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ORIGINAL RESEARCH

Risk Factors for Mortality and Antimicrobial Regimens in Pediatric Intensive Care Unit Patients with Carbapenem-Resistant *Enterobacteriaceae* Infections: A Six-Year Retrospective Study

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Purpose: Limited data are available on the characteristics, risk factors, and antimicrobial treatment of critically ill pediatric patients with carbapenem-resistant *Enterobacteriaceae* (CRE) infections. This study was to identify the risk factors for 30-day mortality in pediatric intensive care unit (PICU) patients with CRE infections and compare the clinical outcomes of different antimicrobial regimens.

Methods: A retrospective, observational cohort study was performed on patients admitted to the PICU with positive CRE cultures between January 2016 and December 2021.

Results: For the 56 patients, the overall 30-day mortality was 50% (n=28). Multivariable logistic regression analysis revealed that pediatric critical illness score (PCIS; HR = 0.879; 95% CI, 0.827–0.935; $P < 0.001$) and serum albumin levels (HR = 0.921; 95% CI, 0.860–0.987; $P = 0.019$) were independently associated with 30-day mortality. At the same time, there was no significant difference in 30-day mortality (42.9% versus 45.5%, $P = 0.854$) or clinical efficiency rate (53.4% versus 40.9%, $P = 0.374$) between with and without polymyxin B therapy.

Conclusion: The study revealed PCIS and serum albumin levels were the independent mortality-related risk factors of CRE infections in critically ill pediatric patients. Treatment with polymyxin B could not reduce 30-day mortality. Future prospective cohort studies are needed to investigate the optimal antimicrobial regimens for CRE infection in PICU patients.

Keywords: carbapenem-resistant*Enterobacteriaceae*, pediatric intensive care unit patients, mortality, risk factors, antimicrobial regimens

Introduction

With the worldwide prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE), it has become a significant problem in terms of public health.[1,2] Multi-drug resistance profile of CRE leads to considerable mortality. The overall 30-day mortality of CRE infections is approximately 30–50% in adult patients,[3–5] and as high as 52% in children.[6–8] Several factors such as immunocompromised status, sepsis/septic shock, and neutropenia have been reported to be significant risk factors for 30-day mortality in adult patients with CRE infection.[5,9,10] However, limited data are available on the characteristics and risk factors of children with CRE infections, especially critically ill pediatric patients.

In addition, antimicrobial options against CRE infections are limited, and only a few antibiotics are available, including carbapenems, polymyxins, quinolone, aminoglycosides, and tigecycline.[11,12] Due to significant adverse effects

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of some antibiotics, such as musculoskeletal adverse reactions of quinolones and ototoxicity and nephrotoxicity of aminoglycosides.[13,14] And serious underlying diseases and complications, the treatment of CRE infections in pediatric intensive care unit (PICU) patients is a real challenge for clinicians.

This study aimed to identify the risk factors for 30-day mortality in PICU patients with CRE infections and to compare the clinical outcomes of different antimicrobial regimens for CRE infections.

Materials and Methods

Study Design and Patient Selection

We conducted a retrospective, observational cohort study of hospitalized patients with positive CRE cultures in PICU between January 2016 and December 2021. Inclusion criteria were (ⅰ) patients with positive cultures of CRE; (ⅱ) > 1 month old and < 18 years old. Exclusion criteria were (ⅰ) age < 1 month old or >18 years old; (ⅱ) polymicrobial infections; (ⅲ) hospital stay after positive culture of CRE < 24 h; (ⅳ) without clinical manifestation of CRE infection, which were determined by 3 experienced clinicians. The study was approved by the ethics review committee of the research project of the First Affiliated Hospital of Zhengzhou University (2022-KY-0168) and waived informed consent given the retrospective nature.

The primary outcome was all-cause mortality on day 30 after the onset of CRE infection. Clinical efficiency of antibiotic therapies was also analyzed.

Microbiology

The Vitek® 2 COMPACT automated system (France Biomerieux) was employed for bacterial identification and drug sensitivity tests. The biological samples included blood, sputum, urine, bronchial-alveolar lavage fluid, abdominal drainage fluid, cerebrospinal fluid, and skin sanies. Carbapenem-resistant *Enterobacteriaceae* was defined as *Enterobacteriaceae* were resistant to ≥ 1 carbapenem antibiotics. Minimum inhibitory concentration (MIC) breakpoint ≥ 4 mg/L for meropenem/imipenem/doripenem or ≥ 2 mg/L for ertapenem was defined as carbapenem resistance.[15] Isolated with MIC ≤ 2 mg/L were considered susceptible to polymyxins.[16] Meanwhile, in accordance with the US FDA, MIC ≥ 8 mg/L represented bacterial resistance to tigecycline.[17]

Study Definitions

The severity of infection was assessed by pediatric critical illness score (PCIS) on the day of positive cultures of CRE.[18] Pediatric index of mortality (PIM) 3 and pediatric risk of mortality (PRISM) III on the day of admission to PICU were used to predict the risk of mortality from CRE infection. Probability of death was determined by the PIM3 score, which was calculated from this formula (probability of death = exp (PIM3 score)/[1+exp (PIM3 score)]).[19] Immunosuppression included immunosuppressive therapy and primary immune deficiency diseases. Multi-site infection was defined as the isolation of pathogens from ≥ 2 sites. Clinical efficiency was defined as clinical or microbiological improvement, including remission or resolution of infection symptoms and clearance of pathogenic microorganisms, which were determined by 3 experienced clinicians.

Data Collection

Data extracted from the electronic medical record, included demographics (age, weight, and gender), PCIS, underlying disease, invasive procedures (central venous catheterization, urinary catheterization, gastric catheterization), clinic features, infection sites and sensitivity of pathogenic bacteria, and blood biochemical indices on the day of positive cultures of CRE. Antimicrobial regimens and clinical efficiency were assessed at the end of CRE treatment. Thirty-day all-cause mortality was recorded from the day of positive cultures of CRE.

Statistical Analysis

Continuous variables were presented as median (interquartile ranges, IQR), and were analyzed by Mann–Whitney *U*-test. The Categorical variables were presented as numbers (%) and were analyzed by the Chi-square test or Fisher's exact test.

To determine risk factors for mortality, baseline feature between deceased and survived patients at the 30-day point were compared using univariate analysis. Risk factors with $P<0.1$ were included into a Cox proportional hazards model to establish independent predictors for the 30-day mortality. Statistical analyses were performed with SPSS software (version 26; SPSS Inc., Chicago, IL, USA). All tests were two-tailed, with the significance level set at 0.05.

Results

Patient Overview

During the study period, a total of 116 patients with CRE infection were included. Finally, 60 patients were excluded and 56 patients were enrolled in the analysis (Figure 1). Patient characteristics were shown in Table 1. The median patient age was 10 years (IQR, 2.7–11.7 years) and 39 (69.6%) were male. The highest proportion of pathogen was *Klebsiella pneumoniae* (n=37, 66.1%), followed by *Escherichia coli* (n=16, 28.6%), *Klebsiella oxytoca* (n=1, 1.8%), *Citrobacter freundii* (n=1, 1.8%), and *Raoultella planticola* (n=1, 1.8%). Among them, 12 patients (21.4%) had multi-site infections. The sites of CRE infection included bloodstream (n=29, 51.8%), pulmonary (n=27, 48.2%), intraperitoneal infection (n=5, 8.9%), and others (n=7, 12.5%; urinary tract n=2; intracranial n=2; skin n=3). The resistance rate to meropenem was over 90%, while the rest 10% was resistant to imipenem or ertapenem (Table S1). All isolated pathogens were susceptible to polymyxin B and 96.4% of them were susceptible to tigecycline.

Risk Factors for 30-Day Mortality in CRE-Infected Pediatric Patients

The overall 30-day mortality was 50% (n=28, Table 1). Among them, 25 children had infection-related mortality. As to the other 3 children, one died of pneumothorax and 2 died of pulmonary hemorrhage, unexpectedly (Table S2). Risk factors for 30-day mortality associated with CRE infection were investigated by Cox regression analysis. Since the probability of death was calculated by PIM3 score, only the probability of death was included in further analysis. Cox regression results suggested that serum albumin level (hazard ratio [HR] = 0.921; 95% confidence level [CI], 0.860–0.987; $P = 0.019$) and PCIS (HR = 0.879; 95% CI, 0.827–0.935; $P < 0.001$) were correlated with 30-day mortality (Figure 2), which was consistent with the result of infection-related mortality analysis (Figure S1).

Furthermore, the area under the curve (ROC) of PCIS and serum albumin level for the perspective of 30-day mortality was 0.804 (95% CI, 0.692–0.916; $P = 0.001$) and 0.754 (95% CI, 0.627–0.881; $P = 0.001$), respectively (Figure 3). The

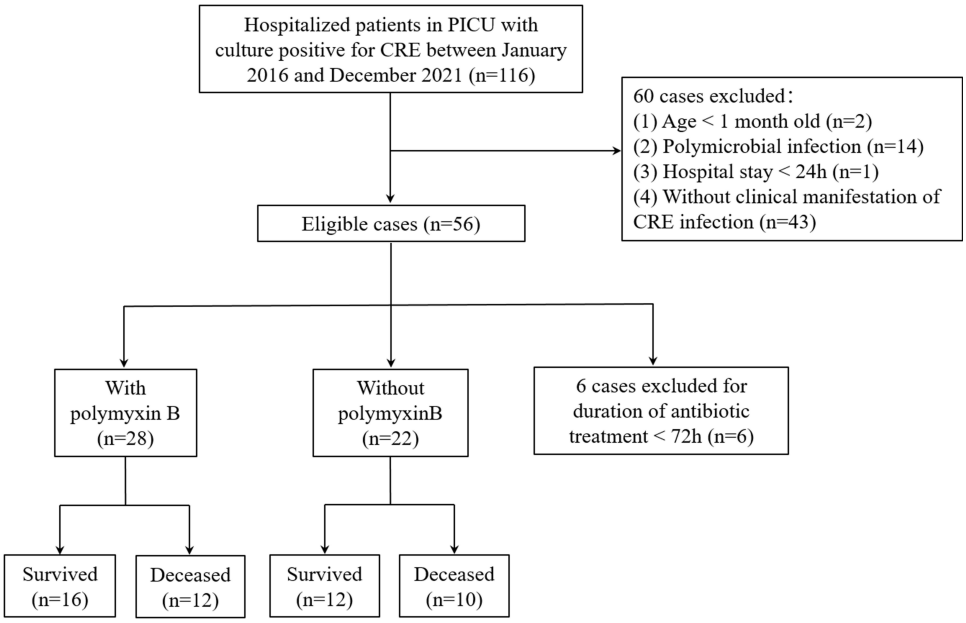

Figure 1 Flow chart of included patients with CRE infections. CRE, carbapenem-resistant *Enterobacteriaceae*; PICU, pediatric intensive care unit.

Table 1 Patient Characteristics

Characteristic	Total (n = 56)	Deceased (n = 28)	Survived (n = 28)	*P*
Age (year)	10.0 (2.7–11.7)	10.7 (3.7–12.5)	7.5 (2.2–10.9)	0.272
Weight (kg)	28.0 (14.0–41.8)	33.0 (17.3–41.8)	20.5 (13.0–46.0)	0.486
Male (%)	39 (69.6%)	22 (78.6%)	17 (60.7%)	0.146
PCIS	88.0 (80.5–92.0)	84.0 (78.0–90.0)	92.0 (86.5–96.0)	<0.001
PIM3 score	−2.6 (−3.6– −2.0)	−2.4 (−3.2– −1.7)	−2.8 (−4.2– −2.1)	0.098
Probability of death	6.9 (2.6–12.1)	8.7 (4.1–16.0)	5.5 (1.5–10.8)	0.098
PRISM III score	12.0 (7.3–16.8)	15.0 (12.0–18.0)	9.0 (5.0–12.0)	0.003
Septic shock, n (%)	13 (23.2%)	7 (25.0%)	6 (21.4%)	0.752
MODS, n (%)	18 (32.1%)	12 (42.9%)	6 (21.4%)	0.086
Mechanical ventilation, n (%)	20 (35.7%)	8 (28.6%)	12 (42.9%)	0.265
CPR, n (%)	8 (14.3%)	4 (14.3%)	4 (14.3%)	1.0
Surgery, n (%)	10 (17.9%)	5 (17.9%)	5 (17.9%)	1.0
Underlying disease, n (%)				
Hematological system disease	29 (51.8%)	19 (67.9%)	10 (35.7%)	0.016
Accidental injury	8 (14.3%)	1 (3.6%)	7 (25.0%)	0.051
Congenital malformation	7 (12.5%)	1 (3.6%)	6 (21.4%)	0.101
Immunodeficiency	3 (5.4%)	2 (7.1%)	1 (3.6%)	0.553
Others	9 (16.1%)	5 (17.9%)	4 (14.3%)	0.716
Immunosuppression, n (%)	38 (67.9%)	22 (78.6%)	16 (42.1%)	0.086
Invasive procedures, n (%)				
Central venous catheterization	40 (71.4%)	19 (67.9%)	21 (75.0%)	0.554
Urinary catheterization	27 (48.2%)	11 (39.3%)	16 (57.1%)	0.181
Gastric catheterization	33 (58.9%)	13 (46.4%)	20 (71.4%)	0.057
Infection sites, n=68(%)				
Bloodstream	29 (51.8%)	16 (57.1%)	13 (46.4%)	0.422
Pulmonary	27 (48.2%))	12 (42.9%)	15 (53.6%)	0.522
Intraperitoneal	5 (8.9%)	1 (3.6%)	4 (14.3%)	0.160
Others	7 (12.5%)	4 (14.3%)	3 (10.07%)	0.686
Meropenem MIC (mg/L)				
≥ 16	48 (85.7%)	24 (85.7%)	24 (85.7%)	0.766
4–8	3 (5.4%)	1 (3.6%)	2 (7.1%)	
≤2	5 (8.9%)	3 (10.7%)	2 (7.1%)	
Multi-site infection, n (%)	12 (21.4%)	5 (17.9%)	7 (25.0%)	0.515
Serum albumin	32.3 (27.6–36.8)	28.1 (25.2–33.6)	34.3 (29.5–38.8)	0.001
Creatinine	27.0 (16.3–40.5)	36.5 (18.3–54.0)	24.4 (16.0–34.5)	0.037
Lactate dehydrogenase	383.0(176.3–789.8)	471.0(215.5–852.8)	291.0(163.5–762.0)	0.334
Alamine aminotransferase	41.0 (18.3–66.8)	41.0 (14.0–98.5)	41.5 (21.3–59.5)	0.670
Total bilirubin	14.8 (6.8–49.3)	16.6 (7.4–70.6)	13.4 (6.3–32.2)	0.248
White blood cells	5.7 (0.3–12.4)	1.5 (0.2–11.3)	9.3 (0.3–13.0)	0.127
Hemoglobin	85.5 (74.2–95.7)	79.2 (70.3–94.5)	89.5 (76.2–96.8)	0.108
Platelet	49.5 (7.3–201.3)	28.5 (5.5–123.3)	143.0 (28.5–295.8)	0.006
C-reactive protein	120.0 (46.4–200.0)	168.1 (87.4–200.0)	95.7 (34.5–164.8)	0.043
Procalcitonin	2.5 (0.4–9.4)	4.6 (0.6–16.4)	1.1 (0.3–4.6)	0.068

Note: Categorical variables were presented as numbers (%), and continuous variables were presented as median (interquartile ranges).
Abbreviations: PCIS, pediatric critical illness score; PIM, paediatric index of mortality; PRISM, pediatric risk of mortality score; MODS, multiple organ dysfunction syndrome; CPR, cardiopulmonary resuscitation.

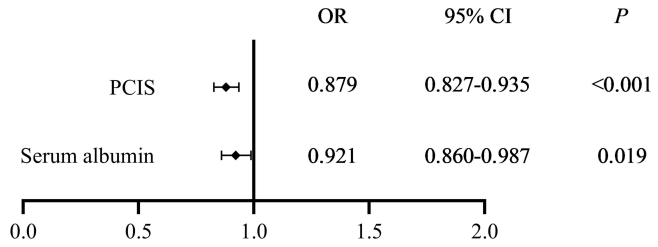

Figure 2 Cox regression of factors associated with 30-day mortality. HR, hazard ratio; CI, confidence interval; PCIS, pediatric critical illness score; MODS, multiple organ dysfunction syndrome.

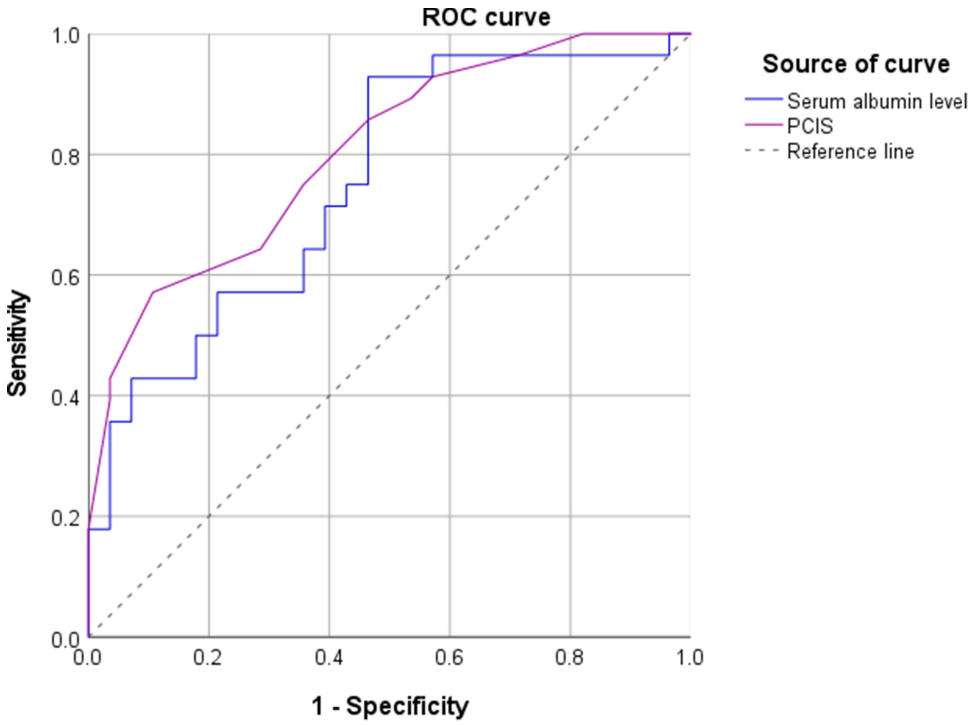

Figure 3 The area under the area under the curve of risk factor for the survive of CRE infections. CRE, carbapenem-resistant *Enterobacteriaceae*; PCIS, pediatric critical illness score.

optimum cut-off value of PCIS was 91, and its sensitivity and specificity were 57.1% and 46.4%, respectively. And the optimum cut-off value of serum albumin level was 28.4 g/L corresponding to 92.9% sensitivity and 46.2% specificity.

The Impacts of Different Antimicrobial Regimens on the 30-Day Mortality

Since 6 children received antibiotics treatment for less than 72 h, a total of 50 patients were included in the subgroup analysis. To investigate the effect of antimicrobial regimens on the 30-day mortality, patients were divided into polymyxin B group (n =28) and without polymyxin B group (n =22, Table 2). The 30-day mortality between patients with and without polymyxin B was no statistically significant difference (42.9% versus 45.5%, $P = 0.854$). The survival curves of the two treatment groups were shown in Figure 4. At the same time, there was also no statistically significant difference (53.4% versus 40.9%, $P = 0.374$; Table 3) for clinical efficiency.

Discussion

We performed an observational cohort study that evaluated risk factors for 30-day mortality of CRE infections in PICU patients over a 6-year study period. The overall 30-day mortality of PICU patients with CRE infections was 50% and the most frequently isolated pathogen was *K. pneumoniae* (n=37, 66.1%), which was consistent with previous domestic and

Table 2 Comparison of Characteristics and Treatment Between Patient with and without Polymyxin B

Characteristic	With Polymyxin B (n = 28)	Without Polymyxin B (n = 22)	*P*
Age (year)	9.8 (4.1–12.6)	9.9 (1.3–11.3)	0.197
Weight (kg)	32.0 (17.3–47.5)	23.3 (9.8–38.5)	0.120
Male (%)	19 (67.9%)	15 (68.2%)	0.981
PCIS	90.0 (86.0–93.5)	86.0 (80.0–96.0)	0.530
PIM3 score	−2.8 (−3.5– −2.2)	−2.6 (−4.2– −1.5)	0.845
Probability of death	5.9 (2.9–10.4)	7.3 (1.5–18.1)	0.845
PRISM III	12.0 (7.5–17.5)	11.5 (8.0–15.0)	0.583
Septic shock, n (%)	6 (21.4%)	5 (22.7%)	0.912
MODS, n (%)	12 (42.9%)	4 (18.2%)	0.076
Mechanical ventilation, n (%)	13 (46.4%)	7 (31.8%)	0.295
CPR, n (%)	5 (17.9%)	3 (13.6%)	1.0
Surgery, n (%)	4 (14.3%)	5 (22.7%)	0.481
Underlying disease, n (%)			
Hematological system disease	16 (57.1%)	9 (40.9%)	0.254
Accidental injury	3 (10.7%)	5 (22.7%)	0.277
Congenital malformation	2 (7.1%)	5 (22.7%)	0.217
Immunodeficiency	1 (12.5%)	0	0.371
Others	6 (21.4%)	3 (13.6%)	0.476
Immunosuppression, n (%)	20 (71.4%)	12 (54.5%)	0.217
Invasive procedures, n (%)			
Central venous catheterization	22 (78.6%)	15 (68.2%)	0.406
Urinary catheterization	18 (64.3%)	8 (36.4%)	0.050
Gastric catheterization	21 (75.0%)	11 (50.0%)	0.068
Infection sites, n=68 (%)			
Bloodstream	16 (57.1%)	8 (36.4%)	0.144
Pulmonary	13 (46.4%)	14 (63.6%)	0.226
Intraperitoneal	4 (14.3%)	1 (4.5%)	0.254
Others	3 (10.7%)	3 (13.6%)	0.752
Meropenem MIC (mg/L)			
≥ 16	23 (82.1%)	19 (86.4%)	0.906
4–8	2 (7.1%)	1 (4.5%)	
≤2	3 (10.7%)	2 (9.1%)	
Multisite infection, n (%)	8 (28.6%)	4 (18.2%)	0.512
Serum Albumin	32.2 (28.1–37.5)	33.0 (27.4–35.9)	0.977
Creatinine	27.5 (18.0–50.9)	25.5 (15.5–46.3)	0.358
Lactate dehydrogenase	342.0(194.3–805.5)	455.5(161.8–813.3)	0.860
Alamine aminotransferase	35.0 (15.5–57.5)	56.0 (21.0–68.8)	0.168
Total bilirubin	13.2 (6.8–37.5)	14. 5(6.1–33.5)	0.845
White blood cells	6.0 (0.3–14.2)	6.0 (0.3–11.9)	0.710
Hemoglobin	83.0 (77.8–96.5)	87.7 (70.8–100.0)	0.914
Platelet	56.5 (8.0–197.5)	57.0 (10.3–242.0)	0.625
C-reactive protein	106.2(43.6–200.0)	114.1 (38.2–200.0)	0.761
Procalcitonin	2.3 (0.4–7.7)	0.9 (0.3–15.4)	0.558
Deceased, n (%)	12 (42.9%)	10 (45.5%)	0.854

Note: Categorical variables were presented as numbers (%), and continuous variables were presented as median (interquartile ranges).
Abbreviations: PCIS, pediatric critical illness score; PIM, paediatric index of mortality; PRISM, pediatric risk of mortality score; MODS, multiple organ dysfunction syndrome; CPR, cardiopulmonary resuscitation.

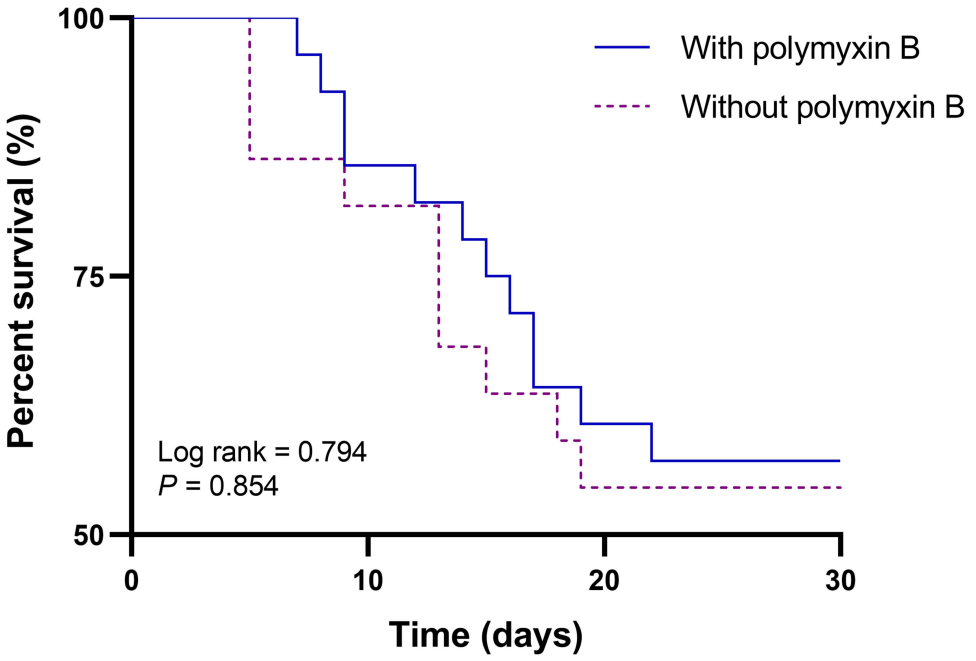

Figure 4 Survival rates of patients treated with polymyxin B and without polymyxin B.

international epidemiologic data.[3–8,20] In this study, hematological system disease, PCIS, serum albumin, platelet count, serum creatinine, and C-reactive protein were associated with mortality (Table 1). While only PCIS and serum albumin levels were the independent mortality-related risk factors in the Cox regression analysis (Figure 2).

For PICU patients, PIM3, PRISM III, and PCIS are commonly used mortality prediction models in pediatric patients.[21–23] In this study, PCIS, as a pediatric scoring system based on China's national conditions, showed a better correlation with 30-day mortality than PIM3 and PRISM III scores (Table 1). This may be because PCIS was assessed on the day of positive cultures of CRE, whereas PIM3 and PRISM III scores were assessed within 1 h and 24 h of PICU admission, respectively. Without dynamically assessing the scores at different time points, PIM3 and PRISM scores could not reflect the variable of diseases, leading to the inability to accurately predict the outcome. Nevertheless, PCIS does not include etiological scores, which may inaccurately predict the severity of the disease.[22,23] Since this study only selected PICU patients with CRE infection, which model is more suitable for PICU patients needs to be further studied.

Table 3 The Impacts of Different Therapy on the 30-Day Mortality

Antimicrobial Regimen	No.	Deceased (%)	*P*	Efficiency (%)	*P*
With polymyxin B	28	12 (42.9%)	0.854	15 (53.4%)	0.374
+Carbapenem	23	11		11	
+Carbapenem+Tigecycline	1	0		1	
+Tigecycline	1	0		1	
+Cefperazone/Sulbactam	2	1		1	
Monotherapy	1	0		1	
Without polymyxin B	22	10 (45.5%)		9 (40.9%)	
Carbapenem	14	5		6	
Cefoperazone/Avibatam	2	1		2	
Cefoperazone/Avibatam+Carbapenem	1	1		0	
Cefperazone/Sulbactam+Tigecycline	2	2		0	
Cefperazone/Sulbactam	1	1		0	
Carbapenem+Cefperazone/Sulbactam	1	0		0	
Carbapenem+Tigecycline	1	0		1	

In general, blood biochemical indexes are also important signals reflecting the pathological status of diseases. This study showed that children who deceased were more likely to have lower albumin levels than survivors (28.1 versus 34.3 g/L, $P = 0.001$; Table 1). Low albumin levels or the more serious condition known as hypoalbuminemia, refers to serum albumin < 30 g/L, is a common clinical complication in critically ill patients.[24] It is mainly caused by the following two reasons: a) inadequate intake and/or synthesis, such as liver disease and malnutrition; b) excessive consumption and/or loss, such as long-term fever, burns, nephrotic syndrome, etc. Low albumin levels can not only reflect the ailing physical condition but also affect the pharmacokinetics of drugs with high protein binding rates, thus affecting drug efficacy and clinical outcomes.[24]

Previous studies have identified several risk factors associated with the mortality of CRE infection, including sepsis/septic shock, immunosuppression or immunocompromised status, mechanical ventilation, and invasive procedures.[8–10,25] Nevertheless, in our cohort more children suffered immunosuppression in the deceased group than those in the survived group, but it had no statistically significant difference ($P = 0.086$; Table 1). Other factors were not predictive of higher mortality.

To date, there are few universal standards of treatment for CRE infection in children.[26] Due to limited available CRE-active antibiotics and for safety reasons, carbapenem-containing combination therapy tended to be the mainstay of treatment options.[10] In this study, 41 children were treated with carbapenem. With regard to other antibacterial agents, polymyxin B was relaunched in China in 2018 for the treatment of drug-resistant Gram-negative infections. While pediatric data related to polymyxin B are limited.[26] A systematic review of studies suggested that the microbiologic cure and survival of colistin were consistent with those reported in neonates and pediatrics in which multidrug-resistant Gram-negative bacteria were treated with other antibiotics,[27,28] which was also found in this study (Table 3). However, due to the large time span of this study, new treatments and medications may affect mortality, such as extracorporeal membrane oxygenation and ceftazidime-avibactam.

In recent years, novel β-lactam-β-lactamase inhibitor agents (eg, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam) are gradually being used in the treatment of CRE infection in children.[26] Among them, only ceftazidime-avibactam was available in China since 2019. In adults, retrospective studies have supported the preferential use of ceftazidime-avibactam over polymyxins for CRE infections.[29,30] In our cohort, only three patients used ceftazidime-avibactam, and two showed clinical efficacy and survived (Table 3). However, although ceftazidime-avibactam is effective for most KPC- and OXA-48-producing *Enterobacteriaceae*, it has a narrow antibacterial spectrum which is not available against metallo-beta-lactamase (MBL)-producing *Enterobacteriaceae*,[31] which is playing an increasingly important role in infections caused by CRE, especially in children.[32] These findings in children require confirmation by randomized controlled trials in the future.

This study had several limitations. Firstly, this was a single-center retrospective study with a relatively small sample size. Therefore, the power of the analysis to identify risk factors of mortality and potential treatment regimens was limited. Secondly, the pharmacokinetics of antibiotics and drug-resistance genes in the bacteria isolated were not tested, which also could affect clinical outcomes.

Conclusion

In conclusion, the overall 30-day mortality of PICU patients with CRE infections was considerably high. PCIS and serum albumin levels were the independent mortality-related risk factors of CRE infections. There was no significant difference in the 30-day mortality between the antimicrobial regimens that did or did not contain polymyxin B. Future prospective cohort studies are needed to investigate the optimal antimicrobial therapies for CRE infection in critically ill pediatric patients.

Ethical Statement

This study has been approved by the ethics review committee of the research project of the First Affiliated Hospital of Zhengzhou University (2022-KY-0168) and waived informed consent given the retrospective nature. All samples were collected as part of routine management/surveillance and were anonymized prior to research use.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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