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Impact of Oxacillinase-48 (OXA-48) and New Delhi Metallo-β-Lactamase (NDM) Co-existence on Mortality in Critically Ill Patients with *Klebsiella pneumoniae* Bloodstream Infections: A Prospective Controlled Study

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ABSTRACT

Objective: Carbapenem-resistant *Klebsiella pneumoniae* (CRKp) is associated with high mortality rates due to carbapenemase production. Türkiye is endemic for oxacillinase-48–producing carbapenemase (OXA-48), and New Delhi metallo-β-lactamase-1 (NDM-1) has also recently emerged. This study aimed to investigate mortality risk factors and carbapenemase types in patients with CRKp bacteremia.

Materials and Methods: This prospective study included 83 adult patients with CRKp bacteremia at Kayseri City Training and Research Hospital between September 2023 and March 2024. The control group consisted of patients without infection from the same hospital units. Pathogens were identified using the Vitek 2 system. Susceptibility to ceftazidime-avibactam and colistin was determined using disk methods. Carbapenemase genes were detected by polymerase chain reaction (PCR).

Results: In the multivariable logistic regression analysis, central venous catheter use, rectal colonization, and prior piperacillin–tazobactam use were identified as significant risk factors for CRKp bacteremia. Among the isolates, 95% carried OXA-48, 48.2% carried NDM, and 3.6% carried *Klebsiella pneumoniae* carbapenemase (KPC); OXA-48 and NDM co-production was detected in 45.7% of isolates. Verona integron-encoded metallo-β-lactamase (VIM) and Imipenemase metallo-β-lactamase (IMP) were not detected. Fourteen-day mortality was 25.3%. Respiratory system-related bacteremia was identified as an independent predictor of mortality, whereas clinical response on day 5 was independently associated with lower mortality. No difference was observed between monotherapy and combination therapy.

Conclusion: This study demonstrates that OXA-48 remains the most prevalent carbapenemase type in CRKp bloodstream infections in Türkiye, while NDM is increasing rapidly and frequently co-occurs with OXA-48, worsening clinical outcomes. Strengthening infection control measures, promoting the prudent use of antibiotics, and ensuring access to new treatment agents are crucial for reducing the spread and impact of CRKp infections.

Keywords: Carbapenemase, New Delhi metallo-β-lactamase-1 (NDM), oxacillinase-48 (OXA-48).

INTRODUCTION

The global epidemic of antibiotic resistance is endangering public health. The incidence and prevalence of carbapenem-resistant Gram-negative bacteria have increased significantly worldwide over the past decade.[1] The 2014 antimicrobial resistance report from the World Health Organization (WHO) indicates that carbapenem-resistant *Klebsiella pneumoniae* (CRKp) is present in all regions of the world.[2] According to Türkiye's 2021 National Antimicrobial Resistance and Surveillance System report on healthcare-associated infections, the rate of carbapenem resistance among *K. pneumoniae* strains increased from 63.5% in 2021 to 73.43% in 2024.[3,4]

Carbapenemases are β-lactamases that hydrolyze at least one carbapenem and represent one of the primary mechanisms of carbapenem resistance. These enzymes can also hydrolyze other β-lactam antibiotics in addition to carbapenems.[5,6] Oxacillinase-48 (OXA-48) is the most commonly detected carbapenemase enzyme in CRKp strains in Türkiye.[7] Although data on carbapenemase-producing pathogens in Türkiye are limited, other carbapenemases, such as New Delhi metallo-β-lactamase (NDM-1), the NDM-1/OXA-48 co-production, Verona integron-encoded metallo-β-lactamase (VIM), and Imipenem metallo-β-lactamase (IMP), have also been identified in outbreak settings.[7–9]

The development of CRKp infection is influenced by multiple factors, and patients often present with one or more risk factors. Recognized risk factors include severe underlying diseases (such as solid tumors, diabetes mellitus, and hemiplegia), high disease severity, invasive procedures, prolonged stay in the intensive care unit (ICU), prior colonization, advanced age, and prior use of intravenous broad-spectrum antibiotics. Identifying risk factors associated with mortality is important for optimizing patient management and recognizing high-risk individuals.[10]

There are limited safe and effective alternative treatment options for healthcare-associated CRKp bacteremia, contributing to high mortality and morbidity rates that vary across years and regions.[11] Despite the use of various antibiotic combinations and the development of novel agents, treatment options may vary depending on the specific carbapenemase genes present. However, there is no consensus on the optimal treatment strategy for CRKp infections. When new drugs are unavailable or contraindicated, monotherapy or combination therapy with existing antibiotics may be the only viable option.[12]

The aim of this study was to evaluate episodes of bloodstream infections caused by CRKp in our hospital and to determine associated risk factors, the carbapenemase genotypes of the causative agents, and their relationship with patient prognosis. Additional objectives were to assess disease severity and mortality outcomes, to evaluate the effectiveness of monotherapy versus combination therapy, and to examine the relationship between carbapenemase resistance patterns and genotypes.

KEY MESSAGES

- This study evaluated the risk factors and clinical outcomes of bloodstream infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKp).
- OXA-48 carbapenemase remains the most prevalent type in CRKp bloodstream infections in Türkiye, whereas NDM is rapidly increasing, often co-occurring with OXA-48 and leading to poorer clinical outcomes.
- Given the limited treatment options and the high morbidity and mortality associated with CRKp, rational antibiotic use and strict infection-control practices are essential to prevent further resistance.

MATERIALS AND METHODS

Study Design and Participant Selection

This study was designed as a single-center, prospective observational cohort study. A total of 83 patients who were treated in the Kayseri City Training and Research Hospital Department of Infectious Diseases and Clinical Microbiology between September 7, 2023 and March 7, 2024, and who had CRKp isolated from blood cultures were evaluated. The control group consisted of patients admitted to the intensive care unit who had stayed for at least 48 hours, had similar demographic and clinical characteristics to the case group, and showed no evidence of infection. In total, 81 patients were enrolled in the study.

Based on previous literature, we evaluated mortality occurring within 14 days. The infection-related mortality period was defined as 14 days. Patients who developed CRKp-associated bloodstream infections were categorized into two groups according to their 14-day survival status: survivors and non-survivors. Risk factors for mortality were analyzed, and the genotypic characteristics of carbapenemase production in the causative strains were examined.

Ethics Committee Approval

Ethics approval was obtained from the Kayseri City Hospital Clinical Research Ethics Committee (Approval Number: 904, Date: 05.09.2023).

Patients and Data Collection

Clinical, laboratory, and demographic data of the patients were recorded. Risk factors for CRKp-associated bloodstream

infection were identified by comparing the clinical and demographic characteristics of the study groups. The study group consisted of patients aged 18 years and older who developed bloodstream infection due to CRKp while being followed at Kayseri City Training and Research Hospital. Pregnant women, patients under 18 years of age, and patients with polymicrobial infections (defined as isolation of *K. pneumoniae* together with other bacterial or fungal species) were excluded from the study. For each patient included in the case group, control patients were selected from individuals admitted to critical care units who had stayed in the intensive care unit for at least 48 hours, had similar demographic and clinical characteristics to the case group, and showed no evidence of infection. Microsoft Excel was used to record the following data for both study and control groups: demographic characteristics; comorbidities; rectal *K. pneumoniae* carriage within the three months prior to infection; risk scores calculated at hospital admission and on the day of bacteremia onset; interventional procedures and their durations; changes in key laboratory parameters and clinical response on the fifth day of targeted therapy after bacteremia diagnosis; empirical antibiotic therapy administered after diagnosis and its duration; appropriateness of empirical antibiotic therapy according to antimicrobial susceptibility results; microbiological response status on day 5 after treatment initiation; 14-day mortality following bacteremia diagnosis; antibiotic susceptibility results and minimum inhibitory concentration (MIC) values; and carbapenemase resistance genes (OXA-48, NDM, *Klebsiella pneumoniae* carbapenemase [KPC], VIM, and IMP).

Microbiological and Molecular Analyses

Bacteremia was diagnosed based on laboratory and clinical findings consistent with blood culture results. Blood culture samples sent to the microbiology laboratory from various departments during the study period were loaded into the BacT/Alert 3D automated blood culture system. Blood culture bottles were incubated in the device for seven days until a positive signal was detected. Bottles that yielded a positive signal during the incubation period were further processed.

Following Gram staining, samples were inoculated onto blood agar (Oxoid) and Eosin Methylene Blue (EMB) agar (Oxoid). After incubation for 18-24 hours, grown colonies were evaluated by Gram staining and then identified using an automated system (VITEK 2 Compact; bioMérieux, France). The isolates were identified as *K. pneumoniae*, and their sensitivities were evaluated. For isolates identified as carbapenem-resistant, sensitivity was re-evaluated using a meropenem disk test to confirm resistance.

A total of 83 isolates identified as *K. pneumoniae* were included in the study. Carbapenem-resistant isolates were additionally tested for ceftazidime-avibactam susceptibility using the disk diffusion method and for colistin susceptibility using the disk elution method. All antibiogram evaluations were performed and interpreted according to the clinical breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), version 14.0 (2024).[13] Species identification of the obtained strains was further confirmed by 16S rRNA gene sequencing analysis at the Molecular Microbiology Laboratory of the Turkish Public Health Institution.

Statistical Analyses

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Prior to the initiation of this prospective observational cohort study, an a priori sample size calculation was conducted using PASS software (NCSS, LLC, USA). The calculation was based on the primary study hypothesis regarding the difference in 14-day mortality between treatment groups. Assuming an anticipated effect size of 0.60 for mortality outcomes, a two-sided alpha level of 0.05, and a statistical power of 95%, the minimum required sample size was estimated to be at least 35 patients per group.

Histogram analyses and the Shapiro-Wilks test were used to assess the normality of continuous variables. Parametric data are presented as mean ± standard deviation, and the Student's t-test was used to compare differences between groups. The Mann-Whitney U test was used to evaluate differences between groups, and non-parametric data are presented as median (range). The chi-square test was used to compare categorical variables, which are reported as numbers and percentages.

To identify factors associated with the outcome, logistic regression analyses were performed. First, univariate logistic regression analyses were conducted for all potential independent variables. Variables with a p value <0.20 in the univariate analysis were considered candidate variables and were subsequently included in the multivariable logistic regression model. A backward stepwise likelihood ratio method was used to derive the final model. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

The linearity of the logit assumption for continuous variables was assessed using the Box–Tidwell test. Multicollinearity among independent variables was evaluated using the variance inflation factor (VIF), with VIF values >5 considered indicative of significant multicollinearity. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. A p value <0.05 was considered statistically significant in all analyses.

Table 1. Demographic and clinical characteristics of the study population

Characteristics	CRKp n=83 (%)	Control n=81 (%)	p
Age, mean (±SD)	69.4±16.5	70.1±15.8	0.781
Male sex	37 (44.6)	42 (51.9)	0.438
APACHE II score (on admission), mean (±SD)	17.7±6.6	16.1±6.7	0.125
SOFA Score (on admission), mean (±SD)	3.6±3.1	2.3±2.0	0.001
Charlson Comorbidity Index (on admission), mean (±SD)	5.5±3.0	5.0±2.7	0.232
Invasive procedures			
Central venous catheter	70 (84.3)	17 (21.0)	<0.001
Intubation	40 (48.2)	10 (12.3)	<0.001
Tracheostomy	11 (13.3)	–	–
Urinary catheter	82 (98.8)	77 (95.1)	0.207
Decubitus	21 (25.3)	–	
Drainage catheter	9 (10.8)	1 (1.2)	0.025
Percutaneous endoscopic gastrostomy	12 (14.5)	–	–
Nephrostomy	4 (4.8)	2 (2.5)	
Surgery	20 (24.1)	2 (2.5)	<0.001
Other (chest tube, etc.)	2 (2.4)	3 (3.7)	0.630
Rectal *K. pneumoniae* carriage	49 (59.8)	2 (2.5)	<0.001
Prior antibiotic use			
Beta-lactam/beta-lactamase inhibitor	44 (53.0)	14 (17.9)	<0.001
Carbapenem	57 (68.7)	13 (16.0)	<0.001
Quinolone	13 (15.7)	11 (13.6)	0.706
Aminoglycoside	13 (15.7)	1 (1.2)	–
Polymyxin	13 (15.7)	–	–
Tigecycline	8 (9.6)	–	–
Ceftazidime–avibactam	4 (4.8)	–	–

APACHE: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; SD: Standard deviation; CRKp: Carbapenem-resistant *Klebsiella pneumoniae*.

RESULTS

The case group consisted of 46 (55.4%) female and 37 (44.6%) male patients, with a mean age of 69.4±16.5 years. Age and sex distributions were similar between the case and control groups. The Sequential Organ Failure Assessment (SOFA) score at admission was higher in the case group than in the control group (p=0.007). In the case group, the most common comorbidities were hypertension (38 patients, 45.8%), diabetes mellitus (32 patients, 38.6%), congestive heart failure (19 patients, 22.9%), chronic kidney disease (14 patients, 16.9%), chronic obstructive pulmonary disease (10 patients, 12%), solid tumors (9 patients, 10.8%), and hematological malignancies (3 patients, 3.6%). There was no significant difference in comorbidities between the case and control groups.

Central venous catheterization, intubation, and surgical procedures were more frequent in the case group than in the control group (p<0.001). The rate of rectal *K. pneumoniae* carriage was also significantly higher in the case group. Regarding prior antibiotic use, beta-lactams or beta-lactam/beta-lactamase inhibitors (53%), carbapenems (68.7%), quinolones (15.7%), and aminoglycosides (15.7%) were used significantly more frequently in the case group (Table 1).

In the univariable logistic regression analysis for infection, central venous catheter use increased the risk of infection approximately eightfold (odds ratio [OR]: 7.80, 95% confidence interval [CI]: 2.30–26.52; p=0.001). Rectal *K. pneumoniae* carriage showed the strongest association, increasing the risk

Table 2. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infections

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
APACHE II score (on admission), mean (±SD)	1.06 (0.95–1.19)	0.297		
SOFA score (on admission), mean (±SD)	0.97 (0.74–1.28)	0.850		
Central venous catheter	7.80 (2.30–26.52)	0.001	8.42 (2.53–27.99)	0.001
Intubation	2.25 (0.55–9.26)	0.262	3.12 (0.86–11.29)	0.082
Rectal *K. pneumoniae* carriage	41.01 (6.03–278.74)	<0.001	50.65 (9.62–266.77)	<0.001
Piperacillin–tazobactam use	7.38 (2.24–24.28)	0.001	6.16 (2.02–18.78)	0.001
Carbapenem use	1.96 (0.55–7.02)	0.303		

APACHE: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; SD: Standard deviation; OR: Odd ratios; CI: Confidence interval.

more than fortyfold (OR: 41.01, 95% CI: 6.03–278.74; p<0.001). Piperacillin–tazobactam use was also significantly associated with infection (OR: 7.38, 95% CI: 2.24–24.28; p=0.001). Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, intubation, and carbapenem use were not significantly associated with infection. In the multivariable logistic regression analysis, central venous catheter use (OR=7.803; p=0.001), rectal colonization (OR=41.009; p<0.001), and piperacillin–tazobactam use (OR=7.377; p=0.001) were significantly associated with infection. Other variables, including APACHE II score, SOFA score, intubation, and carbapenem use, lost statistical significance after adjustment. The final model demonstrated good calibration according to the Hosmer–Lemeshow test (χ^2=1.677; p=0.976) (Table 2).

OXA-48 was detected in 95% of CRKp strains, NDM in 48.2%, and KPC in 3.6%, while co-production of OXA-48 and NDM was observed in 45.7% of strains. None of the isolates harbored VIM or IMP (Fig. 1).

Among patients with CRKp-associated bloodstream infection, the 14-day mortality rate was 25.3%. There was no significant difference in age between survivors and non-survivors. Similarly, no significant differences were observed between the two groups in terms of comorbidities. The APACHE II score on the day of bloodstream infection onset was higher in the survivor group (p=0.032).

When comparing the sources of bacteremia between survivors and non-survivors, respiratory tract–related bacteremia was more frequent in the non-survivor group (p=0.003). The most common source of bacteremia overall was central venous catheters, followed by the respiratory system. In 17 patients, *K. pneumoniae* was isolated from sputum cultures within 72 hours prior to blood culture growth. These cases were classified as respiratory-associated bacteremia, including pneumonia and ventilator-associated pneumonia.

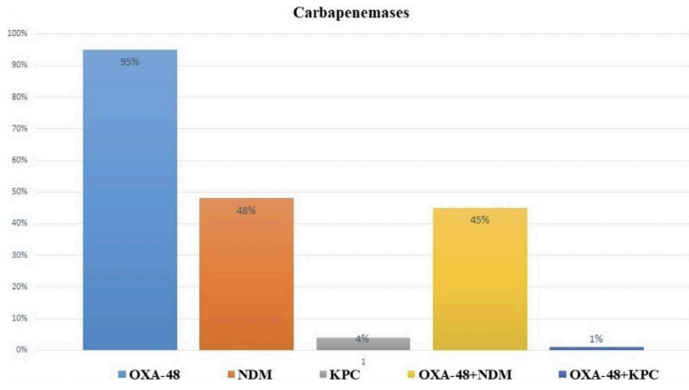

Figure 1. Distribution of carbapenemases.

OXA-48: Oxacillinase-48; NDM; New Delhi metallo-β-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase.

In the analysis of carbapenemase enzymes according to 14-day mortality, co-production of OXA-48 and NDM was more frequent in the non-survivor group (p=0.026). Empirical therapy was administered more frequently in non-survivors (47.6%), and the most commonly prescribed empirical antibiotic was a carbapenem (38.1%). There was no notable difference between survivors and non-survivors regarding the appropriateness of empirical therapy (p=0.38).

Targeted therapy was used more frequently in survivors (80.6%) (p=0.011). Ceftazidime-avibactam was the most frequently used antibiotic in monotherapy, whereas the most commonly administered combination therapy was carbapenem plus polymyxin. Carbapenem plus aminoglycoside was the second most frequently used combination regimen. No statistically significant difference was observed between survivors and non-survivors with respect to either monotherapy or combination

Table 3. Characteristics of survivors and non-survivors

	Non-survivors n=21	Survivors n=62	p
Age, mean (±SD)	68.6±19.0	69.7±15.8	0.790
Comorbidities			
Hypertension	9 (46.9)	29 (46.8)	0.756
Diabetes	10 (47.6)	22 (35.5)	0.323
Congestive heart failure	7 (33.3)	12 (19.4)	0.188
Chronic obstructive pulmonary disease	3 (14.3)	4 (6.5)	0.362
Chronic kidney disease	2 (9.5)	12 (19.4)	0.298
Solid tumor	1 (4.8)	8 (12.9)	0.300
Hematological malignancy	–	3 (4.8)	–
APACHE II score, mean (±SD) (day of bacteremia)	19.6±7.9	24.4±9.9	0.032
SOFA score, mean (±SD) (day of bacteremia)	5.2±4.2	7.6±5.4	0.056
Charlson Comorbidity Index, mean (±SD) (day of bacteremia)	5.3±2.7	5.6±3.0	0.792
Source of bacteremia			
Central catheter	7 (33.3)	25 (40.3)	0.570
Primary bacteremia	4 (19.0)	10 (16.1)	0.758
Respiratory tract	9 (42.9)	8 (12.9)	0.003
Urinary tract infection	1 (4.8)	13 (21.0)	0.087
Other (skin, soft tissue, and intra-abdominal)	1 (4.8)	6 (9.7)	0.484
Carbapenemases			
OXA-48	21 (100)	58 (93.5)	0.233
NDM	14 (66.7)	26 (41.9)	0.076
KPC	1 (4.8)	2 (3.2)	0.744
OXA-48 + NDM	14 (66.7)	24 (38.7)	0.026
OXA-48 + KPC	1 (4.8)	–	–
Treatment			
Empirical treatment	10 (47.6)	11 (17.7)	0.006
Carbapenem	8 (38.1)	9 (14.5)	0.030
Beta-lactam/beta-lactamase inhibitor	1 (4.8)	1 (1.6)	0.416
Cephalosporin	1 (4.8)	1 (1.6)	0.416
Appropriateness of empirical treatment	1 (4.8)	7 (11.3)	0.381
Targeted treatment	11 (52.4)	50 (80.6)	0.011
Monotherapy	1 (4.8)	14 (22.6)	0.067
Ceftazidime–avibactam	1 (4.8)	13 (21.0)	0.087
Trimethoprim-sulfamethoxazole	–	1 (1.6)	–
Combination therapy	9 (42.9)	37 (59.7)	0.180
Carbapenem + polymyxin	5 (23.8)	17 (27.4)	0.746
Carbapenem + aminoglycoside	3 (14.3)	8 (12.9)	0.872
Carbapenem + tigecycline	–	3 (4.8)	–
Carbapenem + trimethoprim-sulfamethoxazole	–	1 (1.6)	–
Ceftazidime–avibactam + polymyxin	1 (4.8)	2 (3.2)	0.744
Ceftazidime–avibactam + trimethoprim-sulfamethoxazole	–	1 (1.6)	–
Polymyxin + tigecycline	–	3 (4.8)	–
Beta-lactam/beta-lactamase inhibitor + aminoglycoside	1 (4.8)	–	–
Trimethoprim-sulfamethoxazole + fosfomycin	–	1 (1.6)	–
Carbapenem + polymyxin + tigecycline	–	1 (1.6)	–
Clinical response on day 5 of treatment	4 (19.0)	35 (56.5)	0.003

APACHE: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; SD: Standard deviation; OXA-48: Oxacillinase-48; NDM: New Delhi Metallo-β-Lactamase; KPC: *Klebsiella pneumoniae* carbapenemase.

Table 4. Risk factors for mortality in patients with carbapenem-resistant *Klebsiella pneumoniae* infections

	Univariate analysis	Multivariate analysis
Congestive heart failure	1.39 (0.42–4.63), p=0.59	
APACHE II score, mean (±SD) (day of bacteremia)	1.01 (0.94–1.09), p=0.77	
SOFA score, mean (±SD) (day of bacteremia)	0.95 (0.80–1.12), p=0.55	
Respiratory tract	4.98 (1.61–15.39), p=0.005	5.92 (1.41–24.77), p=0.015
Urinary tract infection	0.63 (0.22–1.79), p=0.38	
NDM	2.35 (0.87–6.35), p=0.091	1.88 (0.57–6.19), p=0.300
OXA-48 + NDM	3.28 (1.17–9.21), p=0.024	2.41 (0.72–8.07), p=0.150
Empirical treatment	1.31 (0.47–3.63), p=0.60	
Carbapenem	0.144 (0.006-3.365), p=0.228	
Targeted treatment	0.075 (0.003-1.641), p=0.100	
Monotherapy	1.62 (0.59–4.44), p=0.35	
Ceftazidime–avibactam	0.37 (0.14–1.02), p=0.054	0.46 (0.14–1.55), p=0.210
Combination therapy	0.72 (0.26–1.97), p=0.52	
Clinical response on day 5 of treatment	0.18 (0.06–0.49), p=0.001	0.16 (0.05–0.48), p=0.001

APACHE: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; OXA-48: Oxacillinase-48; NDM: New Delhi Metallo-β-Lactamase.

therapy. On the fifth day of treatment, the survivor group demonstrated a better clinical response (Table 3).

Fourteen-day mortality risk factors were evaluated using logistic regression analysis. In univariable analyses, respiratory source of infection, NDM production, OXA-48+NDM co-production, ceftazidime–avibactam therapy, and clinical response on day 5 were associated with mortality at p<0.20 and were therefore included in the multivariable model. In the final model, respiratory source of infection remained an independent predictor of mortality (OR: 5.92, 95% CI: 1.41–24.77; p=0.015), whereas clinical response on day 5 was independently associated with lower mortality (OR: 0.16, 95% CI: 0.05–0.48; p=0.001). The model demonstrated good calibration (Hosmer–Lemeshow p=0.48) and excellent discriminative ability (area under the curve [AUC]=0.86) (Table 4).

DISCUSSION

K. pneumoniae infections have increased in recent years and represent a serious public health issue due to limited treatment options and high mortality rates. According to the WHO, CRKp is classified among bacteria of critical priority, along with carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, for which the development of new antibiotics is urgently needed.[14]

Due to the limited range of available treatment options, the aim of this study was to investigate the clinical and molecular characteristics of patients who developed CRKp bacteremia in order to contribute to the development of strategies for reducing CRKp infections, identifying associated risk factors, and optimizing treatment approaches. The study included 83 patients with CRKp bacteremia and 81 patients in the control group.

Although risk factors vary across studies of CRKp infections and bacteremia, the most commonly reported factors include prior history ICU admission, previous antibiotic or carbapenem use, prolonged hospitalization, renal dysfunction, gastrointestinal colonization, mechanical ventilation or tracheostomy, history of surgery, and gastric catheterization.[15–23] In the present study, central venous catheter use and rectal *K. pneumoniae* carriage were also identified as risk factors for CRKp bacteremia.

Antibiotic selective pressure is believed to contribute to the emergence of antibiotic-resistant infections.[24] A meta-analysis by Liu et al.[25] demonstrated that prior use of quinolones, carbapenems, aminoglycosides, anti-pseudomonal agents, and glycopeptides was associated with the development of CRKp infections. Similarly, in our study, prior use of piperacillin–tazobactam was found to increase the likelihood of carbapenem resistance.

The 14-day mortality rate in our cohort was 25.3%. Notably, respiratory source-related bacteremia was significantly more frequent among non-survivors (p=0.003), suggesting that pulmonary infections may serve as a reservoir for more virulent or resistant strains. In Italy, a study conducted between 2015 and 2018 reported a 14-day mortality rate of 32.4% among 102 ICU patients with bloodstream infections caused by

KPC-producing CRKp.[26] In a study conducted in South Korea between 2016 and 2019, the 14-day and 30-day mortality rates for carbapenem-resistant *Enterobacteriaceae* bacteremia were 34.0% and 42.2%, respectively.[27] In several meta-analyses, mortality in cases of CRKp-associated infections has been estimated to range from 37.2% to 42.1%.[28,29]

Studies assessing CRKp bacteremia have identified various risk factors for mortality. Commonly reported predictors include ICU admission, mechanical ventilation, septic shock, high comorbidity-mortality or bacteremia scores (APACHE II, SOFA, and Pitt bacteremia score), absolute neutrophil count <500/mm^3, the presence of immunosuppressive comorbidities, inappropriate empirical antibiotic therapy, and colistin resistance.[7,26,27,30–33] In the present study, respiratory tract-related bacteremia was identified as an independent predictor of mortality, whereas clinical response on day 5 was independently associated with reduced mortality. Interestingly, the APACHE II score was higher in the survivor group (p=0.032), a finding that appears paradoxical. This discrepancy may reflect confounding factors such as small sample size, patient heterogeneity, or differences in the intensity of clinical management between groups.

Aslan et al.[34] evaluated 124 patients with bacteremia and detected OXA-48 in 85.5%, NDM in 3.2%, and OXA-48 + NDM in 8.9% of cases, while no KPC-producing strains were identified. A multicenter study conducted between 2018 and 2019, including 187 patients with CRKp bacteremia, reported OXA-48-like genes in 79.1%, OXA-48-like genes + NDM in 15.5%, NDM alone in 5.9%, and KPC in 3.2% of cases.[7] In another study conducted in Ankara, Bursa, and Trabzon Zarakolu et al.[8] detected OXA-48 in 62.6%, NDM in 9.2%, OXA-48 + NDM in 6.9%, and KPC in 14.5% of 131 bacteremia cases. In our study, the distribution of resistance genes was as follows: OXA-48 in 95%, NDM in 48%, KPC in 4%, OXA-48 + NDM in 45.7%, and OXA-48 + KPC in 1%. This is the first study to report such a high rate of OXA-48 + NDM co-occurrence. We believe this finding is particularly important for Türkiye and will influence empirical treatment strategies.

Another study investigated the clonal and genetic relationships of carbapenem- and colistin-resistant isolates in a large hospital in Sofia, Bulgaria. Co-production of NDM-5 and OXA-232 was detected in 72% of 14 isolates, which were susceptible only to cefiderocin. In our study, NDM was detected in 48% of cases, and OXA-48 + NDM co-production was observed in 45.7%. The lack of effective therapeutic options complicates the management of infections caused by these strains, and their rapid spread emphasizes the urgent need for effective control measures.[35]

A retrospective two-year study conducted in a tertiary hospital in Romania evaluated CRKp-resistant infections and reported that the predominant carbapenemases were OXA-48 + NDM (49.4%), highlighting an increasing frequency of this combination. In our study, the OXA-48 + NDM co-production rate was 45.7%. The Romanian study emphasized the need for caution in the management of infected patients and in preventing the spread of these infections, as well as the need for strengthening public health policies promoting rational antibiotic use and a One Health approach.[36]

Studies investigating the efficacy of antibiotic therapy in CRKp bacteremia have produced conflicting results. While some studies suggest that certain antibiotic combination therapies may influence mortality, others have found no difference.[7,19,26,33,34,37–39] In the INCREMENT study (International Network for Optimal Resistance Monitoring and Epidemiology of Carbapenemase-Producing *Enterobacteriaceae*), which included 437 patients with carbapenem-resistant *Enterobacteriaceae* bacteremia from 10 countries, monotherapy was compared with combination therapy. The 30-day mortality rate did not differ significantly between the groups; however, lower 30-day mortality was observed in patients who received at least one effective antibiotic within five days of bacteremia onset.[37]

Another study conducted at Hacettepe University between 2014 and 2018 compared 30-day mortality rates among 124 patients with CRKp bacteremia who received appropriate treatment (defined as initiation of at least one active antibiotic within five days of bacteremia onset) and those who did not. Mortality was lower in the group that received appropriate treatment. Furthermore, within this group, patients receiving monotherapy (primarily carbapenem and, less frequently, colistin) were compared with those receiving combination therapy (carbapenem- and colistin-based regimens), and no significant difference in 30-day mortality was observed between the two groups.[34]

In our study, empirical carbapenem use was more common among non-survivors, underscoring the limited efficacy of carbapenems in the treatment of CRKp infections. In contrast, targeted therapy based on susceptibility results was significantly more frequent among survivors (p=0.011), highlighting the importance of early microbiological diagnosis and individualized treatment. Pathogen-directed therapy was associated with improved 14-day survival. No statistically significant difference in 14-day survival was observed between survivors and non-survivors with respect to ceftazidime-avibactam monotherapy or combination regimens (including carbapenem-based, polymyxin-based, ceftazidime-avibactam-based, and other combinations). These findings are consistent with previous studies questioning the

superiority of combination therapy. The absence of an optimal standardized treatment regimen continues to be a major challenge in the management of CRKp infections.

CONCLUSION

Central venous catheter use, rectal *K. pneumoniae* carriage, and prior piperacillin–tazobactam use were identified as risk factors for CRKp-associated bloodstream infections. Respiratory system-related bacteremia emerged as an independent predictor of mortality, whereas clinical response on day 5 was independently associated with reduced mortality. No significant difference in mortality was observed between patients receiving monotherapy and those receiving combination therapy. CRKp bacteremia has limited treatment options, is difficult to manage, and is associated with high morbidity and mortality. Therefore, rational antibiotic use, strict adherence to hand hygiene, appropriate use of personal protective equipment, and rigorous implementation of hospital infection-control protocols are essential to prevent the emergence and spread of resistance.

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REFERENCES

1. World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS) report: 2022. https://www.who.int/publications/i/item/9789240062702 Accessed February 25, 2026.
2. Sawai T, Mitsuhashi S, Yamagishi S. Drug resistance of enteric bacteria. XIV. Comparison of beta-lactamases in gram-negative rod bacteria resistant to alpha-aminobenzylpenicillin. Jpn J Microbiol 1968;12(4):423-34. [CrossRef]
3. Turkish Ministry of Health, Directorate General of Public Health. Summary Report of the National Health Service-Associated Infections Surveillance Network (USHIESA) 2023. Turkish. https://hsgm.saglik.gov.tr/depo/birimler/bulasici-hastaliklar-ve-erken-uyari-db/Dokumanlar/Raporlar/USHIESA_OZET_RAPOR_2023_03.07.2024.pdf Accessed February 25, 2026.
4. Republic of Turkey Ministry of Health, General Directorate of Public Health, Department of Infectious Diseases and Early Warning. National Healthcare-Associated Infections Surveillance Network (USHIESA) Summary Report 2022. https://hsgm.saglik.gov.tr/depo/birimler/bulasici-hastaliklar-ve-erken-uyari-db/Dokumanlar/Raporlar/USHIESA_OZET_RAPORU_2022.pdf Accessed February 25, 2026.
5. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. Clin Microbiol Rev 2007;20(3):440-58, table of contents. [CrossRef]
6. Poirel L, Pitout JD, Nordmann P. Carbapenemases: molecular diversity and clinical consequences. Future Microbiol 2007;2(5):501-12. [CrossRef]
7. Isler B, Özer B, Çınar G, Aslan AT, Vatansever C, Falconer C, et al. Characteristics and outcomes of carbapenemase harbouring carbapenem-resistant Klebsiella spp. bloodstream infections: a multicentre prospective cohort study in an OXA-48 endemic setting. Eur J Clin Microbiol Infect Dis 2022;41(5):841-7. [CrossRef]
8. Zarakolu P, Eser ÖK, Otlu B, Gürpınar Ö, Özakın C, Akalın H, et al. In-vitro activity of fosfomycin against Escherichiacoli and Klebsiellapneumoniae bloodstream isolates and frequency of OXA-48, NDM, KPC, VIM, IMP types of carbapenemases in the carbapenem-resistant groups. J Chemother 2022;34(4):235-40. [CrossRef]
9. Süzük Yıldız S, Şimşek H, Bakkaloğlu Z, Numanoğlu Çevik Y, Hekimoğlu CH, Kılıç S, et al.; National Carbapenemase Surveillance Study Group. The Epidemiology of Carbapenemases in Escherichia coli and *Klebsiella pneumoniae* Isolated in 2019 in Turkey. Mikrobiyol Bul 2021;55(1):1-16. Turkish. [CrossRef]
10. Borer A, Saidel-Odes L, Eskira S, Nativ R, Riesenberg K, Livshiz-Riven I, et al. Risk factors for developing clinical infection with carbapenem-resistant *Klebsiella pneumoniae* in hospital patients initially only colonized with carbapenem-resistant *K pneumoniae*. Am J Infect Control 2012;40(5):421-5. [CrossRef]
11. Xu M, Fu Y, Kong H, Chen X, Chen Y, Li L, et al. Bloodstream infections caused by *Klebsiella pneumoniae*: prevalence of blaKPC, virulence factors and their impacts on clinical outcome. BMC Infect Dis 2018;18(1):358. [CrossRef]

12. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect 2022;28(4):521-47. [CrossRef]
13. European Committee on Antimicrobial Susceptibility Testing. EUCAST clinical breakpoint table. https://www.eucast.org/clinical_breakpoints/ Accessed February 25, 2026.
14. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al.; WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018;18(3):318-27. [CrossRef]
15. Wang Z, Qin RR, Huang L, Sun LY. Risk Factors for Carbapenem-resistant *Klebsiella pneumoniae* Infection and Mortality of *Klebsiella pneumoniae* Infection. Chin Med J (Engl) 2018;131(1):56-62. [CrossRef]
16. Jiao Y, Qin Y, Liu J, Li Q, Dong Y, Shang Y, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection/colonization and predictors of mortality: a retrospective study. Pathog Glob Health 2015;109(2):68-74. [CrossRef]
17. Dai G, Xu Y, Kong H, Xie W, Wang H. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection and associated clinical outcomes. Am J Transl Res 2021;13(6):7276-81.
18. Zhang S, Yang Z, Sun L, Wang Z, Sun L, Xu J, et al. Clinical Observation and Prognostic Analysis of Patients With *Klebsiella pneumoniae* Bloodstream Infection. Front Cell Infect Microbiol 2020;10:577244. [CrossRef]
19. Xiao T, Zhu Y, Zhang S, Wang Y, Shen P, Zhou Y, et al. A Retrospective Analysis of Risk Factors and Outcomes of Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia in Nontransplant Patients. J Infect Dis 2020;221(Suppl 2):S174-83. [CrossRef]
20. Huang W, Qiao F, Deng Y, Zhu S, Li J, Zong Z, et al. Analysis of risk factors associated with healthcare-associated carbapenem-resistant *Klebsiella pneumoniae* infection in a large general hospital: a case-case-control study. Eur J Clin Microbiol Infect Dis 2023;42(5):529-41. [CrossRef]
21. Zhu Q, Xu J, Chen X, Ren Y, Zhao L. Risk factors and molecular epidemiology of bloodstream infections due to carbapenem-resistant *Klebsiella pneumoniae*. Diagn Microbiol Infect Dis 2023;106(3):115955. [CrossRef]
22. Holmes CL, Anderson MT, Mobley HLT, Bachman MA. Pathogenesis of Gram-Negative Bacteremia. Clin Microbiol Rev 2021;34(2):e00234-20. [CrossRef]
23. Meatherall BL, Gregson D, Ross T, Pitout JD, Laupland KB. Incidence, risk factors, and outcomes of *Klebsiella pneumoniae* bacteremia. Am J Med 2009;122(9):866-73. [CrossRef]
24. Mouloudi E, Massa E, Papadopoulos S, Iosifidis E, Roilides I, Theodoridou T, et al. Bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae* among intensive care unit patients after orthotopic liver transplantation: risk factors for infection and impact of resistance on outcomes. Transplant Proc 2014;46(9):3216-8. [CrossRef]
25. Liu P, Li X, Luo M, Xu X, Su K, Chen S, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection: A meta-analysis. Microbial Drug Resistance 2018;24(2):190-198. [CrossRef]
26. Falcone M, Bassetti M, Tiseo G, Giordano C, Nencini E, Russo A, et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing *Klebsiella pneumoniae*. Crit Care 2020;24(1):29. [CrossRef]
27. Ahn JY, Ahn SM, Kim JH, Jeong SJ, Ku NS, Choi JY, et al. Clinical Characteristics and Associated Factors for Mortality in Patients with Carbapenem-Resistant *Enterobacteriaceae* Bloodstream Infection. Microorganisms 2023;11(5):1121. [CrossRef]
28. Agyeman AA, Bergen PJ, Rao GG, Nation RL, Landersdorfer CB. A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant *Klebsiella pneumoniae* infections. Int J Antimicrob Agents 2020;55(1):105833. [CrossRef]
29. Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*. Ann Clin Microbiol Antimicrob 2017;16(1):18. [CrossRef]
30. Meng H, Han L, Niu M, Xu L, Xu M, An Q, et al. Risk Factors for Mortality and Outcomes in Hematological Malignancy Patients with Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections. Infect Drug Resist 2022;15:4241-51. [CrossRef]
31. Balkan II, Alkan M, Aygün G, Kuşkucu M, Ankaralı H, Karagöz A, et al. Colistin resistance increases 28-day mortality in bloodstream infections due to carbapenem-resistant *Klebsiella pneumoniae*. Eur J Clin Microbiol Infect Dis 2021;40(10):2161-70. [CrossRef]
32. Chen J, Ma H, Huang X, Cui Y, Peng W, Zhu F, et al. Risk factors and mortality of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection in a tertiary-care hospital in China: an eight-year retrospective study. Antimicrob Resist Infect Control 2022;11(1):161. [CrossRef]

33. Manesh A, Shankar C, George MM, Jasrotia DS, Lal B, George B, et al. Clinical and Genomic Evolution of Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections over Two Time Periods at a Tertiary Care Hospital in South India: A Prospective Cohort Study. Infect Dis Ther 2023;12(5):1319-35. [CrossRef]
34. Aslan AT, Kırbaş E, Sancak B, Tanrıverdi ES, Otlu B, Gürsoy NC, et al.; Study Group for Carbapenem Resistance (SCARE). A retrospective observational cohort study of the clinical epidemiology of bloodstream infections due to carbapenem-resistant *Klebsiella pneumoniae* in an OXA-48 endemic setting. Int J Antimicrob Agents 2022;59(4):106554. [CrossRef]
35. Markovska R, Stankova P, Popivanov G, Gergova I, Mihova K, Mutafchiyski V, et al. Emergence of blaNDM-5 and blaOXA-232 Positive Colistin- and Carbapenem-Resistant *Klebsiella pneumoniae* in a Bulgarian Hospital. Antibiotics (Basel) 2024;13(7):677. [CrossRef]
36. Lazar DS, Nica M, Dascalu A, Oprisan C, Albu O, Codreanu DR, et al. Carbapenem-Resistant NDM and OXA-48-like Producing *K. pneumoniae*: From Menacing Superbug to a Mundane Bacteria; A Retrospective Study in a Romanian Tertiary Hospital. Antibiotics (Basel) 2024;13(5):435. [CrossRef]
37. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, et al.; REIPI/ESGBIS/INCREMENT Investigators. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing *Enterobacteriaceae* (INCREMENT): a retrospective cohort study. Lancet Infect Dis 2017;17(7):726-34. [CrossRef]
38. Fang Y, Zhong Q, Chen Y, Hang Y, Fang X, Xiao Y, et al. Ceftazidime/Avibactam, Polymyxin or Tigecycline as a Rescue Strategy for the Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* in Bloodstream Infection: A Retrospective Cohort Study. Infect Drug Resist 2023;16:2963-71. [CrossRef]
39. Tumbarello M, Trecarichi EM, Corona A, De Rosa FG, Bassetti M, Mussini C, et al. Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by *Klebsiella pneumoniae* Carbapenemase-producing *K. pneumoniae*. Clin Infect Dis 2019;68(3):355-64. [CrossRef]