestyles. Therefore, it is important to focus on the prevention and control of CRO infections in elderly patients with sepsis. For the high-risk elderly population, basic nursing can be strengthened to reduce infection risks [33]. During clinical treatment, attention should be paid to the responses of patients of different genders, with particular emphasis on the special physiological periods of women to avoid an increase in infection risk [34].

From the perspective of underlying diseases, COPD patients could be seriously affected by carbapenem resistance [35]. This group of individuals exhibits a high level of bacterial colonization due to recurrent respiratory infections and chronic inflammation. Their long-term use of antibiotics can lead to an imbalance in the airway microbiome, increasing the risk of colonization and infection by drug-resistant strains, while suppressed immune function further heightens the risk of infection [36]. Immunocompromised patients are more susceptible to infections caused by carbapenem-resistant bacteria, facing a higher risk of infection and greater challenges in treatment [37, 38]. Diabetes is a chronic metabolic disease, and patients with poor blood glucose control show a defect in pathogen recognition [39]. Hyperglycemia in diabetic patients can impair the pathogen-clearing activity of white blood cells, including macrophages [40, 41]. Studies have shown that hyperglycemic patients exhibit higher resistance rates to carbapenem drugs in Enterobacteriaceae [42, 43].

In terms of clinical test indicators, high white blood cell counts in sepsis patients are associated with CRO infections, as they reflect the massive proliferation of pathogenic bacteria and a strong inflammatory response, which may trigger or exacerbate infections [44]. Elevated urea nitrogen and creatinine are high-risk factors for CRO infections, which increase the susceptibility of sepsis patients to acute kidney injury and renal failure. Research by Shitong Qiang and others has also confirmed that kidney function indicators in CRKP-infected patients are higher than those in CSKP-infected patients [45]. Hemoglobin is crucial for immune regulation and other aspects [46, 47]; patients with low hemoglobin demonstrate poor immune system function and are prone to infections with CRE. Hypernatremia causes hypertension [48], and studies by Vasiliki Gogou et al. indicate that hypertensive patients carrying the OXA-23 gene in Acinetobacter have increasing resistance to carbapenem drugs year by year [49].

Antibiotic usage represents a key risk factor. Previous use of carbapenem drugs and cephalosporins has been associated with an increased risk of CRKP infection. Some studies have shown that carbapenem resistance in Gram-negative bacteria is positively correlated with the usage of these antibiotics [50]. Research by Michael J. Satlin et al. also confirmed that the use of cephalosporins increases the risk of CRE bloodstream infections, consistent with the findings of this study [51]. This may be due to broad-spectrum antibiotics altering the gut microbiota, promoting the growth of antibiotic-resistant

microorganisms, producing enzymes, and affecting outer membrane porin proteins, which ultimately lead to CRE infection [52]. Therefore, the formulation of treatment plans with carbapenem drugs and cephalosporins should be cautious, with attention paid to the diversification of antibiotic treatments for resistant infections.

In treating sepsis patients, clinicians can make more precise decisions using a nomogram and intervention thresholds. A nomogram calculates the specific probability of the patient developing a CRO infection based on risk factors. For example, after severe patients are admitted to the ICU, doctors collect information regarding their age, underlying diseases (such as diabetes, chronic obstructive pulmonary disease), laboratory test results (white blood cell count), and used medications. The information then corresponded to a nomogram for calculating scores, which are used to determine the probability of patient infection with carbapenem-resistant microorganisms. If a patient's infection probability is 60%, exceeding the predetermined intervention threshold of 40%, the doctor will take proactive measures, such as adjusting the antibiotic regimen, selecting more targeted and higher-level drugs, and enhancing isolation precautions to prevent the spread of resistant bacteria. If the probability is below the threshold, doctors can closely monitor the patient's condition, maintain conservative treatment, and continuously monitor indicators to avoid unnecessary medications and side effects. Through nomograms, doctors could obtain a quantitative basis for decision-making, enabling them to make scientific decisions within a limited time frame, thus improving patient prognosis.

Dynamic nomograms exhibit significant innovative advantages compared to static models. They provide real-time access to the latest patient data, aiding clinical decision-making, whereas static models struggle to update data promptly. They also allow for convenient online parameter updates, overcoming the complexities and time consumption of adjusting parameters in static models. In addition, they can be tailored to different institutions and patient populations, offering doctors a clear, interactive experience. Multiple risk factors for CRO infection in septic patients have been identified, yet a risk prediction model for CRO infection in these patients is currently lacking. In this study, we developed a nomogram based on the identified risk factors, allowing clinicians to dynamically evaluate the risk in sepsis patients.

This study is subject to several limitations. First of all, this study may have overlooked some potential risk factors, because we used the MIMIC-IV database, which has obvious limitations. It also lacks external validation. This data set only comes from specific medical institutions or research groups, and the predictive model constructed based on it has not been widely validated in external populations. The characteristics of patients, disease conditions, and medical interventions vary greatly across different regions, making it difficult for the model to accurately reflect the reality of patients in external regions, resulting in insufficient generalization ability. Therefore, it is unable to effectively predict the risk of CRO in a broader scope. Secondly, this data set exhibits regional bias. The data sources are concentrated in specific regions and are not truly representative of different regions globally. Finally, retrospective studies carry an inherent risk of confounding bias, even after statistical adjustments. As a result, the model may perform poorly in different patient populations, medical environments, or data collection methods, making it unable to accurately predict CRO infection situations. This may limit the model's promotion in actual clinical applications.

Therefore, in our future research, we will adopt a prospective multicenter study approach, utilizing multicenter clinical data for some prospective clinical studies. To enhance the quality and efficiency of healthcare services, we will comprehensively integrate external validation mechanisms into hospital workflows. This mechanism can accurately verify critical patient data, reduce misdiagnosis and treatment delays while also enhancing information security management to prevent information risks.

Conclusion

In this study, we have developed a personalized risk prediction model for CRO infections in sepsis patients, which exhibits outstanding accuracy and predictive performance. It is an intuitive and quantifiable decision-making tool that helps doctors integrate multiple factors and quickly assess the risk of patient infection with CRO, enabling appropriate treatment decisions and improving consistency in clinical judgment and accuracy in medical decision-making. Furthermore, with the risk of infection visually presented by the nomogram, doctors can better explain the condition to patients, improving patient compliance with treatment. In addition, it offers a valuable reference for tailoring CRO infection prevention and control strategies to sepsis patients.

Appendix

See Fig. 5.

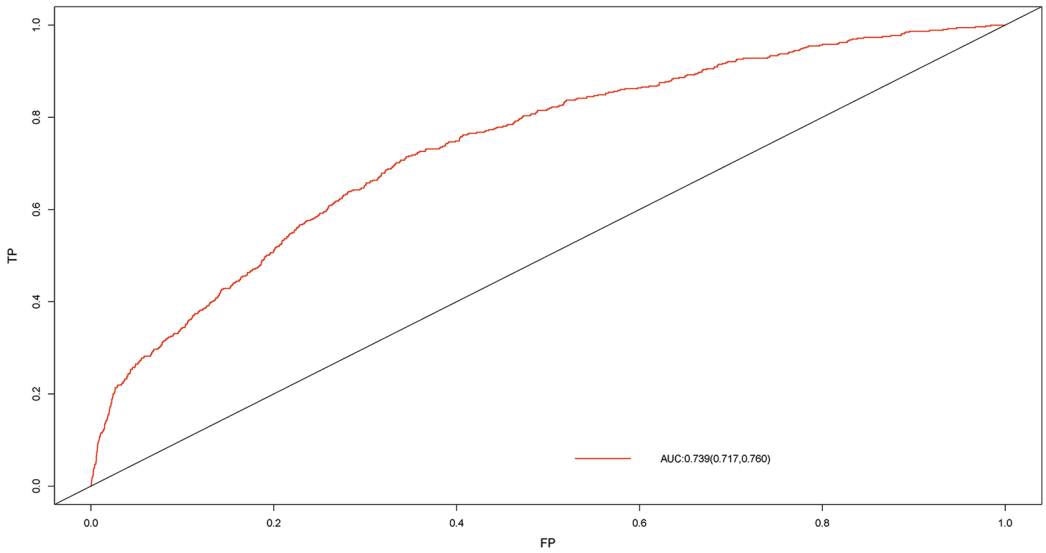

Fig. 5 Sensitivity analysis performance of dataset models after medianinterpolation

Abbreviations

ROC	Receiver operating characteristic
AUC	Area under the curve
CRO	Carbapenem-resistant organism
CRPA	Carbapenem-resistant *Pseudomonas aeruginosa*
CRKP	Carbapenem-resistant *Klebsiella pneumoniae*
CRE	Carbapenem-resistant *Escherichia coli*
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
WHO	World Health Organization
MDR	Multidrug-resistant
CHINET	China Antimicrobial Surveillance Network
ICU	Intensive care unit
SD	Standard deviation
95% Cis	95% Confidence intervals
DCA	Decision curve analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02448-z.

Supplementary Material 1: Table S1. Basic characteristics of sepsis patients infected with CRO. Table S2. Univariate and multivariate logistic regression analysis of independent predictors of CRO infection in sepsis patients.

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Not applicable.

Author contributions
All authors contributed to the study conception and design. Writing—original draft preparation: Ronghua Liu; Writing—review and editing: Xiang Li; Conceptualization: Jie Yang; Methodology: Yue Peng; Formal analysis and investigation: Ronghua Liu; Resources: Xiaolu Liu; Supervision: Ronghua Liu, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
The data for this study were obtained from the MIMIC-IV online intensive care medical database, a collaborative effort between Beth Israel Deaconess Medical Center (BIDMC) and the Massachusetts Institute of Technology (MIT). Given that patient privacy information is encrypted in the database, no patient consent or ethical approval was necessary for this study. The researchers have successfully passed an online examination and have been granted a certification number (record number: 12313185).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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