

# Microbiological Characteristics, Risk Factors, and Short-Term Mortality of Carbapenem-Resistant *Enterobacteriaceae* Bloodstream Infections in Pediatric Patients in China: A 10-Year Longitudinal Study

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**Background:** Carbapenem-resistant *Enterobacteriaceae* (CRE) is rapidly becoming a major threat to hospitalized children worldwide. The purpose of this study was to summarize etiological characteristics and identify risk factors relevant to CRE bloodstream infection (BSI) and short-term mortality among pediatric patients in China.

**Methods:** In this study, we included 370 inpatients  $\leq 17$  years old with BSI caused by *Enterobacteriaceae* in China from January 2013 to December 2022. By collecting data on demographics, etiological features, and clinical outcomes, we conducted an in-depth analysis.

**Results:** Among the 370 BSI patients with infections caused by *Enterobacteriaceae*, 35 patients (9.46%) were caused by CRE. Among these CRE strains, *Klebsiella pneumoniae* (49.46%) was the most important pathogen of BSI in pediatric patients, followed by *Escherichia coli* (31.62%) and *Enterobacter cloacae* (5.95%). The most frequent carbapenemase was NDM (23/35, 65.71%), followed by KPC (8/35, 22.86%). The overall 28-day mortality rate of children with an *Enterobacteriaceae* BSI episode was 1.89% (7/370), of which CRE BSI patients (3/35, 8.57%) were significantly higher than CSE patients (4/335, 1.19%,  $P < 0.001$ ). Congenital malformation (OR: 8.162, 95% CI: 3.859–16.680,  $P < 0.001$ ) and catheter-related (OR: 6.645, 95% CI: 3.159–13.28,  $P < 0.001$ ) were associated with the development of CRE BSI in pediatric patients. A multivariate analysis showed that the infection of CRE (OR 7.758, 95% CI 1.869–29.62,  $P = 0.021$ ) were independent risk factors for 28-day mortality of *Enterobacteriaceae* BSI. When the MIC of any carbapenems was  $\geq 8$   $\mu\text{g/mL}$ , the mortality rate in the ICU was higher ( $P < 0.05$ ).

**Conclusion:** Congenital malformation, previous cephalosporin/carbapenems administration, and catheter-related conditions were closely related to the development of CRE BSI. The mortality rate of CRE BSI was higher. NDM was the predominant carbapenemase-producing mechanism in children.

**Keywords:** carbapenem-resistant *Enterobacteriaceae*, bloodstream infection

## Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) is increasingly isolated and poses a great threat to hospitalized children worldwide.<sup>1,2</sup> Oncologic conditions, premature infants, and hospitalization in the intensive care unit (ICU) are frequently reported in available case series of pediatric CRE infections.<sup>3–5</sup> Specifically, bloodstream infections (BSIs) caused by CRE are exceptionally intractable problems in children, with significant morbidity and mortality.<sup>6</sup>

Due to the limited treatment options available for children,<sup>7,8</sup> the treatment of CRE BSI is challenging for the pediatrician. The key to successful prevention and treatment of CRE infection is to implement infection control measures and early identification of high-risk patients. Most of the information available on risk factors, clinical characteristics, therapeutic options, and prognosis was provided by adult population studies. It is reported risk factors for CRE-BSI in adults include extended hospital stay, critical illness, medical device intervention, long-term use of broad-spectrum antibiotics, and residency in nursing homes.<sup>9–11</sup> There is still little research information on CRE-BSI in children.<sup>12,13</sup>

This study is aimed to summarize the etiological features and determine risk factors for CRE-BSI and predictors of 28-day mortality associated with the infection in a pediatric cohort.

Therefore, we conducted a retrospective analysis spanning 10 years. The 10-year time frame enhances the value of the epidemiological characteristics of CRE infections. Studies with a long-time span help to identify and validate long-term risk factors associated with the development of CRE BSI and allow for a more accurate assessment of the mortality rate of CRE BSI, which is crucial for guiding clinical treatment and prevention measures.

## Methods

This study was carried out in the First Affiliated Hospital of Sun Yat-sen University from January 2013 to December 2022. A total of 370 episodes were enrolled in this study. Patients aged  $\leq 17$  years old with confirmed *Enterobacteriaceae* BSI were included. Based on the established criteria, *Enterobacteriaceae* BSI is defined as the presence of at least one positive blood culture with infectious symptoms and signs. Only the first phase of BSI was included. Patients with multi-bacterial BSI or patients with incomplete medical records were excluded. The included patients were followed up for 28 days from the date of the first positive blood culture.

CRE was defined as an isolate with a minimum inhibitory concentration (MIC) of  $\geq 2$   $\mu\text{g/mL}$  for ertapenem (ETP) or  $\geq 4$   $\mu\text{g/mL}$  for imipenem (IMP) or meropenem (MEM), according to the CLSI criteria (Clinical and Laboratory Standards Institute, 2022). Death within 28 days after the first positive blood culture was considered as the outcome evaluation.

The collected data included basic information, underlying diseases, length of hospital stay, admission to the intensive care unit (ICU), invasive surgery, immunosuppressive treatment 90 days prior to the onset of BSI, antibiotic treatment one month prior, pathogen characteristics, and patient outcomes.

## Microbiological methods

Bact/ALERT<sup>®</sup> VIRTUO<sup>®</sup> blood cultures incubation (bioMérieux, Marcy l'Etoile, France) was used to incubate the blood specimen. Vitek 2 system (bioMérieux, Marcy l'Etoile, France) was used to identify the strains. Gram-negative susceptibility (GNS) cards (bioMérieux, Marcy l'Etoile, France) was employed to examine the antibiotic susceptibility tests for the strains. Antibiotic susceptibility testing results were interpreted according to the criteria recommended by the Clinical and Laboratory Standards Institute (CLSI, 2022). *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 were used as the quality control strains for antibiotic susceptibility testing. The carbapenemase was examined by immunochromatographic assay NG-test CARBA 5 kit (FOSUN DIAGNOSTICS, Changsha, China). This assay is able to detect the five most common carbapenemase among carbapenemase in *Enterobacteriaceae*: KPC (*Klebsiella pneumoniae* carbapenemase), NDM (New Delhi metallo- $\beta$ -lactamase), IMP (imipenemase metallo- $\beta$ -lactamase), VIM (Verona integron-encoded metallo- $\beta$ -lactamase) and OXA-48 like (oxacillinase-48-like type carbapenemase).

## Statistical Analysis

Numerical expressions for categorical variables are presented as percentages and figures. For continuous variables, the mean and standard deviation (SD) are provided for those following a normal distribution or the median with the interquartile range (IQR) for distributions that are not normal. Comparisons of categorical data were conducted using the Chi-square or Fisher's exact test as appropriate. Continuous data were evaluated using the Student's *t*-test or the Mann–Whitney *U*-test, depending on their distribution. The outcomes from the univariate analyses included the Odds ratio (OR), the 95% confidence interval (CI), and the P-value. Variables that demonstrated significance with a P-value of less than 0.05 were subsequently included in the binary logistic regression model to identify multivariate factors associated with the risk of CRE bloodstream infections (BSIs). The potential risk determinants for 28-day mortality

due to CRE-BSI were examined using Cox logistic regression. The Forward LR method was employed in the multi-variable assessment, integrating both binary logistic and Cox logistic regression. Survival curves were plotted using the Kaplan–Meier method to conduct survival analysis.

In the context of statistical testing throughout these analyses, a P-value threshold of less than 0.05 was indicative of statistical significance. The software utilized for all statistical evaluations was GraphPad Prism, version 10.0.

## Result

### Clinical and Demographic Characteristics of Patients

Among these 370 hospitalized children enrolled in the study, 35 (9.46%) presented a BSI by CRE. The 28-day mortality rate of children with an *Enterobacteriaceae* BSI episode was 1.89% (7/370). It was significantly higher for patients with CRE BSI (3/35, 8.57%) than for patients with CSE BSI (4/335, 1.19%,  $P = 0.021$ ). The overall ICU-stay rate of children with an *Enterobacteriaceae* BSI episode was 8.11% (30/370), which was also significantly higher for patients with CRE BSI (7/35, 20.0%) than patients with CSE BSI (23/335, 6.87%,  $P = 0.0151$ ).

In terms of the age distribution, preschool pediatric patients have a higher rate of CRE BSI, especially before the age of 6 years (OR: 2.921, 95% CI: 1.432–5.888,  $P = 0.0041$ ). These pediatric patients with CRE BSI had a significantly higher rate of congenital malformations including congenital heart disease, biliary atresia, absence of kidney (OR: 8.162, 95% CI: 3.859–16.680,  $P < 0.001$ ) and indwelling catheters (OR: 6.645, 95% CI: 3.159–13.28,  $P < 0.001$ ), as well as early long-term exposure to antibiotics, particularly carbapenems, which caused patients more likely to develop CRE BSI. The clinical and demographic characteristics of cohort patients with *Enterobacteriaceae* BSI isolates are shown in Table 1.

**Table 1** Demographic Characteristics and Risk Factors of BSI Caused by CRE and BSI Patients Caused by CSE

	Total:n=370(%)	CSE:n=335(%)	CRE:n=35(%)	P value	OR	95% CI
Demographic variables						
Male sex	209(56.48)	192(57.31)	17(56.60)	0.321		
Age						
0–27 Days	15(4.05)	15(4.48)	0(0.00)	0.201		
1–12 Months	55(14.86)	46(13.73)	9(25.71)	0.058		
1–6 Years	125(33.78)	105(31.34)	20(57.14)	0.004	2.921	1.432–5.888
7–14 Years	121(32.70)	116(34.63)	5(14.29)	0.014	0.315	0.130–0.802
15–17 Years	54(14.59)	53(15.82)	1(2.86)	0.042	0.157	0.015–0.944
Co-morbidities						
Hematological tumors	110(29.72)	103(30.75)	7(20.00)	0.244		
Congenital malformation	53(14.32)	33(9.85)	20(57.14)	<0.001	8.162	3.859–16.680
Premature delivery	18(4.86)	18(5.37)	0(0.00)	0.396		
Solid organ tumors	35(9.46)	33(9.85)	2(5.71)	0.557		
Laboratory examination						
Neutropenia ( $ANC < 0.5 \times 10^9$ )	167(45.14)	159(47.46)	8(22.86)	0.007	0.328	0.153–0.740
PCT >2 ng/mL	165(44.59)	149(44.48)	16(45.71)	1.000		
CRP >10 mg/mL	153(41.35)	121(36.12)	32(91.43)	<0.001	18.870	6.154–59.400
Antibiotics before isolation						
$\beta$ -Lactam/lactamase combinations	28(7.57)	25(7.46)	3(8.57)	0.739	1.163	
cephalosporins	46(12.43)	36(10.75)	10(28.57)	0.006	3.322	1.505–7.283
carbapenems	98(26.48)	81(24.18)	17(48.57)	0.011	2.510	1.268–4.906
quinolones	27(7.30)	24(7.16)	3(8.57)	0.732		
antifungal	67(18.1)	58(17.31)	9(25.71)	0.073		
others	76(20.54)	71(21.19)	5(14.26)	0.389		

(Continued)

**Table 1** (Continued).

	Total:n=370(%)	CSE:n=335(%)	CRE:n=35(%)	P value	OR	95% CI
Invasive operation						
Puncture	138(37.29)	127(37.91)	11(31.43)	0.582		
Catheter	90(24.23)	68(20.30)	22(62.86)	<0.001	6.645	3.159–13.28
Mechanical ventilation	23(6.22)	19(5.67)	4(11.43)	0.256		
Surgery	28(7.57)	24(7.16)	4(11.43)	0.322		
Pathogen isolated from other sites	24(6.49)	17(5.07)	7(20.00)	0.004	4.676	1.820–12.45
ICU stay(days)	30(8.11)	23(6.87)	7(20.00)	0.015	3.391	1.320–8.268
Mortality	7(1.89)	4(1.19)	3(8.57)	0.021	7.758	1.869–29.62

**Note:** Data are expressed as n (%) or median (IQR).

**Abbreviations:** ANC, absolute neutrophil count; PCT, procalcitonin; CRP, C-reaction protein; ICU, intensive care unit.

## Microbiological Characteristics of Enterobacteriaceae Strains

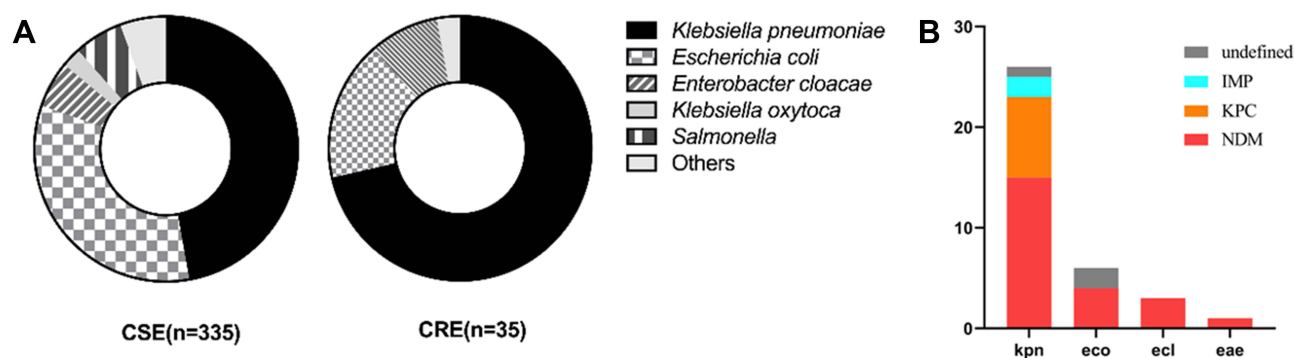
The characteristics of strains are shown in Figure 1A. The top three species causing overall *Enterobacteriaceae* BSI in children were *Klebsiella pneumoniae* (Kpn, 183/370, 49.46%), *Escherichia coli* (Eco, 117/370, 31.62%), and *Enterobacter cloacae* (Ecl, 22/370, 5.95%). This ranking was consistent in both CRE BSI and CSE BSI. In addition, Other *Enterobacteriaceae* species involved were *Klebsiella oxytoca* (8/335, 2.39%), *Salmonella* bacteria (20/335, 5.97%), and other pathogens.

Most of the CRE strains (32/35, 91.43%) were found to produce carbapenemases. The most frequent carbapenemase was NDM (23/35, 65.71%), followed by KPC (8/35, 22.86%). Two Kpn isolates showed IMP positive, and one co-harbored NDM and IMP (Figure 1B). The susceptibility testing results of isolates with statistically significant differences of MIC ( $P < 0.05$ ) were compared in Figure 2. CRE isolates showed more common resistance to other types of antibiotics than CSE isolates. The results were displayed in the form of minimum inhibitory concentration (MIC) for piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, amikacin, and ciprofloxacin. The MIC of piperacillin-tazobactam, ceftazidime, cefepime, and aztreonam was higher in the CRE strain ( $P < 0.0001$ ), while amikacin was higher in the CSE strain ( $P < 0.001$ ).

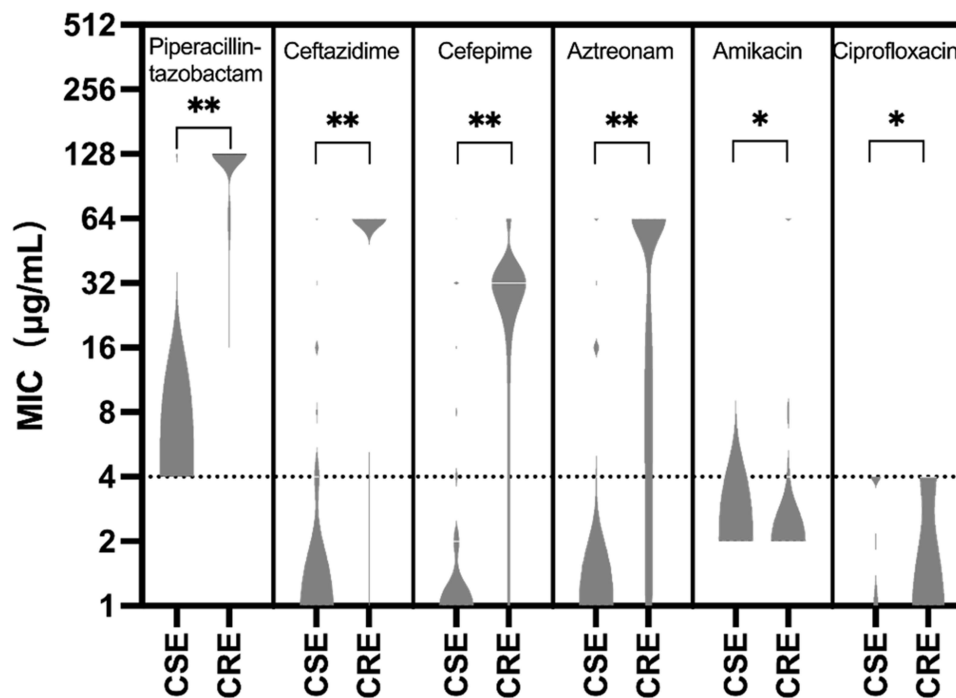
Table 2 presented the antimicrobial resistance patterns of 35 CRE strains, categorized based on the type of carbapenemase they produced. The findings revealed that CRE strains harboring NDM-type carbapenemases exhibited the most sensitive in vitro to colistin and tigecycline. While strains producing KPC-type carbapenemases demonstrated enhanced in vitro susceptibility to ceftazidime-avibactam, as well as to colistin and tigecycline.

## Risk Factors and Outcome of CRE BSI versus CSE BSI

The univariate analysis identified potential risk factors for CRE BSI among pediatric patients, including congenital malformations, such as congenital heart disease, biliary atresia, and absence of kidneys (OR 8.162, 95% CI



**Figure 1** (A) Microbiological characteristics of CRE and CSE strains, (B) Characteristics of carbapenemase in CRE strains.

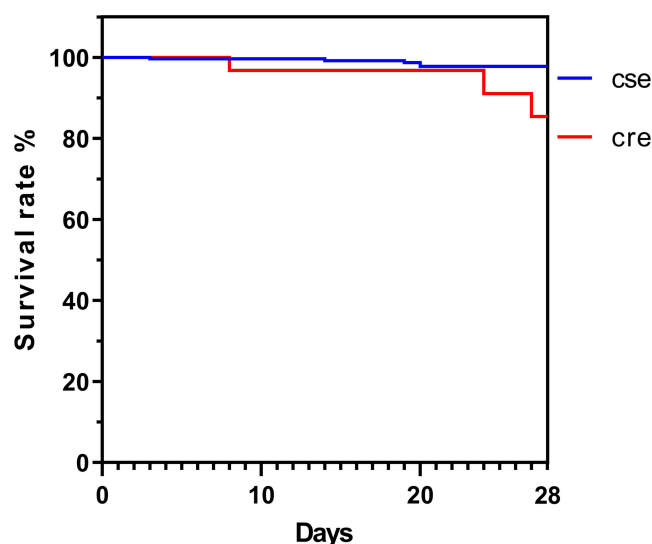


**Figure 2** Partly susceptibility testing results of CSE and CRE isolates in MIC ( $\mu\text{g/mL}$ ), the dashed horizontal line at 4  $\mu\text{g/mL}$ : breakpoint for the aforementioned drug  
\* $P < 0.001$ , \*\* $P < 0.0001$ .

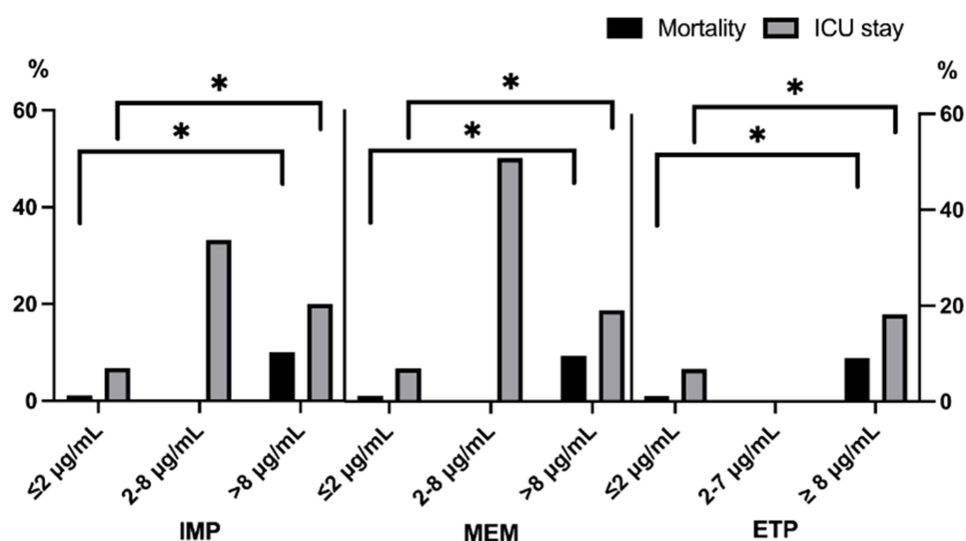
3.859–16.680,  $P < 0.001$ ), abnormal CRP values (OR 18.870, 95% CI 6.154–59.400,  $P < 0.001$ ), and pathogens isolated from other sites (OR 4.674, 95% CI 1.820–12.450,  $P = 0.004$ ). Further, ICU stays before BSI onset (OR 3.391, 95% CI 1.320–8.268,  $P = 0.015$ ), catheter input (OR 6.645, 95% CI 3.159–13.280,  $P < 0.001$ ), prior exposure to carbapenems (OR 2.510, 95% CI 1.268–4.906,  $P = 0.011$ ) and cephalosporins (OR 3.322, 95% CI 1.505–7.283,  $P = 0.006$ ) were identified associated with CRE BSI.

**Table 2** Resistance of CRE Strains Stratified for Carbapenemase Type to Specific Antimicrobials

Antibiotic	NDM (n=22)	KPC (n=8)	IMP (n=1)	NDM+IMP (n=1)	Undefined (n=3)
Piperacillin-tazobactam	100.0%	100.0%	100.0%	100.0%	100.0%
Ceftazidime	100.0%	100.0%	100.0%	100.0%	66.7%
Cefoperazone/Sulbactam	100.0%	87.5%	100.0%	100.0%	66.7%
Cefepime	95.5%	100.0%	100.0%	100.0%	66.7%
Aztreonam	86.4%	87.5%	100.0%	100.0%	100.0%
Imipenem	100.0%	87.5%	100.0%	100.0%	33.3%
Meropenem	100.0%	100.0%	100.0%	100.0%	66.7%
Ertapenem	90.9%	100.0%	100.0%	100.0%	100.0%
Ceftazidime-Avibactam	90.9%	0.0%	100.0%	100.0%	0.0%
Amikacin	9.1%	37.5%	0.0%	0.0%	0.0%
Tobramycin	9.1%	25.0%	100.0%	0.0%	0.0%
Ciprofloxacin	4.5%	37.5%	0.0%	100.0%	0.0%
Levofloxacin	31.8%	37.5%	0.0%	100.0%	0.0%
Doxycycline	27.3%	12.5%	0.0%	0.0%	0.0%
Minocycline	31.8%	12.5%	0.0%	0.0%	0.0%
Polymyxin	0.0%	0.0%	0.0%	0.0%	0.0%
Tigecycline	0.0%	0.0%	0.0%	0.0%	0.0%



**Figure 3** The 28-day survival rate of CRE BSI versus CSE BSI in the Kaplan–Meier curve.



**Figure 4** Effect of ETP, MEM, IMP drug susceptibility of isolated strains affect mortality and ICU hospitalization, \*:  $P < 0.001$ .

The 28-day mortality rate of CRE BSI relative to CSE BSI was compared in Figure 3. Kaplan–Meier survival analysis showed a significant difference in the 28-day survival rate between CRE BSI patients and CSE BSI patients, with CRE patients having a higher mortality rate (8.57% vs 1.19%,  $P < 0.001$ ).

The susceptibility of carbapenem antibiotics to the isolated strains was detected, and it was found that different MICs significantly affected the mortality and ICU hospitalization of patients ( $P < 0.05$ ) (Figure 4). When the MIC of carbapenems was  $\geq 8$  µg/mL, the admission rate and mortality rate in the ICU were higher.

## Discussion

In this retrospective observational study, we analyzed 370 children with BSI caused by *Enterobacteriaceae* and found that nearly 10% of patients developed BSI caused by CRE. According to the China Antimicrobial Resistance Surveillance Network (CHINET), the detection rate of CRE strains in China has increased from 2.7% in 2012 to 9.7% in 2022. Our research findings are marginally elevated, which could be attributed to the more severe condition of BSI patients, who are more prone to developing CRE infections. Notably, the incidence of CRE BSI was the highest in the



age group under 6 years of age. This may be because the majority of patients in this study came from the hematology-oncology ward. Children with hematologic cancers have an early onset of disease, weakened immunity, and long-term exposure to prophylactic antibiotics. It is reported that carriers of carbapenem-resistant *Enterobacteriaceae* in children with hematologic disorders with neutropenia are at high risk of bloodstream infection.<sup>14</sup>

Among the 35 CRE strains, *Klebsiella pneumonia* remained the most important pathogen of BSI in pediatric patients, followed by *Escherichia coli* and *Enterobacter cloacae*. We also found that NDM was the predominant carbapenemase-producing mechanism in children, which was consistent with CHINET's data. However, Ruvinsky's research found that in Argentina, KPC is the most dominant enzyme form in children, indicating that carbapenemase-producing *Enterobacteriaceae* has different molecular and epidemiological characteristics in different geographical regions.<sup>14,15</sup> In China, the main mechanism causing carbapenem resistance was KPC-producing among adults,<sup>16,17</sup> and ceftazidime/avibactam (CZA) is widely used to treat CRE infection with KPC-producing CRE, which is ineffective against NDM-producing isolates.<sup>18</sup> In fact, for children suspected of CRE bloodstream infection, after determining the pathogen and enzyme production mechanism, CZA combined with aztreonam can be considered for the treatment of metallo-enzyme-producing strains including NDM and IMP.<sup>19</sup>

According to our study, we showed that congenital malformation (including congenital heart disease, biliary atresia, absence of kidney), previous cephalosporin, and carbapenems administration were independent risk factors for CRE BSI. Patients with congenital malformations typically undergo surgical procedures, more frequent exposure to healthcare, longer antibiotic treatment times, and more medical interventions. All these factors will increase the risk of infection.<sup>20,21</sup> Laura et al<sup>1</sup> reported that 84% of CRE BSI children had underlying diseases and most of them (46%) suffered from hematological malignancies or solid tumors. The 28-day mortality rate (8.57%) of the CRE group was also lower than previous reports.<sup>2,22</sup> Recently, Montagnani et al reported that 4 out of 9 children in Italy (44.4%) died of CRE BSI.<sup>3</sup> Another study showed that the CRE-BSI-related mortality rate in the Indian pediatric population was 52%.<sup>1</sup> Therefore, closely monitoring the epidemic characteristics of CRE infection in local children is beneficial for early identification of infection risks and improving cure rates.

The relationship between meropenem MIC and increased patient mortality has been previously reported.<sup>23,24</sup> Similarly, in our study, the MIC values of carbapenems in CRE strains can also predict a higher mortality rate in children. In adults, it is suggested that improved survival in patients receiving combinations of two or more in vitro active antibiotics, mainly in patients with a higher probability of death.<sup>25,26</sup> This result has been inferred as a prediction for pediatric patients.<sup>4</sup>

The limitation of this study is that it was a retrospective study conducted in a single center, which may affect the ability to summarize research results. Further large-scale prospective multicenter investigations are needed.

In conclusion, congenital malformations, prior administration of cephalosporins/carbapenems, and the presence of indwelling catheters were associated with the development of CRE bloodstream infections (BSI). NDM was the primary carbapenemase-producing mechanism contributing to carbapenem resistance. Consequently, given the varying characteristics of patients infected with different strains of carbapenem-resistant *Enterobacteriaceae* (CRE), it is essential to apply individualized antimicrobial therapy.

## Impact

1. The key message of the article is that we summarized etiological characteristics and identify risk factors relevant to CRE bloodstream infection and short-term mortality among pediatric patients in China.
2. Our study provides new insights into the etiology and risk factors of CRE bloodstream infections among pediatric patients, including congenital malformation, CRP levels, and catheter-related conditions. Our findings suggest that CRE infections are associated with a higher mortality rate compared to carbapenem-susceptible *Enterobacteriaceae* (CSE) infections and that NDM was the most common carbapenemase-producing mechanism among the CRE isolates.
3. In terms of impact, our study may have a significant impact on the management of CRE infections in pediatric patients by providing clinicians with a better understanding of the disease and its risk factors. This information may lead to improved patient outcomes and reduce the burden of CRE infections in pediatric patients.

## Abbreviations

CRE, Carbapenem-resistant Enterobacteriaceae; CSE, Carbapenem-susceptible Enterobacteriaceae; BSI, Bloodstream infection; ICU, Intensive care unit; MIC, Minimum inhibitory concentration; ANC, absolute neutrophil count; PCT, procalcitonin; CRP, C-reaction protein; Kpn, *Klebsiella pneumoniae*; Ecl, *Enterobacter cloacae*; Eco, *Escherichia coli*.

## Data Sharing Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board and Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University and conducted according to the Declaration of Helsinki (Approved No. of ethics committee: [2024]-200). The ethics committee approved the waiver of informed consent owing to the retrospective nature of the review. All research data were de-identified and anonymously analyzed.

## Consent for Publication

NA

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## Disclosure

The authors declare that they have no competing interests.

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