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ORIGINAL ARTICLE

Detection and distribution of carbapenemase-encoding genes in clinical *Klebsiella pneumoniae* isolates from Kayseri, Türkiye

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ABSTRACT

Background and Objectives: Carbapenem Resistance *Klebsiella pneumonia* (CRKP), mostly caused by carbapenemase enzymes, poses a serious public health threat due to limited treatment options. This study aimed to genotypically identify carbapenemase-encoding genes in CRKP isolates recovered from fecal swabs and to correlate these genotypes with phenotypic antibiotic resistance profiles.

Materials and Methods: In this study, fecal samples from 150 hospitalized patients were screened for *K. pneumoniae.* Phenotypic testing included the Phoenix automated system, CHROMagar KPC, biochemical tests, and disk diffusion assays. Genotypic analysis was performed using the BD MAX Checkpoint CPO PCR test, marking its first use in Kayseri, Türkiye, to detect carbapenemase genes in this pathogen.

Results: Out of 150 fecal samples, 47 tested positive for *K. pneumoniae*, with 28 (59.6%) identified as carbapenem-resistant (CRKP). Molecular analysis identified five distinct carbapenemase gene patterns among these resistant isolates. The most prevalent gene, $bla_{\text{OXA-48}}$, was found alone in 60.7% of CRKP isolates, followed by bla_{NDM} in 3.6%; bla_{KPC} was not detected. Co-occurrence of genes was observed as follows: $bla_{\text{OXA-48}}$/bla_{NDM} (14.3%), $bla_{\text{OXA-48}}$ with bla_{VIM}/bla_{IMP} (10.7%), and $bla_{\text{OXA-48}}$ with bla_{NDM} and bla_{VIM}/bla_{IMP} (10.7%) in CRKP clinical isolates.

Conclusion: The study found that bla_{KPC} was consistently absent, while $bla_{\text{OXA-48}}$ was highly prevalent and exhibited co-occurrences of carbapenemase genes. It underscored the need for strict hospital surveillance and effective infection control to prevent the spread of CRKP strains. Rapid molecular methods, such as the BD MAX multiplex PCR, have shown promise in accurately and efficiently identifying carbapenemase genes.

Keywords: Carbapenems; Carbapenemases; Genes; *Klebsiella pneumoniae*

INTRODUCTION

Healthcare-associated infections (HAIs) are frequently caused by multidrug-resistant *Klebsiella pneumoniae* (MDR *K. pneumoniae*), which is responsible for an estimated 6-17% of these infections globally. In immunocompromised or critically ill patients, this pathogen is associated with severe diseases, including liver abscesses, bloodstream infections, pneumonia, and urinary tract infections (1).

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Isolates of *K. pneumoniae* from Türkiye exhibited resistance rates of 75.4% to third-generation cephalosporins, 43.1% to aminoglycosides, 68.0% to quinolones, and 38.7% to all three drug classes (2). Because of the increasing prevalence of MDR, carbapenems are overused because patients have fewer treatment options. There is an urgent need for new antimicrobial drugs against carbapenem-resistant *K. pneumoniae* (CRKP), a pathogen the World Health Organization (WHO) has identified as one of the greatest threats to human health (3).

The rapid and troubling spread of CRKP strains poses a serious public health concern, especially in regions with weak healthcare systems such as the Middle East, South Asia, and parts of Africa, where its prevalence may approach 20%. In contrast, CRKP affects between 3% and 7% of people in the US and Europe. About 50% of deaths are linked to CRKP bloodstream infections (4). Reports show that Türkiye's CRKP rate has increased annually from 29.5% in 2016 to 48.2% in 2020, with yearly rates of 29.5%, 32.5%, 34.4%, 39.4%, and 48.2%, respectively. The National Health Service-Associated Infections Surveillance Network study (5) found that the overall weighted average of CRKP infections in 2021 was 63.57%, highlighting the urgent need for action.

The emergence of CRKP pathogens undermines the effectiveness of beta-lactam antibiotics, particularly carbapenems, which are crucial last-resort treatments for severe infections due to their rapid bactericidal action and extensive spectrum of activity. *K. pneumoniae* resists β-lactam antibiotics primarily through the production of extended-spectrum β-lactamases (ESBLs), which confer resistance to monobactams and cephalosporins, and carbapenemases (6)—a diverse group of enzymes capable of hydrolyzing various β-lactams, including carbapenems, rendering them ineffective (7-9).

K. pneumoniae produces a variety of class A, B, and D carbapenemase types. *K. pneumoniae* carbapenemases (KPCs), which have been reported in the United States, Colombia, Brazil, Argentina, Italy, Poland, China, Taiwan, Israel, and Greece, are the most common class A carbapenemases (10).

In the Asia-Pacific area and Southern Europe, class B carbapenemases, such as Imipenemase (IMP) and Verona integron-related metallo-β-lactamase (VIM), have been common since the early 2000s in several countries (10). New Delhi metallo-beta-lactamase (NDM), another class B carbapenemase, has spread rapidly and become a global threat since it was first discovered in 2008 in Sweden. It was identified in a strain of *K. pneumoniae* recovered from a patient who had previously been hospitalized in India. The United States, the United Kingdom, and many other nations have since reported cases, especially in relation to travel to India and Pakistan (11). Class D carbapenemases, known as oxacillinases (OXA), were first identified in Türkiye in 2003 (12). The enzyme has been reported in Türkiye, Morocco, Libya, Egypt, Tunisia, Algeria, and India (10).

Understanding the distribution of carbapenemase genes and resistance patterns remains challenging despite advancements in phenotypic and genotypic techniques for carbapenemase identification, especially in understudied areas like Kayseri, Türkiye. This information is essential for developing antimicrobial stewardship programs and targeted infection control strategies. Although phenotypic methods (such as the modified Hodge test, Carba NP, and Blue CARBA) and genotypic methods (such as PCR, sequencing (13), and the BD MAX Checkpoint CPO assay) exist for carbapenemase detection, their use and validation in specific geographic settings are limited. This study intends to fill the gap by assessing carbapenemase genes and carbapenem resistance patterns in CRKP isolates from Erciyes University Hospital in Kayseri, Türkiye, using both phenotypic and genotypic methodologies. The objectives are to ascertain the prevalence of carbapenem resistance in *K. pneumoniae* isolates in hospitalized patients, investigate the distribution of $bla_{\text{OXA-48}}$, bla_{VIM}/bla_{IMP}, bla_{KPC}, and bla_{NDM} genes in these isolates, and evaluate the concordance between phenotypic and genotypic methods for carbapenemase detection.

MATERIALS AND METHODS

Isolation, selection and identification. A total of 150 *K. pneumoniae* isolates were collected from fecal samples at Erciyes University Hospital and processed for standard clinical diagnostics. Isolates from hospitalized patients with confirmed infections across various hospital units were anonymized, and no further clinical data were collected. This study employed isolates acquired through standard diagnostic methods without any further intervention or collection of patient data. The identification of *K. pneumoniae* involved culturing fecal swabs on MacConkey

agar (BD-Becton Dickinson) and KPC chromogenic agar (RTA Laboratories), followed by incubation at 37°C for 24 hours. Presumptive *K. pneumoniae* colonies were confirmed, and the isolates were identified using the Phoenix automated identification system (BD-Becton Dickinson). The findings were validated by standard biochemical assays, encompassing triple sugar iron agar (TSI), citrate utilization, and motility-indole-ornithine decarboxylase (MIO) tests (BD-Becton Dickinson).

Antimicrobial susceptibility testing (AST). This was performed using the Kirby-Bauer disc diffusion method on Mueller-Hinton agar (BD-Becton Dickinson, USA), following EUCAST guidelines. 10 µg discs of imipenem, ertapenem, and meropenem were provided by Oxoid, UK. Minimum inhibitory concentrations (MICs) were determined using the broth microdilution method. Other antibiotic classes were tested using the Phoenix automated antimicrobial susceptibility testing (AST) system (BD-Becton Dickinson, USA).

Carbapenemase gene detection. This was carried out using the BD MAX Check-Points CPO assay, an automated, real-time PCR-based system (BD-Becton Dickinson, USA). This qualitative assay evaluates the five most common carbapenemase genes—$bla_{\text{OXA-48}}$, bla_{NDM}, bla_{VIM}/bla_{IMP} (shared channel), and bla_{KPC}—according to the manufacturer's protocol, which includes cell lysis, DNA extraction, amplification, and identification. Positive results were determined based on Ct values as specified by the manufacturer. The BD MAX system produced results for 24 samples in 2.5–3 hours, including extraction and PCR, thereby significantly reducing turnaround time.

RESULTS

Bacterial identification and phenotypic characterization. Out of 150 randomly collected fecal samples, 47 isolates were identified as *K. pneumoniae*. Identification was based on distinctive colony morphology on MacConkey agar, featuring mucous, moist, sticky, large, shiny, and dark pink colonies. Biochemical tests confirmed this identification by demonstrating citrate utilization, fermentation of three sugars (lactose, glucose, and sucrose) with gas production, and absence of motility. On KPC chromogenic agar, 28 isolates demonstrated carbapenem resistance, characterized by large metallic blue colonies with a mucous texture, whereas 19 isolates were susceptible to carbapenems.

Demographic and clinical information. As detailed in Table 1, among the 47 samples tested, 21 male samples (44.7%) were positive for *K. pneumoniae* infection, while 8 (17.0%) were negative. In contrast, among females, 8 out of 18 (44.4%) tested positive, and 10 (55.6%) tested negative ($p = 0.055$). This finding indicates a possible trend toward a gender-based differences in infection rates, although it is not statistically significant.

Of the 21 individuals aged 30 or younger, 13 (61.9%) tested positive for *K. pneumoniae* infection, while 8 (38.1%) tested negative. In the over-30 age group, 15 of 26 (57.7%) were positive, and 11 (42.3%) were negative, indicating no significant association between age groups and infection status ($p = 0.769$). The distribution of *K. pneumoniae* infections across hospital units shows no significant association ($p = 0.616$). Cases were fairly evenly distributed across all units.

Antimicrobial susceptibility testing (AST). Using the disc diffusion method, we found that 96.4% of *K. pneumoniae* isolates were resistant to ertapenem, imipenem, and meropenem. Using the broth microdilution method, the MICs for CRKP isolates were as follows: imipenem 4-8 µg/mL, meropenem >8 µg/mL, and ertapenem 1 µg/mL. The Phoenix automated system demonstrated complete multidrug resistance (100%) to 19 antibiotics, including ertapenem, meropenem, imipenem, amikacin, amoxicillin-clavulanate, ampicillin, ampicillin-sulbactam, cefazolin, cefepime, ceftazidime, ceftolozane-tazobactam, ceftriaxone, cefotaxime, ciprofloxacin, colistin, gentamicin, levofloxacin, tazobactam, and trimethoprim-sulfamethoxazole.

Carbapenemase genes. The BD MAX Check-Points CPO assay was used to analyze the isolates. This molecular analysis identified carbapenemase genes in 28 of the 47 *K. pneumoniae* isolates, all of which had previously been confirmed as carbapenem-resistant through culture-based methods. Five distinct carbapenemase gene profiles were detected. The most common gene was $bla_{\text{OXA-48}}$ found in 17 isolates (60.7%), followed by bla_{NDM} alone (3.6%). Several co-occurrence patterns were also observed. The most frequent double co-occurrence was $bla_{\text{OXA-48}}$ with bla_{NDM}, found in 4 isolates (14.3%), followed by

Table 1. Statistical analysis of *K. pneumoniae* infection and carbapenemase gene distributions in relation to clinical variables.

	Variables	*K. pneumoniae* infection (n/47)		P-value	Carbapenemase genes (n/47)		P-value
		Positive	Negative		Positive	Negative	
Gender	Male	21	8	0.055	20	9	0.095
	Female	8	10		8	10	
Age group	≤30 years	13	8	0.769	13	8	0.769
	>30 years	15	11		15	11	
Hospital units	Critical Care Units*	12	5	0.616	10	7	0.832
	Surgical Units**	10	7		11	6	
	Medical Units***	7	6		7	6	
Multidrug resistance	Positive	47		-	28	18	1.0
	Negative	-			1	0	
Carbapenem resistance	Positive	28	0	0.00001	24	4	0.00001
phenotype	Negative	1	18		3	16	

*Critical Care Units include ICU, Pediatric ICU, and Neonatal ICU.

**Surgical Units include General Surgery, Neurosurgery, and Anesthesia.

***Medical Units include Hematology, Medical Oncology, Bone Marrow, and Nephrology.

bla_{OXA-48} with bla_{VIM}/bla_{IMP} (10.7%). A triple co-occurrence of bla_{OXA-48}, bla_{NDM}, and bla_{VIM}/bla_{IMP} (10.7%) was also detected. A notable finding from the PCR analysis was the complete absence of the bla_{KPC} gene in all 28 carbapenemase-resistant isolates (Table 2 and Fig. 1).

The distribution of carbapenemase genes across different parameters is presented in Table 1. Among males, 31.0% (9/29) tested negative and 69.0% (20/29) tested positive. Among females, 55.6% (10/18) tested negative and 44.4% (8/18) tested positive. There was no statistically significant association between the presence of the carbapenemase gene and gender (p = 0.095). Both infection and gene positivity rates were higher in males, but these differences were not statistically significant.

Gene detection was not significantly associated with age group (p = 0.769). The distribution of carbapenemase genes across hospital units did not show a significant association with unit type (p = 0.832).

None of the isolates that tested positive for carbapenemase genes were MDR-negative; however, this finding was not statistically significant (p = 1.0). The lack of a significant association between MDR status and the presence of the carbapenemase gene indicates that not all MDR isolates are associated with carbapenemase production.

None of the 28 isolates that exhibited phenotypic resistance to carbapenem were gene-negative; all tested positive for carbapenemase genes. Only 5.3% (1/19) of the isolates that were phenotypically carbapenem-susceptible were carbapenemase gene-positive, while 94.7% (18/19) were carbapenem-resistant and carbapenemase gene-positive. There was evidence of a highly significant association (p = 0.00001) between the carbapenem resistance phenotype and the presence of carbapenemase genes. This finding supports the use of phenotypic resistance as a reliable marker of gene carriage. The results highlight the therapeutic challenges and the urgent need for prompt molecular diagnostics and antimicrobial stewardship to guide treatment decisions by demonstrating that CRKP isolates exhibit a multidrug-resistant profile.

DISCUSSION

The global rise in antibiotic resistance, particularly in carbapenemase-producing *K. pneumoniae*, poses a significant public health threat due to its severe impact on morbidity and mortality. Antibiotic resistance in *K. pneumoniae* is a considerable obstacle in therapeutic management. The excessive and improper use of antibiotics substantially exacerbates this global issue (14).

Rapid identification of carbapenemase producers is

Table 2. Carbapenemase gene co-occurrence in CRKP isolates

Carbapenemase genes detected via BD MAX assay	Count of *K. pneumoniae* (%)
bla_{OXA-48}	17 (60.7)
bla_{KPC}	0
bla_{NDM}	1 (3.6)
bla_{OXA-48} + bla_{NDM}	4 (14.3)
bla_{OXA-48} + bla_{VIM}/bla_{IMP}	3 (10.7)
bla_{OXA-48} + bla_{NDM}+ bla_{VIM}/bla_{IMP}	3 (10.7)
Number of Carbapenem-resistant *K. pneumonia* (CRKP)	28 (59.6)
Number of Carbapenem-susceptible *K. pneumonia* (CSKP)	19 (40.4)
Study total isolates	47 (100.00)

crucial for managing severe infections and preventing the spread of carbapenem-resistant *K. pneumoniae* (CRKP) in healthcare settings. Molecular methods are the most effective tools for detecting carbapenemase due to their speed and accuracy (15). This study found that 28 of 47 *K. pneumoniae* isolates exhibited carbapenemase genes as identified by the BD MAX Check-Points CPO assay. Carbapenemase genes can be directly identified from clinical specimens due to the assay's high specificity and sensitivity (16).

The BD MAX assay was positive for carbapenemase genes in 59.6% of CRKP isolates (28/47) and negative in 40.4% (19/47). All isolates had been confirmed as *K. pneumoniae* prior to testing. The scale of the problem is significant, with resistant strains in Europe causing an estimated 90,000 infections and 7,000 deaths annually (17).

The global proliferation of antibiotic resistance constitutes a significant public health threat, particularly with carbapenemase-producing *K. pneumoniae*, due to its association with increased morbidity and mortality rates (18). Our data indicate that isolates of carbapenemase-producing *K. pneumoniae* from hospitalized patients are significantly more prevalent in the intensive care unit (ICU) (32.14%) and the neurosurgery unit (28.57%).

Patients in these high-acuity units are at heightened risk for acquiring and transmitting drug-resistant organisms. Our findings align with earlier research from Egypt (Cairo), the US (Chicago), Italy (Molise), and Poland (Torun), which also reported a high prevalence of *K. pneumoniae* in ICU settings (13, 19-21). The persistence and dissemination of CRKP is linked to its capacity to colonize various hospital surfaces, including patient tables, beds, and medical equipment (13). *K. pneumoniae* isolates at Erciyes University Hospital exhibited a significant level of resistance (96.6%) to imipenem, ertapenem, and meropenem, as determined by disk diffusion and Phoenix system results, consistent with findings from a study conducted in the Netherlands (22). The resistance was primarily associated with the bla_{OXA-48} gene, identified in 27 of 28 carbapenemase-positive isolates. In this study, bla_{OXA-48} was the only gene detected in 60.7% of isolates, while bla_{NDM} gene was identified in 3.6%. The presence of bla_{OXA-48} and bla_{NDM} was also noted. The distribution of carbapenemase genes was as follows: bla_{OXA-48} + bla_{NDM} (14.3%), bla_{OXA-48} + bla_{NDM} + bla_{VIM}/bla_{IMP} (10.7%), and bla_{OXA-48} + bla_{VIM}/bla_{IMP} (10.7%). No statistically significant correlations were detected between *K. pneumoniae* infection or the presence of carbapenemase genes and gender, age group, or hospital unit. A highly significant association was observed between phenotypic carbapenem resistance and the identification of carbapenemase genes ($p = 0.00001$). The minor significance observed for gender ($p = 0.055$) may warrant further investigation with an expanded sample size to clarify potential gender-related differences.

The co-occurrence of bla_{OXA-48} and bla_{NDM} has been documented in Türkiye, with a noted increase in prevalence over time. Initial reports of bla_{OXA-48} co-existing with bla_{NDM} in Istanbul, Türkiye, date back to 2013 (23), with subsequent studies reporting varying co-occurrence rates in Kayseri and other areas (24-27). The findings of this study align with the observed trend of increasing co-detection of these genes. Additionally, the co-occurrence of bla_{OXA-48} with bla_{VIM}/bla_{IMP} was observed in 10.7% of isolates. One isolate harboring bla_{OXA-48} and bla_{VIM}/bla_{IMP} demonstrated susceptibility to carbapenem, as determined by disk diffusion. The bla_{KPC} gene was absent in all examined isolates, consistent with previous

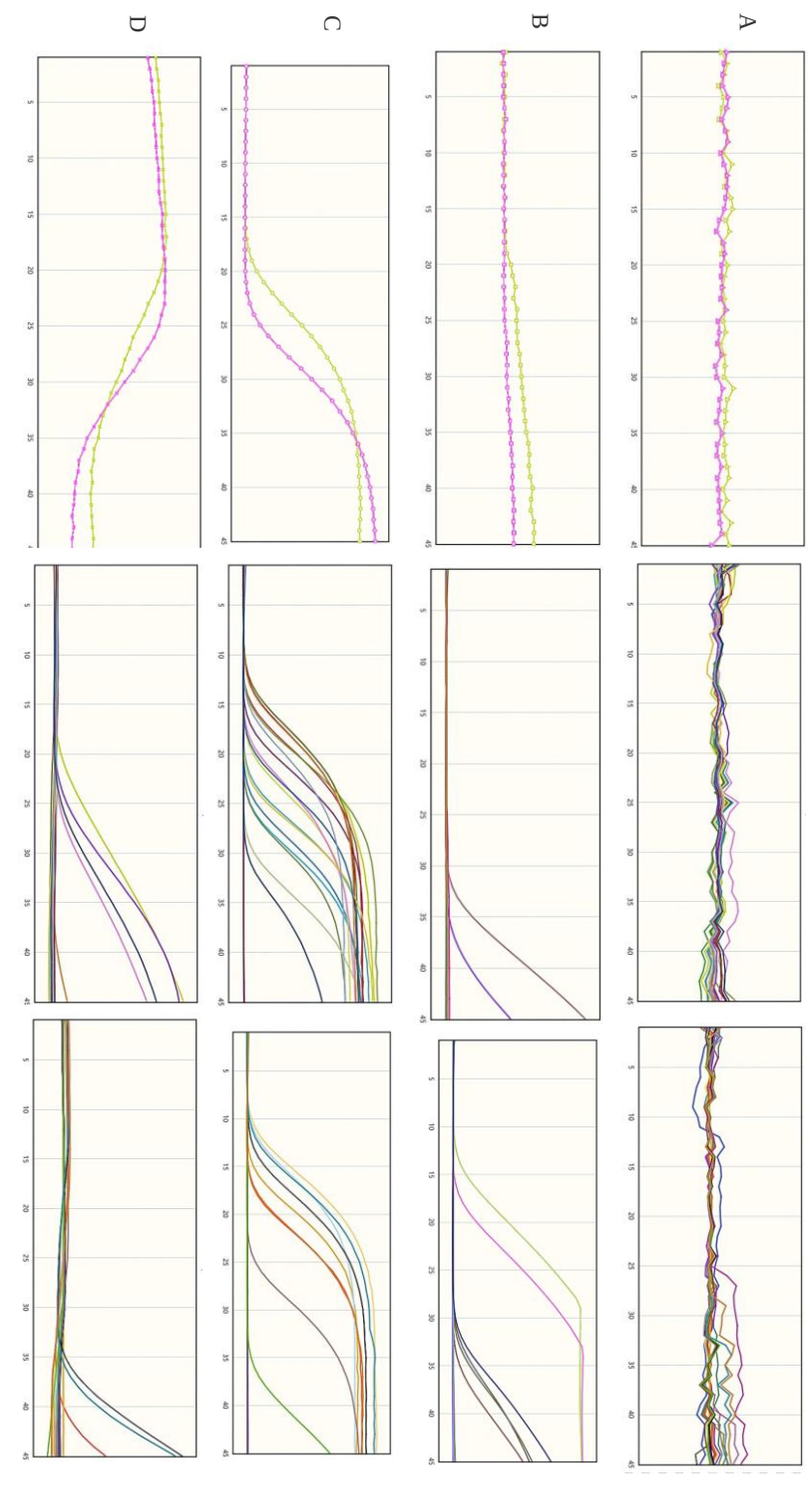

Fig. 1. BD MAX carbapenemase gene detection wavelengths: (A) *bla*$_{KPC}$ (475/520 nm), (B) *bla*$_{VIM}$/*bla*$_{IMP}$ (530/565 nm), (C) *bla*$_{OXA-48}$ (585/630 nm), (D) *bla*$_{NDM}$ (630/665 nm).

findings from Türkiye (28). The absence of *bla*$_{KPC}$ in Türkiye may be attributed to several factors, such as the high prevalence of alternative resistance mechanisms in *K. pneumoniae*, limited transferability of *bla*$_{KPC}$-harboring plasmids, gene inactivation through mutation, changes in bacterial traits during dissemination and replication, and the implementation of effective preventive measures in healthcare settings (29). This study did not address the details of the infection control protocols at Erciyes University Hospital. The strict implementation of such measures, including hand hygiene, contact precautions, patient

isolation, and environmental decontamination, is crucial for preventing the transmission of carbapenemase-producing organisms (CPOs), which may explain the absence of bla_{KPC} in our research samples. Additional processes that may contribute to carbapenem resistance include increased efflux pump activity, reduced outer membrane permeability, modified carbapenem-binding proteins, and decreased porin production (30).

The identification of CRKP isolates co-producing bla_{OXA-48}, bla_{NDM}, and bla_{VIM}/bla_{IMP} is a significant observation, reflecting the spread of CRKP strains with complex resistance characteristics. This contrasts with studies in other regions—for example, in Korea, bla_{KPC} is the predominant carbapenemase gene, followed by bla_{NDM}, bla_{OXA-48}, and bla_{OXA-48}+ bla_{NDM}, with no detection of bla_{VIM}/bla_{IMP} (31). In contrast, a study conducted in Antalya, Türkiye, identified bla_{OXA-48} as the most common gene, followed by bla_{VIM}, bla_{NDM}, and bla_{IMP}, with no detection of bla_{KPC} (32). A multi-center study conducted in Türkiye also reported various combinations of bla_{OXA-48}, bla_{NDM}, bla_{VIM}/bla_{IMP} in *Klebsiella* spp. isolates (33).

This study has several limitations that warrant consideration. The sample size of 150 fecal isolates from hospitalized patients in Kayseri, Türkiye, may limit the generalizability of our findings to broader populations or other geographic regions. Additionally, focusing exclusively on hospitalized patients may restrict the comprehension of the prevalence and distribution of carbapenemase-encoding genes in community settings. This study delineates the incidence of specific carbapenemase genes, thereby augmenting the current understanding of the molecular epidemiology of CRKP in hospital settings. These findings are essential for influencing local antimicrobial stewardship programs, guiding empirical treatment strategies, and implementing targeted infection control measures to mitigate the spread of multidrug-resistant bacteria. The study underscores the urgent need for continuous surveillance and research to address the escalating issue of carbapenem resistance in clinical settings.

CONCLUSION

K. pneumoniae poses a considerable risk among ESKAPE pathogens due to its ability to resist antibiotics, especially in the case of carbapenem-resistant strains (CRKP). These strains pose a significant healthcare challenge by undermining the effectiveness of treatments for severe infections. The situation has been exacerbated by the emergence of resistance to last-resort antibiotics such as carbapenems, colistin, and tigecycline, necessitating immediate action to combat this growing public health crisis. This study investigated carbapenemase-encoding genes in *K. pneumoniae* isolates from Kayseri, Türkiye, revealing a high prevalence of bla_{OXA-48} and the co-occurrence of various carbapenemase genes. The absence of blaKPC-producing *K. pneumoniae* at Erciyes University Hospital indicates that effective infection control measures may mitigate its dissemination. Rapid molecular approaches, such as the BD MAX multiplex PCR, have exhibited efficacy and precision in identifying carbapenemase genes, demonstrating substantial agreement with conventional culture methods. These findings help clarify the antibiotic resistance landscape in Kayseri, Türkiye, particularly the emergence and spread of CRKP, offering essential insights for targeted therapeutic approaches and enhanced antibiotic stewardship to address this public health concern.

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