

Clinical determinants, molecular resistance patterns, and 90-day mortality in carbapenem-resistant *Klebsiella pneumoniae* infections in intensive care units: a one-year prospective cohort study

Betül Altunbaş¹

drbetulsenn@outlook.com

Afyonkarahisar Sağlık Bilimleri Üniversitesi

Neşe Demirtürk¹

Afyonkarahisar Sağlık Bilimleri Üniversitesi

Yeliz Çetinkol²

Afyonkarahisar Sağlık Bilimleri Üniversitesi

Cengiz Demir²

Afyonkarahisar Sağlık Bilimleri Üniversitesi

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Clinical determinants, molecular resistance patterns, and 90-day mortality in carbapenem-resistant *Klebsiella pneumoniae* infections in intensive care units: a one-year prospective cohort study

Betül Altunbaş^{1*}, Neşe Demirtürk¹, Yeliz Çetinkol², Cengiz Demir²

¹ Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Türkiye

² Department of Medical Microbiology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Türkiye

*** Corresponding Author:**

Betül Altunbaş, MD

Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Türkiye

E-mail: drbetulsenn@outlook.com

ORCID: 0000-0001-8587-8514

Abstract

Background

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has emerged as a growing health threat in intensive care units (ICUs), where infections often have limited therapeutic options and demonstrate high mortality. However, the relative contribution of antimicrobial resistance versus host-related factors to clinical outcomes remains unclear. This study aimed to evaluate the clinical determinants, molecular resistance patterns, and 90-day mortality associated with CRKP infections in patients admitted to the ICU.

Methods

Conducted between October 2023 and October 2024 in several ICUs of a single tertiary-care hospital, this prospective cohort study included adult patients with culture-confirmed *K. pneumoniae* infections. They were classified into CRKP (n = 96) and carbapenem-susceptible (CSKP, n = 57) groups. Demographic characteristics, comorbidities, invasive procedures, prior antibiotic exposure, and clinical outcomes were recorded. Polymerase chain reaction was used for detecting carbapenemase genes (*OXA-48*, *NDM*, *KPC*, *VIM*, *IMP*), and multivariate logistic regression was performed to identify independent risk factors for carbapenem resistance and 90-day mortality.

Results

Univariate analysis revealed that advanced age, hemodialysis, steroid use, central venous catheterization, and mechanical ventilation were significantly associated with CRKP. In the multivariate analysis, age, central venous catheterization, and recent Gram-negative infection (within the previous 3 months) independently predicted carbapenem resistance. The predominant resistance gene was *OXA-48* (67.1%), followed by *NDM* (49.4%) and *KPC* (31.7%); all *NDM*-positive isolates harbored *OXA-48*. The 90-day mortality rate did not significantly differ between the two groups (CRKP, 51.9%; CSKP, 66%). Advanced age, malignancy, chronic kidney disease, and mechanical ventilation independently predicted mortality. *IMP* was the only resistance gene significantly associated with mortality.

Conclusions

Carbapenem resistance was associated with distinct clinical and molecular characteristics but was not independently linked to increased 90-day mortality in ICU patients with *K. pneumoniae* infections. Host-related factors and invasive support measures strongly determined clinical outcomes. Rapid molecular detection of resistance genes and optimization of invasive device management remain essential for improving ICU infection control and patient prognosis.

Keywords: CR-KP infections, Epidemiology, Resistance genes

Background

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has recently become one of the most concerning multidrug-resistant pathogens worldwide [1–3]. The rapid dissemination of carbapenemase-producing strains, particularly in intensive care units (ICUs), has significantly limited therapeutic options and further complicated infection management. According to the World Health Organization, new

antimicrobial strategies should be urgently developed for carbapenem-resistant Enterobacterales [1].

Frequent invasive procedures, broad-spectrum antibiotic exposure, prolonged hospitalization, and the presence of critically ill patients with multiple comorbidities have made ICUs a high-risk environment for CRKP transmission [2, 3]. CRKP-induced infections, including ventilator-associated pneumonia, bloodstream infections, urinary tract infections, and intra-abdominal infections, are associated with increased morbidity, healthcare costs, and mortality [4–6]. Reported mortality rates for CRKP infections are 30%–70%, particularly in bacteremia and severe sepsis cases [4–6].

Carbapenemase enzymes such as KPC (class A), metallo- β -lactamases (NDM, VIM, and IMP; class B), and OXA-48-like enzymes (class D) primarily mediate carbapenem resistance in *K. pneumoniae* [5, 8]. Carbapenemase genes' epidemiology varies geographically. For instance, *OXA-48* has been widely reported in Mediterranean and Middle Eastern countries, *KPC* in North America and parts of Europe, and *NDM* in South Asia [7–9]. Understanding local molecular resistance patterns is crucial for guiding empirical therapy and infection control strategies.

Numerous studies have identified risk factors associated with CRKP acquisition (e.g., prior carbapenem exposure, invasive device use, mechanical ventilation, and prolonged ICU stay); however, the relative contribution of antimicrobial resistance itself to mortality remains largely unknown [6, 10]. Some investigations suggest that carbapenem resistance independently increases mortality, whereas others indicate that host-related factors, illness severity, and underlying comorbidities determine patient outcomes [6, 10].

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Therefore, this one-year prospective cohort study aimed to:

1. Identify clinical risk factors for carbapenem-resistant *K. pneumoniae* (CRKP) infection,
2. Characterize carbapenemase gene distribution, and
3. Determine the independent predictors of 90-day mortality caused by such infection.

By integrating clinical and molecular data, we sought to clarify whether carbapenem resistance or patient-related factors primarily drive CRKP mortality in ICU settings.

Methods

Study Design and Setting

This one-year prospective cohort study was conducted between October 1, 2023, and October 1, 2024, in multiple ICUs of a tertiary-care university hospital. Such ICUs included anesthesiology and reanimation, neurosurgery, general surgery, pulmonology, cardiovascular surgery, and coronary and internal medicine ICUs.

Study Population

We included adult patients (≥ 18 years old) with culture-confirmed *K. pneumoniae* isolated from clinical specimens. Only the first isolate per patient during the study period was analyzed. Patients were classified into two groups according to carbapenem susceptibility: CRKP group (study group) and carbapenem-susceptible *K. pneumoniae* (CSKP) group (control group).

Colonization and infection were distinguished according to clinical, microbiological, and radiological criteria consistent with the Centers for Disease Control and Prevention's definitions for healthcare-associated infections.

Microbiological Procedures

We used an automated system (VITEK 2®, bioMérieux) for identifying bacteria and antimicrobial susceptibility. Antimicrobial susceptibility results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. Carbapenemase genes (*OXA-48*, *NDM*, *KPC*, *VIM*, and *IMP*) were detected using polymerase chain reaction (PCR) assays.

Data Collection

The following data were collected: demographic profile, comorbidities (malignancy, chronic kidney disease [CKD], diabetes mellitus [DM]), invasive procedures (mechanical ventilation, central venous catheterization, urinary catheterization), prior antibiotic exposure, ICU stay duration, and infection type. The primary outcome was 90-day all-cause mortality.

Statistical Analysis

Continuous variables, expressed as mean $\pm$ SD or median (interquartile range), as appropriate, were compared using Student's t-test or Mann–Whitney U test. Meanwhile, categorical variables, expressed as number (percentage), were compared using the chi-square or Fisher's exact test.

Variables with a p-value < 0.05 in the univariate analysis were included in the multivariate logistic regression models to identify independent predictors of carbapenem resistance and 90-day mortality. Furthermore, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A two-sided p-value < 0.05 was considered statistically significant. Statistical data were analyzed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA).

Results

Study Population

This study included 153 ICU patients with culture-confirmed *K. pneumoniae* infection across the one-year study period. Among them, 96 (62.7%) demonstrated carbapenem-resistant isolates (CRKP group), whereas 57 (37.3%) exhibited carbapenem-susceptible isolates (CSKP group). The CRKP isolates were evaluated as infectious and colonization agents in 79 and 17 patients, respectively. Of the 79 infectious disease cases, 78 were healthcare-associated and 1 was community-acquired. Furthermore, 69 of the 96 CRKP isolates showed monomicrobial growth, whereas 27 showed polymicrobial growth. Meanwhile, the CSKP isolates were classified as infectious and colonization agents in 50 and 7 patients, respectively. Of the 50 infectious disease cases, 40 were healthcare-associated and 10 were community-acquired. In addition, 37 of the 57 CSKP isolates showed monomicrobial growth, whereas 20 showed polymicrobial growth.

Figure 1 shows a flowchart of these data. Table 1 lists the demographic and clinical characteristics of patients in the study and control groups. The mean age was higher

in the CRKP group than in the CSKP group. Sex distribution did not differ significantly between these groups. In the study group, sex ($p = 0.770$), age ($p = 0.671$), and hospitalization department ($p = 0.747$) showed no significant difference between the infection and colonization groups. Conversely, a statistically significant difference was found in the clinical specimens examined ($p = 0.001$). Specifically, the infection rate was significantly higher in direct endotracheal aspirate (DTA) samples (87%), while the colonization rate was higher in urine samples (58.3%).

Table 1. Clinical and demographic characteristics of patients in the study and control groups

Characteristic	Category	Infection Study n (%)	Infection Control n (%)	p	Colonization Study n (%)	Colonization Control n (%)	p	p*
Age	Median (years)	66	72	-	75	72	-	-
	≥65	42 (53.2)	34 (68.0)	0.103	10 (58.8)	4 (57.1)	1.000	1.000
	<65	37 (46.8)	16 (32.0)	-	7 (41.2)	3 (42.9)	-	-
Sex	Male	54 (68.4)	29 (58.0)	0.261	11 (64.7)	3 (42.9)	0.393	0.626
	Female	25 (31.6)	21 (42.0)	-	6 (35.3)	4 (57.1)	-	-
ICU type	Medical ICU	28 (35.4)	16 (32.0)	0.708	3 (17.6)	1 (14.3)	1.000	1.000
	Anesthesiology ICU	25 (31.6)	7 (14.0)	0.035	4 (23.5)	3 (42.9)	0.374	0.788
	Pulmonology ICU	12 (15.2)	7 (14.0)	1.000	1 (5.9)	0 (0.0)	1.000	1.000
	General Surgery ICU	10 (12.7)	9 (18.0)	0.450	3 (17.6)	1 (14.3)	1.000	0.533
	Neurosurgery ICU	3 (3.8)	5 (10.0)	0.260	6 (35.3)	2 (28.6)	1.000	0.601
	Coronary ICU	1 (1.3)	4 (8.0)	0.074	-	-	-	1.000
	Cardiovascular Surgery ICU	0 (0.0)	2 (4.0)	0.148	-	-	-	1.000
Clinical Specimen	DTA	40 (50.6)	13 (26.0)	0.006	6 (35.3)	0 (0.0)	0.130	0.340

Characteristic	Category	Infection Study n (%)	Infection Control n (%)	p	Colonization Study n (%)	Colonization Control n (%)	p	p*
	Wound	15 (19.0)	6 (12.0)	0.337	2 (11.8)	1 (14.3)	1.000	1.000
	Blood	12 (15.2)	15 (30.0)	0.049	-	-	-	0.015
	Urine	5 (6.3)	8 (16.0)	0.130	7 (41.2)	3 (42.9)	1.000	0.003
	BAL	4 (5.1)	1 (2.0)	0.648	0 (0.0)	1 (14.3)	0.292	1.000
	Catheter	2 (2.5)	1 (2.0)	1.000	0 (0.0)	1 (14.3)	0.292	0.457
	Sputum	1 (1.3)	3 (6.0)	0.298	0 (0.0)	1 (14.3)	0.292	0.535
	Peritoneal Fluid	0 (0.0)	2 (4.0)	0.148	2 (11.8)	0 (0.0)	1.000	0.094
	Pleural Fluid	0 (0.0)	1 (2.0)	0.388	-	-	-	1.000

*p-values were calculated using Fisher's exact test for group comparisons within the same variable category. Abbreviations: ICU, intensive care unit; DTA, direct endotracheal aspirate; BAL, bronchoalveolar lavage.

Clinical Characteristics and Risk Factors for Carbapenem Resistance

In the univariate analysis, advanced age, hemodialysis, steroid use, central venous catheterization, and mechanical ventilation were significantly associated with carbapenem resistance (Table 2). In the multivariate logistic regression analysis, central venous catheterization and Gram-negative infection history within the previous 3 months were independent predictors of CRKP infection (Table 3).

Table 2. Univariate analysis for carbapenem resistance

Variable	OR	95% CI	p
Age	0.98	0.96–1.00	0.046
Sex	1.56	0.75–3.26	0.314
Diabetes Mellitus	1.55	0.70–3.46	0.377
Immunosuppression	0.49	0.22–1.07	0.110

Variable	OR	95% CI	p
Malignancy	0.64	0.30–1.38	0.348
Chronic Kidney Disease	1.86	0.56–6.20	0.459
Hemodialysis	7.08	1.57–32.03	0.009
Steroid use	3.70	1.30–10.50	0.019
Central venous catheterization	9.85	2.66–36.46	<0.001
Mechanical ventilation	6.05	2.64–13.84	<0.001
Recent surgery	0.97	0.48–1.97	1.000
Antimicrobial use in the last 3 months	2.90	1.04–8.08	0.066
Resistant GN infection in the last 3 months	1.96	0.81–4.74	0.199
ICU admissions in the last 3 months	2.08	1.01–4.27	0.068
Hospitalizations in the last 3 months	1.35	0.57–3.18	0.646

Abbreviations: OR, odds ratio; CI, confidence interval; GN, Gram-negative; ICU, intensive care unit.

Table 3. Multivariate analysis for carbapenem resistance

Variable	OR	95% CI	p
Age	0.96	0.93–0.99	0.020
Sex	1.17	0.40–3.44	0.770
Immunosuppression	0.34	0.04–2.89	0.320
Malignancy	1.67	0.22–12.55	0.620
Hemodialysis	2.12	0.18–3.42	0.090
Steroid use	2.09	0.36–12.01	0.410
Central venous catheterization	14.26	1.46–139.27	0.020
Mechanical ventilation	1.44	0.43–4.87	0.560
Antimicrobial in the last 3 months	0.94	0.06–14.60	0.960
Resistant GN infection in the last 3 months	25.59	1.32–495.09	0.030
ICU admissions in the last 3 months	0.37	0.09–1.58	0.180
Hospitalizations in the last 3 months	0.30	0.05–1.70	0.170

Abbreviations: OR, odds ratio; CI, confidence interval; GN, Gram-negative; ICU, intensive care unit.

Infection Types and Treatment

The most common infection types were pneumonia, bloodstream infection, and urinary tract infection. Combination antibiotic therapy was more frequently used in the CRKP group, particularly in those with pneumonia and bloodstream infections,

whereas monotherapy was more common in those with urinary tract infections. Treatment approaches were compared between the study and control groups according to infection diagnosis (Table 4). The CRKP group had longer hospital stays than the CSKP group.

Table 4. Comparison of treatment preferences according to infection diagnosis in the study and control groups

Infection Diagnosis	Study Combined n (%)	Study Monotherapy n (%)	Control Combined n (%)	Control Monotherapy n (%)	p
Ventilator-associated pneumonia	36 (76.6)	11 (23.4)	4 (23.5)	13 (76.5)	0.000
Bloodstream infection	12 (92.3)	1 (7.7)	4 (26.7)	11 (73.3)	0.001
Soft-tissue infection	8 (80.0)	2 (20.0)	0 (0.0)	4 (100.0)	0.015
Surgical site infection	5 (100.0)	0 (0.0)	2 (28.6)	5 (71.4)	0.028
Urinary tract infection	3 (75.0)	1 (25.0)	1 (14.3)	6 (85.7)	0.088

Carbapenemase Gene Distribution

Among CRKP isolates, the most frequently detected carbapenemase gene was *OXA-48* (67.1%), followed by *NDM* (49.4%), *KPC* (31.7%), *IMP* (7.6%), and *VIM* (5.1%). All *NDM*-positive isolates coharbored *OXA-48*. Table 5 summarizes the distribution of these genes. Analysis of the relationship between comorbidities and gene distribution showed that *OXA-48* and *KPC* gene prevalence was significantly increased in patients undergoing hemodialysis and those receiving steroids ($p < 0.05$).

Table 5. Beta-lactamase gene distribution of CRKP isolates detected in the study group

Gene	Category	Infection n (%)	Colonization n (%)
<i>OXA-48</i>	Positive	53 (67.09)	10 (58.8)
<i>NDM</i>	Positive	39 (49.30)	9 (52.9)

Gene	Category	Infection n (%)	Colonization n (%)
<i>KPC</i>	Positive	25 (31.65)	6 (35.2)
<i>IMP</i>	Positive	6 (7.50)	1 (5.9)
<i>VIM</i>	Positive	4 (5.06)	2 (11.8)
<i>OXA-48 + NDM</i>	Positive	39 (49.30)	9 (52.9)
<i>OXA-48 + KPC</i>	Positive	1 (1.27)	1 (5.9)
<i>OXA-48 + KPC + NDM</i>	Positive	1 (1.27)	1 (5.9)

According to the chi-square analysis results, the relationship between prognosis and carbapenemase gene positivity was significant only for *IMP* positivity ($\chi^2[2] = 9.18$, $p = 0.010$). Mortality rate was highest in the *IMP*-positive group. For other genes (*OXA-48*, *KPC*, *NDM*, *VIM*), no significant difference was found between prognosis groups ($p > 0.05$; Table 6).

Table 6. Carbapenemase gene positivity rates according to prognosis group

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Prognosis	Total Patients (n)	<i>OXA-48</i> n (%)	<i>KPC</i> n (%)	<i>NDM</i> n (%)	<i>VIM</i> n (%)	<i>IMP</i> n (%)
Healing	10	5 (50.0%)	5 (50.0%)	4 (40.0%)	1 (10.0%)	1 (10.0%)
Mortality	25	20 (80.0%)	4 (16.0%)	14 (56.0%)	2 (8.0%)	5 (20.0%)
Infection nonresponse, treatment change	44	28 (63.6%)	16 (36.4%)	21 (47.7%)	1 (2.3%)	0 (0.0%)

The gene combination *NDM + OXA-48* ($n = 35$) was the most frequently detected, followed by *KPC* positivity alone ($n = 22$) and *OXA-48* positivity alone ($n = 12$). Only one case showed triple-gene positivity (*KPC + NDM + OXA-48*), and only two cases showed no gene combination. According to gene combination, the 90-day mortality rate was 100% in cases with quadruple gene positivity, 75% in cases with *OXA-48* positivity alone, and 50% in cases without a gene combination. While the mortality rate was close to 50% in the *NDM + OXA-48* combination, it was 37.5% in cases with *KPC* positivity alone.

In terms of hospitalization duration, cases with triple-gene positivity had the longest hospital stay. In other combinations, the average hospitalization duration ranged from 30 to 42 days.

90-Day Mortality Rate

Among patients with infection, the 90-day mortality rate was lower in the study group than in the control group (51.9% [41/79] vs. 66.0% [33/50]), but this difference was not statistically significant ($p = 0.144$).

In the multivariate analysis, the independent predictors of 90-day mortality were advanced age, malignancy, CKD, and mechanical ventilation (Table 8). Carbapenem resistance was not independently associated with increased mortality. Tables 7 and 8 list the univariate and multivariate analysis results, respectively.

Table 7. Univariate analysis results for 90-day mortality rate

Variable	OR	95% CI	p
Age	1.05	1.03–1.08	<0.001
Sex	0.92	0.44–1.91	0.820
Diabetes Mellitus	1.41	0.65–3.06	0.391
Immunosuppression	1.62	0.72–3.62	0.244
Malignancy	2.43	1.08–5.48	0.031
Chronic Kidney Disease	12.60	1.60–99.04	0.016
Hemodialysis	1.91	0.68–5.33	0.219
Steroid use	1.45	0.61–3.44	0.404
Foley catheter use	2.14	0.57–8.00	0.257
Central venous catheterization	0.93	0.33–2.63	0.896
Mechanical ventilation	1.78	0.83–3.82	0.140
Recent surgery	1.55	0.77–3.12	0.223
Antimicrobial in the last 3 months	1.41	0.52–3.83	0.497
Resistant GN infection in the last 3 months	0.71	0.29–1.75	0.456
ICU admissions in the last 3 months	0.70	0.35–1.43	0.329
Hospitalizations in the last 3 months	0.91	0.38–2.15	0.823

Abbreviations: OR, odds ratio; CI, confidence interval; GN, Gram-negative; ICU, intensive care unit.

Table 8. Multivariate analysis results for 90-day mortality rate

Variable	OR	95% CI	p
Age	1.05	1.02–1.08	<0.001

Variable	OR	95% CI	p
Malignancy	2.54	1.02–6.29	0.044
Chronic Kidney Disease	9.54	1.17–78.07	0.035
Mechanical ventilation	3.40	1.35–8.58	0.009
Recent surgery	1.31	0.57–3.02	0.527

Note: ORs are adjusted values; 95% CI was calculated using the Wald method. Abbreviations: CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval.

Discussion

In this one-year prospective cohort study involving ICU patients with culture-confirmed *K. pneumoniae*, carbapenem-resistant isolates accounted for nearly two-thirds of all cases. Independent predictors of carbapenem resistance included advanced age, central venous catheterization, and a recent history of Gram-negative infection. Molecular analysis demonstrated that *OXA-48* was the predominant carbapenemase gene, frequently coexisting with *NDM*. Despite marked differences in resistance profiles, carbapenem resistance itself was not independently associated with increased 90-day mortality.

Furthermore, the 90-day mortality rate was higher in the CSKP (control) group than in the CRKP (study) group, although the difference was not statistically significant. Tumbarello et al. [11] reported a 30-day mortality rate of 41.6% for CRKP, while Giannella et al. [12] found high rates of morbidity and mortality associated with these infections. The higher mortality observed in our control group, contrary to previous studies, may be explained by our limited sample size, the exclusive inclusion of ICU patients, or confounding factors including differences in age, infection severity, comorbidities, and treatment initiation timing.

This study identified advanced age, malignancy, CKD, and mechanical ventilation as the principal determinants of mortality. According to a meta-analysis by Qian et al. [13], septic shock, congestive heart failure, chronic obstructive pulmonary disease (COPD), CKD, DM, mechanical ventilation, and inappropriate empirical antimicrobial treatment are factors associated with mortality in CRKP infections. Consistent with these findings, our study found that DM and CKD were more prevalent in patients who died than in those who did not. Therefore, in *Klebsiella* infections, comorbidities may play a more significant role in mortality than carbapenem resistance itself.

The predominance of *OXA-48* observed in our cohort aligns with the molecular epidemiology of carbapenem-resistant Enterobacterales reported in Turkey and other Mediterranean countries [14, 15]. In this geographical region, *OXA-48*-like enzymes have become endemic, representing the dominant carbapenemase in *K. pneumoniae* isolates. Its high frequency and coexistence with *NDM* detected in our study further highlight the evolving complexity of resistance mechanisms. Karabay et al. reported that all eight collected *K. pneumoniae* isolates produced *NDM-1*, with *OXA-48* detected in two, and that six of the eight strains showed 95% clonal similarity by Rep-PCR [16]. Similarly, our study found a high frequency of *OXA-48* and *NDM* co-occurrence, with all *NDM*-positive cases also testing positive for *OXA-48*. In Turkey, *OXA-48* and *NDM* co-occurrence was first reported in a patient from Urfa [17]. Coexistence of multiple carbapenemase genes is associated with broader resistance phenotypes, fewer therapeutic options, and increased challenges in antimicrobial stewardship programs.

Although *VIM* and *IMP* positivity were relatively uncommon, the *IMP* positivity and mortality association observed in our study suggests that specific resistance mechanisms have distinct clinical implications beyond antimicrobial susceptibility patterns alone.

Our major finding was the strong association between invasive medical interventions and carbapenem resistance. According to Lin et al.'s meta-analysis, mechanical ventilation is a significant risk factor for multidrug-resistant and extensively drug-resistant infections [18]. Moreover, central venous catheterization emerged as one of the strongest independent predictors of CRKP infection [19]. Ben-David et al. stated that central venous catheterization and mechanical ventilation are significant predisposing factors for colonization in patients with CRKP-induced bacteremia [20]. This observation agrees with previous investigations demonstrating that invasive devices facilitate both colonization and infection by multidrug-resistant Gram-negative organisms. Central venous catheters may serve both as direct portals of entry and indicators of greater disease severity and prolonged ICU exposure. Similarly, univariate analyses revealed that mechanical ventilation was significantly more common among patients with CRKP, reflecting the well-established relationship between ventilator support and resistant pathogen acquisition in critical care settings.

Prolonged healthcare exposure may play an important role in carbapenem resistance development. Tumbarello et al. demonstrated that CRKP infections are associated with higher mortality and prolonged hospital stays compared with infections caused by susceptible strains despite appropriate treatment, and that delayed or absent appropriate treatment has an adverse impact on hospitalization duration [21]. Additionally, Zhang et al. observed that hospital stay was significantly longer in the CRKP group than in the CSKP group [22]. In our cohort, patients with CRKP generally experienced longer hospitalization before microbiological isolation compared with those with CSKP. Extended ICU stays may increase cumulative exposure to broad-spectrum antibiotics, invasive

procedures, healthcare personnel contact, and environmental reservoirs of resistant organisms. Our finding supports previous reports identifying hospitalization duration as a key determinant of CRKP acquisition and reinforces that infection prevention measures remain important throughout prolonged ICU admissions.

Recent Gram-negative bacterial infection was another independent predictor of carbapenem resistance observed in this study, likely reflecting repeated antibiotic exposure and prior selection pressure favoring resistant strains. Among patients with infection, the CRKP group had more individuals with a history of antimicrobial drug use in the preceding 3 months than the CSKP group (91.1% vs. 78%); ICU admission history was also significantly more common in the CRKP group. Likewise, a history of antimicrobial drug use, hospitalization, ICU admission, and infection or colonization with resistant Gram-negative bacteria within the last 3 months was more frequently observed in the CRKP group than in the CSKP group. Wang et al. reported that prior antibiotic use and ICU admission history are risk factors for CRKP infection or colonization. In Zhu et al.'s study, prior hospitalization and antibiotic use emerged as risk factors for carbapenem resistance development [23, 24]. Previous antimicrobial treatment, particularly with broad-spectrum β -lactams and carbapenems, has consistently been identified as a major driver of CRKP emergence. Therefore, our findings further emphasize that antimicrobial stewardship programs are essential in limiting unnecessary antibiotic use and reducing the selection of resistant pathogens.

Interestingly, although carbapenem resistance has traditionally been regarded as a major determinant of poor clinical outcomes, no significant increase in 90-day mortality was observed in the CRKP group versus the CSKP group. Nonetheless, both groups showed high mortality rates, reflecting the critically ill nature of ICU patients. Several contemporary studies have reported similar findings, suggesting that mortality is often driven more strongly by patient-related factors and illness severity than by resistance status alone.

Our multivariate analysis demonstrated that advanced age, malignancy, CKD, and mechanical ventilation independently predicted death within 90 days. Tumbarello et al. reported *K. pneumoniae* carbapenemase (KPC)-associated bloodstream infection, septic shock, inadequate empirical antimicrobial therapy, CKD, and a high APACHE III score as independent predictors of mortality [11]. Chang et al. examined *K. pneumoniae*-associated bloodstream infection and found hematologic malignancies, CP isolation, COPD, and septic shock as risk factors associated with mortality in their multivariate analysis [25]. These findings align with our results.

Another noteworthy observation in our study was the relationship between carbapenemase gene patterns and clinical outcomes. While *OXA-48* alone represented the predominant molecular mechanism, isolates harboring multiple

resistance genes were associated with longer hospital stays and poorer outcomes. In particular, infection cases with multiple carbapenemase genes involved demonstrated the highest mortality rates and the longest hospitalization duration. Regarding carbapenemase gene combinations, 49.37% of the patients tested positive for both *OXA-48* and *NDM*, with all *NDM*-positive cases (100%) testing positive for *OXA-48* concurrently. Therefore, the distribution of carbapenemase genes in Turkey is not limited solely to *OXA-48*; other genes, such as *NDM* and *KPC*, have begun to appear, with the prevalence of gene coexistence gradually increasing [26–28]. Thus, the novel gene combinations identified in our study align with the national literature. In our study, cases testing positive for the triple-gene combination of *KPC* + *NDM* + *OXA-48* had the longest mean length of hospital stay and 100% mortality rate. Li et al. reported that the mean hospitalization duration for infections caused by triple-gene-positive *K. pneumoniae* strains was significantly longer than single-gene-positive cases and that mortality rates exceeded 80% [29]. Therefore, molecular complexity may be associated with clinical burden.

Our study findings have several important clinical implications. First, rapid molecular detection of carbapenemase genes may help early optimize antimicrobial therapy and infection control measures. Second, minimizing unnecessary invasive device use and shortening device duration whenever clinically feasible may reduce CRKP risk. Third, given that host-related factors mainly influenced mortality, comprehensive management strategies should include optimizing underlying comorbidities, organ support, and overall critical care management, extending beyond antimicrobial treatment alone.

This study has several limitations. It was conducted at a single tertiary-care center, thereby limiting our findings' generalizability to other healthcare settings. Severity-of-illness scores, including APACHE II or SOFA, were not incorporated into the multivariate models; therefore, residual confounding may remain. Additionally, the sample size is relatively limited; thus, this study may have insufficiently detected modest mortality differences between resistant and susceptible isolates. Nevertheless, the prospective design of this study, the inclusion of molecular resistance characterization, and the evaluation of long-term mortality outcomes strengthen the validity and clinical relevance of our findings.

Conclusions

In conclusion, CRKP infections in ICU patients were characterized by distinct clinical and molecular features, including the predominance of *OXA-48* and frequent *OXA-48* + *NDM* coexistence. However, carbapenem resistance itself was not independently associated with increased 90-day mortality. Instead, advanced age, malignancy, CKD, and mechanical ventilation emerged as the strongest

predictors of adverse CRKP outcomes. Therefore, host-related factors may outweigh resistance status in determining prognosis and support an integrated approach that combines molecular surveillance, antimicrobial stewardship, invasive device optimization, and comprehensive critical care management.

List of Abbreviations

- **CI:** Confidence interval
- **CKD:** Chronic kidney disease
- **CRKP:** Carbapenem-resistant *Klebsiella pneumoniae*
- **CSKP:** Carbapenem-susceptible *Klebsiella pneumoniae*
- **DM:** Diabetes mellitus
- **ICU:** Intensive care unit
- **OR:** Odds ratio
- **PCR:** Polymerase chain reaction

Declarations

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University (AFSU) Faculty of Medicine (Approval No.: 2011-KAEK-2; September 1, 2023). Given the observational design of the study, informed consent was waived by the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University Faculty of Medicine according to local regulations.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BA and ND contributed to the study design, data collection, and manuscript drafting. YÇ and CD performed microbiological procedures and molecular gene analyses. All authors read and approved the final manuscript.

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Fig. 1. Flowchart of the study population and classification of patients according to carbapenem susceptibility, infection status, and microbiological characteristics.

