

## Original Article

# Phenotypic Detection and Antimicrobial Resistance Profile of Metallo- $\beta$ -Lactamase-Producing *Klebsiella pneumoniae* Clinical Isolates in Tehran, Iran, 2024

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## Abstract

**Background:** *Klebsiella pneumoniae* is a major cause of healthcare-associated infections, and the emergence of carbapenem-resistant and metallo- $\beta$ -lactamase (MBL)-producing strains poses a major therapeutic and infection-control challenge. The aim of this study was to detect metallo- $\beta$ -lactamases (MBLs) and determine the antimicrobial resistance profile of *Klebsiella pneumoniae* Clinical Isolates.

**Materials and Methods:** A total of Forty-four non-duplicate consecutive *K. pneumoniae* isolates were obtained from patients admitted to tertiary care hospitals in Tehran between January 2024 and June 2024. These isolates were cultured from various clinical specimens, including sputum and urine. Antimicrobial susceptibility testing was performed using both disk diffusion (16 disks) and microdilution methods for five antibiotics, imipenem, meropenem, ciprofloxacin, ceftazidime, and colistin, according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Additionally, the combined disk diffusion test (CDDT) was used to confirm the production of metallo- $\beta$ -lactamases (MBLs).

**Results:** The lowest rate of resistance was observed against tigecycline (n = 2, 4.6%), and fosfomycin (n = 7, 15.9%). The resistance rates determined by the broth microdilution method were 31.8% for imipenem, 29.6% for meropenem, 68.2% for Ciprofloxacin, 79.5% for ceftazidime, and 15.9% for colistin. The number of isolates with multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes was 28 (63.6%) and 16 (36.4%), respectively. Using the DDST, 34.09% of *K. pneumoniae* isolates were positive for MBL production.

**Conclusion:** The high prevalence of multidrug-resistant and extensively drug-resistant *Klebsiella pneumoniae* isolates, along with significant MBL production, emphasizes the urgent need for antimicrobial stewardship, continuous monitoring, and effective infection control measures.

**Keywords:** *Klebsiella pneumoniae*, Antibiotic resistance, Metallo-beta-Lactamase, Extensively drug resistance

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## Introduction

*Klebsiella pneumoniae* has emerged as one of the most

clinically significant pathogens associated with both hospital-acquired infections and antimicrobial resistance<sup>1</sup>. *K. pneumoniae* is responsible for various

nosocomial infections, including pneumonia, urinary tract infections, bloodstream infection, and wound infection<sup>2, 3</sup>. *K. pneumoniae* demonstrates remarkable capability in developing and acquiring antibiotic resistance, particularly against  $\beta$ -lactam antibiotics. One of the primary mechanisms antibiotic resistance in *K. pneumoniae* is the production of  $\beta$ -lactamase enzymes (such as MBLs and ESBLs along with carbapenems). Although  $\beta$ -lactam antibiotics, especially carbapenems, represent one of the last and most effective therapeutic options for treating *K. pneumoniae* infection, this pathogen can overcome their antibacterial effects by producing resistance enzymes, including metallo- $\beta$ -lactamases (MBLs) and carbapenemases, leading to antimicrobial resistance<sup>4</sup>. Recent epidemiological evidence indicates that carbapenem-resistant *K. pneumoniae* has become an increasing public health concern in Iran. MBL-producing isolates are predominantly recovered from hospitalized patients (ICUs). The most common clinical specimens include urine, blood, respiratory secretions, and wound samples. These isolates usually exhibit multidrug-resistant (MDR) or extensively drug-resistant (XDR) phenotypes, showing resistance to carbapenems, cephalosporins, fluoroquinolones, and aminoglycosides. Molecular epidemiological studies have identified high-risk clones that contribute to the dissemination of MBL genes via mobile genetic elements such as plasmids. Major risk factors associated with the spread of these organisms include prolonged hospitalization, prior carbapenem exposure, invasive medical procedures, ICU admission, and inadequate infection prevention and control measures. Recent genomic surveillance studies have highlighted the continuous evolution of NDM-harboring plasmids and the emergence of novel high-risk clones, underscoring the necessity of integrating molecular surveillance with antimicrobial stewardship and infection prevention programs<sup>5</sup>. The available evidence suggests that NDM producing *K. pneumoniae* is the predominant MBL-producing pathogen in Iran, highlighting the need for continuous molecular surveillance, robust antimicrobial stewardship programs, and strengthened infection prevention strategies to limit its dissemination<sup>6</sup>. This study was designed to characterize antimicrobial resistance profiles and identify MBL-producing *K.*

*pneumoniae* among clinical isolates from hospitalized patients in hospitals in Tehran, Iran.

## Methods

**Bacterial isolates:** In this descriptive study, *K. pneumoniae* isolates were collected from clinical specimens, including sputum and urine, obtained from hospitalized patients admitted to different wards of the teaching hospitals (Labbafinejad and Shohada Tajrish) in Tehran between January 2024 and June 2024. Each isolate was identified at species level based on the biochemical reactions, including reaction on triple sugar iron (TSI) agar, H<sub>2</sub>S/indole/motility (SIM) medium, methyl red/Voges-Proskauer (MR/VP), urease production on urea agar, growth on Simmons' citrate agar medium, and ornithine decarboxylase (OD) test<sup>7</sup>. All isolates were stored in tryptic soy broth (TSB) tube with 20% glycerol at  $-70^{\circ}\text{C}$ .

**Ethical statement:** This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences "IR.SBMU.MSP.REC.1401.242". To maintain participants' confidentiality, anonymity was respected throughout the study; therefore, no personal identifying information was requested.

**Antimicrobial susceptibility testing:** Antimicrobial susceptibility of all *K. pneumoniae* isolates was determined by the Kirby-Bauer disk diffusion method on Mueller Hinton agar (Merck, Germany) and interpreted as recommended by the Clinical and Laboratory Standards Institute (2024CLSI breakpoints) or Food and Drug Administration (FDA) breakpoints guidelines (for tigecycline) [8, 9]. Antibiotic discs used were as follow: penicillins [piperacillin (PIP, 100  $\mu\text{g}$ )], cepheims [ceftazidime (CAZ, 30  $\mu\text{g}$ )], cefepime (FEP, 30  $\mu\text{g}$ )],  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations [piperacillin/tazobactam (PTZ, 100/10  $\mu\text{g}$ )], carbapenems [imipenem (IPM, 10  $\mu\text{g}$ )], meropenem (MEM, 10  $\mu\text{g}$ )], doripenem (DOR, 10  $\mu\text{g}$ )], ertapenem (ETP, 10  $\mu\text{g}$ )], monobactams [aztreonam (ATM, 30  $\mu\text{g}$ )], , aminoglycosides [Amikacin (AK, 30  $\mu\text{g}$ )], gentamicin (GEN, 10  $\mu\text{g}$ )], Fluoroquinolones [ciprofloxacin (CIP, 5  $\mu\text{g}$ )], inhibitors [trimethoprim sulfamethoxazole (TS, 2.5  $\mu\text{g}$ )], fosfomycins [fosfomycin (FOS, 200  $\mu\text{g}$ )], nalidixic acid (NA, 30  $\mu\text{g}$ )], and tigecycline (TGC, 15  $\mu\text{g}$ ) (Mast Group, Merseyside, UK). The minimum inhibitory

concentrations (MICs) of five antibiotics, including imipenem, meropenem, ciprofloxacin, ceftazidime, and colistin were determined by broth microdilution method on Cation-Adjusted Mueller Hinton broth (Merck, Germany), and the results were analyzed according to the CLSI guidelines. *E. coli* ATCC 25922 was used as a quality control strain for disk diffusion and MIC results<sup>8</sup>. The isolates were categorized based on their resistance profiles using the international standard definitions proposed by Magiorakos et al.: MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories; Extensively drug-resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., the isolate remains susceptible to agents in only one or two categories); and Pandrug-resistant (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories<sup>9, 10</sup>.

**Phenotypic Detection of MBLs:** MBL was detected using the by DDST. MEM and MEM + EDTA, imipenem, and imipenem + EDTA discs were used to detect MBL-producing *K. pneumoniae* isolates. A zone diameter difference of 7 mm between the discs alone and the discs plus EDTA was interpreted as a positive result regarding MBL production<sup>11</sup>. *Pseudomonas aeruginosa* PA40 (Accession number KM359725) and *P. aeruginosa* ATCC 27853 were

used as positive and negative controls for MBL production, respectively.

## Results

**Bacterial isolates:** 44 non-duplicate isolates of *K. pneumoniae* were collected from 20 (45.5%) males and 24 (54.5%) females admitted at Tehran hospitals during the January 2024 to June 2024. The age range of patients was between 10 and 90 years (Figure 1). The origins of isolates were 41 in urine and 3 in sputum.

**Antimicrobial susceptibility test (AST):** In this study, the antibiotic susceptibility patterns of 44 *Klebsiella pneumoniae* isolates were investigated. For aztreonam (ATM), 18 isolates (40.9%) were susceptible, 3 (6.8%) were intermediate, and 23 (52.3%) were resistant. For gentamicin (GM), 29 isolates (65.9%) were susceptible, 2 (4.5%) were intermediate, and 13 (29.5%) were resistant.

For ciprofloxacin (CIP), 14 isolates (31.8%) were susceptible, none (0%) were intermediate, and 30 (68.2%) were resistant. Similarly, for trimethoprim/sulfamethoxazole (TS), 14 isolates (31.8%) were susceptible, none (0%) were intermediate, and 30 (68.2%) were resistant. For amikacin (AK), 29 isolates (65.9%) were susceptible, 1 (2.3%) was intermediate, and 14 (31.8%) were resistant.

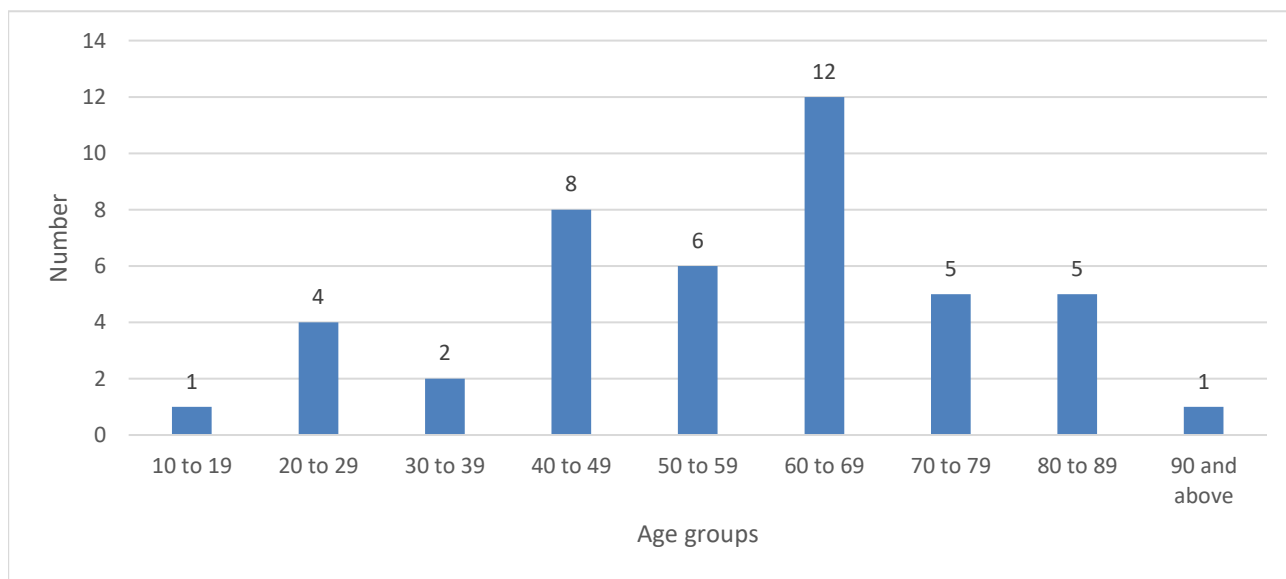


**Figure 1.** Frequency of samples by age group.

The highest resistance rate was observed for ceftazidime (CAZ), with 4 isolates (9.1%) susceptible, 2 (4.5%) intermediate, and 38 (86.4%) resistant. For cefepime (FEP), 19 isolates (43.2%) were susceptible, none (0%) were intermediate, and 25 (56.8%) were resistant. Similarly, for nalidixic acid (NA), 14 isolates (31.8%) were susceptible, none (0%) were intermediate, and 30 (68.2%) were resistant.

For piperacillin (PIP), 8 isolates (18.2%) were susceptible, 5 (11.4%) were intermediate, and 31 (70.4%) were resistant. In contrast, tigecycline (TGC) showed a relatively high susceptibility rate, with 28 isolates (63.6%) susceptible, 14 (31.8%) intermediate, and only 2 (4.6%) resistant.



**Figure 2.** Results of MBL Screening Using the DDST Test, showing that 34.09 % of Imipenem- Resistant Isolates Were MBL Positive. A, IMP (10  $\mu$ g) disc alone; B, disk of IMP (10  $\mu$ g) plus EDTA.

For doripenem (DOR), 20 isolates (45.4%) were susceptible, 6 (13.6%) were intermediate, and 18 (40.9%) were resistant. For ertapenem (ETP), 22 isolates (50.0%) were susceptible, 2 (4.5%) were intermediate, and 20 (45.5%) were resistant. For imipenem (IMI), 27 isolates (61.4%) were susceptible, 2 (4.5%) were intermediate, and 15 (34.1%) were resistant.

For meropenem (MEM), 28 isolates (63.6%) were susceptible, 1 (2.3%) was intermediate, and 15 (34.1%) were resistant. For piperacillin/tazobactam (PTZ), 24 isolates (54.5%) were susceptible, 1 (2.3%) was intermediate, and 19 (43.2%) were resistant. Finally, for fosfomycin (FOS), 30 isolates (68.2%)

were susceptible, 7 (15.9%) were intermediate, and 7 (15.9%) were resistant.

Overall, the highest resistance rate was observed for ceftazidime (86.4%), whereas the lowest resistance rate was observed for tigecycline (4.6%). The highest susceptibility rate was observed for fosfomycin (68.2%). Of the total isolates, 28 (63.6%) were identified as multidrug-resistant (MDR), while 16 (36.4%) were categorized as extensively drug-resistant (XDR). The MIC ranges, MIC<sub>50</sub>, MIC<sub>90</sub>, and the percentages of isolates resistant, intermediate, or susceptible to the five antimicrobial agents are shown in Table 1.

**Metallo- $\beta$ -lactamase phenotype:** The prevalence of MBL-producing *K. pneumoniae* by DDST was 34.09% (n = 15) (Figure 2).

## Discussion

In Iran, the excessive and inappropriate use of antibiotics has significantly contributed to the increasing prevalence of antimicrobial resistance over recent decades<sup>12</sup>. In recent years, clinicians have become increasingly reliant on carbapenems to treat infections caused by multidrug-resistant bacteria. Carbapenem-resistant Enterobacteriaceae (CRE) strains have been associated with multiple nosocomial outbreaks and demonstrate a remarkable ability to spread rapidly within healthcare settings and across local, regional, and international boundaries. Their persistent emergence poses a significant challenge to global public health<sup>13</sup>. CRE strains are increasingly exhibiting resistance to a broad range of antimicrobial classes, posing a significant challenge to effective treatment<sup>12, 14, 15</sup>.

In this study, among the included isolates, the highest rates of resistance belonged to Ceftazidime (n = 38, 86.4%), nalidixic acid (n = 30, 68.2%), Ciprofloxacin (n = 30, 68.2%), and trimethoprim-sulfamethoxazole (Ts) (n = 30, 68.2%). On the other hand, the lowest resistance rates were observed for tigecycline (n = 2, 4.6%) and fosfomycin (n = 7, 15.9%), indicating that these antibiotics are increasingly becoming primary options for the treatment of multidrug-resistant strains of *K. pneumoniae*. The very high resistance rate to third-generation cephalosporins (86.4% ceftazidime) in our study is worrying.

**Table 1.** MIC of the *K. pneumoniae* clinical isolates (n= 44).

| Antibiotic    | MIC( $\mu$ g/ml)      |     |     | No (%)     |              |             |
|---------------|-----------------------|-----|-----|------------|--------------|-------------|
|               | Range                 | 50% | 90% | Resistant  | Intermediate | Susceptible |
| Imipenem      | $\leq 2$ - $\geq 256$ | 4   | 64  | 14 (31.8%) | 2(4.6%)      | 28(63.6%)   |
| Meropenem     | $\leq 2$ -256         | 2   | 64  | 13 (29.6%) | 6(13.6%)     | 25(56.8%)   |
| Ceftazidime   | $\leq 2$ - $\geq 256$ | 32  | 256 | 35 (79.5%) | 1(2.3%)      | 8(18.2 %)   |
| Ciprofloxacin | $\leq 2$ - $\geq 256$ | 8   | 64  | 30 (68.2%) | 0            | 14(31.8%)   |
| Colistin      | $\leq 2$ -128         | 2   | 4   | 7 (15.9%)  | 0            | 37(84.1%)   |

The antimicrobial resistance pattern observed in the present study is comparable to that reported in previous investigations. Kashefieh et al. reported resistance rates of 68% to ceftazidime, 67% to ciprofloxacin, and 70% to trimethoprim-sulfamethoxazole among clinical *K. pneumoniae* isolates in northwestern Iran<sup>16</sup>. In the study by Firoozeh et al. in Kashan, resistance to ceftazidime was reported (50.3%), which is significantly lower than our findings<sup>17</sup>. The observed discrepancy may be due to differences in patient populations, geographical regions, antibiotic prescribing practices, or infection control policies.

Overall, the findings of the present study further support the growing burden of multidrug-resistant *K. pneumoniae* and highlight the urgent need for routine antimicrobial susceptibility testing, continuous surveillance of antimicrobial resistance, implementation of antimicrobial stewardship programs, and strict infection prevention and control measures. These strategies are essential to limit the dissemination of resistant strains and to optimize empirical and targeted antimicrobial therapy.

Our findings demonstrated that 15.9% of the *K. pneumoniae* isolates were resistant to colistin, with MIC values ranging from 2–128  $\mu$ g/mL. Colistin remains a last-line treatment for Gram-negative bacilli; However, colistin-resistant and even pandrug-resistant strains have been reported<sup>18</sup>. Globally, colistin resistance among carbapenem-resistant *K. pneumoniae* has increased from < 2% to 9%, while in Europe it has reached approximately one-third of carbapenem-resistant isolates. Furthermore, multiple outbreaks of colistin-resistant *K. pneumoniae* have been documented worldwide<sup>19, 20</sup>.

A meta-analysis in Iran an average rate of colistin resistance among clinical isolates of 6.9%, but in our

study, the prevalence of colistin resistance was 15.9%, which is significantly higher than the national average. This high rate of resistance could be due to the selection of isolates in our study as well as the antibiotic consumption pattern in the study area<sup>21</sup>.

Similar to our findings, several Iranian studies have reported the emergence of colistin-resistant *K. pneumoniae*, particularly among carbapenem-resistant and MDR isolates. The increased occurrence of resistance in these strains may be associated with selective pressure caused by colistin and other broad-spectrum antibiotics, as well as genetic changes affecting lipopolysaccharide modification pathways and acquisition of plasmid-mediated *mcr* resistance genes<sup>21, 22</sup>.

In contrast, lower rates of colistin resistance have been reported in some international studies. A global systematic review and meta-analysis reported a pooled prevalence of colistin resistance among *K. pneumoniae* bloodstream isolates of approximately 3.1%, which was lower than the prevalence observed in the present study<sup>23</sup>. However, recent reports indicate a gradual increase in colistin resistance worldwide, particularly among MDR and carbapenem-resistant *K. pneumoniae* isolates<sup>24</sup>.

The relatively high prevalence of colistin resistance in the present study may be associated with the high frequency of MDR and XDR isolates among the investigated strains. Therefore, continuous surveillance of colistin susceptibility, molecular investigation of resistance mechanisms, and appropriate antimicrobial stewardship programs are necessary to control the spread of colistin-resistant *K. pneumoniae*.

In the present study, among 44 *Klebsiella pneumoniae* isolates recovered from urine and sputum samples, 63.6% were classified as multidrug-resistant (MDR) and 36.4% as extensively drug-resistant (XDR). The

high prevalence of MDR and XDR isolates indicates the increasing burden of antimicrobial resistance among *K. pneumoniae* clinical isolates.

Our findings are consistent with the study by Soltani et al., who reported a high prevalence of MDR *K. pneumoniae* isolates (58%) in Iran. The similarity may be related to the widespread distribution of resistance genes, particularly ESBL-encoding genes, and the extensive use of broad-spectrum antibiotics. However, differences in XDR rates among studies may be explained by variations in sample types, patient populations, geographical regions, and antibiotic consumption patterns<sup>25</sup>.

Ghasemian et al. also reported a high prevalence of antimicrobial resistance among *K. pneumoniae* isolates in Iran, especially against  $\beta$ -lactam antibiotics, which supports the findings of the present study. The high MDR/XDR rates may be associated with the ability of *K. pneumoniae* to acquire resistance genes through plasmids and integrons, along with the production of ESBLs and other resistance mechanisms<sup>26</sup>. In the present study, the prevalence of MBL-producing *K. pneumoniae* was 34.09%. ESBL and MBL-producing *K. pneumoniae* have been identified worldwide, with reports from Asia, Africa, Americas, the Europe, and Australia<sup>27, 28</sup>. The high rate of ESBL and MBL prevalence in the world and its widespread dissemination is a cause of concern.

The prevalence of MBL-producing *K. pneumoniae* isolates has shown considerable variation among different studies conducted in Iran. Using phenotypic detection methods such as the (DDST), Azizian et al. reported an MBL prevalence of 5% among *K. pneumoniae* isolates in Hamedan<sup>29</sup>. In contrast, Rajabnia et al. reported a higher prevalence, with approximately 30% of isolates identified as MBL producers in Babol<sup>30</sup>. Similarly, Bahmani et al. found that 53.6% of *K. pneumoniae* isolates in sanandaj were MBL producers<sup>31</sup>. The observed discrepancies among these studies may be related to differences in sample size, patient characteristics, clinical specimen sources, antimicrobial exposure, infection control measures, and local epidemiological patterns. These findings highlight the geographic variability of MBL-producing *K. pneumoniae* and the importance of continuous surveillance of carbapenem-resistant isolates in healthcare settings. The lack of molecular

confirmation for MBL genes is a substantial weakness, as phenotypic methods alone are insufficient to confirm MBL production definitively. The analysis of the genes responsible for resistance is currently underway.

## Conclusion

Unnecessary prescribing of antimicrobial drugs in patients is associated with the eradication of normal flora, leading to spread of MDR and XDR isolates. This study revealed the rapid emergence of extensively-drug resistant *K. pneumoniae* isolates in patients. In conclusion, the emergence and dissemination of (MBL)-producing *K. pneumoniae* represent a major global public health threat due to their extensive resistance to multiple classes of antibiotics, particularly carbapenems. The coexistence of MBL genes with other antimicrobial resistance determinants further limits therapeutic options and contributes to the emergence and spread of MDR and XDR strains. Therefore, continuous surveillance, rapid molecular detection, strict infection prevention and control measures, antimicrobial stewardship, and the development of novel therapeutic strategies are essential to curb the dissemination of these high-risk pathogens, preserve the efficacy of existing antibiotics, and improve clinical outcomes.

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## Conflict of Interest

The authors declare no conflicts of interest related to this study.

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