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Risk Factors for Multidrug Resistance in Patients Infected with Carbapenem-Resistant *Klebsiella pneumoniae*: A Nomogram

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Purpose: Our aim was to determine the risk factors for multidrug resistance in patients with carbapenem-resistant *Klebsiella pneumoniae* (CRKP).

Methods: The information of 196 patients with *Klebsiella pneumoniae* infection was collected. The patients were subsequently assigned to the carbapenem-resistant, multidrug-resistant, and non-multidrug-resistant groups. The risk factors for multidrug resistance in CRKP patients were assessed via least absolute shrinkage and selection operator and logistic regression analyses. Moreover, a nomogram was constructed dependent on the identified risk factors, and calibration and decision curves were plotted to detect its accuracy.

Results: Length of stay (LOS) [odds ratio (OR) and 95% confidence interval (CI): 4.558 (1.157–17.961), P = 0.030], intensive care unit (ICU) stay within 30 days [OR and 95% CI: 12.643 (3.780–42.293), P < 0.001], Glasgow Coma Scale (GCS) score [OR and 95% CI: 13.569 (2.738–67.236), P = 0.001], fungal infection [OR and 95% CI: 6.398 (1.969–20.785), P = 0.002], and cardiovascular disease (CVD) [OR and 95% CI: 3.871 (1.293–11.592), P = 0.016] were identified as risk factors for multidrug resistance in CRKP patients. The concordance index (C-index) of the constructed nomogram was 0.950 (95% CI: 0.945–0.955). Moreover, decision curve analysis elucidated the nomogram utilization across a wide range of probability thresholds, ranging from 1% to 100%. Finally, internal validation using random data validated the robustness of the predictive model, yielding a C-index of 0.937.

Conclusion: The LOS, ICU stay within 30 days, GCS score, fungal infection, and CVD were recognized as risk factors for multidrug resistance in CRKP patients. The constructed nomogram could accurately predict multidrug-resistant CRKP infections in patients.

Plain Language Summary:

(1) The LOS, ICU stay within 30 days, GCS, fungal infection, and CVD were identified as risk factors for multidrug resistance in CRKP patients.
(2) The nomogram constructed in this study had high predictive accuracy.
(3) This study provides a reference for the formulation of personalized prevention and therapy strategies.

Keywords: *Klebsiella pneumoniae*, multidrug resistance, carbapenem, prediction model, risk factors

Introduction

Klebsiella pneumoniae (KP) is a gram-negative pathogenic bacterium commonly present in clinical specimens.[1–3] It is the most important conditional pathogenic bacteria in immunocompromised patients and causes respiratory tract infections.[4–6] Besides causing respiratory tract infections, KP can also cause infections in multiple systems, such as the digestive tract, blood, and urinary system.[7–9] During the early stages of KP infection, patients are typically asymptomatic, leading to an underestimation of disease severity in clinical practice.[10] Moreover, treatment outcomes for KP are frequently sub-optimal, contributing to the high mortality rates of patients.[11]

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Recently, with the extensive use and irrational administration of antibiotics, the detection rate of multidrug resistance among CRKP strains has been steadily rising.[12–15] Elevating resistance to colistin in KP uropathogens due to chromosomal mutations and plasmid-mediated *mcr* genes leads to chronic severe and recurrent UTI in clinical settings.[16] Of 240 carbapenem- and colistin-resistant KP isolates in Thailand, 220 isolates (91.7%) were resistant to tigecycline, and most of the isolates were resistant to fosfomycin (70.4%).[17] In 2016, the European Resistance Surveillance Network reported resistance rates of KP to carbapenem drugs ranging between 30.0–66.9% across three countries.[18] Similarly, the 2018 China Bacterial Resistance Monitoring Network data revealed that the KP resistance rates to third-generation cephalosporins and carbapenem drugs in various provinces and cities ranged between 12.3–55.8% and 0.7%–32.5%, respectively.[19] From 2015 to 2019, the KP resistance rates to imipenem and meropenem detected in the departments of critical care and respiratory medicine in Chongqing fuling center hospital were 17.02%, 14.90%, 30.77% and 30.77%, respectively.[20] Therefore, early identification of risk factors for multidrug resistance holds considerable implications for disease prevention and disease progression, as well as for reducing the burden on patients and society.

As a mathematical model featuring an intuitive visual presentation, a nomogram considers the weights of relevant factors and integrates the independent factors for predicting the risk probability of a special clinical event.[21] The nomogram constructed by Chen et al predicated thrombocytopenia as a sign of poor prognosis in patients with bloodstream infections KP.[22] Yang et al constructed a nomogram using independent prognostic factors of CRKP, short hospitalization, and elevated C-reactive protein (CRP)-to-prealbum in ratio, and the nomogram model had a critical possibility for predicting the prognosis of patients with KP meningitis.[23] However, as far as we know, nomograms for the risk prediction of CRKP are still unclear. Herein, we aimed to evaluate risk factors related to multidrug resistance in CRKP patients. In addition, a nomogram was constructed relying on these risk factors. This study provides a reference for clinical medical staff to assist in the development of personalized prevention and therapy strategies.

Materials and Methods

Study Design

This retrospective case-control study was performed at the Beijing Jingmei Group General Hospital. Patients with KP infection admitted to the respiratory department between January 1, 2017, and December 31, 2021, were included. The inclusion criteria were as follows: (a) Adult patients; (b) patients with complete clinical data; (c) presence of KP in blood samples, qualified sputum cultures, or bronchial lavage; (d) exclusion of repeated inclusion of the same patient (only the information of the first infection with KP was considered); and (e) confirmation of multidrug-resistant infections of KP (resistant to three or more types of antibiotics) based on drug sensitivity tests. Patients with incomplete clinical information were excluded from the study. Informed consent from the participants was waived. Our study was authorized by the ethics committee of Beijing Jingmei Group General Hospital (ZZ2022-01).

Data Collection

The following clinical data of patients were gathered: (a) general information: patient admission number, name, gender, age, length of stay (LOS) at the time of KP detection, and history of 30-day intensive care unit (ICU) hospitalization; (b) basic disease history: conditions such as coal worker's pneumoconiosis, malignancies, chronic lung disease, coronary atherosclerotic heart disease, renal insufficiency, hypertension, diabetes, and cerebrovascular disease; (c) laboratory and medication indicators upon admission: procalcitonin (PCT), CRP, and albumin (ALB) levels, oxygenation index, Glasgow Coma Scale (GCS) score, presence of fungal infection, number of hospitalizations within the past year, and use of the following drugs or involvement in the following procedures during hospitalization: carbapenems, immunosuppressants, parenteral nutrition, acid suppressants, hormones, vancomycin, invasive procedures (excluding invasive mechanical ventilation), and mechanical ventilation. The VITEK 2 COMPACT automatic microbial identification system was utilized to identify bacteria and test for drug sensitivity in vitro, with the findings interpreted based on the standards of the American Clinical Laboratory Standardization Committee (2015).[24]

Statistical Analysis

The R software was utilized to carry out statistical analyses. Least absolute shrinkage and selection operator (LASSO) regression analysis was deployed to screen risk factors for multidrug resistance in CRKP patients, while multivariate logistic regression analysis was performed to determine their P-values and odds ratios (OR). A nomogram was provided to predict the likelihood of multidrug resistance in hospitalized CRKP patients. Its concordance index (C-index) was calculated using the RMS program package, and calibration and decision curves were plotted to evaluate its accuracy. Finally, the Cater program package was employed for random internal verification.

Results

In this study, 196 patients with KP infection were included; 4 patients were < 50 years old, 7 patients were > 90 years old, 185 patients were between 51 and 90 years old, 31 were females, and 165 were males. They were divided into two groups, namely the carbapenem-resistant-multidrug-resistant (n = 48), and non-multidrug-resistant (n = 148) groups. Table 1 presents their baseline information, disease history, and laboratory and medication indicators. Eighteen variables, including severe pneumonia, LOS, and ICU stay within 30 days, were statistically different between the two groups.

Table 1 Clinical Data of 196 Patients with Klebsiella Pneumoniae Infection

Characteristics, n (%)		Carbapenem Resistant Multidrug-Resistant Group (n=48)	Non Multidrug-Resistant Group (n=148)	*P* Value
Severe pneumonia	No	14 (29.2)	136 (91.9)	<0.001
	Yes	34 (70.8)	12 (8.1)	
Gender	male	43 (89.6)	122 (82.4)	0.238
	female	5 (10.4)	26 (17.6)	
Age (years)	<50	0 (0.0)	4 (2.7)	0.135
	51–60	5 (10.4)	16 (10.8)	
	61–70	8 (16.7)	48 (32.4)	
	71–80	15 (31.3)	36 (26.3)	
	81–90	17 (35.4)	40 (27.0)	
	>90	3 (6.3)	4 (2.7)	
Length of stay (LOS, Day)	1–7	27 (56.3)	139 (93.9)	<0.001
	>7	21 (43.7)	9 (6.1)	
30-day ICU hospitalization history	No	6 (12.5)	127 (85.8)	<0.001
	Yes	42 (87.5)	21 (14.2)	
Procalcitonin (PCT, ng/mL)	<0.5	27 (56.3)	127 (85.8)	<0.001
	≥0.5	21 (43.8)	21 (14.2)	
Albumin (ALB, g/L)	<20	2 (4.2)	1 (0.7)	<0.001
	21–25	8 (16.7)	10 (6.8)	
	26–30	19 (39.6)	23 (15.5)	
	>30	19 (39.6)	114 (77.0)	
Oxygenation index	<100	3 (6.3)	1 (0.7)	<0.001
	100–199.9	6 (12.5)	5 (3.4)	
	200–299.9	18 (37.5)	29 (19.6)	
	>400	21 (43.8)	113 (76.4)	
Glasgow Coma Scale (GCS)	3–8	20 (41.7)	4 (2.7)	<0.001
	9–12	11 (22.9)	8 (5.4)	
	13–15	17 (35.4)	136 (91.9)	

(*Continued*)

Table 1 (Continued).

Characteristics, n (%)		Carbapenem Resistant Multidrug-Resistant Group (n=48)	Non Multidrug-Resistant Group (n=148)	*P* Value
Fungal infection	No	15 (31.3)	112 (75.7)	<0.001
	Yes	33 (68.8)	36 (24.3)	
Pneumoconiosis	No	34 (70.8)	99 (66.9)	0.611
	Yes	14 (29.2)	49 (33.1)	
Carbapenems	No	24 (50.0)	135 (91.2)	<0.001
	Yes	24 (50.0)	13 (8.8)	
Immunosuppression	No	46 (95.8)	148 (100.0)	0.095
	Yes	2 (4.2)	0 (0.0)	
Parenteral nutrition	No	35 (72.9)	142 (95.9)	<0.001
	Yes	13 (27.1)	6 (4.1)	
Acid suppressants	No	22 (45.8)	119 (80.4)	<0.001
	Yes	26 (54.2)	29 (19.6)	
Glucocorticoids	No	28 (58.3)	118 (79.7)	0.003
	Yes	20 (41.7)	30 (20.3)	
Vancomycin	No	39 (81.3)	145 (98.0)	<0.001
	Yes	9 (18.7)	3 (2.0)	
Malignant tumors	No	41 (85.4)	119 (80.4)	0.436
	Yes	7 (14.6)	29 (19.6)	
Invasive procedure	No	16 (33.3)	104 (70.3)	<0.001
	Yes	32 (66.7)	44 (29.7)	
Mechanical ventilation	No	36 (75.0)	136 (91.9)	0.001
	Invasive	9 (18.8)	3 (2.0)	
	Non invasive	3 (6.2)	9 (6.1)	
Chronic lung disease	No	26 (54.2)	71 (48.0)	0.456
	Yes	22 (45.8)	77 (52.0)	
Coronary atherosclerosis Heart disease	No	25 (52.1)	98 (67.1)	0.061
	Yes	23 (47.9)	46 (32.9)	
Renal injury	No	34 (70.8)	144 (97.3)	<0.001
	Yes	14 (29.2)	4 (2.7)	
Hypertension	No	20 (41.7)	87 (58.8)	0.038
	Yes	28 (58.3)	61 (41.2)	
Diabetes mellitus	No	38 (79.2)	122 (82.4)	0.612
	Yes	10 (20.8)	26 (17.6)	
Cardiovascular disease (CVD)	No	13 (27.1)	104 (70.3)	<0.001
	Yes	35 (72.9)	44 (29.7)	

Risk Factors for Multidrug Resistance in CRKP Patients

The LASSO regression, an advanced variable selection algorithm for multi-collinear or high-dimensional data, has proven superiority in reducing multicollinearity among variables, and it is especially appropriate for dealing with a large number of clinical factors and preventing overfitting.[25] Herein, LOS [OR: 4.558, 95% confidence interval (CI): 1.157–17.961, P = 0.030], ICU stay within 30 days (OR: 12.643, 95% CI: 3.780–42.293, P < 0.001), GCS score (OR: 13.569, 95% CI: 2.738–67.236, P = 0.001), fungal infection (OR: 6.398, 95% CI: 1.969–20.785, P = 0.002), and CVD (OR: 3.871, 95% CI: 1.293–11.592, P = 0.016) were identified as significant risk factors for multidrug resistance in

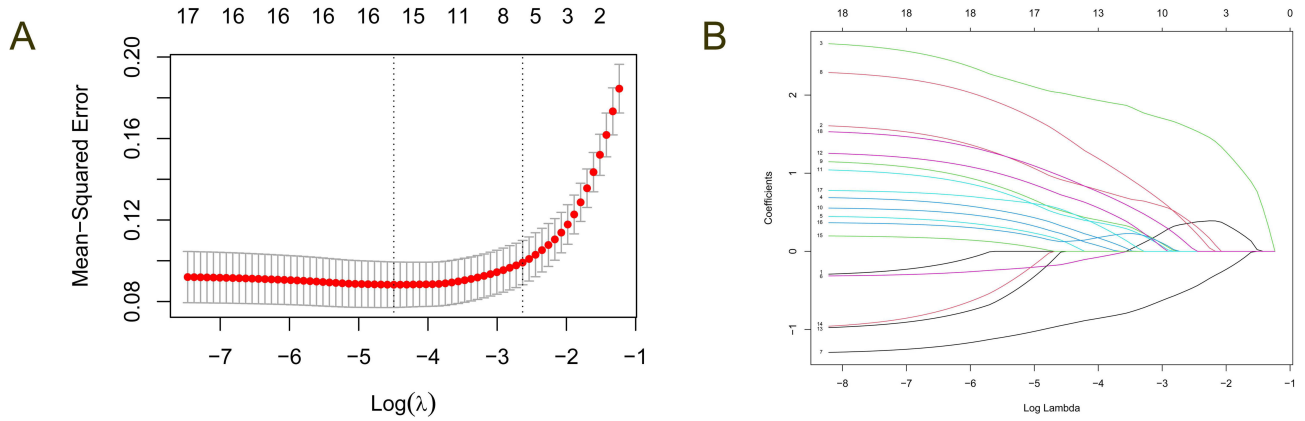

Figure 1 Least absolute selection and shrinkage operator (LASSO) regression analysis. (**A**) Tuning parameter (λ) selection in the LASSO model was conducted using 10-fold cross-validation via minimum criteria. (**B**) LASSO coefficient profiles of the 18 features.

CRKP patients. The LASSO regression analysis determined that KP infection was significantly associated with severe pneumonia, LOS, ICU stay within 30 days, GCS score, fungal infection, and cardiovascular disease (CVD) (Figure 1A and B). Meanwhile, the multivariate logistic regression analysis revealed significant associations between KP infection and LOS [OR and 95% CI: 4.558 (1.157–17.961), P = 0.030], ICU stay within 30 days [OR and 95% CI: 12.643 (3.780–42.293), P < 0.001], GCS score [OR and 95% CI: 13.569 (2.738–67.236), P = 0.001], fungal infection [OR and 95% CI: 6.398 (1.969–20.785), P = 0.002], and CVD [OR and 95% CI: 3.871 (1.293–11.592), P = 0.016, Table 2].

Construction of the Nomogram

Nomograms, visual clinical predictive models, are simple statistical visual tools that can be utilized as regression algorithms to predict a specific finding probability.[26,27] They have gained popularity due to their advantages of straightforward visualization and comprehensibility. Herein, the nomogram constructed could accurately predict carbapenem-resistant and multidrug-resistant KP infection in patients. The LOS, ICU admission within 30 days, GCS score, fungal infection, and CVD were used to construct a nomogram (Figure 2A). The LOS > 7 days corresponded to 58 points, ICU admission within 30 days scored 97 points, GCS scores between 3–8 accounted for 100 points, GCS scores between 9–12 scored 40 points, fungal infection (Yes) was attributed 71 points, CVD (Yes) scored 52 points. Therefore,

Table 2 Logistic Regression Analysis

Variables	β	Odds Ratio (95% CI)	*P*-value
Length of stay (LOS)			
1–7	0	1 (Reference)	
>7	1.517	4.558 (1.157, 17.961)	0.030
ICU (Within 30 days)			
NO	0	1 (Reference)	
Yes	2.537	12.643 (3.780, 42.293)	<0.001
Glasgow Coma Scale (GCS)			0.006
13–15	0	1 (Reference)	
9–12	1.030	2.802 (0.650, 12.076)	0.167
3–8	2.608	13.569 (2.738, 67.236)	0.001
Fungal infection			
No	0	1 (Reference)	
Yes	1.856	6.398 (1.969, 20.785)	0.002
Cardiovascular disease (CVD)			
No	0	1 (Reference)	
Yes	1.354	3.871 (1.293, 11.592)	0.016

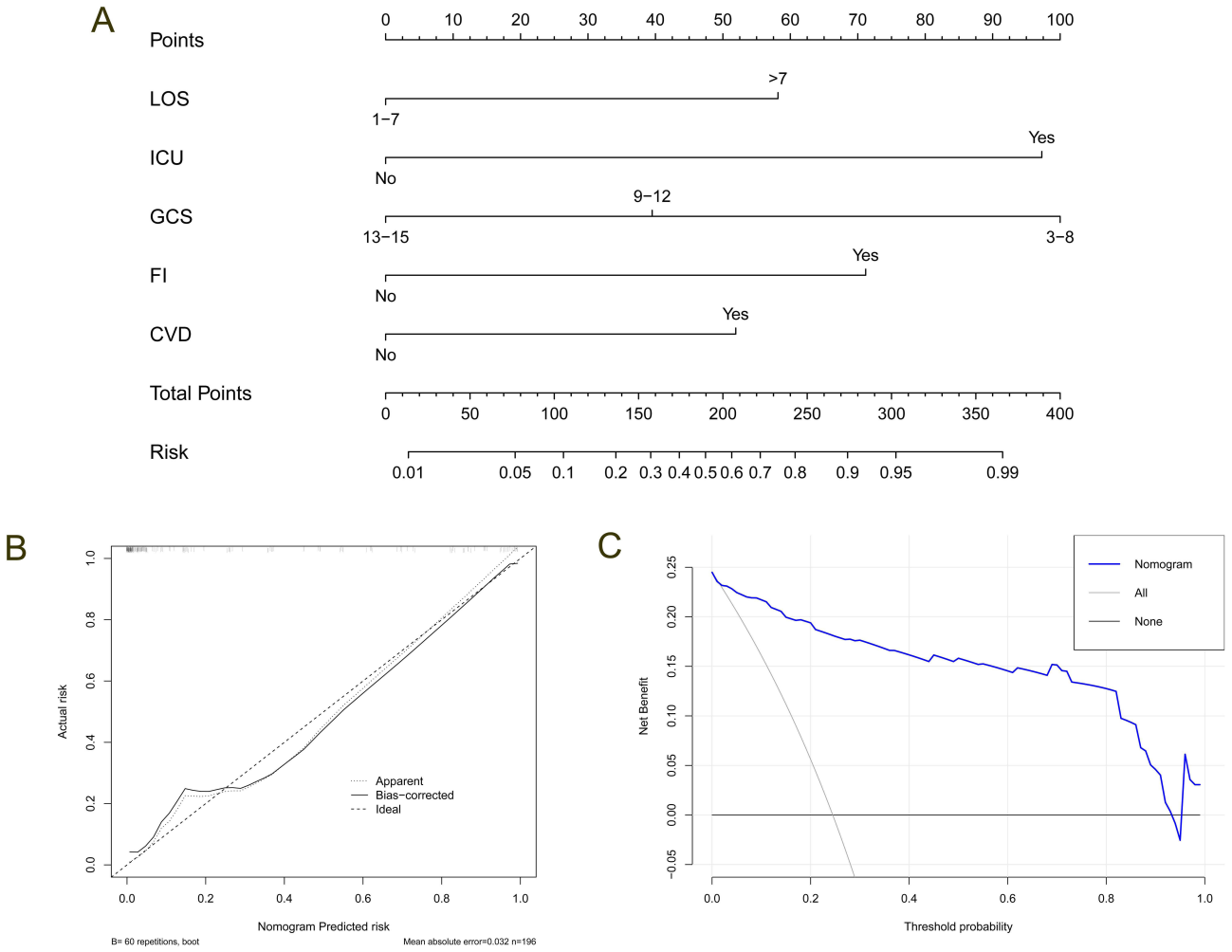

Figure 2 Nomogram. (**A**) Nomogram construction. (**B**) Calibration curve. (**C**) Decision curve.

a patient with a fungal infection hospitalized for > 7 days and admitted to the ICU within 30 days, as well as a GCS score of 3–8 points and a history of CVD, totaling a score of 378, has a risk of developing multidrug resistance of over 99%. Moreover, the C-index is commonly employed for assessing the prediction model performance.[28] The C-index (95% CI) of the predictive model was 0.950 (0.945, 0.955), highlighting its high accuracy of the constructed nomogram. Figure 2B and C illustrate the calibration and decision curves of the predictive model, respectively, with the profit of the decision curve ranging from 1% to 100%. In addition, internal random data verification yielded a C-index of 0.937, indicating a very high level of accuracy.

Discussion

Recently, the prevalence of KP resistance has significantly elevated both domestically and internationally.[29–32] Herein, the detection rate of CRKP was 24.49% among patients infected with KP, indicating that KP resistance was also related to regions and departments. Consequently, there is a pressing need to timely and accurately identify such high-risk patients in order to delay disease progression, mitigate the risk of bacterial resistance, optimize drug management protocols, regulate the use of antibacterial drugs, and enhance awareness for preventing infections.

In the present study, LOS, ICU stay within 30 days, GCS score, fungal infection, and CVD were recognized as risk factors for multidrug resistance in CRKP patients. Worsening patient conditions and disease progression are typically accompanied by an extended length of hospitalization, increasing the likelihood of ICU admission. Patients admitted to ICUs often display rapidly changing conditions and inevitably necessitate various invasive operations to maintain life. Intubation or tracheostomy

can easily damage normal tissues and lower patient immunity, thereby facilitating the invasion and adherence of opportunistic pathogens to the respiratory tract's inner wall, resulting in biofilm formation. This significantly heightens the KP risk, turning from colonization to infection and from mild to severe disease in ICU patients. Furthermore, prolonged exposure to healthcare settings substantially increases the risk of nosocomial transmission of drug-resistant bacteria.[33] Zhang et al enrolled ICU patients with multidrug-resistant bacterial infections and evinced that the length of ICU stay and the rates of antibiotic use were higher in the multidrug-resistant bacterial group than in the control group. Moreover, the resistance rate of KP to carbapenem drugs was significantly positively correlated with the frequency and intensity of carbapenem use.[34] In addition, patients with low GCS scores are more prone to undergoing invasive procedures such as tracheal intubation and tracheotomy, resulting in local mucosal damage to the respiratory tract, which increases the risk of bacterial inhalation and colonization. Additionally, these patients frequently experience longer hospital stays, higher rates of ICU admission, longer durations of antibiotic use, and more frequent administration of carbapenems, thereby significantly increasing the risk of resistance. A previous study identified low GCS scores as a risk factor for pulmonary infection,[35] with a GCS score ≤ 8 being a risk factor for multidrug-resistant KP infection.[36] Consequently, it is imperative to enhance the ICU medical staff's comprehension of the sensory control degree connected to invasive devices/operations, to master the indications for employing diverse invasive devices and tubes, and to conduct accurate daily assessments to prevent unnecessary utilization and redundancy of multiple tubes. During bacterial infection, PCT is synthesized by neuroendocrine cells, monocytes, macrophages, and lung tissues and is released into the blood.[37] After 2 h of intravenous injection of low-dose endotoxin in healthy volunteers, serum PCT levels rapidly increased, peaking at 12–48 h.[38] Zhang et al documented that PCT levels were significantly higher in the CRKP group compared with those in the non-CRKP group,[39] in line with our results, indicating that LOS, ICU stay within 30 days, GCS score, fungal infection, and CVD are risk factors for multidrug resistance in CRKP patients. Therefore, hospitals have to establish essential preventive measures to mitigate the risk factors for drug-resistant bacteria, including the optimization of the configuration of ICU space, timely isolation of infected patients, paying close attention to CVD patients, and sufficient disinfection of ICU equipment, which may decrease the CRKP infection rate.

At present, there are no effective strategies for completely preventing multidrug resistance in KP. Once multidrug resistance develops, effective treatment options are limited. The nomogram can offer a valuable tool for accurately and intuitively assessing the risk of multidrug resistance in patients with CRKP, thereby facilitating adjustments in treatment strategies, enhancing adherence to catheter care protocols among medical staff, raising awareness of infection control measures, and minimizing factors driving resistance.[40] A nomogram was established in this study to predict the multidrug resistance risk in CRKP patients, and calibration and decision curves were plotted to detect the predictive model accuracy. The results exposed a C-index (95% CI) of 0.950 (0.945, 0.955), indicating the high accuracy of the predictive model. Moreover, the slope of the calibration curve was close to 1, further validating the predictive accuracy of the generated nomogram.

Although several independent risk factors of multidrug resistance have been identified in CRKP patients which had a particular reference value for medical workers to determine the individual risk. Our study has several limitations that merit acknowledgment. First, the data were sourced from a hospital, resulting in a relatively narrow disease spectrum and a limited sample size, which may introduce bias into the results. Second, the model was not externally validated, and the possibility of overfitting cannot be excluded. Thus, we will continually recruit patients to complete the external validation. Lastly, our model was based on a hospital that primarily contained Chinese patients. Therefore, the generalizability of the model to the global population remains unclear.

Conclusion

The LOS, ICU stay within 30 days, GCS score, fungal infection, and CVD were recognized as risk factors for multidrug resistance in CRKP patients. Thus, hospitals have to employ essential preventative strategies to alleviate the risk factors for drug-resistant bacteria and reduce the CRKP infection rate. The constructed nomogram could accurately predict carbapenem- and multidrug-resistant KP infection in patients, which also allowed for individualized prediction of high-risk patients.

Ethics Approval and Consent to Participate

Our study was performed in compliance with the principles of the Declaration of Helsinki, reviewed and authorized by the Beijing Jingmei Group General Hospital (No. ZZ2022-01). As this research is retrospective, involving only de-identified data from existing patient records, the ethics committee waived the requirement for informed consent. The waiver was granted because the study poses minimal risk to patient privacy and does not involve direct patient interaction.

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Disclosure

The authors report no conflicts of interest in this work.

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