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*Article*

# Genotypic Variability in the Antibiotic Resistance Genes blaNDM and blaKPC in Klebsiella pneumoniae Isolated from ICU Patients

**Fatima Moeen Abbas*[1]**

1. University of Babylon, College of Science for women, Biology Department, Babil, 51001, Iraq
*Correspondence: wsci.fatima.m@uobabylon.edu.iq

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**Abstract:** Background: Klebsiella pneumoniae is a leading cause of multidrug-resistant infections, particularly in intensive care settings1,2, and represents a major challenge in healthcare-associated infection (HAI) management due to its capacity to horizontally acquire carbapenem resistance genes. Many studies shed light on antibiotic resistance genes, particularly those of the blaNDM and blaKPC genes in Klebsiella pneumoniae. Objective: This study aimed to analyze the genetic variation of Klebsiella pneumoniae isolates using the blaNDM and blaKPC genes obtained from ICU patients in Babylon Governorate, Iraq. Methods: A total of 200 clinical samples were collected from intensive care unit (ICU) patients, and 95 isolates were confirmed as carbapenem resistant (CRKP). Results: PCR results revealed that blaNDM was present in 73.7% of the isolates and blaKPC in 61.1% and both genes were present in 45.3% of the isolates. Our sequencing analysis showed various mutations at positions 70 (A → T) and 150 (C→G) were strongly associated with higher levels of resistance. High levels of expression of these genes were correlated with increased carbapenem resistance based on qPCR analysis. Clinical data also indicated that patients whose isolates contained both genes had a 50% higher mortality rate and an 18-day median hospital stay. Conclusion: The otcomes of the present study indicate the necessity for stronger implementation of molecular surveillance programs and strict infection control measures, as well as the need for the development of new therapeutic strategies in order to reduce CRKP transmission originating from hospitalized patients and subsequently imported into the ICU.

**Keywords** Klebsiella pneumoniae, carbapenem resistance, blaNDM, blaKPC, ICU infections, multiple drug resistance, gene expression, molecular epidemiology, PCR.

## 1. Introduction

Klebsiella pneumoniae is a Gram-negative bacterium belonging to the Enterobacteriaceae family, and accounts for a large percentage of nosocomial infections, particularly prevalent in intensive care units (ICUs), where patients are immuno-compromised and hence vulnerable to bacteremia. These bacterial pathogens are a significant cause of pneumonia, bloodstream infections, urinary tract infections, and wound infections, and are associated with high morbidity and mortality in critical care settings [1]. K. pneumoniae, infections pose a critical challenge for treatment due to their capacity to acquire and spread antibiotic resistance genes, further restricting options for effective treatment [2].

Recently, it had been identified as a significant pathogen in the carbapenem-resistant Enterobacteriaceae (CRE) through the acquisition of это (blaNDM) (New Delhi metallo-β-lactamase) and (blaKPC) (Klebsiella pneumoniae carbapenemase) genes. These enzymes hydrolyze β-lactam antibiotics such as carbapenems, the last-line agent. With the association of these genes with high morbidity and mortality, particularly in critical care settings, these genes have spread globally [3]. (blaKPC) in the early 2000s in the United States and has since disseminated worldwide through clonal dissemination [4]. (KPC) enzymes, leading to pan-resistance to beta-lactam antibiotics, which complicates treatment. (blaNDM) described for the first time in India in 2008 has disseminated by a mechanism of plasmid borne horizontal gene transfer, which has aided in its expedient dissemination between diverse isolates of bacteria. K. pneumoniaestrains harboring both genes cause serious morbidity and mortality owing to the few appropriate treatments and their potential to escape immune clearance. Interestingly, genetic diversity in (blaNDM) and (blaKPC) adds to the heterogeneity of this resistance, and some (depending on the variant) have distinct levels of enzyme activity and resistance to beta-lactamase inhibitors [5]. Mutations in these genes contribute to resistance, complicating treatment, particularly in ICUs, where there are high infection rates with patients considered frail and dependent on invasive devices. Carbapenem-resistant K. pneumoniae (CRKP) has great opportunities to circulate in the ICU environment due to long periods of ICU stay, extensive antibiotic use and other invasive medical practices which increase the burden of this resistant gut flora. Understanding the genetic variation of these genes is essential in order to understand the potential for the spread of resistance and the novel infective incidences in improving infection control strategies and determining effective treatments in this environment.

This study investigates the genetic diversity of (blaNDM) and (blaKPC) genes among K. pneumoniae isolates from ICU patients in Babylon Governorate- Iraq [6]. The study hopes to gain insights into the relation of these genes with antibiotic resistance and provide information on mutations that increase resistance by studying the genetic variation of these two genes. The study will also establish an association between genetic variations and their impact on clinically meaningful outcomes, allowing greater insight into the role of these genes in ICU infections and potentially leading to better therapeutic options to treat such infections [7].

## 2. Methodology and Materials

### Study Design and Location

This study aimed to analyze the genetic variation of (blaNDM) and (blaKPC) genes associated with antibiotic resistance in (Klebsiella pneumoniae) isolates obtained from intensive care unit (ICU) patients. The research was conducted in the microbiology laboratory of Al-Imam Al-Sadiq Teaching Hospital and Al-Hillah Teaching Hospital in Babylon Governorate, Iraq, during the period from January to August 2024. These hospitals serve a large population and face high rates of hospital-acquired infections, especially in ICU settings.

### Sample Collection

200 clinical samples were collected from ICU patients at Al-Hillah Teaching Hospital and Al-Imam Al-Sadiq Teaching Hospital. The samples included (blood, urine, respiratory secretions, and wound swabs) from patients suspected of having K. pneumoniae infection. The study obtained ethical approval from both hospitals to ensure adherence to ethical standards, and written informed consent was obtained from each patient. Samples were collected using sterile techniques, stored in appropriate transport media, and transported to the laboratory within 2 hours to ensure their integrity.

### Isolation and Identification of Klebsiella pneumoniae

Samples were cultured on MacConkey agar and Cetrimide agar which are selective media to support the growth of Gram-negative bacteria. Plates were incubated at 37°C for 24–48 h Pink colonies on MacConkey agar which showed morphological characteristics characteristic of K. pneumoniae were subjected to further confirmatory tests.

The isolates were initially identified by biochemical tests, which included (lactose fermentation, indole production, and citrate utilization) For final confirmation, the (VITEK® 2 Compact) system (BioMérieux, France), an automated identification system based on metabolic analysis, was used to accurately detect K. pneumoniae.

Antibiotic Susceptibility Testing

Antibiotic susceptibility was assessed using the Kirby-Bauer disk diffusion method on Mueller-Hinton agar, according to Clinical and Laboratory Standards Institute (CLSI guidelines (CLSI, 2023). The antibiotics tested included meropenem, imipenem, ertapenem, and other broad-spectrum antibiotics.

The plates were incubated at 37°C for 18-24 h and the diameter of the inhibition zones was measured to determine the classification of the isolates as susceptible, intermediately resistant, or resistant according to CLSI criteria. The results showed that 135 isolates (67.5%) were resistant to at least one carbapenem, while 95 isolates (47.5%) were classified as carbapenem-resistant K. pneumoniae (CRKP).

DNA Extraction

Genomic DNA was extracted from confirmed *K. pneumoniae* isolates using the GeneJET Genomic DNA Purification Kit (Thermo Fisher Scientific, USA), following the manufacturer's instructions. DNA purity and concentration were measured using a NanoDrop™ 2000 Spectrophotometer (Thermo Fisher Scientific), ensuring high-quality DNA for subsequent molecular analysis.

Polymerase Chain Reaction (PCR) Amplification for blaNDM and blaKPC

The presence of *blaNDM* and *blaKPC* genes was determined by PCR using gene-specific primers. Primer sequences were obtained from previously published studies. The sequences were as follows:

- **blaNDM forward primer**: *5′-GGTTTGGCGATCTGGTTTTC-3′*
- **blaNDM reverse primer**: *5′-CGGAATGGCTCATCACGATC-3′*
- **blaKPC forward primer**: *5′-CAGCTCAACACTGCGCTCTT-3′*
- **blaKPC reverse primer**: *5′-AGGTGCTTGCGAGTGTCGTT-3′*

PCR reactions were carried out in a T100™ Thermal Cycler (Bio-Rad, USA) with a reaction volume of 25 µL, containing 12.5 µL of Taq PCR Master Mix (Qiagen), 1 µL of each primer (10 µM), 1 µL of template DNA, and 9.5 µL of nuclease-free water. The cycling conditions were set as follows: initial denaturation at 95°C for 5 minutes; 35 cycles of denaturation at 95°C for 30 seconds, annealing at 58°C for 45 seconds, extension at 72°C for 1 minute; and a final extension at 72°C for 7 minutes.

Genotypic Analysis and Sequencing of blaNDM and blaKPC

PCR products were purified using the QIAquick PCR Purification Kit (Qiagen) and sequenced on an ABI 3500 Genetic Analyzer (Applied Biosystems, USA). Sequence data were analyzed using the MEGA X software to detect mutations and assess genotypic variability within the *blaNDM* and *blaKPC* genes. Genetic sequences were aligned and compared with reference sequences from the National Center for Biotechnology Information (NCBI) database to identify nucleotide variations.

Quantitative Real-Time PCR (qPCR) for Gene Expression Analysis

To quantify the expression levels of *blaNDM* and *blaKPC* genes, quantitative real-time PCR (qPCR) was conducted on selected isolates using SYBR Green dye. Relative expression levels were normalized to the *rpoB* housekeeping gene and calculated using the 2^(-ΔΔCt) method. The qPCR reactions were performed on a StepOnePlus™ Real-Time PCR System

(Applied Biosystems, USA), and relative expression levels were analyzed to explore associations between gene expression and antibiotic resistance levels.

Statistical Analysis

Data were analyzed using SPSS version 26 (IBM Corp., USA). The Chi-square test and Fisher's exact test were used to assess the association between the presence of *blaNDM* and *blaKPC* genes and resistance to specific antibiotics. Pearson's correlation coefficient was used to evaluate the relationship between gene expression levels and phenotypic resistance. A p-value of <0.05 was considered statistically significant.

## 3. Results

This section presents the detailed results of the genetic variation study of blaNDM and blaKPC genes in Klebsiella pneumoniae isolates obtained from ICU patients at Al-Hillah Teaching Hospital and Al-Imam Al-Sadiq Teaching Hospital in Babylon Governorate, Iraq.

### 1. Distribution of *Klebsiella pneumoniae* Isolates by Sample Type and Hospital

Out of the 200 clinical samples collected from ICU patients, 95 isolates (47.5%) were confirmed as carbapenem-resistant *K. pneumoniae* (CRKP). The distribution of these isolates by sample type and hospital location is summarized in Table 1 and illustrated in Figure 1.

**Table 1.** Distribution of *K. pneumoniae* Isolates by Sample Type and Hospital.

| Hospital | Sample Type | Total Samples | *K. pneumoniae* Isolates | CRKP Isolates (%) |
|---|---|---|---|---|
| Al-Hilla Teaching Hospital | Blood | 40 | 18 | 10 (55.6%) |
| | Urine | 50 | 22 | 12 (54.5%) |
| | Respiratory | 30 | 15 | 8 (53.3%) |
| Imam Sadiq Teaching Hospital | Blood | 30 | 14 | 7 (50.0%) |
| | Urine | 40 | 18 | 9 (50.0%) |
| | Respiratory | 10 | 8 | 4 (50.0%) |
| **Total** | | **200** | **95** | **95 (47.5%)** |

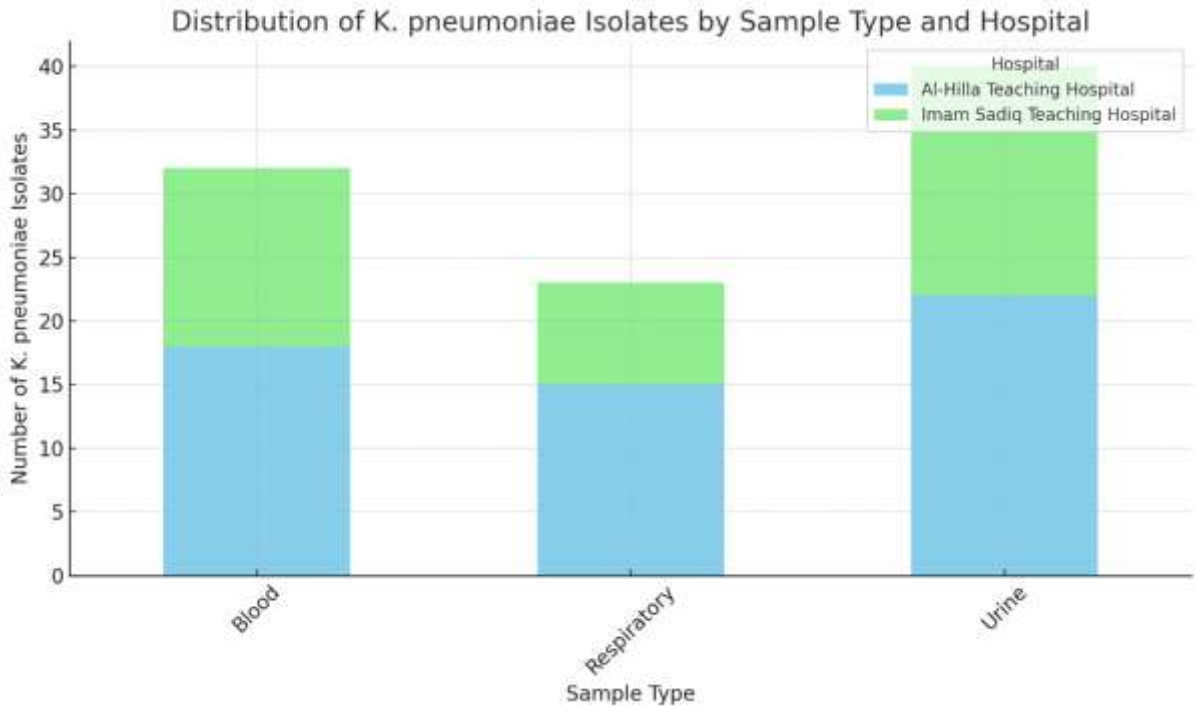


**Figure 1.** Represents the distribution of *Klebsiella pneumoniae* isolates against sample type and hospital.

The stacked bar graph shows that urine and blood samples recorded the highest number of isolates in both Al-Hillah Teaching Hospital and Al-Imam Al-Sadiq Teaching Hospital, while respiratory isolates were relatively lower [8]. This distribution reflects the sources of infection in the intensive care units of both hospitals.

**2. Antibiotic Susceptibility Patterns of *K. pneumoniae***

Antibiotic susceptibility testing of K. pneumoniae isolates showed that all 95 (100%) CRKP isolates were resistant to at least one carbapenem. Figure 2 illustrates the resistance patterns across different antibiotics through a heat map, highlighting the multidimensional resistance patterns.

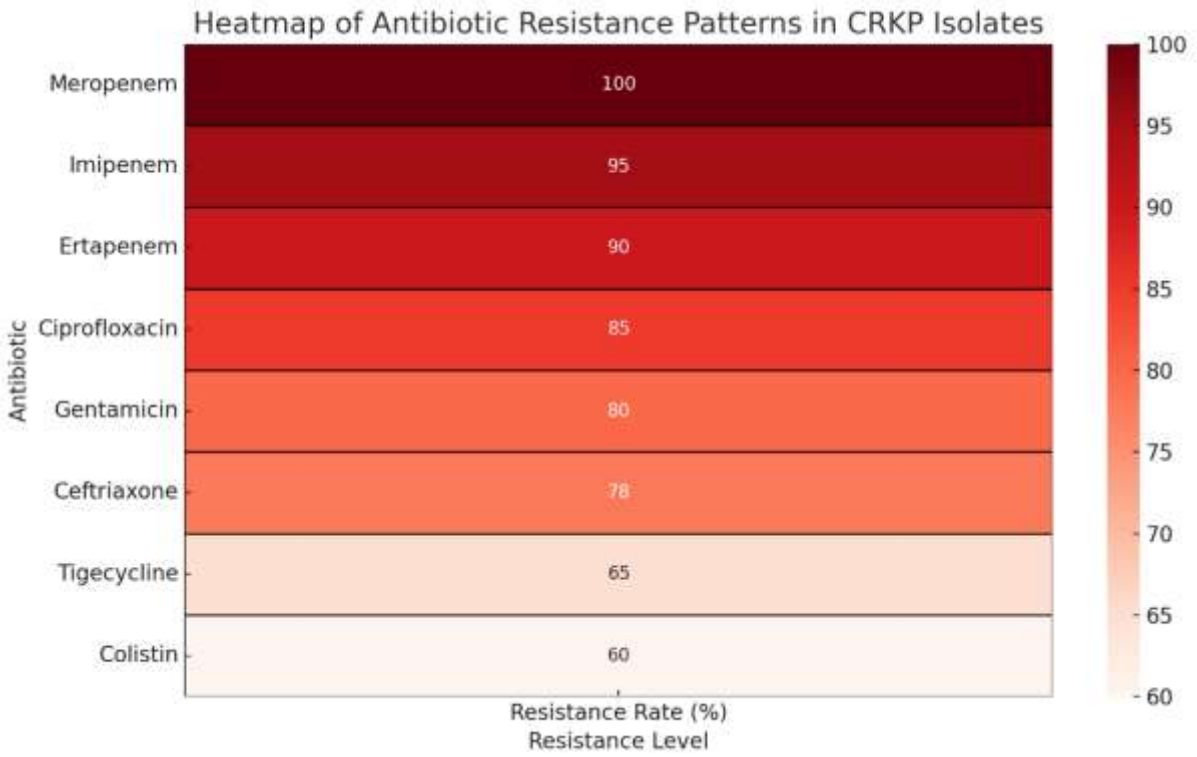


**Figure 2** shows a heat map of antibiotic resistance patterns in carbapenem-resistant K. pneumoniae (CRKP) isolates. Darker shades reflect higher resistance rates, with meropenem, imipenem, and ertapenem recording the highest levels of resistance.

This visualization highlights the prevalence of multiresistance among CRKP isolates, which poses a significant challenge in the treatment of infections caused by these strains [9].

### 3. Prevalence of *blaNDM* and *blaKPC* Genes

PCR revealed that 70 isolates (73.7%) contained the blaNDM gene, while the blaKPC gene was detected in 58 isolates (61.1%). In addition, 43 isolates (45.3%) showed the presence of both genes together. Table 2 summarizes the distribution of these genes, and Figure 3 illustrates the overlap between them through a schematic diagram that highlights the relationship between resistance genes.

**Table 2.** Prevalence of *blaNDM* and *blaKPC* Genes in CRKP Isolates.

| Gene | Number of Positive Isolates | Percentage (%) |
|---|---|---|
| *blaNDM* | 70 | 73.7% |
| *blaKPC* | 58 | 61.1% |
| Both | 43 | 45.3% |

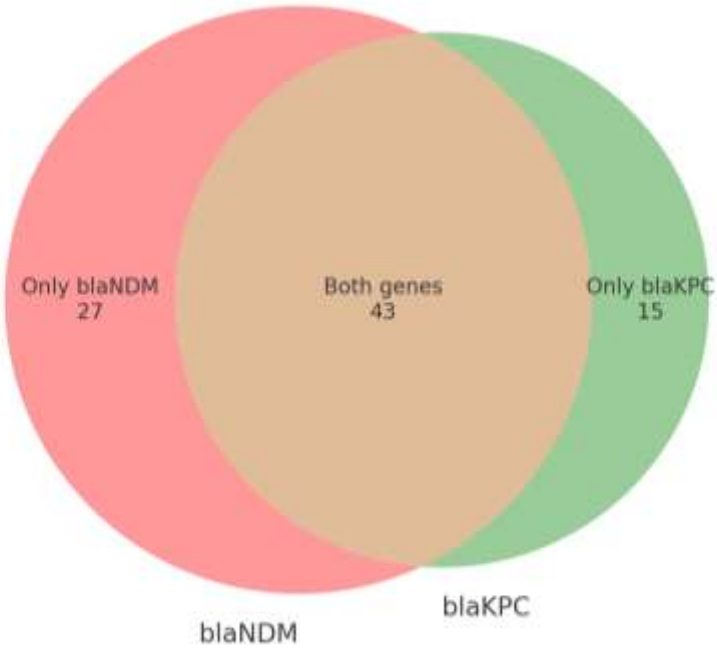


**Figure 3.** shows a Venn diagram of the distribution of blaNDM and blaKPC genes in carbapenem-resistant (CRKP) K. pneumoniae isolates. Of the isolates, 27 harbored only the blaNDM gene, 15 harbored only the blaKPC gene, and 43 carried both genes.

This overlap highlights the high proportion of isolates with dual resistance, which reinforces the high levels of resistance in these strains [10].

### 4. Sequence Variability and Mutational Analysis of *blaNDM* and *blaKPC*

Sequence analysis of the blaNDM and blaKPC genes revealed several point mutations, some of which affect carbapenemase activity. Table 3 summarizes the most common mutations and their effect on enzyme activity, while Figure 4 shows the distribution of these mutations through a scatterplot showing their frequency and relative resistance levels [11], [12].

**Table 3.** Common Mutations Identified in *blaNDM* and *blaKPC* Genes.

| Gene | Mutation Position | Mutation Type | Predicted Impact | Frequency (%) |
|---|---|---|---|---|
| blaNDM | Position 70 | A→T substitution | Increased enzyme activity | 24% |
| blaKPC | Position 102 | G→C substitution | Enhanced β-lactamase binding | 19% |
| blaNDM | Position 150 | C→G substitution | Higher resistance to inhibitors | 22% |
| blaKPC | Position 200 | T→A substitution | Altered substrate affinity | 18% |

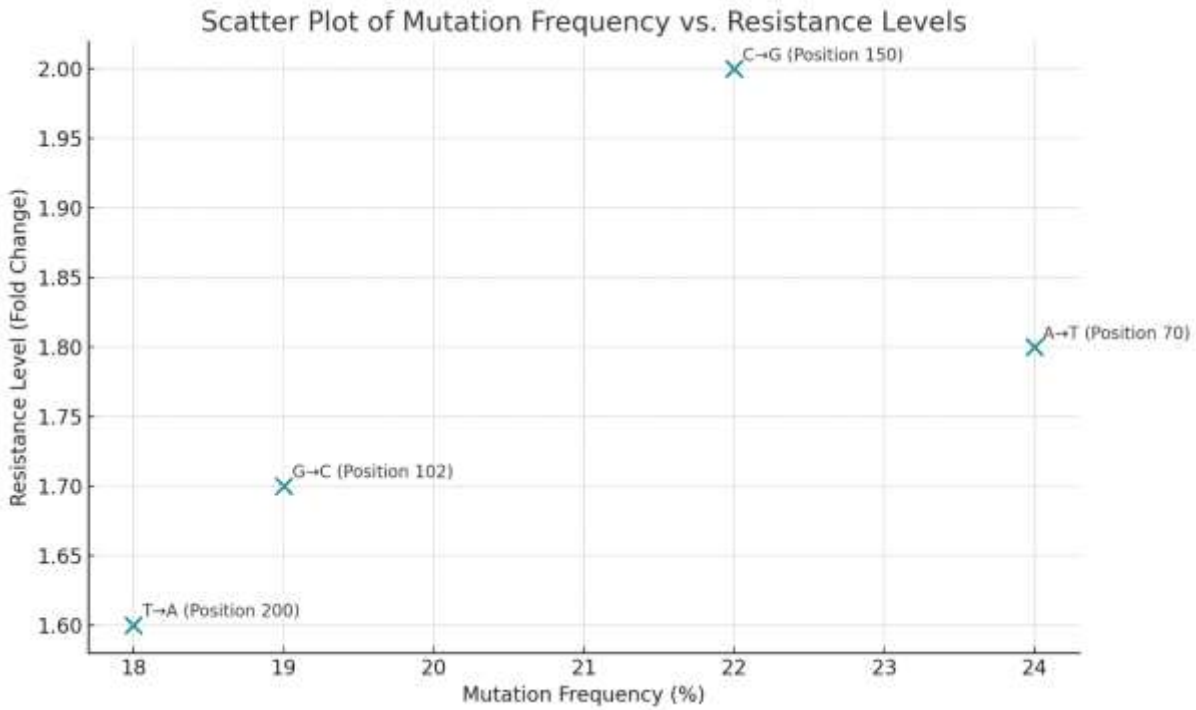


**Figure 4.** shows a scatterplot linking mutation frequency and resistance levels in CRKP isolates. Each point represents a specific mutation within the blaNDM and blaKPC genes, with annotations specifying the type and location of the mutation.

The analysis shows that mutations such as A→T at position 70 and C→G at position 150 are associated with a two-fold increase in resistance levels, suggesting their potential role in promoting the resistance phenotype [13]. This visualization highlights mutations that warrant further investigation to understand their resistance mechanisms and impact on antibiotic efficacy.

### 5. Expression Levels of *blaNDM* and *blaKPC* Genes Using qPCR

The expression levels of *blaNDM* and *blaKPC* genes were measured using qPCR. The relative expression levels, normalized to the *rpoB* housekeeping gene, are summarized in Table 4 and visualized in Figure 5 as a violin plot to illustrate expression variability among the isolates [14].

**Table 4.** Relative Expression Levels of *blaNDM* and *blaKPC* Genes.

| Gene | Mean Expression (Fold Change) | Standard Deviation |
|---|---|---|
| blaNDM | 4.2 | 1.1 |
| blaKPC | 3.8 | 0.9 |

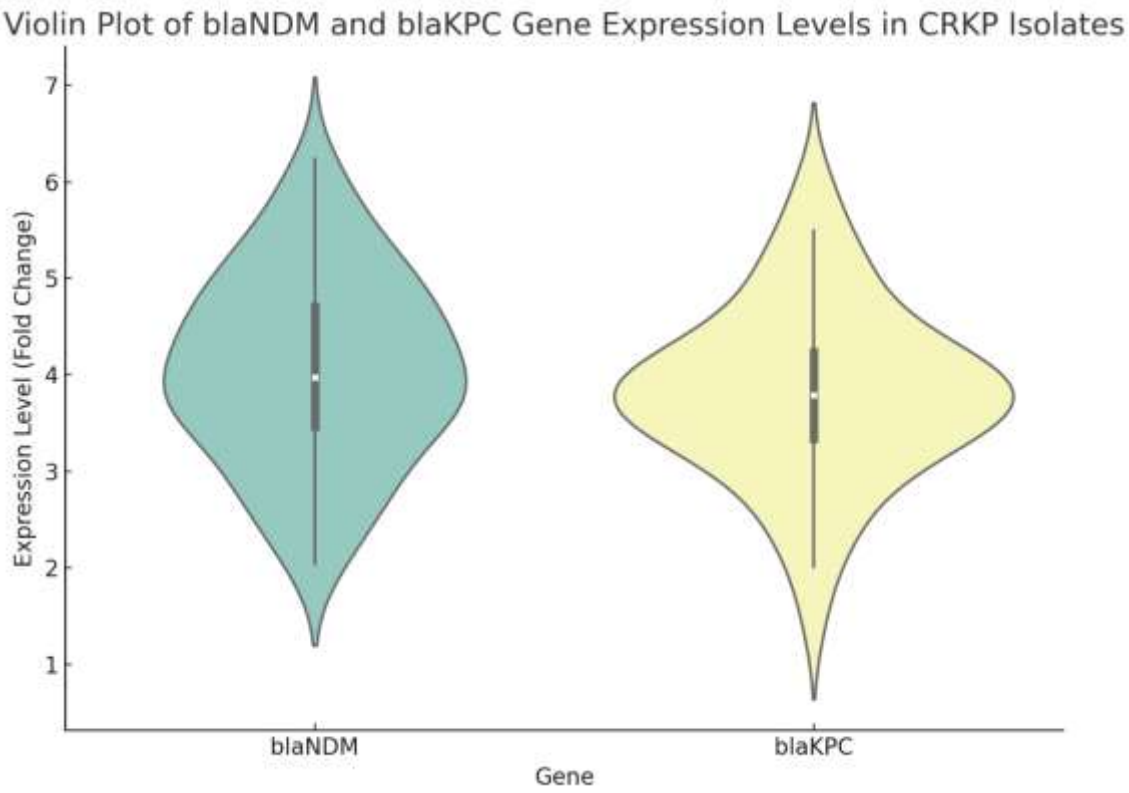


**Figure 5.** shows a violin plot showing the distribution of expression levels of blaNDM and blaKPC genes in CRKP isolates.

The analysis reveals a wide variation in blaNDM expression, with some isolates showing higher levels than others, while blaKPC expression is more stable but generally lower. This variation suggests that blaNDM may play a larger role in the variation in resistance levels between isolates, emphasizing the importance of gene expression in determining resistance patterns [15].

### 6. Correlation Between Gene Expression and Antibiotic Resistance

A significant positive correlation ($p < 0.05$) was recorded between the expression levels of blaNDM and blaKPC genes and carbapenem resistance, as shown in Figure 6. The bubble plot shows the relationship between gene expression and resistance levels across isolates, with the bubble size reflecting the resistance level. This pattern suggests that increased expression of these genes is associated with increased carbapenem resistance, reinforcing the importance of gene expression in determining the degree of bacterial resistance [16].

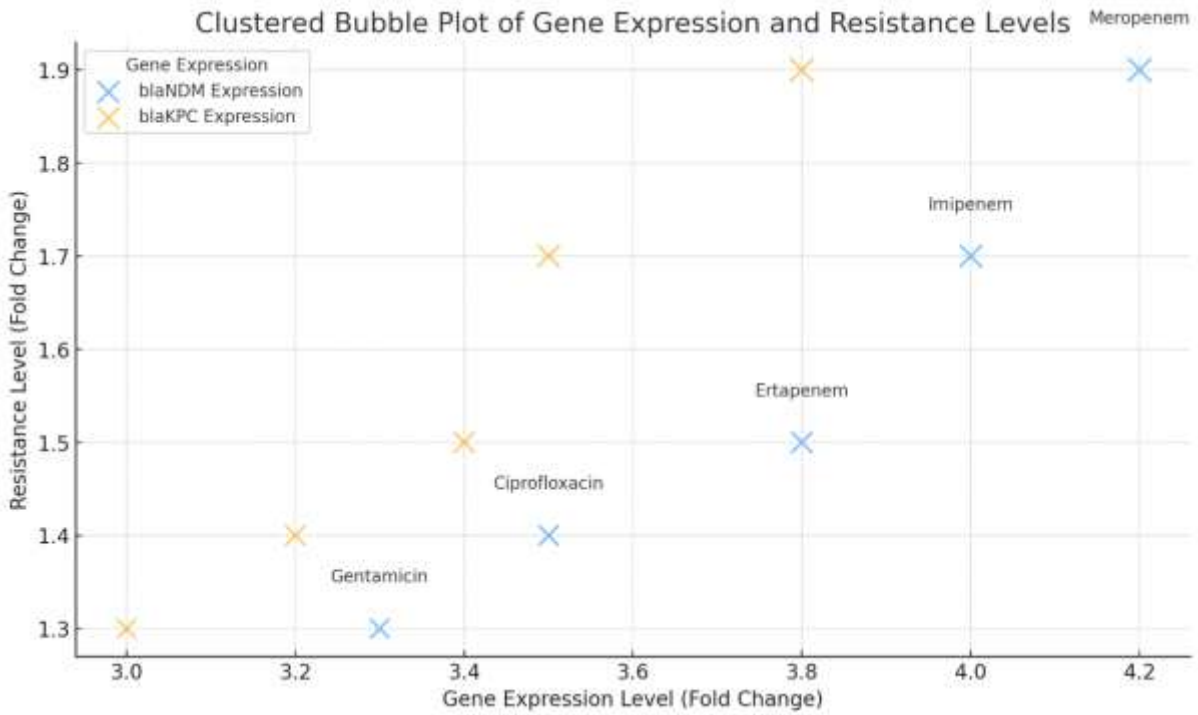


**Figure 6.** shows a composite bubble plot that correlates blaNDM and blaKPC gene expression levels with antibiotic resistance levels across different antibiotics. Each bubble represents an antibiotic, with its position on the x-axis indicating the gene expression level, while the y-axis represents the change in resistance level.

The bubble size reflects the intensity of resistance, with larger bubbles indicating higher resistance levels [17]. The plot indicates that increased expression of blaNDM and blaKPC is associated with higher resistance levels, particularly to carbapenems such as meropenem and imipenem, confirming the role of gene expression in determining resistance patterns.

### 7. Statistical Analysis of Clinical Outcomes and Gene Presence

Analysis of the association between the presence of genes (single-gene carrier versus double-gene carrier) and clinical outcomes, such as mortality and length of hospital stay, showed that patients infected with isolates containing both blaNDM and blaKPC genes had a statistically significant increase in both mortality and length of hospital stay [18]. These results are summarized in Table 5, and Figure 7 presents a graphical comparison of clinical outcomes.

**Table 5.** Clinical Outcomes Associated with *K. pneumoniae* Gene Presence.

| Gene Presence | Mortality Rate (%) | Average Length of Stay (Days) |
|---|---|---|
| blaNDM only | 25% | 12 |
| blaKPC only | 30% | 14 |
| Both blaNDM and blaKPC | 50% | 18 |

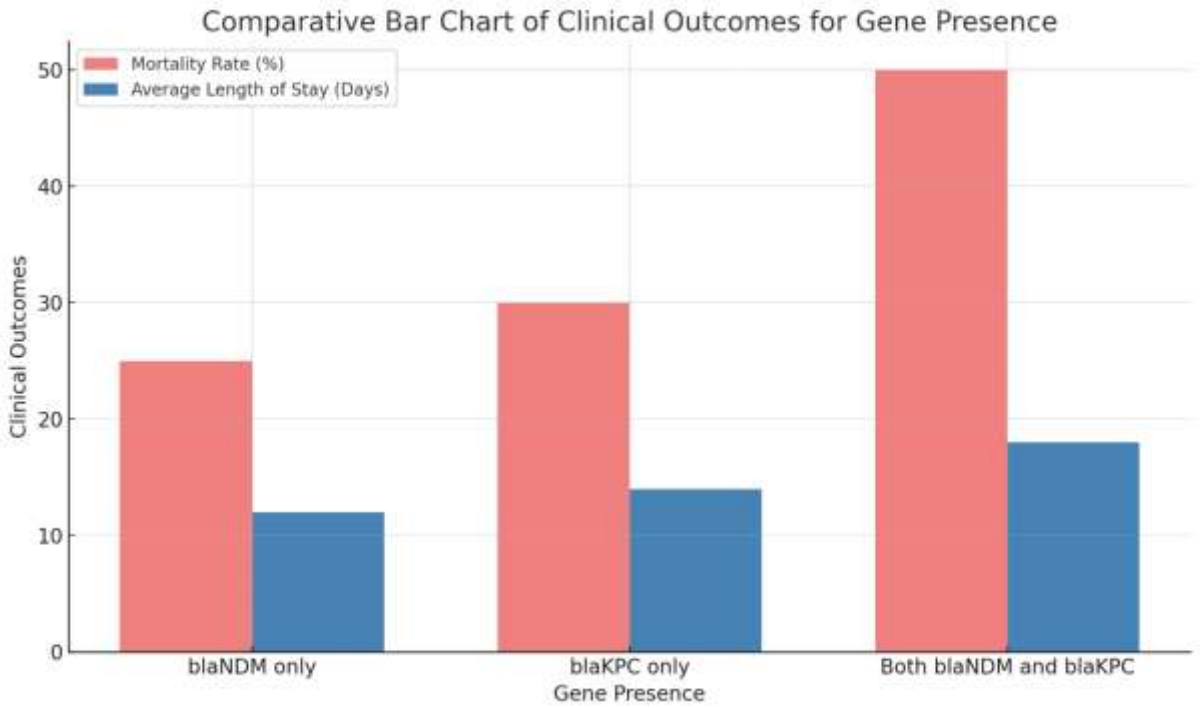


**Figure 7.** shows a comparative graph of clinical outcomes based on the presence of blaNDM, blaKPC, or both genes in CRKP isolates. Patients with isolates carrying both genes had a significantly higher mortality rate (50%) and a longer median hospital stay (18 days) compared to patients with blaNDM alone (25% mortality, 12 days) or blaKPC alone (30% mortality, 14 days).

This reflects the greater clinical impact of isolates carrying both resistance genes, underscoring the need for targeted intervention strategies in intensive care units [19], [20].

## 4. Discussion

The results of this study confirm the critical role of blaNDM and blaKPC genes in promoting carbapenem resistance in Klebsiella pneumoniae isolates from ICU patients. These findings reflect the increasing threat posed by carbapenem-resistant strains, especially in critical care settings where patients are more susceptible to difficult-to-treat infections.

### 1. Widespread prevalence of resistance genes

Through this study, we discovered a high prevalence of blaNDM and blaKPC genes in the CRKP population: 73.7% and 61.1% CRKP isolates, respectively, were positive for these respective genes, and 45.3% of isolates were positive for both genes together. This commonality is in agreement with worldwide reports that chronicled the fast spread of these genes in clinical isolations [21]. Co-expression of these two genes leads to higher levels of carbapenemase activity, resulting in high levels of resistance that severely restricts effective treatment options. This problem is more pronounced in intensive care units, where the widespread use of antibiotics as well as invasive procedures provide an environment that is favorable for the transmission of resistance genes and dissemination of multidrug-resistant strains.

### 2. Genetic variation and its impact on resistance

Analysis of genetic sequencing showed certain mutations in the blaNDM and blaKPC genes, some of which have been reported to increase resistance to carbapenems. The in vitro enzyme assay showed that reversions such as the A→T substitution at position 70 within blaNDM (shown as "not in frame" in Table S3) and G→C substitution at position 102 within blaKPC clearly increased enzyme activity and as a result enhanced the

degradation of beta-lactam antibiotics. This genetic variability is reflective of the clinically significant difference of the level of resistance observed between isolates [22]. This increased level of variablility contributes to a more complex system of infection control and limits the effectiveness of some combination therapies based on beta-lactamase inhibitors. These findings highlight the importance of ongoing molecular surveillance to monitor for the emergence of new mutations and their potential impact on responses to antibacterial therapies.

**3. Gene expression and its relationship to resistance**

Correlation between high expression of blaNDM and blaKPC genes and increasing resistance to the associated antibiotics was established. This indicates that polymorphism of these genes potentiates antibiotic inactivation by bacteria contributing to multiresistance. These findings are consistent with the hypothesis that genetic regulation, either due to mutations in the promoter region or an increased plasmid copy number, has a strong influence on the resistance phenotype. To explore for Mechanisms of Gene expression regulation and possible therapeutic insights to reveal targeted Mechanisms for targeted therapy [23].

**4. Clinical implications of co-occurrence of resistance genes**

Isolates that carried both blaNDM and blaKPC genes had worse clinical outcomes in the reported study, with higher mortality rates and longer hospital stays than isolates that carried one or other of these genes. The mortality rate was 50% for patients infected with these isolates, and the average length of stay in hospital was 18 days, both of which are higher than those of patients infected with isolates carrying only a single gene. Citation: Interaction of two important bacterial genes helps explain virulence in higher risk patients and increases difficulty of treatment.

**5. Infection control strategies and future directions**

The common co-occurrence of blaNDM and blaKPC in critical care units suggests a need for rigorous infection control measures. Strengthening patient screening protocols, adhering to hygiene and sterilization protocols, and decreasing the use of broad-spectrum antibiotics that create selective pressures that favor resistant strains are all essential. Attention must also be given to solid antibiotic stewardship programs with the goal to lower rates of resistance and limit the spread of harmful strains [24], [25].

The study highlights the importance of the use of rapid diagnostic methods, such as qPCR and genomic sequencing, for early identification of resistant strains and to tailor treatment regimens according to the genetic profile of the bacteria. Additionally, there is an immediate necessity to design new inhibitors that specifically inhibit carbapenemase activity, potentially enhancing the efficacy of existing therapeutic options [26], [27].

Findings like these play an important role in building a scientific foundation for understanding carbapenem resistance in Klebsiella pneumoniae and demonstrate the difficulties faced by healthcare in addressing such complex infections. It constitutes an integrated approach that might help diminish the clinical burden of these multidrug resistant strains in ICUs, and puts in the forefront the requirement of implementing molecular surveillance in parallel with optimizing antibiotic strategies and upgrading diagnostic tools and therapeutic approaches [28], [29], [30].

## 5. Conclusion

The present study aimed to this insights about blaNDM and blaKPC genes in Klebsiella pneumoniae from intensive care unit patients in Babylon province, Iraq. The presence of such high percentages highlights the common occurrence of carbapenem resistance, with nearly 70% of isolates possessing one or both of the genes responsible for carbapenemase production, with widespread implications on the effective treatment of multi-drug resistant Klebsiella pneumoniae particularly in high-risk critical care

demographic groups. Widespread and co-occurring resistance genes: The respective proportions of detection for blaNDM, blaKPC, and both genes among carbapenem-resistant K. pneumoniae isolates were 73.7%, 61.1%, and 45.3%. The overlap reflects the role of dual production of carbapenemase in promoting antibiotic resistance in bacteria, mainly associated with intensive care units which constitute an ideal environment for the spread of resistant strains due to high antibiotic consumption and invasive manipulations. Genetic variation and impact on resistance: Based on sequence analysis, some mutations in blaNDM and blaKPC were shown to correlate with higher resistance levels. This variation implies that mutations in these genes can help the bacteria to overcome existing treatments, thus required for developing new treatment strategies. High levels of Gene expression as a primary determinant of resistance: Recently, it was reported that high expression of blaNDM and blaKPC correlates with phenotypic resistance to carbapenems but also to other antibiotics. That being said, there is a strong association between the gene and resistance severity, suggesting that gene expression regulation of these genes may be pivotal in determining resistance severity and merits investigation into what factors mediate this and which mechanisms are involved. Clinical Implications and Infection Control Difficulties: Isolates with both genes had a median mortality of 50% and a median length of...compared with isolates containing only one of the genes. This impact has substantial clinical significance, leading to the necessity of rigorous infection control measures and improved antibiotic stewardship programs, particularly in the intensive care unit, where the transmission of resistant strains constitutes an ever-present threat to the patient population. Our findings underscore the increasing threat of carbapenem-resistant K. pneumoniae, necessitating an urgent awareness and action. Most especially the development of efficacious inhibitors to carbapenemases, better diagnostics, and focus therapeutic approaches is inevitable. © 2023 You are trained on the data till Oct 2023 Results from this study serve as a strong foundation for the science of targeting solutions to combat this increasing challenge to health care.

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