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Correlation between intestinal CRE colonization and consequent systemic infection in hospitalized patients in China

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It is generally believed that Carbapenem-resistant Enterobacterales (CRE) colonization is primarily responsible for systemic infection in humans. However, there is no consensus on whether decolonization should be recommended in clinical practice. In China, the specific situation of CRE colonization and consequent systemic infection in hospitalized patients necessitates further exploration. We conducted a cohort study and analyzed various clinical characteristics of inpatients with intestinal CRE colonization. A risk prediction model for consequent CRE infection was established and externally validated. Our prediction model is freely available online at https://creinfection.shinyapps.io/dynnomapp/. 839 intestinal CRE colonization samples from inpatients were included. 317 cases of intestinal CRE colonization were enrolled, 25.9% of whom developed systemic infections. The consequent CRE infection rates of *Klebsiella pneumoniae* and *Escherichia coli* were 27.0% and 32.3%. The departments at high risk for subsequent CRE infection were respiratory medicine, hematology, and intensive care unit. Secondary infection after intestinal CRE colonization in inpatients can significantly prolong the length of hospital stay (26 days vs. 33 days, $P < 0.001$), increase the total medical cost (144735.34¥ vs. 281852.34¥, $P < 0.001$), and has poor (85.11% vs. 52.44%, $P < 0.001$) efficacy and high mortality (5.96% vs. 18.29%, $P = 0.001$). Our study makes a significant contribution to comprehensively specify CRE infection, because these results can facilitate early identification of high-risk hospitalized patients, timely implementation to decolonize treatment interventions, ultimately achieve the goal of CRE nosocomial infection prevention and control.

Keywords Carbapenem-resistant Enterobacterales, CRE, Colonization, Infection, Prediction model

Abbreviations

CRE	Carbapenem-resistant enterobacterales
ICU	intensive care unit
CDC	Centers for disease control and prevention
KPC-Kp	Carbapenemase-producing *Klebsiella pneumoniae*
NHSN	National healthcare safety network
OR	odds ratio
95% CI	95% confidence interval
ROC	receiver operating curve
AUC	area under the curve

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WBC	white blood cell
HB	Hemoglobin
PLT	platelet
NE	neutrophilicgranulocyte
ALB	albumin
TBIL	total bilirubin
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
Cr	creatinine
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
PCT	procalcitonin

The number of cases of infection caused by Carbapenem-resistant Enterobacterales (CRE) continues to increase globally, with a particularly high incidence in susceptible groups such as children, the elderly, transplant recipients, and immunosuppressed individuals, especially when these patients are hospitalized[1–3]. In recent years, the treatment of patients infected with CRE has also faced considerable difficulties, and is associated with poor prognosis and high mortality. As early as 2013, due to the high hazards of CRE infection, the Centers for Disease Control and Prevention (CDC) listed CRE as the first "emergency" level of drug-resistant bacteria[4]. According to the European CDC's 2022 report on bacterial resistance surveillance in 41 European countries, the resistance rate of *Escherichia coli* to carbapenems was low, and only six countries, namely Belarus, North Macedonia, Russia, Serbia, Turkey, and Ukraine, had a resistance rate higher than 1.0%. However, the resistance rate of *Klebsiella pneumoniae* to carbapenems rose from 6.2% in 2012 to 10.0% in 2020, with six countries or regions, namely Belarus, Georgia, Greece, Moldova, Russia, and Ukraine, showing resistance above 50.0%. Moreover, the isolation rate of Carbapenem-resistant *Klebsiella pneumoniae* in Greece was the highest, reaching 66.3%[5]. The CDC estimates that as of 2017, approximately 13,100 hospitalized patients in the United States were infected with CRE, among which 1,100 died, leading to a case fatality rate of 8.4%[1]. These findings demonstrate that CRE infection has gradually become a major global public health threat, causing an enormous economic burden of disease to society at large. Consequently, there are severe challenges to the prevention, control, and treatment of CRE nosocomial infections.

It is generally believed that CRE colonization is primarily responsible for infection, and patients with CRE colonization have a significantly high risk of infection[6]. The Italian CHIMERA multicenter cohort study evaluated the characteristics of secondary infections caused by carbapenemase-producing Klebsiella pneumoniae (KPC-Kp). Among 1,071 patients, bloodstream infections (BSI) accounted for 54% of all KPC-Kp infections, and rectal swab samples constituted 67% of all colonization samples. The all-cause mortality rate was 34% in patients with KPC-Kp infections and 21% in colonized patients[7]. This suggests that decolonization therapy of CRE is important to prevent the morbidity and mortality associated with these infections. However, relevant studies have shown that among 1806 patients with CRE colonization, the overall risk of infection with CRE was 16.5% (299/1806)[8]. Therefore, most CRE carriers will not be infected with CRE, and if excessive decolonization is performed in clinical practice, it may lead to a waste of medical resources and abuse of antibiotics. Thus, there is no general consensus among experts on the specific timing and the degree of decolonization therapy. However, in China, the current situation of consequent infection in patients with CRE colonization is not yet fully clear. Hence, the population characteristics, clinical features, and related risk factors of consequent systemic infection in patients with CRE colonization need to be further explored.

CRE colonization in the intestinal tract usually precedes or coexists with CRE infection[6]. Under normal circumstances, colonized CRE, gut microbiota, and the host interact in a dynamic equilibrium state. When the gut microbiota is disturbed due to causes such as diet, drugs, and diseases, the normal intestinal flora loses resistance to colonized CRE, thus increasing the risk of CRE infection[9,10]. Clinically, in high-risk groups, such as patients with hematological tumor, hematopoietic stem cell transplantation, and organ transplantation, the proportion of intestinal CRE colonization increases significantly, and the intestinal CRE colonization rate in such hospitalized patients ranges from 6.8–45.4%[9–12]. The World Health Organization recommends that for asymptomatic patients with CRE colonization, pathogenic surveillance should be guided by the epidemiology and risk assessment of each region/country[13,14]. In other words, early identification of patients with CRE colonization can be used to further track and prevent the prevalence and spread of CRE in hospitals[15]. Currently, the preferred screening sites recommended by the American CDC and the European Society for Clinical Microbiology are intestinally-derived samples (including feces and rectal swabs)[13,16]. Stool is the best screening specimen, and stool CRE detection is relatively convenient and easy to popularize clinically. Therefore, we conducted a cohort study to understand the association between intestinal CRE colonization and consequent CRE systemic infection in hospitalized patients. Our study focused on all CRE-positive specimens from January 1, 2013 to October 1, 2022, and the patients were from all clinical departments of Xiangya Hospital, Central South University. This wide range of observation groups improves the value of the results as a clinical reference. The main objective of our study was to identify the population characteristics, clinical features, pathogenic characteristics, and risk factors of systemic infection after CRE colonization in inpatients, and to establish a risk prediction model for consequent infection in CRE carriers. It is crucial to investigate these factors to facilitate early identification of high-risk hospitalized patients, provide timely implementation of decolonization treatment interventions, and ultimately achieve the goal of prevention and control of CRE nosocomial infection.

Materials and methods

Sample collection and testing

Collect fecal specimens from ICU patients and ensure they are sent for testing within 2 h of collection, with immediate performance of the test. If immediate testing is not feasible, the specimen should be stored in a refrigerator at 4 °C for no longer than 3 days. For specimens requiring preservation beyond this period, freezing is recommended. All sample processing, result analysis, and reporting is conducted in clinical laboratory. Sample detection mainly included: (1) Identification of pathogens: The Merieux Vitek-2 Compact fully automated bacterial identification instrument was utilized; (3) Phenotypic confirmation test: The NG-Test CARBA 5 (NG Biotech, France) was employed to detect five common types of carbapenemases: KPC, NDM, IMP, VIM, and OXA-48 ; (3) Antimicrobial susceptibility testing: Isolates exhibiting resistance or intermediate resistance to carbapenem antibiotics were defined as resistant strains. The quality control strains referenced by our hospital's microbiology laboratory are Escherichia coli ATCC 25,922 and Klebsiella pneumoniae ATCC 700603.

Study subjects and design

The subjects of the study were inpatients with positive stool CRE screening at Xiangya Hospital, Central South University, from January 1, 2013 to October 1, 2022. If the same patient was hospitalized several times, the hospitalization data at the time of the first report was selected. If the samples from the same patient were positive multiple times, the first positive result was taken as the starting point of the research until the patient was discharged. All specimens used met the following inclusion criteria: (1) positive stool CRE screening results; (2) no CRE infection diagnosed prior to positive stool screening; (3) no CRE colonization of other sites before positive stool screening; and (4) hospitalization time $\geq$ 48 h. Additionally, the exclusion criteria were as follows: (1) pregnant patients, (2) patients discharged within 48 h after a positive stool CRE screening, (3) contaminated or unqualified clinical specimens, and (4) missing clinical data.

Study groups and definition

The positive samples of stool CRE screening were monitored through the nosocomial infection real-time monitoring and management system. Samples were included or excluded according to the criteria described in the Methods section. Finally, hospitalized patients with intestinal CRE colonization were included in the study. The clinical data of the patients were collected. The patients were divided into the "CRE infection group" and the "non-CRE infection group" based on whether the patients subsequently developed CRE systemic infection. CRE infection was diagnosed as positive CRE detection in the patient's blood culture or other sterile sites, which can be confirmed as infection. Otherwise, the samples from suspected contamination sources, such as urine, stool, sputum, and wound secretion, were judged according to the standards provided by the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN)[17]. In this study, systemic infection was defined as common infections in various systems of the organism, including bloodstream infection, pulmonary infection, abdominal infection, urinary tract infection, skin and soft tissue infection, surgical site infection, gastrointestinal system infection, and central nervous system infection. CRE colonization means that the samples from suspected contamination sources test positive for CRE; if they do not meet the above diagnostic criteria for CRE infection, it is judged as CRE colonization. After admission, if the fecal CRE screening was positive and the patient did not meet the criteria for infection, then it was diagnosed as intestinal CRE colonization.

Patient groups and clinical variables

As shown in Fig. 1, from January 2013 to October 2022, a total of 839 specimens from inpatients with positive stool CRE screening at Xiangya Hospital, Central South University, were comprehensively analyzed through the Lan Qing Ting Hospital Infection Real-time surveillance and Management Platform 7.0 version. Screening was conducted strictly in accordance with the inclusion and exclusion criteria, and the number of hospitalized patients with intestinal CRE colonization finally included in this study was 317. The patients were divided into a CRE infection group and a non-CRE infection group according to whether the patients subsequently developed systemic CRE infection. Then, the population characteristics, clinical characteristics, incidence, and influencing factors of the two groups of patients were further explored. Meanwhile, data from 2013 to 2021 were used to develop the risk prediction model, and data from patients in 2022 were used to validate the model.

The clinical variables evaluated comprised age, sex, length of hospital stay and cost, department, underlying diseases, comorbidities, clinically invasive procedures, colonization and infection strain type, infection site, therapy, and efficacy. The first relevant laboratory tests on admission were mainly routine blood, liver and kidney function, and inflammatory indicators. Comorbidities, underlying diseases, invasive procedures, special drugs, and antibiotic use before infection were collected.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 26.0), and GraphPad Prism (version 9.5.1). Normally distributed measurement data are represented by the mean $\pm$ standard deviation ($\bar{x} \pm S$), skewed distribution measurement data are represented by the median and interquartile range, namely M (P25, P75), and count data are expressed as absolute frequencies and percentages, such as n (%). The normally distributed quantitative variables were analyzed by Student's t-test, the skewed distribution quantitative variables were analyzed by Wilcoxon rank sum test, and the qualitative variables were analyzed by chi-squared test or Fisher's exact test. P-values < 0.05 were considered significant. According to the results of univariate association analysis, factors with P-values < 0.05 were selected for multivariate analysis. Multivariate analysis was performed by logistic regression analysis, and the odds ratio (OR) and 95% confidence interval (CI) were calculated. The fitting effect of multivariate binary logistic regression analysis was evaluated by receiver operating curve (ROC).

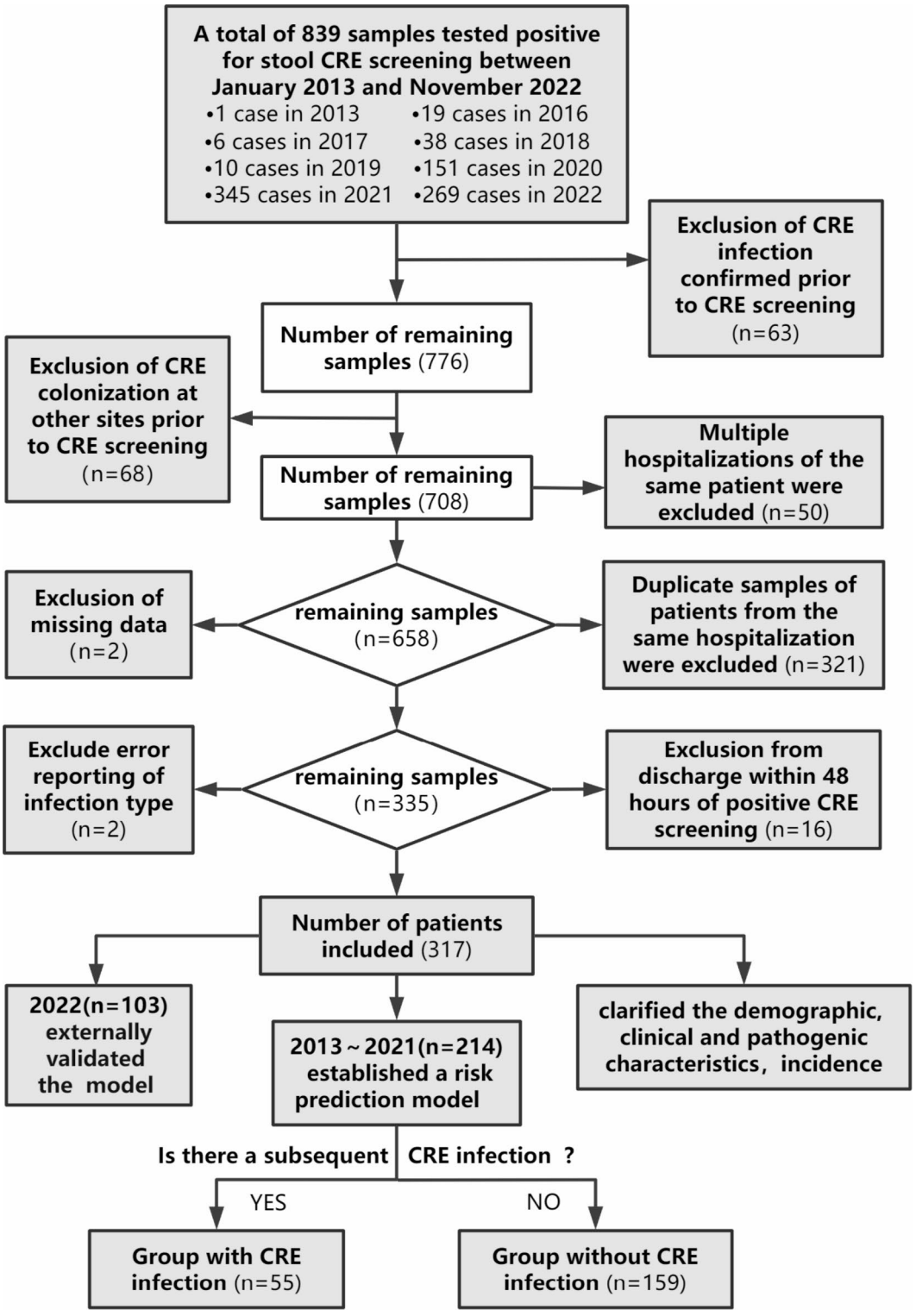

Fig. 1. Flowchart of sample screening and patient grouping.

R was used to draw the nomogram and calibration curve of the risk prediction model of systemic infection after intestinal CRE colonization in hospitalized patients. Meanwhile, the external verification of the model proved that the model had good prediction efficiency.

Results

Baseline data comparison

In all, 317 hospitalized patients with intestinal CRE colonization were included in this study, including 82 patients with consequent CRE infection and 235 patients without CRE infection. Patients in the CRE infection group had a longer average hospital stay ($Z=3.606$, $P<0.001$) and a significantly higher total hospital cost than patients in the non-CRE infection group ($Z=7.415$, $P<0.001$). Additionally, the antibiotic exposure time ($Z=2.647$, $P=0.008$) and cost ($Z=7.341$, $P<0.001$) greatly increased in the CRE infection group. The two groups showed no significant differences in age and sex between the two groups. Regarding the first laboratory examination after a positive intestinal CRE screening in hospitalized patients, we found that the white blood cell count ($Z=3.277$, $P=0.001$) and the procalcitonin index ($Z=5.152$, $P<0.001$) of the two groups of patients were significantly different. However, the albumin level of the CRE infection group was significantly lower than that of the non-CRE infection group ($t=8.341$, $P<0.001$). The two groups showed no significant difference in other blood routine indices and biochemical indices (see Table 1).

Distribution of departments

The details of the department distribution of patients in this study are shown in Fig. 2. The samples of inpatients colonized with intestinal CRE came from 26 clinical departments of Xiangya Hospital, Central South University,

Variable	No CRE infection group ($n=235$, 74.13%)	CRE infection group ($n=82$, 25.87%)	χ^2/Z/t	*P*
Baseline information				
Male [n (%)]	169 (71.9%)	62 (75.6%)	0.420	0.517
Age [M (P_{25}, P_{75})]	49.12 ± 22.66	53.7 ± 22.86	1.560	0.120
Total hospitalization time (days)	26 (14, 41)	33 (21.5, 57.5)	3.606	< 0.001*
Total hospitalization cost	144735.34 (72240.34, 243762.98)	281852.34 (210793.16, 445289.05)	7.415	< 0.001*
Antibacterial cost	11204.00 (2666.40, 30188.91)	61881.80 (23401.49, 91582.75)	7.341	< 0.001*
Total antibacterial exposure time (days)	23 (12, 37)	29 (17, 47.5)	2.647	0.008*
Laboratory examination				
WBC [M (P_{25}, P_{75})]	6.40 (4.00, 10.10)	10.30 (2.95, 15.9)	3.277	0.001*
HB [$\bar{x} \pm S$]	100.52 ± 27.41	93.31 ± 23.49	1.741	0.083
Plt [M (P_{25}, P_{75})]	175 (71.25, 260)	184 (66, 349)	0.387	0.699
NE# [M (P_{25}, P_{75})]	4.70 (2.20, 9.00)	7.70 (1.65, 12.80)	1.797	0.072
ALB [$\bar{x} \pm S$]	34.17 ± 7.39	28.31 ± 4.20	8.341	< 0.001*
TBIL [M (P_{25}, P_{75})]	9.7 (7.03, 14.48)	16.4 (6.9, 30.8)	1.320	0.187
ALT [M (P_{25}, P_{75})]	21.9 (11.45, 41.18)	31.3 (17.2, 64)	1.022	0.307
AST [M (P_{25}, P_{75})]	32.65 (21.4, 57.88)	43.3 (29, 77.4)	1.186	0.236
BUN [M (P_{25}, P_{75})]	6.85 (4.78, 11.81)	7.86 (4.69, 14.11)	0.961	0.336
Cr [M (P_{25}, P_{75})]	80.05 (58, 127.53)	75.10 (62, 123.20)	0.240	0.810
CRP [M (P_{25}, P_{75})]	73.85 (22.33, 120.67)	89.90 (30.3, 130)	1.110	0.267
ESR [$\bar{x} \pm S$]	55.43 ± 35.53	56.13 ± 33.37	0.105	0.916
PCT [M (P_{25}, P_{75})]	0.27 (0.10, 0.76)	1.30 (0.25, 10.88)	5.152	< 0.001*
Classification of colonizing strains †				
Klebsiella pneumoniae	149 (63.40%)	58 (69.88%)	1.440	0.230
Escherichia coli	42 (17.87%)	14 (16.87%)	0.030	0.863
Enterobacter cloacae	16 (6.81%)	4 (4.82%)	0.383	0.536
Klebsiella aerogenes	6 (2.55%)	2 (2.41%)	< 0.001	1.000
Klebsiella oxytoca	7 (2.98%)	0 (0.0%)	1.309	0.253
Citrobacter freundii	1 (0.43%)	2 (2.41%)	2.629	0.165
Citrobacter krusei	1 (0.43%)	0 (0.0%)	0.350	1.000
Serratia marcescens	0 (0.0%)	1 (1.20%)	2.875	0.259
Unclassified CRE	13 (5.53%)	2 (2.41%)	0.695	0.404

Table 1. Basic data of patients in the CRE infection and no CRE infection groups. *CRE* Carbapenem-resistant Enterobacterales, *WBC* white blood cell, *HB* Hemoglobin, *PLT* platelet, *NE* neutrophilicgranulocyte, *ALB* albumin, *TBIL* total bilirubin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *Cr* creatinine, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin. * $P<0.05$, indicating a significant difference. † Among them, 15 samples were unable to isolate specific strains.

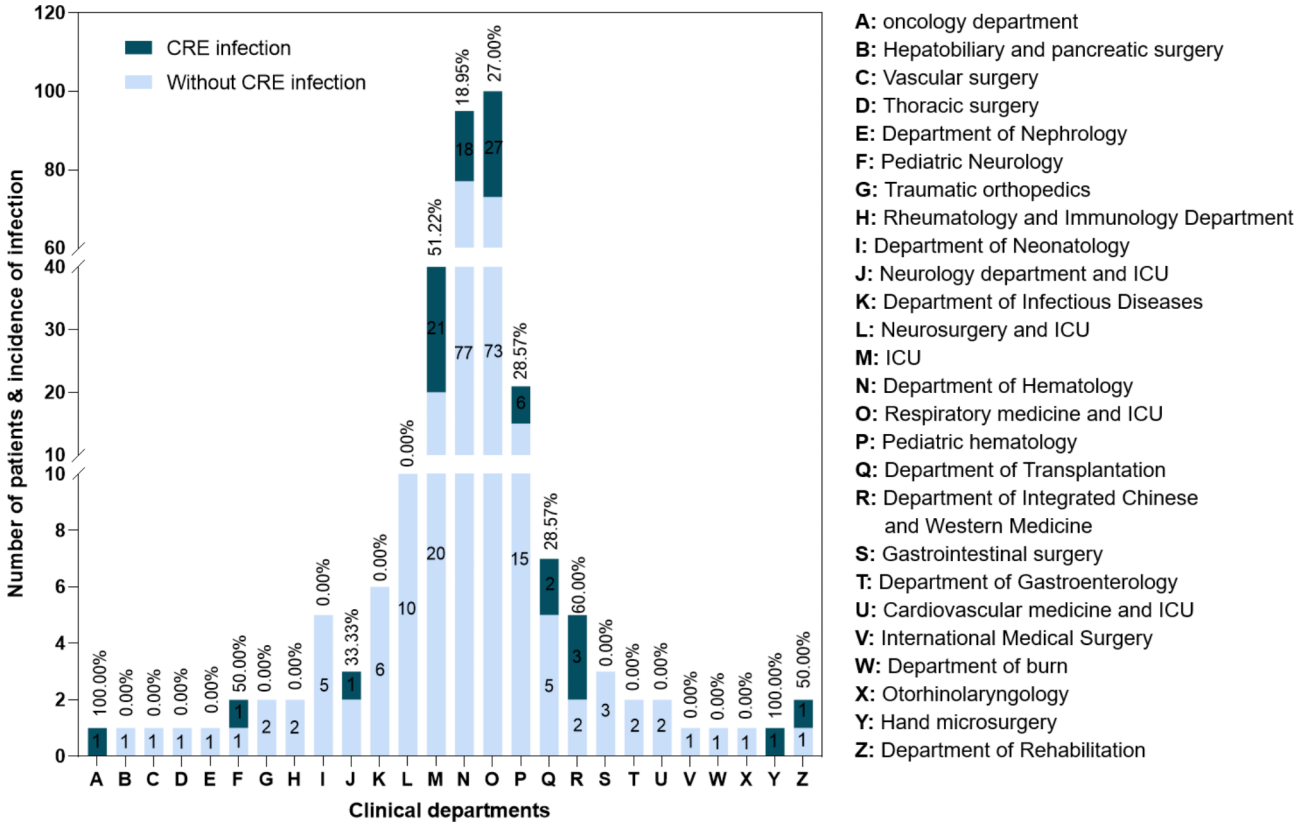

Fig. 2. Departmental distribution of patients and incidence of infection.

mainly in the departments of respiratory medicine, hematology, intensive care unit (ICU), and pediatric hematology, with 100 cases (31.55%), 94 cases (29.65%), 42 cases (13.25%), and 21 cases (6.62%), respectively. Among them, the patients with consequent CRE infection were mainly in the department of respiratory medicine ($n=27$, 33.3%), the department of hematology ($n=17$, 20.99%) and the department of critical care medicine ($n=21$, 13.25%). Simultaneously, the incidence of consequent infection of intestinal CRE colonization among patients in different departments was also different. The incidence of consequent CRE infection in the ICU, department of respiratory medicine, department of hematology, and department of pediatric hematology was 51.22, 18.95, 27.00, and 28.57%, respectively.

Pathogens and infections

Classification of colonizing strains

As shown in Fig. 3A, a total of 317 strains of patients with positive stool CRE screening were included in this study. The two groups showed no significant difference in the classification of colonizing strains. Among them, *Klebsiella pneumoniae* was the main pathogen ($n=149$, 63.40% vs. $n=58$, 69.88%), followed by *Escherichia coli* ($n=42$, 17.87% vs. $n=14$, 16.87%) and *Enterobacter cloacae* ($n=16$, 6.81% vs. $n=4$, 4.82%). Notably, no specific strain was isolated in 15 patients and both *Escherichia coli* and *Klebsiella pneumoniae* were isolated in one patient (Table 1).

Types of CRE strains detected

We analyzed the types of pathogens responsible for consequent infections in hospitalized patients with intestinal CRE colonization. A total of 81 strains were detected, among which *Klebsiella pneumoniae* was the most common, accounting for 69.77%, followed by *Escherichia coli* and *Enterobacter cloacae*, accounting for 16.28% and 5.81%, respectively. Simultaneously, we found that the infection rates of consequent infections of different strains were also different. Among them, *Klebsiella pneumoniae* was 28.99% (60/207), *Escherichia coli* was 25.00% (14/56), and *Enterobacter cloacae* was 25% (5/20) (Fig. 3A).

Sources of CRE strain detected

As shown in Fig. 3B, the analysis of the detected pathogenic bacteria sites after intestinal CRE colonization in hospitalized patients and consequent infection revealed that the main specimen sources included the lungs ($n=38$), blood flow ($n=32$), digestive tract ($n=17$), urinary tract ($n=9$), pleural ascites and postoperative drainage fluid ($n=6$), catheter-related infection ($n=1$), surgical site ($n=3$), skin and soft tissue ($n=2$), and cerebrospinal fluid ($n=38$). Furthermore, the site of CRE infection was consistent with the source of the sample. The most common was pulmonary infection, accounting for 33.04%, followed by bloodstream infection

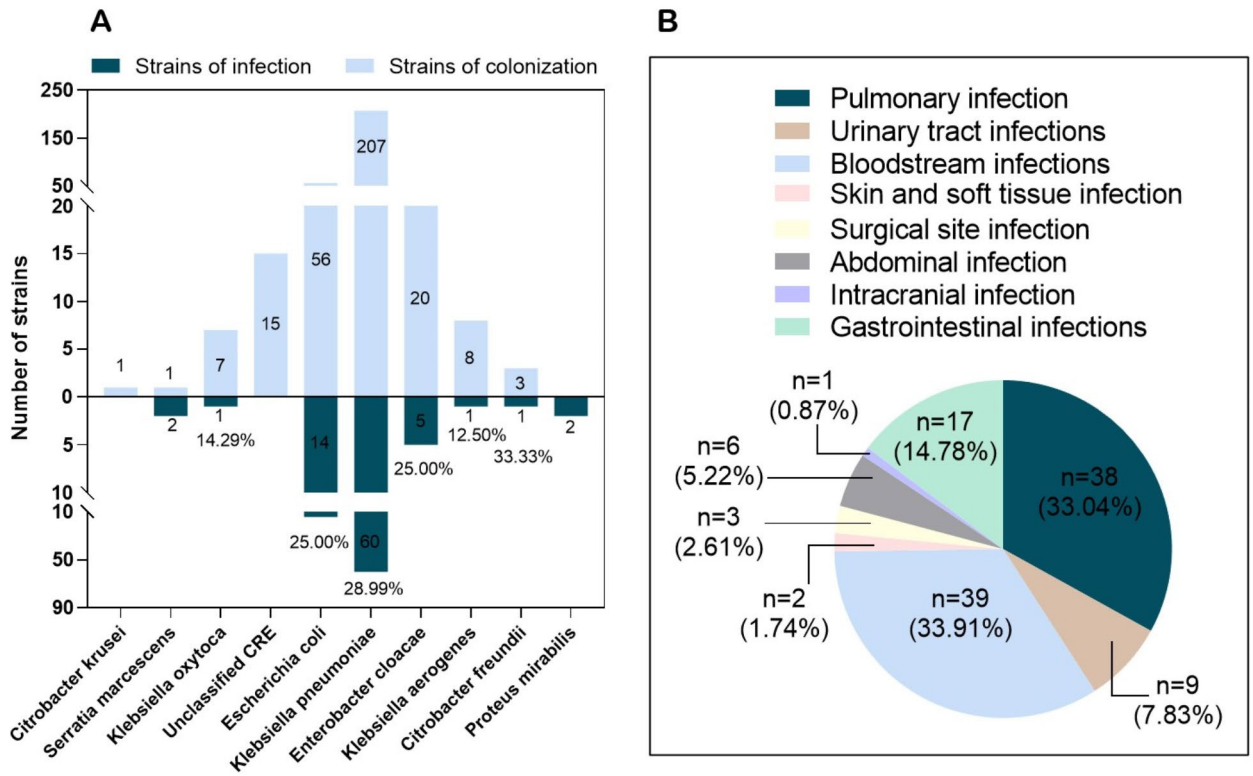

Fig. 3. Types and sources of CRE strains. Figure 3(**A**) shows the classification of colonized and infection strains. Two strains were detected in two patients, and three strains were detected in one patient. Of these 15 patients with unclassified CRE colonization, two cases detected *Proteus mirabilis* infection. Figure 3(**B**) shows the consequent infections of different CRE colonizing sites. *CRE*, Carbapenem-resistant Enterobacterales.

at 27.83%, and digestive tract infection and urinary tract infection, which accounted for 14.78% and 7.83%, respectively. However, intracranial infection was rarest, and only one patient was detected to have pathogens from cerebrospinal fluid.

Clinical characteristics of patients

Underlying diseases and complications

As shown in Table 2, among the 214 inpatients from January 1, 2013 to September 31, 2021, the patients in the two groups had numerous comorbidities and underlying diseases, usually involving multiple organs or systems, and almost all categories of diseases were included. In both the CRE and non-CRE infection groups, the most common underlying clinical disorder was pulmonary lesion, with 115 cases in the non-CRE infection group (72.3%), and 41 cases in the CRE infection group (74.5%). Univariate analysis showed that the incidence of underlying diseases, including liver and digestive tract lesions, combined with other infections, agranulocytosis ≥ 7 days, and hypoalbuminemia, was significantly different between the two groups, while there was no significant difference in other comorbidities. Furthermore, we found that the incidence of consequent CRE infection varied with different underlying diseases and complications. Among the underlying diseases, liver disease was reported in 43.4%, and digestive tract disease was reported in 36.8%. The incidence of consequent systemic CRE infection with other infections was 30.6%, agranulocytosis ≥ 7 days was 39.6%, and hypoproteinemia was 61.9%.

Clinical invasive operation

In terms of the invasive operation performed in the two groups in hospitalized patients before CRE infection, the most common invasive operation was arteriovenous catheterization ($n = 157$, 98.7% vs. $n = 55$, 100%), followed by indwelling catheter ($n = 91$, 57.2% vs. $n = 39$, 70.9). Among them, when the patients had an indwelling gastrojejunal tube or ostomy tube ($\chi^2 = 5.106$, $P = 0.024$), invasive respiratory assisted ventilation ($\chi^2 = 6.431$, $P = 0.011$), and a history of surgery or traumatism within one month ($\chi^2 = 9.393$, $P = 0.002$), the difference between the two groups was significant. For other invasive operations, there was no significant difference between the two groups (Table 2).

Use of drugs and biological agents

By analyzing the use of special drugs before the occurrence of CRE infection in the two inpatient groups, the most common were intestinal probiotics ($n = 115$, 72.3% vs. $n = 30$, 54.5%) and glucocorticoids ($n = 93$, 58.5% vs. $n = 35$, 63.6%). For example, when intestinal probiotics were used ($\chi^2 = 5.914$, $P = 0.015$), the difference between

Variable	No CRE infection group ($n = 159$, 74.30%)	CRE infection group ($n = 55$, 25.70%)	χ^2	*P*-value
Underlying diseases				
Hypertension	48 (30.2%)	19 (34.5%)	0.361	0.584
Diabetes	30 (18.9%)	12 (21.8%)	0.225	0.635
Coronary heart disease	35 (22.0%)	12 (21.8%)	0.001	0.976
Hematological neoplasms	54 (34.0%)	19 (34.5%)	0.006	0.937
Solid tumors	18 (11.3%)	7 (12.7%)	0.078	0.780
Cerebrovascular disease	49 (30.8%)	22 (40.0%)	1.554	0.213
Pulmonary lesions	115 (72.3%)	41 (74.5%)	0.102	0.750
Liver lesions	30 (18.9%)	23 (41.8%)	11.552	0.001*
Urinary system disease	34 (21.4%)	18 (32.7%)	2.859	0.091
Digestive tract lesions	36 (22.6%)	21 (38.2%)	5.050	0.025*
Tuberculosis infection	8 (5.0%)	5 (9.1%)	0.576	0.448
Connective tissue disease	13 (8.2%)	1 (1.8%)	1.786	0.181
Combined with other infections	102 (64.2%)	45 (81.7%)	5.931	0.015*
Combined with agranulocytosis ≥ 7 days	29 (18.2%)	19 (34.5%)	6.245	0.012*
Combined with hypoalbuminemia	40 (72.7%)	65 (40.9%)	16.584	< 0.001*
Clinical invasive operation				
Arteriovenous catheterization	157 (98.7%)	55 (100%)	-	1.000
Various thoracic and abdominal drainage tube	44 (27.7%)	23 (41.8%)	3.802	0.051
Bronchoscopy	66 (41.5%)	27 (49.1%)	0.956	0.328
Indwelling catheter	91 (57.2%)	39 (70.9%)	3.205	0.073
Indwelling gastrojejunal tube or ostomy tube	85 (53.5%)	39 (70.9%)	5.106	0.024*
Blood purification therapy	24 (15.1%)	11 (20.0%)	0.719	0.397
Noninvasive respiratory assisted ventilation	42 (26.4%)	10 (18.2%)	1.506	0.220
Invasive respiratory assisted ventilation	64 (40.3%)	33 (60.0%)	6.431	0.011*
History of surgery or traumatism within one month	66 (41.5%)	36 (65.5%)	9.393	0.002*
Use of drugs and biological agents				
Immunosuppressants	62 (39.0%)	22 (40.0%)	0.017	0.895
Biological agents	10 (6.3%)	4 (7.3%)	< 0.000	1.000
Intestinal probiotics	115 (72.3%)	30 (54.5%)	5.914	0.015*
Glucocorticoids	93 (58.5%)	35 (63.6%)	0.450	0.502
Chemotherapeutic drugs	48 (30.2%)	14 (25.5%)	0.445	0.505
Targeted drugs	11 (6.9%)	5 (9.4%)	0.090	0.764
Antibacterial agents				
Cephalosporins	27 (17.0%)	9 (16.4%)	0.011	0.916
β-lactamase inhibitors and compound preparations	130 (81.8%)	47 (85.5%)	0.390	0.532
Aminoglycosides	33 (20.8%)	10 (18.2%)	0.168	0.681
Quinolones	60 (37.7%)	25 (45.5%)	1.017	0.313
Carbapenems	116 (73.0%)	46 (83.6%)	2.534	0.111
Tigecycline	32 (20.1%)	19 (34.5%)	4.681	0.031*
Polymyxin	22 (13.8%)	19 (34.5%)	11.315	0.001*
Ceftazidime avibactam	4 (2.5%)	2 (3.6%)	< 0.001	1.000
Trimethoprim-sulfamethoxazole	81 (50.9%)	25 (45.5%)	0.493	0.483
Glycopeptides	63 (39.6%)	32 (58.2%)	5.702	0.017*
Antifungal	92 (57.9%)	43 (78.2%)	7.425	0.007*
Use time ≥ 15 days	115 (72.3%)	34 (61.8%)	2.134	0.144
Oral combined with intravenous route	93 (60.0%)	20 (36.4%)	9.125	0.003*

Table 2. Univariate analysis of risk factors for consequent infection in CRE intestinal carriers. *$p < 0.05$, indicating a significant difference.

the two groups was significant. As shown in Table 2, there was no significant difference between other special drugs and measures used before infection, including immunosuppressants, biological agents, glucocorticoids, chemotherapeutic drugs, and targeted drugs.

Antimicrobial agents and therapeutic effect

Use of antimicrobial agents before infection

Analysis of antibiotic use before the diagnosis of CRE infection revealed significant differences in the use of four types of antibiotics between the two groups, namely tigecycline ($\chi^2 = 4.681$, $P = 0.031$), polymyxin ($\chi^2 = 11.315$, $P = 0.001$), glycopeptides ($\chi^2 = 5.701$, $P = 0.017$), and antifungals ($\chi^2 = 7.425$, $P = 0.007$). However, there were no significant differences in the use of cephalosporins, β-lactamase inhibitors and compound preparations, quinolones, carbapenems, ceftazidime avibactam, trimethoprim-sulfamethoxazole, and aminoglycosides before infection between the two groups. Furthermore, when both oral and intravenous antibiotics were administered, there was a significant difference between the two groups compared to intravenous antibiotics alone ($\chi^2 = 9.125$, $P = 0.003$) (Table 2).

Fig. 4 shows the curative effect and outcome of the two groups. We found that the effective rate in the non-CRE infection group was significantly higher than that of the CRE infection group, at 85.11% (200/235) and 52.24% (43/82), respectively. The inefficiency rate of the CRE infection group was 47.56%, which was significantly higher than that of the group without consequent CRE infection. Furthermore, we found that inpatients who developed CRE infection after intestinal CRE colonization had relatively poor prognosis, with a mortality rate of 18.3% ($\chi 2 = 11.129$, $P = 0.001$).

Establishing a risk prediction model

Multivariate logistic regression analysis

Based on the previous univariate analysis results of underlying diseases and comorbidities, invasive procedures, special drugs and preparations, and the use of antibiotics, a total of 14 influencing factors with P-values < 0.05 were selected and included in the multivariate logistic regression analysis. Then, a total of eight independent influencing factors of consequent CRE system infection in patients with intestinal CRE colonization were obtained. We found that taking probiotics and oral administration combined with intravenous use of antibiotics were protective factors of CRE infection after intestinal CRE colonization in hospitalized patients, while complicated with liver disease, combined with agranulocytosis ≥ 7 days, hypoproteinemia, invasive respiratory-assisted ventilation, history of surgery/trauma within one month, and use of antifungal drugs were independent risk factors (Fig. 5). Finally, we established a risk prediction model of systemic infection after intestinal CRE colonization in inpatients. The results are displayed using forest plots.

External evaluation and validation of the model

We also evaluated the performance of the model in terms of discrimination, calibration, and clinical adaptability. The proposed prediction model was externally validated using data of inpatients from Xiangya Hospital Central South University from October 1, 2021 to October 1, 2022. Figure 6 shows the ROC curve used to evaluate the fitting effect of the model. The area under the curve (AUC) for the model and validation data was 0.883

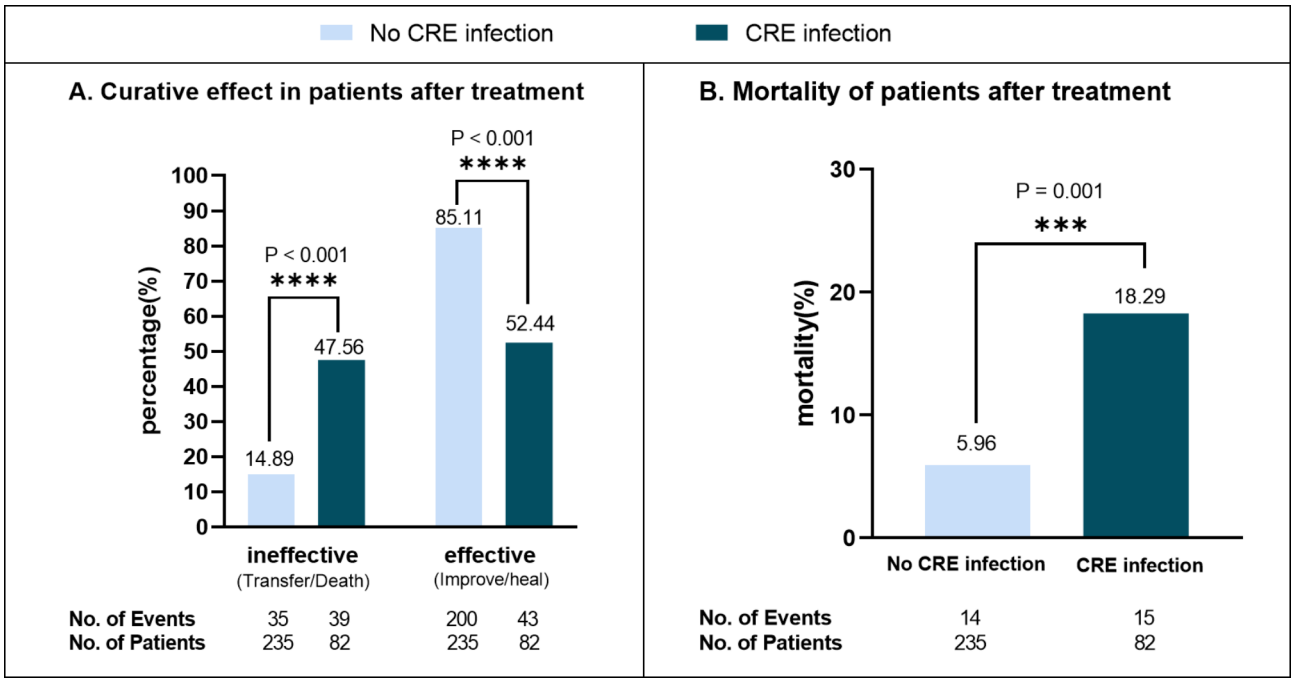

Fig. 4. Curative effect and outcome of patients in the two groups after treatment.

Variables	CRE infection	Non-CRE infection	Odds Ratio（95% CrI）
	no. of events		
complicated with liver disease	30/159	23/55	3.232（1.327，7.872）
invasive respiratory assisted ventilation	64/159	33/55	4.806（1.583，14.590）
history of surgery or trauma within 1 month	66/159	36/55	4.650（1.905，11.348）
taking probiotics	115/159	30/55	0.338（0.142，0.803）
use of antifungal drugs	92/159	43/55	7.764（2.624，22.975）
combined with agranulocytosis ⩾ 7 days	29/159	19/55	12.55（3.408，46.219）
combined with hypoproteinemia	65/159	40/55	4.254（1.797，10.071）
oral administration combined with intravenous use of antibiotics	93/159	20/55	0.152（0.061，0.377）

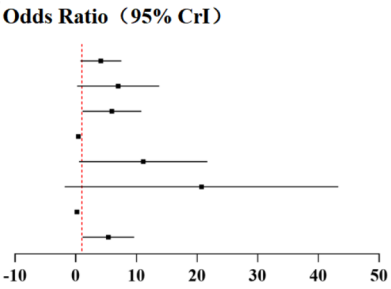

Fig. 5. Multivariate logistic regression analysis of risk factors for consequent infection in CRE intestinal carriers and forest plots.

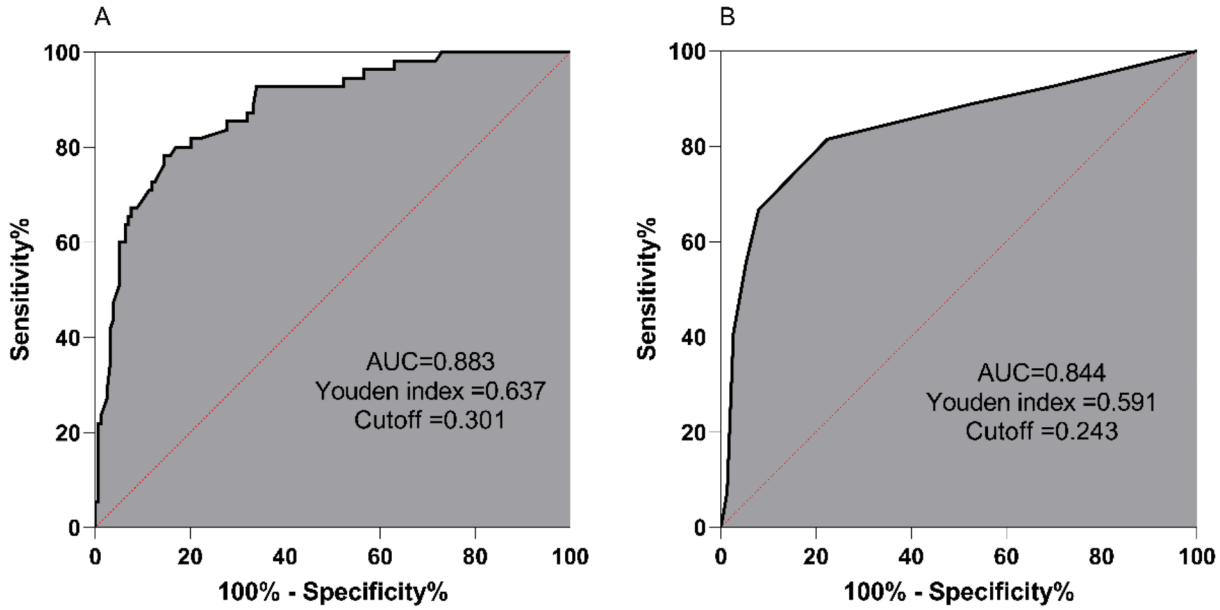

Fig. 6. Multivariate logistic regression analysis of risk factors for consequent infection in CRE intestinal carriers and forest plots.

(95% CI: 0.831–0.934) and 0.844 (95% CI: 0.745–0.943), respectively. Furthermore, Fig. 7A and B show the calibration curves of the prediction model and validation sample, respectively, indicating that the model has a good consistency between the predicted probability and the actual occurrence probability, demonstrating a relatively accurate predictive value. As shown in Fig. 7C and D, the decision curve of the prediction model for both modeling and validation cohorts yielded a higher net clinical benefit than the treat-all and treat-none strategies in the entire range of thresholds. These results demonstrate that the model has excellent prediction performance. Finally, the nomogram of the risk prediction model is shown in Fig. 8. Additionally, we have developed a dynamic nomogram to further strengthen our work, which can be accessed freely at the following URL: https://creinfection.shinyapps.io/dynnomapp/.

Discussion

Of the 317 inpatients with CRE colonization in this study, 25.9% consequently developed systemic CRE infection, which is relatively higher than the percentage reported in previous research[8,18]. We attribute this primarily to two factors: firstly, our study population is predominantly ICU patients, who, compared to those in general wards, are at a higher risk of CRE infection due to their exposure to a more resistant environment, poorer baseline conditions, and more severe illnesses. Secondly, while previous studies have largely focused on bloodstream infections, our research includes infections from various systems, providing a more comprehensive range of infection types. With respect to the types of colonized strains in the two groups, *Klebsiella pneumoniae* was the first, with 67.9% in the non-CRE infection group and 72.7% in the CRE infection group, which is generally

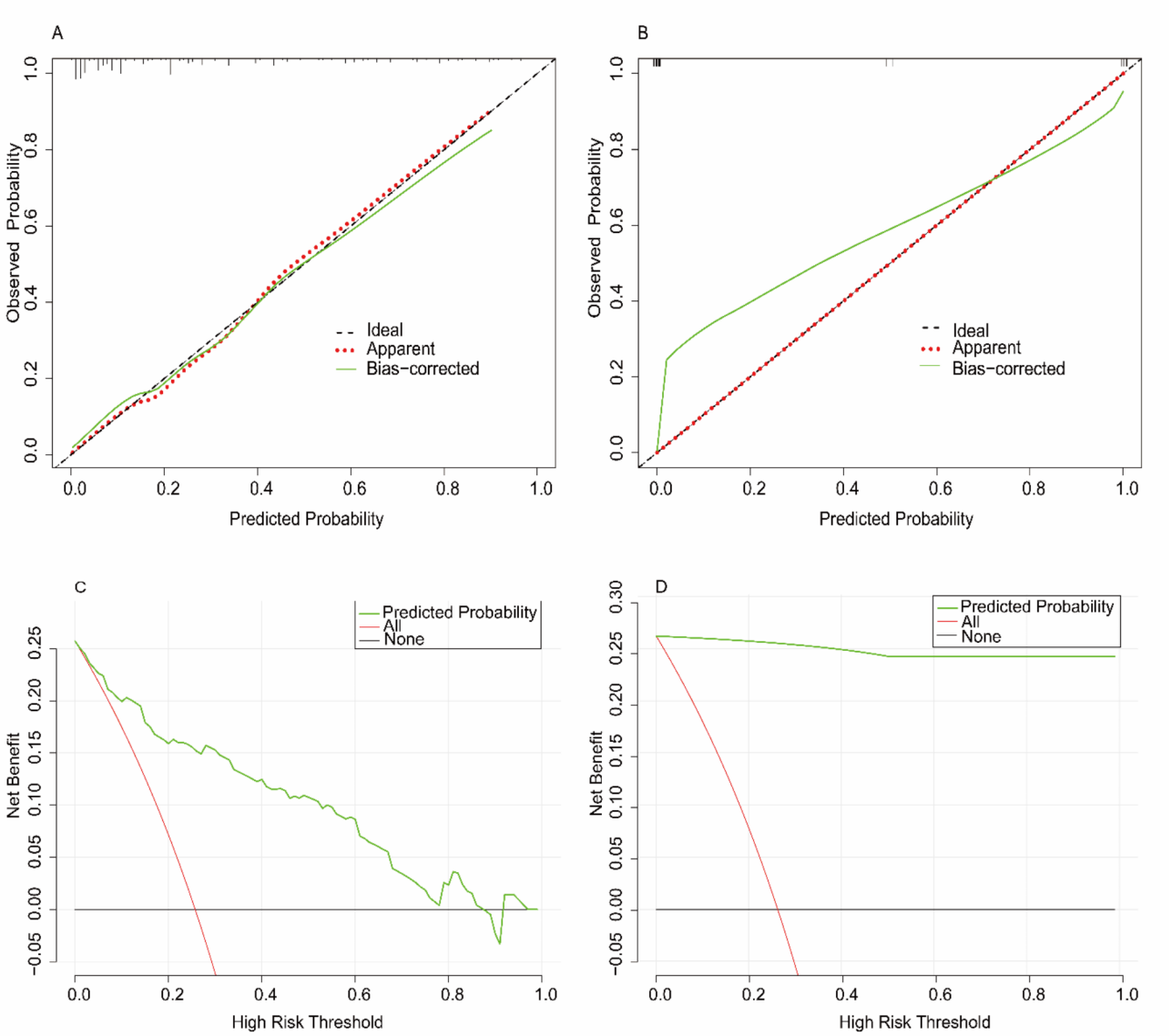

Fig. 7. Calibration curves and decision curve analysis of the model. Figure 7(**A**). Calibration curves of the risk prediction model for infection after CRE colonization. (**B**). Calibration curves of the validation sample for infection after CRE colonization. (**C**). Decision curve analysis of the prediction model for infection after CRE colonization. (**D**). Decision curve analysis of the validation cohorts for infection after CRE colonization.

consistent with the results of other studies[19–22]. In contrast to previous studies, we focused on systemic infection, and the sites of consequent CRE infection were consistent with the source of samples. The most common site was the respiratory system, accounting for 35%, followed by the bloodstream, digestive system, and urinary system, accounting for 21%, 18%, and 10% respectively. In contrast, the distribution of CRE infection specimens in our hospital is generally similar to those reported in related studies, while the proportion of the sources of digestive system specimens is significantly different[8,23]; this may be due to the fact that the subjects of this study are inpatients with intestinal CRE colonization. Notably, considering that pulmonary infections are the most common, aspiration of gastrointestinal contents may represent a mechanism that links intestinal colonization with the occurrence of CRE infections in the critically ill cohort[24]. Therefore, special attention should be paid so as to avoid aspiration when performing related clinical operations such as tracheal intubation, gastric tube insertion, fiberoptic bronchoscopy, and gastroscopy.

The incidence of CRE colonization and infection in clinical departments also varied. In this study, the colonization or infection of CRE mainly occurred in respiratory medicine, hematology, and ICU, which is consistent with relevant studies[8,24], and the incidence of consequent CRE infection was 26.7%, 21.8%, and 45.0%, respectively. Often, most patients in these departments have poor immunity, complex conditions, long hospitalization time, and more frequent use of antibiotics, which lead to patients being more susceptible to the surrounding drug-resistant environment and greatly increases the risk of CRE colonization and consequent CRE infection in hospitalized patients. In fact, most of the patients in the above high-risk departments had a history

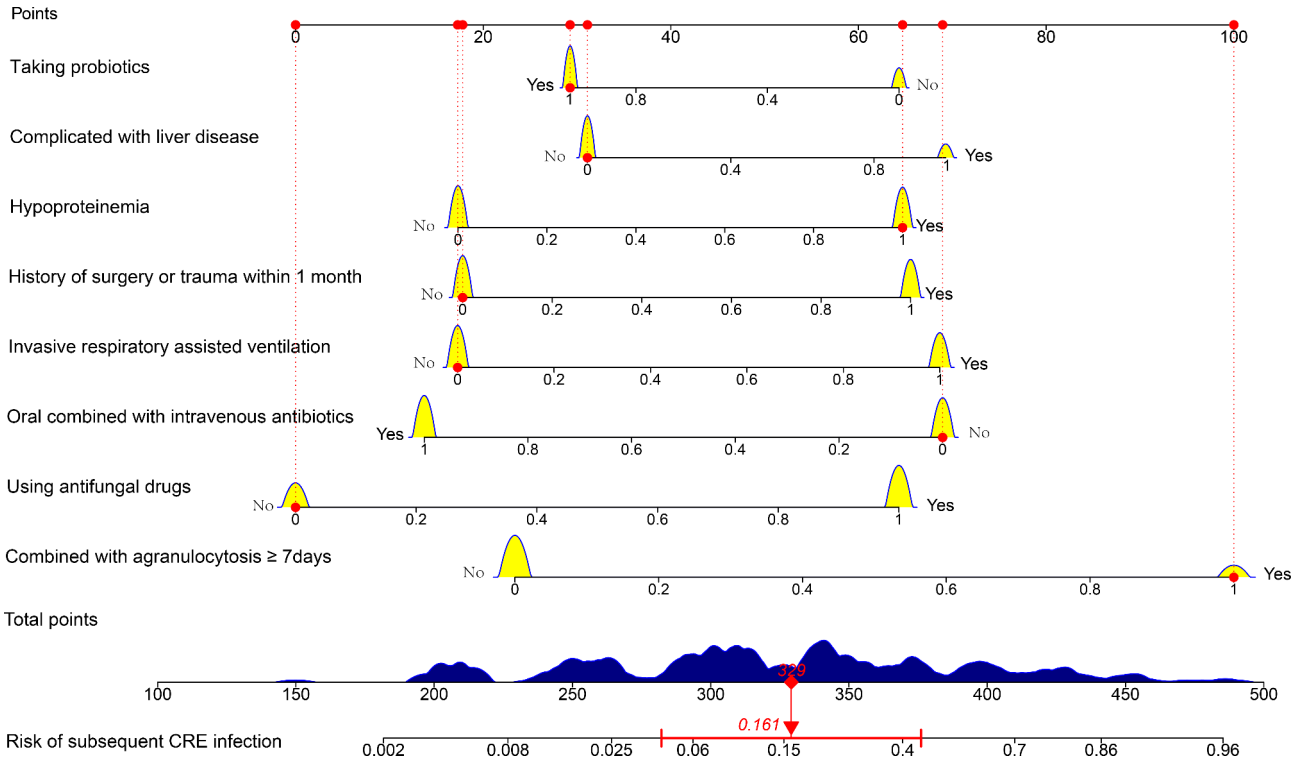

Fig. 8. Nomogram for the occurrence of infection after CRE colonization. The figure shows the relevant data for patient No. 142.

of invasive operations. We found that the most common was arteriovenous catheterization. Indwelling catheter, especially deep venous catheterization, may greatly increase the opportunistic infection of colonized bacteria into the blood, thus further increasing the risk of CRE bloodstream infection[25]. Other invasive operations included patients with an indwelling gastrojejunal tube or ostomy tube, assisted ventilation with invasive breathing, and a history of surgery or trauma in the past three months, which may be the influencing factors of intestinal CRE colonization and consequent development of CRE infection in hospitalized patients, similar to the findings of previous related studies[8,24,26]. Invasive operations can destroy the body's natural barrier and directly or indirectly place pathogens into the human body, resulting in flora translocation, thus increasing the possibility of bacterial colonization or infection. Therefore, for the high-risk departments, unnecessary invasive operations must be minimized, and relevant measures should be taken to monitor, prevent, and control CRE infection, so as to put an end to CRE infection from the source[13,27].

Our research found that, combined with liver disease (mainly including liver insufficiency, liver failure, liver cirrhosis, and liver transplantation), agranulocytosis ≥ 7 days and hypoalbuminemia were independent risk factors for consequent infection of intestinal CRE colonization in hospitalized patients, which is consistent with the findings of relevant studies[28,29]. Clinically, many patients have comorbidities or multiple underlying diseases. Studies have shown that patients with CRE colonization combined with advanced liver cirrhosis can manifest increased intestinal permeability and impaired reticuloendothelial system function, while those with organ transplantation and allogeneic hematopoietic cell transplantation often manifest a combination of neutropenia and intestinal rejection[28,30,31]. Thus, the risk of bacterial translocation and infection after intestinal CRE colonization is significantly increased in such patients. At the same time, laboratory examinations revealed that the CRE infection group had significantly lower levels of albumin, which was caused by factors such as albumin redistribution due to increased vascular permeability, reduced albumin synthesis under pathological conditions, and increased consumption in critically ill patients. Moreover, the plasma protein binding rate is significantly reduced in patients with hypoalbuminemia, which makes antibacterial drugs less effective, forming a vicious circle and inducing CRE infection or leading to poor prognosis[32,33]. Therefore, to reduce the risk of infection in patients with CRE colonization, it is necessary to promptly correct hypoproteinemia and regularly monitor blood drug concentration. In addition, we found that probiotic administration was a protective factor against consequent CRE infection (OR = 0.338). In the state of CRE colonization, when patients suffer from intestinal flora disorders caused by diet, inflammatory bowel disease, antibiotics, and more, intestinal flora translocation of colonizing bacteria will occur due to intestinal mucosal damage, which leads to further infection[6,9,10]. The use of probiotics may reduce this risk. Relevant studies have shown that probiotics may have anti-inflammatory, immunomodulatory, inhibiting abnormal cell proliferation, and antioxidant activities[34]. Therefore, for patients with intestinal CRE colonization, especially those with other infections and using antibiotics, we should regularly monitor the stool and timely add probiotics to regulate intestinal flora in order to reduce the occurrence of consequent CRE infection.

Notably, we found that the use of tigecycline, polymyxin, glycopeptides, and antifungal agents may influence the consequent development of CRE infection in hospitalized patients with intestinal CRE colonization, of which antifungal agents (OR = 7.764) were an independent risk factor. Another study also showed that tigecycline was an independent risk factor for consequent infection after CRE colonization[26]. The use of antibiotics is closely related to infection. Considering colonization and infection, it is particularly important to clarify the use of antibacterial agents before CRE infection. We consider the following reasons for our findings. First, the drugs may have been administered because of coexisting infections that did not respond well to treatment. Second, the clinical effect of monotherapy against CRE infection is not good, and most treatment schemes include a two-drug combination, a three-drug combination, or a carbapenem-containing combination[13]. Third, in our study, the whole CRE was analyzed instead of specific strains, which may have affected the results because of differences in the drug sensitivity of specific strains. Furthermore, we found that combined oral and intravenous antibiotic administration is a protective factor against consequent infections in hospitalized patients with intestinal CRE colonization (OR = 0.152). Indeed, many patients were given oral antibiotics due to severe intestinal microbiota imbalance caused by diarrhea, which would inevitably lead to intestinal mucosal damage if not treated in time. Studies have shown that the realization of intestinal barrier function chiefly includes the adhesion of tight junction proteins to epithelial cells, the secretion of mucus by intestinal immune cells, antibodies, and antibacterial effector molecules[35,36]. If this barrier function is impaired for any reason, the risk of infection by colonizing bacteria in the gut will significantly increase[36,37].

We found that the consequent CRE infection in patients with intestinal CRE colonization significantly prolonged the length of hospital stay and the total hospitalization cost, and also greatly increased the cost and curative time of antibiotics, which is consistent with related studies[8,38]. Moreover, hospitalized patients who subsequently develop CRE infection after intestinal CRE colonization have relatively poor efficacy (85.11% vs. 52.44%) and high mortality (6.0% vs. 18.3%). The relevant literature also reported that approximately 36% of patients who developed infection after CRE colonization died within 90 days[24]. In liver transplant patients, the mortality rate for fatal CRE infection after colonization is 78%[28]. In patients with hematological malignancies complicated with bloodstream infection, the 30-day-related fatality rate caused by CRE is as high as 51%[39], while in patients receiving hematopoietic stem cell transplantation, the overall 90-day mortality rate of patients infected with CRE is even higher, at approximately 58%[40]. It follows that the consequent CRE infection in patients with intestinal CRE colonization increases the antibiotic exposure and economic burden of patients, and also increases the medical burden of the country.

In this study, we comprehensively analyzed the correlation between intestinal CRE colonization and consequent systemic infection in hospitalized patients from the aspects of population, clinical characteristics, incidence, risk factors, and disease economics, and established a risk prediction model for systemic infection after intestinal CRE colonization in hospitalized patients, which is highly valuable. It is helpful to improve clinicians' understanding of intestinal CRE colonization and consequent infection, assist them in making risk assessment before empirical treatment of intestinal CRE colonization, and then take corresponding intervention measures to prevent CRE infection. This study also provides a reference for the rational use of antibiotics, which has a good clinical guiding significance. However, the present study also has certain limitations. First, as a single-center cohort study, there are selection bias and information bias. Second, the statistical significance of some variables in the multivariate analysis may have been obscured due to the uneven distribution of sample sizes between the two groups. Therefore, prospective case–control studies or cohort studies with a large scale and multiple centers could be conducted in the future. Moreover, whether CRE colonization should be treated and the timing of decolonization still need further exploration. The gut microbiota of CRE colonization and consequent infection also deserves further study. This study has a prime reference value for early identification of high-risk patients and prediction of the possibility of infection, which is of great significance for the clinical prevention and control of CRE colonization, and the inhibition of consequent systemic infection.

Conclusions

In this study, we explored the correlation between intestinal CRE colonization and consequent systemic infection in inpatients in a large teaching hospital. A total of 317 cases of intestinal CRE colonization were included, with an incidence of consequent systemic CRE infection of 25.9%. It was found that *Klebsiella pneumoniae* and *Escherichia coli* were the main bacterial strains that followed intestinal CRE colonization in hospitalized patients. The main sites of infection were the lungs and blood stream. High-risk departments mainly included respiratory medicine, hematology, and ICU. CRE infection occurring after intestinal CRE colonization in inpatients can significantly prolong the length of hospital stay and increase the total cost. Additionally, the CRE infection group had poor efficacy and high mortality. The established risk prediction model for intestinal infection after CRE colonization in hospitalized patients had a good prediction efficiency for high-risk departments.

Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
All methods were conducted in accordance with the relevant guidelines and regulations. All experimental protocols were approved by the Ethics Committee of Xiangya Hospital, Central South University. Informed consent was obtained from all patients and/or their legal guardian.

Additional information
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