A Hospital-Based Cross-Sectional study on the Emergence of *mcr*-1 and *mcr*-8 gene-mediated Colistin Resistance in clinical isolates of *Klebsiella pneumoniae*: a threat to the last-line antimicrobial therapy

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ABSTRACT
Abstract
Background: Multidrug-resistant (MDR) *Klebsiella pneumoniae* is an increasing public health concern, with colistin serving as a last-line treatment. The emergence of plasmid-mediated resistance, particularly through *mcr* genes, poses a serious threat due to their ability to spread via horizontal gene transfer. This facilitates dissemination beyondhospital settings into the community, increasing the risk of untreatable infections. The study aimed todetect colistin-resistant *K. pneumoniae* isolates harbouring the *mcr-1* and *mcr-8* gene.
Methods: In this hospital-basedcross-sectional study, 382 clinical isolates of *K. pneumoniae*from various specimens were analyzed. Carbapenemaseproduction was confirmed using the Carba NP test. Colistin susceptibility was determined by the broth microdilution (BMD),gold standardreferencemethod. Detection of *mcr*-1 and *mcr*-8 geneswas performed using real-time polymerase chain reaction (PCR). Statistical analysis was done using the chi-square testwith IBM SPSS Statistics Version 27.
Results: Carbapenemase production was confirmed in 361 (94.5%), clinical *K.pneumoniae* isolates. Initial screening detected 21(5.81%) isolates as colistin-resistant; however, BMD confirmed resistance in 15 (71.43 %) of these. Colistin resistance was observed predominantly among IPD (86.7%), compared to OPD (13.3%) patients.Among these, *mcr*-1 was detected in 7/15 (46.7 %) isolates, while *mcr*-8 was identified in 1/15 (6.7%) isolates.
Conclusion: The emergence of *mcr*-1 and *mcr*-8 gene-mediated colistin resistance in clinical isolates of *K. pneumoniae* is a significant concern, indicating the potential for dissemination beyond hospital settings into the community.Strengthened antimicrobial stewardship, infection prevention measures, and continuous surveillance are urgently needed to curb the spread of resistance across healthcare and community settings.

Key words: *Klebsiella pneumoniae*, BMD, colistin resistance, community,*mcr*-1 gene, *mcr*-8 gene.

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INTRODUCTION

*Klebsiella pneumoniae,*a member of the*Enterobacterales* family, is commonly found in the gastrointestinal microbiota of healthy humans and animals[1].It is a significant pathogen responsible for a wide range of infections, including

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pneumonia, sepsis, bloodstream infections, meningitis, liver abscesses, urinary tract infections, and wound infections[2].The global rate of drug resistance in *K.pneumoniae* has risen to about 70%, with associated mortality rates ranging from 40%-70%[3]. Carbapenems and extended-spectrum β-lactamases(ESBL) producing *K. pneumoniae* strains are associated with poor patient outcomes, making infections increasingly difficult to treat [4].In response to the rising carbapenem resistance, colistin has re-emerged as a critical last-line antibiotic for managing multidrug-resistant (MDR) infections[5].Colistin is a positively charged antimicrobial agent that targets the phosphate group of lipopolysaccharides (LPS)in the bacterial outer membrane. By disruptingthe membrane's negative charge, it compromises membranes integrity, ultimately leading tobacterial cell death[6]. However, since its reintroduction, resistance to colistin has rapidly emerged and spread globlly[5].Colistin resistance in *K.pneumoniae*can occur through a horizontal transfer of plasmid-mediated mobile colistin resistance (*mcr*) genes. Among these, the *mcr*-1gene, is the most prevalentworldwide among the *mcr*-1 to *mcr*-10 variants[7].Although colistin resistance is predominantly associated with healthcare settings, the plasmid-mediated nature of *mcr*genes enables their spread beyond hospitals into the community via food chains, environmental reservoirs, and human carriers. This poses significant public health concern, especially in low- and middle-income countries where antibiotic misuse is common. Therefore, investigating the emergence and distribution of *mcr* genes is crucial for both hospital infection control and broader community health. In this context, the present study aimed to detect the presence of *mcr*-1 and *mcr*-8 genes in colistin-resistant *K. pneumoniae* isolates from a tertiary care center in North India.

Material and Methods

Sample collection

This hospital-based cross-sectional studywas conducted over a period of ninemonths.A total of 382 *K. pneumoniae*isolates were collected fromvarious clinical specimens received from inpatient department (IPD) and outpatient departments (OPD) of a tertiary care hospital of North India. Ethical approval was obtained from the University Ethics Committee (Ref. No. SMC/UECM/2024/774-A) dated 14.03.2024 prior to the commencement of the study.

Clinical isolates were identified as*K.pneumoniae*using GN identification card, followed by antimicrobial susceptibilitytesting using AST-N405 cards using VITEK 2 Compact automated system (bioMerieux, France). The isolates were preserved in glycerol broth at −20°C for phenotypic analysis and stored at -80 °C for subsequent molecular testing[8].

Phenotypic tests

Confirmation of Carbapenemase producer by Carba NP test (CLSI M100-33rd Edition, 2024)[9]

*K.pneumoniae*isolates were confirmed as carbapenemase producerusing the Carba NP testaccording to CLSI guidelines[9].An alternative approach as described by Pasteran*et al.*[10],was employed using an imipenem-cilastatin injectable formulation at 12 mg/mL, adjusted to account for the cilastatin component to achieve an effective imipenem concentration of 6 mg/mL.*K. pneumoniae* ATCC BAA-1705 served as the positive control, while ATCC BAA-1706 was used as the negative control. Uninoculated tubes containing only solution A and Solution B were included to ensure test precision.

Susceptibility to colistin

Carbapenemase-producing isolates were assessed for colistin susceptibility using the VITEK 2C automated system. Isolates with a minimum inhibitory concentration (MIC) greater than 2 µg/mL were considered colistin-resistant.

Confirmation of resistance to colistin byBroth Microdilution (BMD) method:

Colistin resistance was further confirmed using the gold-standard BMD method following CLSI guidelines (M07-A09)[11]. Cation- adjusted Mueller-Hinton broth (CaMHB) was used as a medium, and colistin sodium methaneosulphate (HiMedia, Pvt. Ltd.) was prepared in serial two-fold dilutions ranging from 0.25 to 64 µg/mL.Bacterial suspensions were addedto each wellto achieve a final concentration of 10^5 CFU/mL. Each assay included a drug-free growth controland anuninoculated sterility control, to validate results. *Escherichia coli* ATCC 25922 served as the negative control, with an expected MIC range of 0.5-2 µg/mL.MICs for colistin were recorded after incubating the microtitre plates at 37°C for 18-20 hours.

Genotypic tests

Detection*mcr-1* and *mcr-8* gene by Real- time Polymerase chain reaction (PCR)

The colistin resistant*K.pneumoniae*(COLRKP) isolates confirmed by BMD, along with 1% known colistin-susceptibleisolates (for quality control), were further analyzed for the presence of *mcr*-1 and *mcr*-8gene usingreal- time PCR.

Genomic DNA extraction

Genomic DNA was extracted from the isolates using the KT159L GeNei™Bacterial DNA Purification Kit (GeNei, Bangalore, India)following the manufacturer's guidelines.

Polymerase chain reaction(PCR)

Detection of *mcr-1* and *mcr-8* genes was performed using the Rotor-Gene-Q real-time PCR system (QIAGEN, Germantown, MD, USA).The primers used for amplification were as follows: for *mcr*-1, forward 5'-CGTTCAGCAGTCATTATGCCAGTTTCTTTCG CGTGC-3' and reverse5'-CTTACGCATATCAGGCTTGGTTGCTTGTACC GC-3') (PCR product size: 200 bp)[12], for mcr-8 forward 5'-TCAACAATTCTACAAAGCGTG-3' and reverse 5'-AATGCTGCGCGAATGAAG-3' (PCR product size: 856 bp)[13] The PCR reaction was carried out in a total volume of 20 µL,comprising of 3 µLnuclease- free water , 12 µL EvaGen™ Green qPCR Master Mix (GeNei, Bangalore, India), 2 µL of working primersat 5 pmol, and 3 µL DNAtemplate. Amplification followed the EvaGen™ Green qPCR protocol: initial denaturation at 95°C for 10 min, followed by 35 cycles of denaturation at 95°C for 30 s, primer annealing at 58°C for 30s (*mcr*-1) and53°C for30s for (*mcr*-8), elongation at 72°C for 30s, with final elongation step at 72°C for 5 min.DNA from colistin-susceptible *E.coli*ATCC 25922 was used as the negative control.

RESULTS

Carbapenemase production was confirmed in 361 (94.5%)clinical *K.pneumoniae* isolates. Initial screening detected 21(5.81%) isolates as colistin-resistant; however, BMD confirmed resistance in 15 (71.4 %) of these. Most of these colistin-resistant isolates were recovered from male patients11 (73.3%),compared to female patients4 (26.7%) (p0.106), and were more prevalent in the older age group with a mean age of 39 ±1 years, compared to younger age group. (χ^2 = 1.79; p 0.77) [Table 1]

Table 1: Age and Gender-wise distribution of colistin-resistant *K. pneumoniae* isolates (n = 15)

Age group	Male (n=11)	Female (n=4)
1-16 years	1 (6.66%)	0
17-25 years	3 (20%)	1 (6.66%)
26-40 years	2 (13.35)	0
41-60 years	4 (26.67)	2 (13.34%)
>60 years	1 (6.66%)	1 (6.66%)
	11(73.33%).	4(26.66%).

Regarding sample-wise distribution, COLRKP isolates were predominantly obtained from respiratory specimens8 (53.33%),followed by blood 6 (40%) and tissue 1 (6.67%).Among the respiratory samples33.33%) were endotracheal aspirates and 20%were sputum samples. [Figure1]Regarding departmental distribution, majority of COLRKP isolates were obtained from admitted patients(IPD), 13/15 (86.7%), compared to 2/15 (13.3%) from the outpatient department (OPD).(χ^2 = 8.07; p 0.0045)[Table 2]

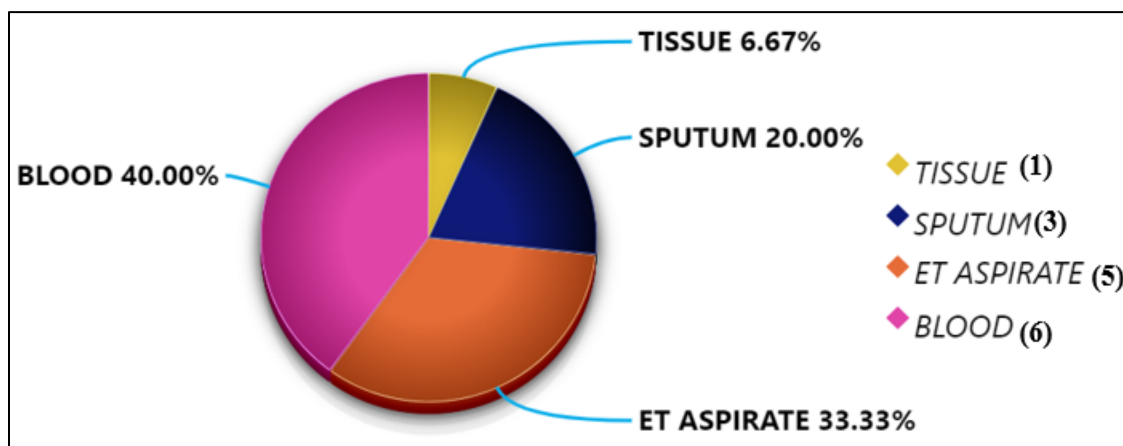

Figure 1: Sample-wise distribution of colistin-resistant *K.pneumoniae* isolates (n = 15)

Table 2: Department-wise distribution of colistin-resistant *K.pneumoniae* isolates(n =15)

Department wise	No. of patients
IPD	13 (86.7%)
OPD	2 (13.3%)
Total	15 (100%)

Among the 15 COLRKP isolates analyzedfor gene detection, 7(46.66%) tested positive for the *mcr*-1 gene [Table 3; Figure 2A &2B]. The *mcr*-8 gene was detected in only1isolate (6.66%)(χ^2 = 4.5; p 0.034). [Table 3; Figure 3], which was negative for *mcr*-1 gene. Neither *mcr*-1 nor*mcr*-8 genes weredetected in 6 isolates whichwere initially identified as colistin resistantby VITEK 2C but found to be susceptible byBMD, nor in the entire 1% of colistin-sensitive isolates tested.

Table 3: Distribution of *mcr*-1 and *mcr*-8 gene amongcolistin-resistant *K.pneumoniae* isolates (n = 15)

Antimicrobial resistance gene for colistin	COLRKP isolates
***mcr*-1gene**	7/15 (46.66%)
***mcr*-8 gene**	1/15 (6.66%)

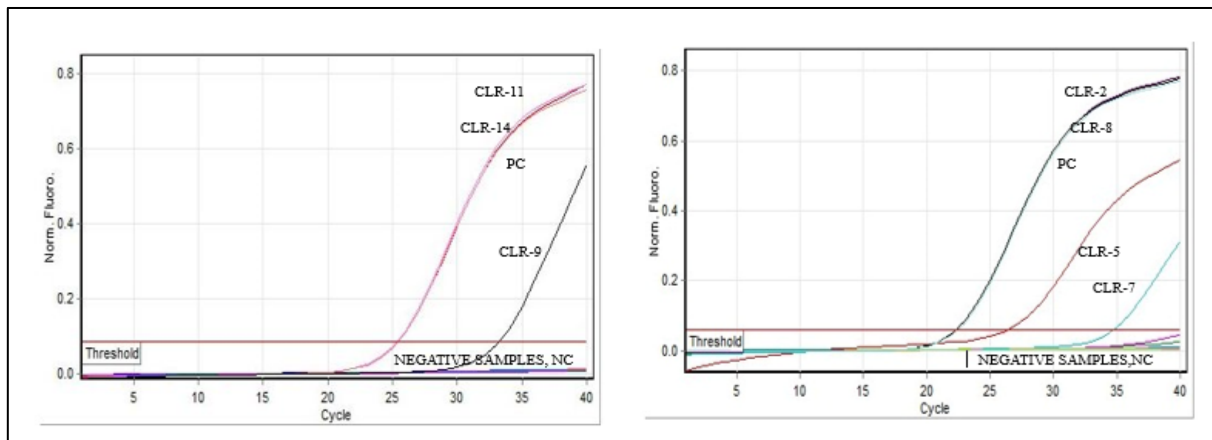

Figure 2 (A) & Figure 2 (B): Amplification curves of the *mcr*-1 gene in *K.pneumoniae.* PC: Positive Control, NC: Negative Control, CLR-2,5,7,8,9,11,14: represents colistin-resistant isolates; Ct value: cycle threshold

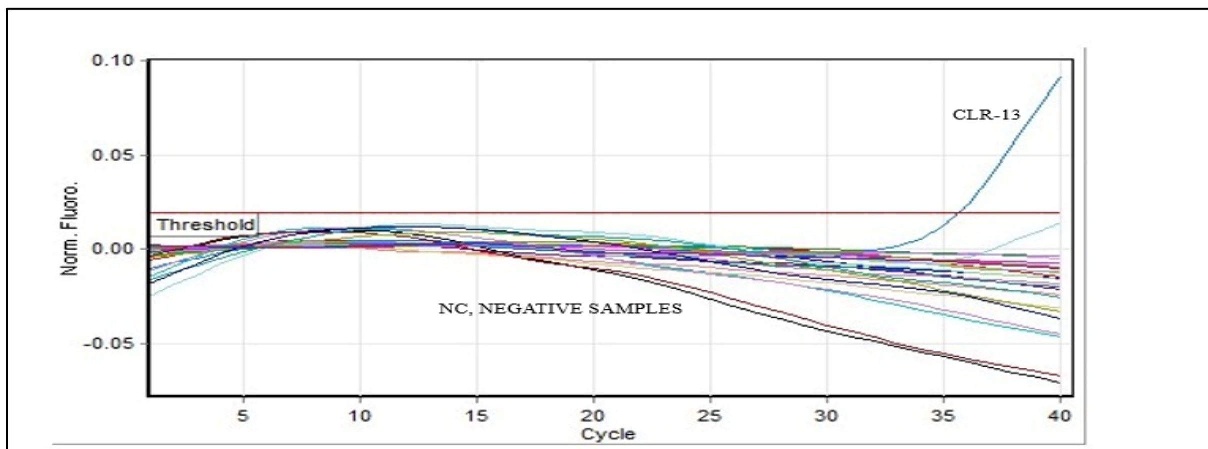

Figure 3:Amplification of the *mcr*-8gene after 40 cycles using the Rotor Gene. A C_t value ≤40 was considered positive for *mcr-8*gene (CLR-13).

DISCUSSION

Antimicrobial resistance (AMR) is a growing global threat, particularly among *Klebsiella* species.Once effectively treated with carbapenems, *K. pneumoniae* has increasingly acquired enzymes capable of degrading these antibiotics, reducing their efficacy. As a result, colistin, a last-resort antibiotic, is increasingly relied upon for treatment[5].In the present study, colistin resistance was confirmed by BMD in 71.43% *K.pneumoniae*isolates, which is higherthan the 56% resistance reported by Torres *et al.*[14]using the same method.

The mean age of patients with COLRKP in our study was 39 ±1 years, with male predominance of (73.3%)[Table1] In comparison, astudy involving 30 hospitalized patients reported a higher mean age of 59.1 ±16.4 years, with 63.3% of the patients being male[15].

In our study,COLRKP isolates were predominantly obtained from respiratory specimens (53.33%), followed by blood (40%) & tissue (6.7%). Similartrends of high colistin-resistant *Klebsiella* speciesisolation from respiratory samples have been reported by other workers[16,17].

In contrast to our finding, Singh *et al.*[18] reported a higher proportion of colistin resistance among OPD isolates (60.7%) compared to IPD isolates (39%), suggesting a shift towards community-associated resistance. In the present study, however, the majority of COLRKP isolates were derived from IPD patients (86.7%), with a smaller proportion from OPD patients (13.3%).

Despite the lower contribution from OPD,its clinical significance remains considerable, as it indicates the potential dissemination of colistin resistance beyond hospital settings into the community. OPD patients, being community-dwelling, may serve as a reservoir for resistant organisms. Moreover, plasmid-mediated *mcr* genes facilitate horizontal gene transfer, Promoting rapid spread of resistance across bacterial populations.

The presence of resistant isolates in OPD patients may also be reflect repeated healthcare exposure, as such individuals often have prior or frequent hospital visits, increasing their risk of acquiring resistant strains. These findingshighlight the emerging concern of community-associated spread of colistin resistance and emphasize the need for continuous surveillance not only in hospital settings but also at the community level.

The emergence of colistin resistanceunderscores the need for judicious use of this antibiotic particularly in treating infectious caused by carbapenem-resistant Enterobacteriaceae.Globally, most studies report the *mcr*-1 gene predominantly in *Escherichia coli,* with *K. pneumoniae* accounting for less than 5% of *mcr*-positive isolates[19,20]In contrast, studies from India indicate a higher prevalence of colistin resistance in *K. pneumoniae* as compared to other bacterial species, suggesting a unique regional pattern[21].Although *mcr*-mediated colistin resistance has been widely reported worldwide, documentation of such cases from India remains relatively limited[22].

In our study, the *mcr*-1 gene was detected in 46.66% of COLRKP isolates [Table 3], which is substantially higher than the 19.1% reportedby Singh *et al.*[22]in 2018. Interestingly, the same group later reported an evenhigherprevalence of 86.36% in 2021[17].These findings underscores the alarming and rising trend of colistinresistance in*K. pneumoniae* over the years, highlighting a significant public health concern given that colistin remains a last resort of antibiotics.

Within the *mcr* gene family, *mcr-1* and *mcr-3* are the most frequently identified genes among Enterobacteriaceae worldwide, whereas as *mcr-8* has been reported relatively rarely. Although the *mcr*genes are present in various members of Enterobacteriaceae and other Gram-negative bacilli, *E. coli* and*K.pneumoniae*remain the predominant hosts[20,21].

In our study, the *mcr*-8 gene was detected in 6.66% of isolates from human samples, raising concernthat this resistance determinant may already be spreading within bacterial populations.These findings align with reports from other regions, Wang *et al*.[24] observed a 7.54% prevalence of *mcr*-8 among COLRKP in China, while Eltai*et al*.[25] reported 11.11% in Qatar.In contrast, Farzana*et al*.[26]documenteda much lower prevalenceof 0.3% of*mcr*-8 genein Bangladesh.Notably, none of the *mcr*positive isolates were identified amongOPD samples, with all detections confined to hospitalized patients.This absencein OPD isolates maysuggest limited community dissemination at present; however, ongoing surveillance is essential to detect potential spread into the community.

Limited data on colistin non-susceptibility in *K.pneumoniae*and the prevalence of the *mcr*-1 gene in India makes it challenging to compare our finding with other Indian studies.Furthermore, to our knowledge, the presence of the *mcr*-8 gene in COLRKP causing human infections has not previously been investigated in India, limiting the scope for comparison.

This study represents the first genotypic analysis reporting the occurrence of both *mcr*-1 and *mcr*-8 genes in COLRKP from this geographical region. The rising incidence of colistin resistance poses a significant therapeutic concern and highlights the need for clinicians to use colistin judiciously. However, this study has certain limitations; due to resource constraints, other *mcr*genespotentially contributing to colistin resistance could not be investigated in these clinical isolates.

CONCLUSION

To conclude, the increasing prevalence of COLRKP in clinical settings represents a growing concern not only for hospital care but also for community health.The detection of plasmid-mediated resistance mechanisms, particularly *mcr*-1 and *mcr-8*,highlight the potential for rapid dissemination beyond healthcare facilities through community reservoirs and environmental pathways. The identification of *mcr*-8 in *K. pneumoniae*from India further emphasizes the emerging threat of transferable colistin resistance. From the public health perspective, these findings underscore the urgent need for integrated surveillance across hospital and community settings,strengthenedantimicrobial stewardship, and adoption of a One Health approach to curb the spread of resistance. Early and accurate detection of colistin resistance is essential to guide appropriate therapy and prevent treatment failure, while limiting the risk of transmission within the broader community.

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Data Availability: The data presented in this study is available upon request.

Ethics Statement: This study has been approved by the University Ethics Committee, via (Ref. No. SMC/UECM/2024/774-A) dated 14.03.2024.

Informed Consent: The samples were included after the informed consent was obtained from the patients.

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