JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Klebsiella pneumoniae infections in the intensive care unit: risk factors related to carbapenem resistance and mortality

Melek Ayan[1], Ali K Çelik[2]

[1] *Microbiology Clinic, Mersin City Training and Research Hospital, Mersin, Turkey*
[2] *Infectious disease Clinic, Mersin City Training and Research Hospital, Mersin, Turkey*

Abstract

Introduction: Nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in intensive care units (ICUs) are increasing worldwide. Morbidity and mortality rates are quite high in these infections due to limited treatment options and various risk factors. We determined the rate of carbapenem resistance, risk factors for carbapenem resistance, mortality rate, and risk factors associated with mortality in nosocomial infections in the adult ICU.

Methodology: We reviewed the medical records of nosocomial infected patients retrospectively, according to the surveillance diagnostic criteria established by the Centers for Diseases Control and Prevention. Bacterial identification and antibiotic susceptibility tests were performed on the Phoenix 100 system (Becton Dickinson, Sparks, MD, USA). During carbapenemase gene analysis, *blaKPC*, *blaOXA-48*, *blaNDM-1*, and *blaIMP* genes were investigated by polymerase chain reaction (PCR). Potential risk factors were statistically analyzed.

Results: Carbapenem resistance was detected in 52/76 of these patients (68.4%). The *OXA-48* gene was present in all isolates, and the combination of *OXA-48* and *NDM-1* was found in 40.4% isolates. The overall mortality rate was 59.2% (45/76). Presence of malignancy; intubation; antibiotic use in the last 3 months; and quinolone, glycopeptide, carbapenem, and antifungal use were determined as risk factors for the development of carbapenem-resistant *K. pneumoniae*. Mechanical ventilation, presence of carbapenemase and pan-resistant status, and glycopeptide use were independent risk factors for mortality.

Conclusions: The data obtained in this study will guide the control measures for this infection and the rational use of antibiotics, and will contribute to the decrease in mortality rates.

Key words: *Klebsiella pneumoniae*; mortality; risk factors.

J Infect Dev Ctries 2025; 19(2):248-257. doi:10.3855/jidc.18775

(Received 23 June 2023 – Accepted 14 April 2024)

Introduction

Klebsiella pneumoniae (*K. pneumoniae*), a member of the family Enterobacteriaceae, is an opportunistic pathogen. *K. pneumonia*e colonizes the gastrointestinal tract, skin, and nasopharynx; and causes community-acquired and nosocomial infections. The bacteria have become increasingly prominent as nosocomial infection agents in recent years. They frequently cause complicated and difficult-to-treat infections such as sepsis, urinary tract infection, catheter-related infection, pneumonia, gallbladder infections, and surgical site infections [1,2].

A major problem experienced in nosocomial infections caused by *K. pneumoniae* is the development of multiple antibiotic resistance following widespread and inappropriate use of antibiotics in the community and in hospitals. Due to limited treatment options in such infections, mortal infections and epidemics that are difficult to control develop, especially in intensive care units (ICUs) [3,4]. Multidrug resistance in *K. pneumoniae* is usually caused by extended spectrum betalactamases (ESBL) and carbapenem resistance through various mechanisms. Carbapenems are antibiotics used to treat serious infections caused by multidrug-resistant bacteria such as *K. pneumoniae*. The main mechanisms of resistance to carbapenems are decreased membrane permeability as a result of porin loss, activation of the efflux pump that provides antibiotic excretion, and, most importantly, production of carbapenemases (carbapenem degrading enzymes) that hydrolyze carbapenems [5]. Although prevalence of carbapenemases varies geographically, they are being reported with increasing frequency all over the world, including in Turkey [6]. It is known that prolonged stay in the ICU or hospital, inadequate immune response, use of invasive devices, and multiple antibiotic use are risk factors for the emergence of resistant strains and mortality [7–10].

The aim of this study was to investigate the risk factors associated with carbapenem resistance and

patient mortality in infections due to *K. pneumoniae* in the ICUs of our hospital.

Methodology

This study was conducted with the approval of Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee (date: 30 June 2022; decision number: 19).

Patients over 18 years of age, who were hospitalized in the ICUs of our hospital between 1 January 2021 and 30 June 2022, and diagnosed with nosocomial infection caused by *K. pneumoniae*, were included in this study. In the case of patients from whom *K. pneumoniae* was isolated from more than one site or more than once, the first isolation data were included in the study. Colonization and community-acquired infections were excluded. Nosocomial infections were defined according to the surveillance diagnostic criteria determined by the United States (US) Centers for Diseases Control and Prevention (CDC) [11]. The medical records of patients infected with carbapenem-susceptible *K. pneumoniae* (CSKP) and carbapenem-resistant *K. pneumoniae* (CRKP) were retrospectively analyzed. Demographics and clinical conditions of these patients were compared. Potential risk factors such as age, gender, invasive procedures performed, comorbidities, and antibiotic exposure in the last three months were analyzed.

In addition to the above risk factors, the effect of presence of carbapenemase and resistance genes, presence of pan-resistant strains, C-reactive protein (CRP) and precalcitonin levels, and the 10- and 90-day mortality in patients were also analyzed. In addition, the effects of resistance genes and presence of resistance to some antibiotics on mortality in CRKP infections were evaluated.

Bacterial identification and antibiotic susceptibility testing

Clinical specimens, except for blood samples, were cultured on 5% sheep blood agar and eosin-methyleneblue (EMB) agar media. Blood samples were added to blood culture bottles (Bactec FXBecton Dickinson®, Maryland, USA) and incubated in an automated system (BACTEC 9120, BD Diagnostic Instrument Systems, Sparks, MD, USA). The flasks that indicated a positive signal were passaged onto 5% sheep blood and EMB agar media, and incubated at 35.5–37 °C for 18–24 hours. Identification and antibiotic susceptibility tests were performed in the automated system Phoenix 100 (Becton Dickinson, Sparks, MD, USA) using NMIC/ID-433 and UNMIC/ID for urine. The results were evaluated according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [12]. Carbapenem-resistant strains were re-studied with the NMIC-505 resistance panel on Phoenix 100 (Becton Dickinson, Sparks, MD, USA) to determine additional antibiotic susceptibilities. The resistance status of 26 antibiotics in 12 antibiotic categories [aminoglycosides (gentamicin, tobramycin, amikacin), antipseudomonal penicillins + β-lactamase inhibitors (piperacillin-tazobactam) carbapenems (ertapenem, imipenem, meropenem), cephalosporins (cefazolin, cefuroxime, cefotaxime, ceftriaxone, ceftazidime, cefepime, cefexime) cephalosporins + β-lactamase inhibitors (ceftalozone-tazobactam, ceftazidime/avibactam) fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin), folate pathway inhibitors (trimethoprim-sulphamethoxazole), penicillins (ampicillin, amoxacillin) penicillins + β-lactamase inhibitors (amoxicillin-clavulanic acid, ampicillin-sulbactam), phosphonic acids (fosfomycin), polymyxins (colistin)] were evaluated with NMIC-505 resistance panel. Strains resistant to 26 antibiotics belonging to 12 antibiotic groups were defined as pan-resistant.

Carbapenemase gene analysis method

Gene analysis of the strains belonging to the patients who were retrospectively examined and included in the study was obtained from the 'Enterobactericae family collection archive' stored at –20 degrees Celsius, where carbapenem resistance was

Table 1. Polymerase chain reaction (PCR) primers.

Primer	Sequence (5'-3')	Product size (bp)
KPC-F[1]	5'-AGGACTTTGGCGGCTCCAT-3	749
KPC-R[2]	5'-TCCCTCGAGCGCGCGAGTCTA-3'	
OXA-48-F [3]	5'-GCGTGGTTAAGGATGAACACAC-3'	438
OXA-48-R [4]	5'-CATCAAGTTCAACCCAACCCAACCG-3'	
IMP-F [5]	5'-GGAATAGAGAGTGGCTTAAYTCTC-3'	232
IMP-R[6]	5'-GGTTTAAYAAAACAACCACC-3'	
NDM-1-F[7]	5′ATGGAATTGCCCAATATTATGC-3'	813
NDM-1-R[8]	5′-TCAGCGCGCAGCTTGTCGGC -3'	

[1]: *Klebsiella pneumonia* carbapenemase – forward; [2]: *Klebsiella pneumonia* carbapenemase – reverse; [3]: Oxasilinase-48 – forward; [4]: Oxasilinase-48 – reverse; [5]: Imipenemase – forward; [6]: Imipenemase – reverse; [7]: New Delhi metallo-beta-lactamases – forward, [8]: New Delhi metallo-beta-lactamases – reverse.

detected with the 'Phoenix 100 (Becton Dickinson, Sparks, MD, USA) automated system. The genes *blaKPC*, *blaOXA-48*, *blaNDM-1*, and *blaIMP*; which are frequently observed in our country, were investigated.

Bacterial genomic DNA was extracted from isolates by using Tissue and Bacterial DNA Purification Kit (Eurx, Gdansk, Poland). DNA samples were stored at –20 °C and 3 µL of DNA was used for multiplex polymerase chain reaction (PCR) with primers for *blaKPC*, *blaOXA-48*, *blaNDM-1*, and *blaIMP* genes (Table 1) in a 50 µL reaction mixture. Amplification was performed with the following thermal cycling conditions: 5 minutes of pre-denaturation at 95 °C; followed by 35 cycles of 1 minute at 95 °C, 1 minute at 52 °C, and 1 minute at 72 °C; and 10 minutes of final elongation at 72 °C. PCR products were analyzed by electrophoresis in a 1% agarose gel at 100 V for 40 minutes in 0.5× TBE and stained with 0.05 mg/L ethidium bromide. The gel was visualized by the Quantum gel documentation system (Vilber Lourmat, Marne La Vallee, France).

Statistical analysis

Statistical Package for Social Sciences (SPSS) for Windows 23.0 (IBM Corp, Armonk, NY, USA) was used for statistical analyses. Descriptive findings were presented as numbers and percentages, means, and standard errors. Comparisons between groups were analyzed by the Chi-square test and significance test of the difference between two means. A *p* value less than 0.05 was considered significant. Odds ratio and 95% confidence interval were also calculated. Normality test was applied for each variable, Multivariate analysis of variance was used to analyze parametric data that fit the normal distribution; t-test was performed in groups of two for comparison of nominal values; and ANOVA analysis was performed in cases involving more than two groups.

Results

Nosocomial infections caused by *K. pneumoniae* were detected in a total of 76 ICU patients, who met the inclusion criteria during the 18-month period. Carbapenem resistance was detected in 52 (68.4%) of these patients.

The average age of the patients was 64.7 years (range 25–94 years) and 56.6% of the patients were male. The majority of the patients in the CRKP subgroup were also men (61.5%).

The most common infections among all patients were urinary tract infection (n = 33, 43.4%), pneumonia (n = 26, 34.2%), and bloodstream infection (n=16, 21%). Growth of CRKP was detected in the peritoneal fluid culture of one patient. Pneumonia was the most common infection in the CRKP group, and urinary tract infection was the most common infection in the CSKP group. The highest mortality rate, in the 76 patients included in our study, was observed among patients with pneumonia, while the highest mortality rate in CRKP group was found among bloodstream infection patients (Table 2).

According to the NMIC-505 resistance panel of 52 CRKP strains, 42 were fosfomycin resistant, 25 were ceftazidime-avibactam resistant, 17 were colistin resistant, and 13 were pandrug-resistant (PDR) bacteria in 12 antibiotic categories.

During PCR analysis of CRKP strains, 30 strains (57.7%) had only the *OXA-48* gene, 21 strains (40.4%) had a combination of *OXA-48* and *NDM-1*, and one strain (1.9%) had the combination of *KPC* and *OXA-48*. The *OXA-48* gene was present in all isolates. None of the strains contained only *NDM-1* or *KPC*. *IMP* was not detected in any isolate.

The results of univariate and multivariate analyses which included possible risk factors such as age and gender, use of invasive devices, enteral nutrition, comorbid diseases, antibiotics used in the last 3 months, and blood transfusion as risks for CRKP development/mortality are shown on Table 3. The presence of malignancy in comorbid diseases and mechanical ventilation among invasive procedures were risk factors for CRKP. Antibiotic use in the last 3 months was significant in CRKP infections; quinolone, glycopeptide, carbapenem, and antifungal use were identified as risk factors. In multiple analyses,

Table 2. Mortality rates according to site of infection and *Klebsiella pneumoniae* resistance status.

Site of infection	Carbapenem resistant *Klebsiella pneumonia* (CRKP) n = 52 / death (%)	Carbapenem sensitive *Klebsiella pneumonia* (CSKP) n = 24 / death (%)	Total number of infections (%) / death (%)
Urinary system	21/9 (42.9%)	12/2 (16.7%)	33 (43.4%) / 11 (33.3%)
Lung	23/21 (91%)	3/2 (66%)	26 (34.2%) / 23 (88.5%)
Blood circulation	7/7 (100%)	9/4 (44.4%)	16 (21%) / 11 (68.8%)
Peritoneum	1/0 (0%)	–	1 (1.3%) / 0 (0%)
Total	52/37 (71.01)	24/8 (33.3)	76/45 (59.2%)

quinolone use was an independent risk factor and was 11.7 times higher in the resistant group compared to the susceptible group (p = 0.008, OR: 11.77, 95% CI: 0.605–25.289).

The results of univariate and multivariate analyses, including possible risk factors associated with 10- and 90-day mortality among patients with CRKP and CSKP, are shown on Table 4. The mortality rate was 59.2% (45/76) in our study. The mortality rate in the CRKP subgroup was 71.15% (37/52), and the mortality rate in the CSKP subgroup was 33.3% (8/24). Mechanical ventilation, parenteral nutrition, cerebrovascular diseases, antibiotic use in the last 3 months, presence of carbapenemase (being CRKP), and pandrug resistance were risk factors for both 10-day and 90-day mortality. In addition to these, coronary artery disease and procalcitonin elevation were risk factors for mortality in the first 10 days, while being over 65 years of age, presence of diabetes mellitus, bladder catheter, and central venous catheter were risk factors for mortality in the first 90 days ($p < 0.05$). In multivariate analysis, mechanical ventilation (1.7-fold), presence of carbapenemase (7.6-fold), and pan-resistant status (8-fold) were independent risk factors for 10-day mortality; while presence of carbapenemase (9.2-fold), pan-resistant status (5.1-fold), and glycopeptide use (5.95-fold) were independent risk factors for 90-day mortality.

Analysis of mortality risk factors in the CRKP subgroup found no effect of carbapenemase resistance genes. Fosfomycin, cefazidime-avibactam, and colistin resistance were risk factors ($p < 0.05$), but not independent risk factors. Pan-resistant status was an independent risk factor for 10- and 90-day mortality (Table 5).

Table 3. Demographics and clinical characteristics of carbapenem resistant *Klebsiella pneumonia* (CRKP) and carbapenem sensitive *Klebsiella pneumonia* (CSKP) groups.

Variables	CRKP (n = 52)	CSKP (n = 24)	Univariate analysis			Multivariate analysis		
			OR	95%	*p*	OR	95%	*p*
Age								
< 65 years	20	8	1.25	0.4485–3.616	0.6666			
≥ 65 years	32	16						
Gender								
Female	20	13	0.5288	0.2121–1.429	0.1991			
Male	32	11						
Invasive procedures								
Mechanical ventilation	33	8	3.474	1.258–10.18	0.0143			> 0.05
Urinary catheter	52	24						> 0.05
Central venous catheter	47	21	1.343	0.3300–5.901	0.7033			> 0.05
Transfusion of blood	33	19	0.4571	0.1669–1.468	0.171			> 0.05
Parenteral nutrition	40	17	1.373	0.4929–3.912	0.5687			> 0.05
Comorbid diseases								
Cerebrovascular disease	7	5	0.5911	0.1684–1.941	0.4127			> 0.05
Chronic obstructive pulmonary disease	6	4	0.6522	0.1861–2.239	0.5387			> 0.05
Malignancy	3	5	0.2327	0.05843–1.045	0.0467			> 0.05
Diabetes mellitus	15	7	0.9846	0.3555–2.637	0.9772			> 0.05
Chronic renal failure	8	3	1.273	0.3231–4.782	0.7397			> 0.05
Hypertension	12	8	0.6	0,2166–1.879	0.3452			> 0.05
Coronary artery disease	4	1	1.917	0.2844–24.36	0.5644			> 0.05
Heart failure	1	1	0.451	0.02335–8.914	0.5701			> 0.05
Immunosuppression	26	7	2.429	0.8690–6.212	0.0885			> 0.05
Antibiotic use in the last 3 months								
Antibiotic use in the last 3 months	44	11	6.5	2.272–17.94	0.0004			> 0.05
Beta lactam / beta lactamase inhibitors	11	1	6.171	0.9235–69.18	0.0591			> 0.05
Cephalosporin	8	5	0.6909	0.2167–2.190	0.5576			> 0.05
Macrolides	2	1	0.92	0.1031–13.86	0.9468			> 0.05
Quinolone	19	1	13.24	2.221–143.6	0.0029	11.773	0.605-25.289	0.008
Glycopeptide	15	1	9.324	1.510–102.4	0.0142			> 0.05
Carbapenem	19	2	6.333	1.439–29.17	0.0106			> 0.05
Polymyxin	3	2	0.6735	0.1307–4.024	0.6751			> 0.05
Aminoglycoside	2	0	Infinity	0.2131–Infinity	0.3302			> 0.05
Antifungal	19	1	13.24	2.221–143.6	0.0029			> 0.05
Metronidazole	1	1	0.451	0.02335–8.914	0.5701			> 0.05
Fosfomycin	1	1	0.451	0.02335–8.914	0.5701			> 0.05

Table 4. Results of univariate and multivariate analyses including possible risk factors associated with 10- and 90-day mortality among patients with carbapenem resistant *Klebsiella pneumonia* (CRKP) and carbapenem sensitive *Klebsiella pneumonia* (CSKP).

Variables	10-day mortality risk factors in *Klebsiella pneumoniae* infections								90-day mortality (General) risk factors in *Klebsiella pneumoniae* infections							
	Mortality (n = 35)	Survival (n = 41)	Univariate analysis			Multivariate analysis			Mortality (n = 45)	Survival (n = 31)	Univariate analysis			Multivariate analysis		
			OR	95%	*p*	OR	95%	*p*			OR		*p*	OR		*p*
Age																
< 65 years	9	19	04008	0.1554–1.024	0.0632				12	16	0.3409	0.1386–0.8756	0.0267			
≥ 65 years	26	22							33	15						
Gender																
Female	12	21	0.4969	0.1919–1.321	0.1377				17	16	0.5129	0.2001–1.258	0.1591			
Male	23	20							29	14						
Invasive procedures																
Mechanical ventilation	24	17	3.08	1.140–7.487	0.0181	1.672	0.454–2.889	0.007	33	8	7.906	2,837–20,40	< 0.0001			> 0.05
Urinary catheter	35	41						> 0.05	45	31	5.16	1.141–26.08	0.0374			> 0.05
Central venous catheter	33	35	2.829	0.6348–14.38	0.2066			> 0.05	43	25	5.16	1.141–26.08	0.0374			> 0.05
Transfusion of blood	21	31	0.4839	0.1917–1.295	0.1445			> 0.05	27	25	0.36	0.1200–1.051	0.0571			> 0.05
Parenteral nutrition	30	27	3.111	1.056–8,590	0.0463			> 0.05	41	16	9.609	2.915–28.82	< 0.0001			> 0.05
Comorbid diseases																
Cerebrovascular disease	2	10	0.1879	0.03945–0.8088	0.026			> 0.05	4	8	0.2805	0.08786–0.9619	0.0468			> 0.05
Chronic obstructive pulmonary disease	5	5	1.2	0.3410–4.212	0.7881			> 0.05	6	4	1.038	0.2929–3.508	0.9565			> 0.05
Malignancy	3	5	0.675	0.1690–2,909	0.6079			> 0.05	4	4	0.6585	0.1802–2.432	0.5752			> 0.05
Diabetes mellitus	13	9	2.101	0.7452–5.695	0.1455			> 0.05	18	4	4.5	1.304–13.31	0.0105			> 0.05
Chronic renal failure	5	6	0.9722	0.2931–3.407	0.9657			> 0.05	7	4	1.243	0.3344–4.087	0.7467			> 0.05
Hypertension	8	12	0.716	0.2401–1.958	0.527			> 0.05	11	9	0.7908	0.3000–2.209	0.6553			> 0.05
Coronary artery disease	5	0	Infinity	1.818–Infinity	0.0123			> 0.05	5	0	Infinity	1.038–Infinity	0.0548			> 0.05
Heart failure	2	0	Infinity	0.5476–Infinity	0.1209			> 0.05	2	0	Infinity	0.3198–Infinity	0.2342			> 0.05
Immunosuppression	14	19	0.7719	.03165–1.844	0.5782			> 0.05	19	14	0.8874	0.3652–2.181	0.7995			> 0.05
Antibiotic use in the last 3 months	34	21	32.38	4.607–345.5	< 0.0001			> 0.05	45	10	Infinity	24.19–Infinity	< 0.0001	0.07	0.006-0.814	0,.034
Antibiotic use in the last 3 months																
Beta lactam/beta lactamase inhibitors	6	6	1.207	0.3204–4.539	0.765			> 0.05	8	4	1.459	0.4317–4.697	0.5668			> 0.05
Cephalosporin	6	8	0.8534	0.2470–2.517				> 0.05	7	7	0.6316	0.2066–1.936	0.4375			> 0.05
Makrolids	1	2	0.5735	0.03857–5.134	0.652			> 0.05	1	2	0.3295	0.02231–2.976	0.3521			> 0.05
Quinolone	11	9	1.63	0.6229–4.532	0.3497			> 0.05	14	6	1.882	0.6034–5.817	0.2527			> 0.05
Glycopeptide	8	8	1.222	0.4147–3.544	0.7214			> 0.05	13	3	3.792	1.014–13.31	0.0435	5.949	1.045–33.876	0.045
Carbapenem	11	10	1.421	0.5444–3.710	0.494			> 0.05	15	6	2.083	0.6831–6.378	0.1805			> 0.05
Polymyxin	4	1	5.161	0.7687–64.48	0.1151			> 0.05	5	0	Infinity	1.038–Infinity	0.0548			> 0.05
Aminoglycoside	2	0	Infinity	0.5476–Infinity	0.1209			> 0.05	2	0	Infinity	0.3198–Infinity	0.2342			> 0.05
Antifungal	6	14	0,399	0.1294–1.237	0.0934			> 0.05	16	4	3.724	1.205–11.11	0.0275			> 0.05
Metranidazole	2	0	Infinity	0.5476–Infinity	0.1209			> 0.05	2	0	Infinity	0.3198–Infinity	0.2342			> 0.05
Fosfomycin	1	1	1.176	0.06031–22.85	0.9096			> 0.05	2	0	Infinity	0.3198–Infinity	0.2342			> 0.05
Gene analysis																
Presence of carbapenemase	28	24	2.833	1.014 to 7.241	0.0448	7.636	2.365–24.659	0.001	37	15	4.933	1.726–13.24	0.0018	9.178	2.227–36.987	0.002
Presence of single gene *OXA-48*	15	15	1.172	0.4847 to 2.837	0.7347			> 0.05	20	10	1.838	0.7400–4.444	0.2091			> 0.05
Presence of combination of *OXA-48* and *NDM-1*	13	8	2.438	0.8354 to 7.256	0.0867			> 0.05	16	5	2.869	0.8931–7.827	0.0627			> 0.05
Presence of combination of *OXA-48* and *KPC*	0	1						> 0.05	1	0	Infinity	0.07654–Infinity	0.4034			> 0.05
Presence of panresistance	10	3	5.067	1.342 to 18.13	0.0142	8.023	1.136–11.63	< 0.0001	13	0	Infinity	3.468–Infinity	0.001	5.112	1.773-14.744	< 0.0001
C reactive protein (CRP) level	13.02 ± 11.52	11.36 ± 9.87			0.258				15.87±11.98	9.89 ± 9.27			0.373			
Procalcitonin (PCT) level	4.33 ± 10.66	8.57 ± 21.39			0.03				5.17±12.27	6.97 ± 18.81			0.068			

Table 5. Analysis of risk factors associated with 10- and 90-day mortality in carbapenem resistant *Klebsiella pneumonia* (CRKP)-associated infections.

Gene analysis	Mortality at 10 days								Mortality at 3 months							
	Death n = 28	Survival n = 24	OR	95% CI	*p*	OR	95% CI	*p*	Death n = 37	Survival n = 15	OR	95% CI	*p*	OR	95% CI	*p*
Presence of single gene *OXA-48*	15	15	0.5769	0.2026–1.777	0.3373			> 0.05	20	10	0.75	0.2255–2.451	0.6563			> 0.05
Combination of *OXA-48* and *NDM-1*	13	8	1.733	0.5628–4.935	0.3373			> 0.05	16	5	1.684	0.5234–5.548	0.4163			> 0.05
Combination of *OXA-48* and *KPC*	0	1						> 0.05	1	0	Infinity	0.04762–Infinity	0.5084			> 0.05
Antibiotic resistance																
Presence of pan-resistance	10	3	5.067	1.342– 18.13	0.0142	1.376	1.983–9.546	< 0.0001	13	0	Infinity	3.468–Infinity	0.001	1.512	0.967–2.364	< 0.0001
Fosfomycin resistance 52/42	24	18	0.0311		0.0311			> 0.05	30	12	3.167	1.271–7.811	0.016			> 0.05
Ceftazidime+avibactam resistance 52/25	19	6	6.927	2.308–21.52	0.0002			> 0.05	21	4	5.906	1.747–17.33	0.0021			> 0.05
Colistin resistance 52/17	11	6	2.674	0.9036–8.631	0.0799			> 0.05	14	3	4.215	1.151–14.70	0.0275			> 0.05

Discussion

The increasing antibiotic resistance in *K. pneumoniae* isolated in Turkey and all around the world, and the prevelance of this resistance among patients in ICUs have led to major problems. CRKP was first reported in the US in 1997, and in Turkey in 2001 [12–14]. In Europe, the prevalence of resistance varies from less than 10% (Scandinavian countries, Netherlands) to more than 50% (Ukraine, Greece). According to the World Health Organization (WHO)'s Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) 2020 report, the rate of carbapenem resistance in *K. pneumoniae* strains in our country is between 25–50% [15,16]. Yeşilbag *et al*. reported that carbapenem resistance in *K. pneumoniae* infections in intensive care units increased from 35% in 2017 to 62.9% in 2019 [17]. In our study, this rate was found to be 68.4% for the years 2021–2022. The high rate of carbapenem resistance in *K. pneumoniae* in the ICUs of our hospital is consistent with its rate of increase across our country.

The most important cause of carbapenem resistance is the production of carbapenemases that hydrolyze carbapenems. Although the prevalence of class A (KPC, GES, SME etc.), class B (IMP, VIM, NDM), and class D (OXA-23, OXA-24, OXA-58, OXA-48) carbapenemases varies geographically, they are being reported with increasing frequency all over the world, and in our country. Groups A and D require the amino acid serine for activity, while group B requires zinc for activity and is known as metallo-beta-lactamase (MBL). MBL cannot be inhibited by beta lactamase inhibitors [6]. *KPC* is endemic in North and South America, Poland, Romania and China; *OXA-48* is endemic in Turkey, North Africa and the Middle East; and *NDM* is endemic in India, Pakistan and Bangladesh [18]. The endemic *OXA-48* was found to be the most common single resistance gene in various studies conducted in Turkey, although combinations of different genes were also reported. In addition, *KPC*, *NDM*, *VIM*, and *IMP* resistance genes were detected alone or in association with different genes [19,20]. In a multicenter study, the single genes found in carbapenem-resistant *K. pneumoniae* were *OXA-48* (83.1%), *NDM* (6.5%), *VIM* (3.2%), *IMP* (1.6%); and the combined genes were *OXA-48* + *NDM* (2.4%), *OXA-48* + *VIM* (2.4%), and *VIM* + *NDM* (0.8%). *KPC* was not detected [20]. In a study conducted from 2012 to 2020, the *OXA-48* was the most common resistance gene and found in 38.8% isolates; the second most common resistance gene *NDM-1* was found to be 11.0% isolates, and the most common resistance gene combination was *OXA-48* + *NDM-1* which was found in 42.3% isolates [21]. Our study was consistent with other studies in our country and all the strains in our study were *OXA-48* positive, and the resistance rates were 57.7% for *OXA-48*, 40.4% for the combination of *OXA-48* and *NDM-1*, and 1.9% for the combination of *KPC* and *OXA-48*. *IMP* was not detected.

Studies have identified many risk factors affecting the development of carbapenem resistance. These factors include history of hospitalization, ICU stay, length of stay, immunosuppressive treatment, steroid use, history of transplantation (organ and stem cell), dialysis, invasive procedures such as intubation, nasogastric tube, parenteral nutrition, tracheostomy, urinary catheter, central venous catheter, antibiotic use, comorbidities such as chronic/acute renal failure, and neurological disease [22–24]. Esen and Leblebicioğlu reported that urinary catheter, nasogastric catheter, intubation, tracheostomy, central venous catheter, mechanical ventilation and emergency surgical procedures significantly increased the risk of nosocomial infection [25]. Budak *et al.* reported that total parenteral nutrition and transfusion of blood products were risk factors [26]. In our study, mechanical ventilation during invasive procedures and presence of malignancy among comorbidities were found to be risk factors for the development of CRKP. No significant factor was identified by multivariate analyses. This may be explained by the fact that our study included patients from the ICU, where invasive procedures were performed in most of the patients.

Risk factors related to antibiotic use in CRKP infections have been reported in various studies as the use of broad-spectrum antibiotics such as carbapenems, aminoglycosides, glycopeptides, quinolones, anti-*Pseudomonas* antibiotics, and antifungals [22]. The use of these antibiotics may lead to selection of carbapenem-resistant strains in the intestinal flora by suppressing susceptible strains. In addition, since almost all patients hospitalized in the ICU were critically ill, carbapenem and glycopeptide combinations were frequently used empirically, and resistant Enterobactericea become dominant in the flora. In our hospital, since carbapenems and vancomycin were among the antibiotics frequently used in the ICU, these were supposed to contribute to the increase in carbapenem resistance in *Klebsiella* strains. In our study, antibiotic use in the last 3 months was significant in CRKP infections; and quinolone, glycopeptide, carbapenem, and antifungal use were risk factors in antibiotic-based statistics. In multivariete analysis, quinolone use was identified as an

independent risk factor and was 11.7 times higher in the resistant group compared to the susceptible group (p = 0.008, OR: 11.77, 95% CI: 0.605–25.289).

Mortality rates in *K. pneumoniae* infections are gradually increasing and there is roughly a 3-fold higher mortality risk in the case of CRKP infections, compared to CSKP [27,28]. In some studies [29–31], the mortality rate of CRKP was within the range of 40 to 50%; however, there are also studies that reported a relatively low mortality rate of 23% [28] and a high mortality rate up to 71.9% [27,32]. In our study, we calculated the mortality rate as 71.1% in patients with CRKP, which is consistent with studies with high mortality rates. Various studies reported that the highest mortality rate in patients with CRKP, in terms of the source of infection, was bloodstream infection and pulmonary infection [28,33,34]. In our study, the highest mortality rate was in bloodstream infection followed by pulmonary infection.

There are studies showing that the factors affecting mortality [advanced age, male gender, presence of CRKP, invasive procedures such as central venous catheter (CVC), mechanical ventilation, bladder catheterization, comorbid diseases such as diabetes mellitus (DM), coronary artery disease (CAD), chronic hearth failure (CHF), chronic renal failure (CRF), cerebrovascular disease (CVD), malignancy, and chronic obstructive pulmonary disease (COPD)] are associated with antibiotics (cephalosporin carbapenem, quinolone, aminoglycoside, antifungal, colistin, glycopeptide) used in the 3-month period before diagnosis [28,32,33,35–37].

In some studies [32,35–38], invasive procedures (mechanical ventilation, CVC, bladder catheter, presence of drain) were reported to have no effect on mortality in CRKP; while in some others [33,38], mechanical ventilation, bladder catheter, and CVC were independent risk factors for mortality. In our study, mechanical ventilation, bladder catheterization, CVC, and total parenteral nutrition (TPN) were risk factors for mortality in univariate analysis, which is consistent with the literature; whereas only mechanical ventilation was an independent risk factor for mortality in multivariate analysis. Although there are reports that blood product use increases mortality [27], we did not determine blood product use as a risk factor for mortality in our study in accordance with other reports in the literature [32,33,37].

Comorbid diseases are also mortality risk factors for CRKP infections as they cause immunosuppression and require multiple and long-term drug use. Contrary to the studies that reported a relationship between malignancy and mortality in CRKP, there are studies [28,32,33,35–37] showing that CRKP mortality increases in the presence of chronic liver disease, renal dysfunction, COPD, ICU stay, and cardiac dysfunction; while malignancy has no effect. In our study, unlike a previous report [33], CVD and CAD were risk factors for mortality in the first 10 days, and DM and CVD were risk factors for mortality in the first 90 days; but no independent risk factor was identified.

There are reports on the relationship between antibiotic use in the 3-month period before the CRKP isolation and mortality. There are studies in the literature reporting a connection between the use of cefoperazone/sulbactam, aminoglycosides, and antifungal agents and CRKP mortality [32,37,39]. In our study, there was significant ($p < 0.001$) association between antibiotic use in the last 3 months and 10-day mortality. In addition, glycopeptide and antifungal use were risk factors, and glycopeptide use was an independent risk factor for 90-day mortality.

In our study, the presence of carbapenemase was determined to be an independent risk factor for mortality in the first 10 days. This result is consistent with other studies showing the association of carbapenemase with mortality. In our study, no relationship was detected between carbapenemase type and mortality. In addition to the reports that are in agreement with our study [32,40,41], there are other studies that report that the mortality rate increases in the presence of the *blaNDM* gene [42].

Among the CRKP cases in our study, 13 were pan-resistant, and all of these patients died within the first 90 days (8 of them before the culture antibiogram results were available). There are a limited number of studies in the literature on the effects of pan-resistant strains on mortality. These studies are generally in the form of case reports and include treatment recommendations such as colistin/high dose tigecycline combination [43] or dual carbapenem ± colistin combination [44,45]. We identified that pan-resistant strains are an independent risk factor for mortality both for the first 10 days and the first 90 days.

There are few studies on the effect of acute phase reactants on CRKP mortality. In one study [46], it was reported that CRP (≥ 150 mg/L), procalcitonin (≥ 5ng/mL) elevation, and leukopenia (< 4,000/L)-thrombocytopenia (< 100,000/L) were associated with CRKP mortality. In addition, elevated procalcitonin was determined to be a risk factor for daily mortality in the first 10 days. More studies should be conducted to show the relationship between CRP and procalcitonin, and mortality.

Conclusions

Carbapenem resistance and related mortality rate were found to be quite high in *K. pneumoniae* infections in the ICUs of our hospital. The period of our research coincided with the coronavirus disease 2019 (COVID-19) pandemic period and the excessive use of antibiotics and antifungals contributed to the increase in carbapenem resistance. Further studies are needed to evaluate the risk factors to support rational antibiotic use and thereby prevent development of carbapenem resistance and reduce the mortality rate.

Authors' contributions

MA: supervision, funding, materials, data collection, critical revision of manuscript, final approval of mansucirpt; AKC, supervision, funding, materials, data collection, data analysis and interpretation, manuscript draft, critical revision, final approval of manuscript.

Availability of data and materials

All data generated and analysed in the study are included in this article

Corresponding author

Melek Ayan, MD.
Mersin City Training and Research Hospital, Korukent Mahallesi,
96015. Sokak, 33240, Toroslar, Mersin, Turkey.
Tel: +905065003487
Fax: +903242251010 / 11
Email: ayanmelek@hotmail.com

Conflict of interests

No conflict of interests is declared.

References

1. Segatore B, Setacci D, Perilli M, Franchino L, Francheschini N, Rossolini GM, Amicosante GF (2004) Antimicrobial susceptibility of clinical isolates of Enterobacteriaceae producing complex β-lactamase patterns including extended-spectrum enzymes. Int J Antimicrob 23: 480–486. doi: 10.1016/j.ijantimicag.2003.10.011.
2. Erdem B, Ustaçelebi Ş (1999) Enterobacteriaceae. In Erdem B, Ustaçelebi Ş, editors. Basic and Clinical Microbiology. Ankara: Gunes Publishing House. 471–515.
3. Koçak CÖ, Hazırolan G (2019) Colistin resistance in carbapenem resistance *Klebsiella pneumoniae* clinical isolates. Journal of Turkish Society of Micobiology 49: 17–23.
4. Sheu CC, Chang YT, Lin SY, Chen YH, Hsueh PR (2019) Infections caused by carbapenem-resistant Enterobacteriaceae: an update on therapeutic options. Front Microbiol 10: 1–13. doi: 10.3389/fmicb.2019.00080.
5. Budak S, Aktaş Z, Erdem H (2012) Carbapenemases in enteric Gram-negative bacteria from laboratory to clinic. Mediterr J Infect Microbes Antimicrob 2012: 1–11. [Article in Turkish].
6. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL (2012) Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. Clin Microbiol Rev 25: 682–707. doi: 10.1128/CMR.05035-11.
7. Aktaş Z, Kayacan CB, Schneider I, Can B, Midilli K, Bauernfeind A (2008) Carbapenem-hydrolyzing oxacillinase, OXA-48, persist in *Klebsiella pneumoniae* in İstanbul, Turkey. Chemotherapy 54: 101–106. doi: 10.1159/000118661.
8. Livermore DM (2009) Has the era of untreatable infections arrived? J Antimicrob Chemother 64 Suppl 1: 29–36. doi: 10.1093/jac/dkp255.
9. Samra Z, Ofir O, Lishtzinsky Y, Madar-Shapiro L, Bishara J (2007) Outbreak of carbapenem resistant *Klebsiella pneumoniae* producing KPC-3 in tertiary medical centre in Israel. Int J Antimicrob Agents 30: 524–529. doi: 10.1016/j.ijantimicag.2007.07.024.
10. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y (2008) Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother 52: 1028–1033. doi: 10.1128/AAC.01020-07.
11. Horan TC, Andrus M, Dudeck MA (2008) CDC/NHSN surveillance definition of health-care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 36: 309–332. doi: 10.1016/j.ajic.2008.03.002.
12. EUCAS (2021) Breakpoint tables for interpretations of MICs and zone diameters. Versiyon 11: 17–23.
13. MacKenzie FM, Forbes KJ, Dorai-John T, Amyes SG, Gould IM (1997) Emergence of a carbapenem resistant *Klebsiella pneumoniae*. Lancet 350: 783. doi: 10.1016/S0140-6736(05)62567-6.
14. Poirel L, Heritier C, Tolün V, Nordmann P (2004) Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniae*. Antimicrob Agents Chemother 48: 15–22. doi: 10.1128/AAC.48.1.15-22.2004.
15. European Centre for Disease Prevention and Control (2020) Antimicrobial resistance in the EU/EEA (EARS-Net) - annual epidemiological report 2019. Stockholm: ECDC. Available: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2019. Accessed: 17 June 2021.
16. Central Asian and European Surveillance of Antimicrobial Resistance (2020) Annual report 2020. Available: https://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/publications/2020/central-asian-and-europeansurveillance-of-antimicrobial-resistance.-annualreport-2020. Accessed: 17 June 2021.
17. Yeşilbağ Z, Tekdöş-Şeker Y, Sevtap Şenoğlu S, Hergünsel GO (2021) *Klebsiella pneumoniae* infections in intensive care unit and risk factors for carbapenem resistance Klimik Journal 34.:25–30. doi: 10.36519/kd.2021.05.
18. Lee CR, Lee JH, Park KS, Kim YB, Jeong BC, Lee SH (2016) Global dissemination of carbapenemase-producing *Klebsiella pneumoniae*: epidemiology, genetic context, treatment options, and detection methods. Front Microbiol 7: 895. doi: 10.3389/fmicb.2016.00895.
19. Süzük YS, Şimşek H, Bakkaloğlu Z, Numanoğlu ÇY, Hekimoğlu CH, Kılıç S, Alp ME (2021) Carbapenemase epidemiology in *Escherichia coli* and *Klebsiella pneumoniae* isolates isolated in Turkey in 2019. Bulletin of Microbiology 55: 1–16.
20. Çakar A, Akyön Y, Gür D, Karatuna O, Öğünç D, Özhak BB, Çöplü N, Çağatay M, Kılıç A, Baysallar M, Bakıcı Z, Çelik C,

Gülay Z, Aydemir Ş, Tünger A, Kılıç H, Erçal BD, Toraman ZA, Zer Y, Büyüktaş A, Ay S, Aktaş Z, Kayacak Ç, Bayramoğlu G, Aydın F, Dündar D, Hasdemir U, Ayaş R, Yanık K, Günaydın M, Güdücüoğlu H, Parlak M (2016) Investigation of carbapenemases in carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* strains isolated in 2014 in Turkey. Bulletin of Microbiology. 50: 21–33. doi: 10.5578/mb.10695.

21. Telli M (2022) Investigation of changes in carbapenem resistance rates and resistance genes in clinical strains of *Klebsiella pneumoniae* between 2012–2020. Journal of Turkish Society of Micobiology 52: 95–102.
22. Liu P, Li X, Luo M, Xu X, Su K, Chen S, Qing Y, Li Y, Qiu J (2018) Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection: a meta-analysis. Microb Drug Resist 24: 190–198. doi: 10.1089/mdr.2017.0061.
23. Zhu WM, Yuan Z, Zhou HY (2020) Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection relative to two types of control patients: a systematic review and meta-analysis. Antimicrob Resist Infect Control 9: 23. doi: 10.1186/s13756-020-0686-0.
24. Yuan Y, Wang J, Yao Z, Ma B, Li Y, Yan W, Wang S, Ma Q, Zhang J, Xu J, Li L, Wang Y, Fan E (2020) Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections and outcomes. Infect Drug Resist 13: 207–215. doi: 10.2147/IDR.S223243.
25. Esen S, Leblebicioglu H (2004) Prevalence of nosocomial infections at intensive care units in Turkey: a multicentre 1-day point prevalence study. Scand J Infect Dis 36:144–148. doi: 10.1080/00365540410019156.
26. Budak S, Oncul O, Aktas Z, Acar A, Ozyurt M, Turhan V, Erdem H, Gorenek L (2014) The determination of carbapenem resistance in *Escherichia coli* and pneumoniae isolates related to nosocomial infections and the evaluation of risk factors. Southeast Asian J Trop Med Public Health 45: 113–122.
27. Hoxha A, Kärki T, Giambi C, Montano C, Sisto A, Bella A, D'Ancona F (2016) Study working group. Attributable mortality of carbapenem-resistant *Klebsiella pneumoniae* infections in a prospective matched cohort study in Italy, 2012-2013. J Hosp Infect 92: 61–66. doi: 10.1016/j.jhin.2015.06.018.
28. Lou T, Du X, Zhang P, Shi Q, Han X, Lan P, Yan R, Hu H, Wang Y, Wu X, Jiang Y, Yu Y (2022) Risk factors for infection and mortality caused by carbapenem-resistant *Klebsiella pneumoniae*: a large multi centre case-control and cohort study. J Infect 84: 637–647. doi: 10.1016/j.jinf.2022.03.010.
29. Wang Z, Qin RR, Huang L, Sun LY (2018) Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection and mortality of *Klebsiella pneumoniae* infection. Chin Med J (Engl) 131: 56–62. doi: 10.4103/0366-6999.221267.
30. Bratu S, Landman D, Haag R, Recco R, Eramo A, Alam M, Quale J (2005) Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York city: a new threat to our antibiotic carmamentarium. Arch Intern Med 165: 1430–1435. doi: 10.1001/archinte.165.12.1430.
31. Gasink LB, Edelstein PH, Lautenbach E, Synnestvedt M, Fishman NO (2009) Risk factors and clinical impact of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. Infect Control Hosp Epidemiol 30: 1180–1185. doi: 10.1086/648451.
32. Büyüktuna SA, Hasbek M, Cem Ç, Ünlüsavuran M, Avcı O, Baltacı S, Fırtına Topcu K, Elaldı N (2020) *Klebsiella pneumonia* infections in the intensive care unit: risk factors related to carbapenem resistance and patient mortality. Mikrobiyol Bul 54: 378–391. [Article in Turkish]. doi: 10.5578/mb.69679.
33. Tian L, Tan R, Chen Y, Sun J, Liu J, Qu H, Wang X (2016) Epidemiology of *Klebsiella pneumoniae* bloodstream infections in a teaching hospital: factors related to the carbapenem resistance and patient mortality. Antimicrob Resist Infect Control 5: 48. doi: 10.1186/s13756-016-0145-0.
34. Hauck C, Cober E, Richter S.S, Perez F, Salata RA, Kalayjian RC, Watkins RR, Scalera NM, Doi Y, Kaye KS, Evans S, Fowler Jr VG, Bonomo RA, van Duin D (2016) Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infections. Clin Microbiol Infect 22: 513–519. doi: 10.1016/j.cmi.2016.01.023.
35. Wu C, Zheng L, Yao J (2022) Analysis of risk factors and mortality of patients with carbapenem-resistant *Klebsiella pneumoniae* infection. Infect Drug Resist 15: 2382–2391. doi: 10.2147/IDR.S362723.
36. Chen Y, Chen Y, Liu P, Guo P, Wu Z, Peng Y, Deng J, Kong Y, Cui Y, Liao K, Huang B (2022) Risk factors and mortality for elderly patients with blood stream infection of carbapenem resistance *Klebsiella pneumoniae*: a 10-year longitudinal study. BMC Geriatrics 22: 573. doi: 10.1186/s12877-022-03275-1.
37. Jiao Y, Qin Y, Liu J, Li Q, Dong Y, Shang Y, Huang Y, Liu R (2015) Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection/colonization and predictors of mortality: a retrospective study. Pathog Glob Health 109: 68–74. doi: 10.1179/2047773215Y.0000000004.
38. Wang Z, Qin RR, Huang L, Sun LY (2018) Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection and mortality of *Klebsiella pneumoniae* infection. Chinese Medical Journal 131: 56–62. doi: 10.4103/0366-6999.221267.
39. Yang H, Ma H, Huang X, Cui Y, Peng W, Zhu F, Ma S, Rao M, Zhang P, Yang H, Su L, Niu R, Pan P (2022) Risk factors and mortality of carbapenem-resistant *Klebsiella pneumoniae* blood stream infection in a tertiary-carehospital in China: an eight-year retrospective study. Antimicrob Resist Infect Control 11: 161. doi: 10.1186/s13756-022-01204-w.
40. Hsu JY, Chuang YC, Wang JT, Chen YC, Hsieh SM (2021). Healthcare-associated carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: risk factors, mortality, and antimicrobial susceptibility, 2017–2019. J Formos Med Assoc 120: 1994–2002. doi: 10.1016/j.jfma.2021.04.014.
41. Verma A, Jain P, Tripathi P, Kalyan RK, Verma S, Venkatesh V (2022) Outcomes in oxacillinases β-lactamases (OXA-48) and New Delhi metallo-β-lactamase (NDM-1)-producing, carbapenem-resistant *Klebsiella pneumoniae* isolates obtained from bloodstream infections. Cureus 14: e27197. doi: 10.7759/cureus.27197.
42. Pudpong K, Pattharachayakul S, Santimaleeworagun W, Nwabor OF, Laohaprertthisan v, Hortiwakul T, Charernmak B, Chusri S. (2022) Association between types of carbapenemase and clinical outcomes of infection due to carbapenem resistance Enterobacterales. Infect Drug Resist 15: 3025–3037. doi: 10.2147/IDR.S363588.
43. Humphries RM, Kelesidis T, Bard JD, Ward KW, Bhattacharya D, Lewinski MA (2010) Successful treatment of pan-resistant *Klebsiella pneumoniae* pneumonia and bacteraemia with a combination of high-dose tigecycline and colistin. J Med Microbiol 59: 1383–1386. doi: 10.1099/jmm.0.023010-0.

44. Oliva A, Mascellino M.A, Cipolla A, D'Abramo A (2015) Therapeutic strategy for pandrug-resistant *Klebsiella pneumoniae* severe infections: short-course treat ment with colistin increases the in vivo and in vitro activity of double carbapenem regimen. Int J Infect Dis 33: 132–134. doi: 10.1016/j.ijid.2015.01.011.
45. Emre S, Moroğlu Ç, Yıldırmak T, Şimşek F, Arabacı Ç, Özkaya Ö, Turgut N, Irmak M (2018) Combination antibiotic therapy in pan-resistant *Klebsiella pneumoniae* infection: a report of two cases. Klimik Journal 31: 169–172. doi: 10.5152/kd.2018.40.
46. Chen J, Yang Y, Yao H, Bu S, Li L, Wang F, Chen F, Yao H (2021) Prediction of prognosis in adult patients with carbapenem- resistant *Klebsiella pneumoniae* infection. Front Cell Infect Microbiol 11: 818308. doi: 10.3389/fcimb.2021.818308.