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Original Research Article

EVALUATION OF CONVENTIONAL METHODS VERSUS MOLECULAR METHODS FOR THE DETECTION OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE: A RETROSPECTIVE STUDY FROM A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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ABSTRACT

Background: The emergence of carbapenem-resistant *Enterobacteriaceae* (CRE), particularly carbapenem-resistant *Klebsiella pneumoniae* (CRKP), poses a formidable challenge to antimicrobial therapeutics worldwide. Timely and accurate detection is critical for appropriate clinical management and infection control. The present study was designed to evaluate and compare conventional phenotypic methods — MacConkey agar with ertapenem disc diffusion and CHROMagar KPC — against the molecular gold standard, Real-Time polymerase chain reaction (RT-PCR) targeting the blaKPC gene, in detecting carbapenem resistance among ESBL-producing *Klebsiella pneumoniae* isolates. **Materials and Methods:** A total of 50 non-duplicate ESBL-producing *Klebsiella pneumoniae* isolates obtained from clinical samples (urine, pus, blood, sputum) over one year (September 2012 – August 2013) were included. Carbapenem resistance was assessed by MacConkey agar with ertapenem (10 µg) disc diffusion and CHROMagar KPC. All resistant isolates were subsequently tested for blaKPC gene by TaqMan probe-based Real-Time PCR. Antibiotic susceptibility, demographic parameters, and risk factors were analysed using SPSS version 20. **Result:** Of the 50 ESBL *Klebsiella pneumoniae* isolates, 11 (22%) were carbapenem-resistant by both MacConkey agar with ertapenem disc and CHROMagar KPC. Of these 11 CRKP isolates, only 2 (18.18%) harboured the blaKPC gene by RT-PCR. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the conventional methods against RT-PCR were 100%, 81.25%, 18.18%, and 100% respectively. Urinary tract infections predominated (63.6%), prior carbapenem exposure was identified as a significant risk factor ($P < 0.05$), and CRKP isolates demonstrated extensive multidrug resistance. **Conclusion:** Conventional phenotypic methods demonstrated high sensitivity and NPV, making them suitable for initial screening of CRKP; however, low PPV underscores that mechanisms other than blaKPC contribute to ertapenem resistance. Molecular methods remain essential for definitive confirmation of blaKPC-mediated resistance, with the two approaches best used in a complementary diagnostic algorithm.

INTRODUCTION

The modern era of antimicrobial chemotherapy was steered in by the discovery of sulphonamides in 1935 and the therapeutic application of penicillin in 1940.[1] The subsequent emergence of β-lactamases led to the development of β-lactamase inhibitors and, ultimately, carbapenems — a group that includes imipenem, meropenem, ertapenem, and doripenem — which rapidly became the last-resort agents for treating severe gram-negative infections.[2] Carbapenems exert their bactericidal effect by binding to penicillin-binding proteins (PBP1 and PBP2), halting cell wall synthesis and triggering autolysis.[3] More than 90% of *Enterobacteriaceae*, including those resistant to third-generation cephalosporins, remain susceptible to carbapenems.[4]

Extended-spectrum β-lactamases (ESBLs) — principally TEM, SHV, and CTX-M types — prevalent in *Klebsiella pneumoniae* and *Escherichia coli*, hydrolyse third- and fourth-generation

cephalosporins but were historically susceptible to carbapenems.[5] However, the emergence of *Klebsiella pneumoniae* carbapenemases (KPC), first described in North Carolina in 2001, represented a qualitative leap in resistance, conferring hydrolytic activity against all β-lactams including carbapenems.[6,7] KPC enzymes belong to Ambler class A serine carbapenemases (Bush group 2f); eleven gene variants (blaKPC-1/2 through blaKPC-12) are recognised, with blaKPC-2 being the most clinically prevalent.[7-13] The plasmid-mediated nature of blaKPC facilitates horizontal transfer among hospital strains, leading to nosocomial outbreaks across the United States and other countries.[8]

In the Indian subcontinent, carbapenem resistance among *Klebsiella pneumoniae* has been increasingly reported, although blaKPC prevalence appears lower compared to Metallo-β-lactamase (MBL) types such as blaVIM and blaNDM-1.[12] Accurate and timely detection of CRKP is pivotal both for directing appropriate antimicrobial therapy and for initiating contact precautions to prevent nosocomial spread.[15,16] Conventional phenotypic assays — disc diffusion on MacConkey agar with ertapenem, CHROMagar KPC, the Modified Hodge Test, and Double Disc Synergy with boronic acid — offer practical and cost-effective approaches for front-line laboratories.[15,16] Molecular assays targeting blaKPC by Real-Time PCR provide definitive gene-level confirmation but require specialised infrastructure and trained personnel.[14,16]

Faced with this diagnostic dilemma, the present retrospective study was undertaken at Tirunelveli Medical College, a tertiary care referral hospital in South India, to evaluate the performance of MacConkey agar with ertapenem disc diffusion and CHROMagar KPC against RT-PCR for blaKPC among ESBL *Klebsiella pneumoniae* clinical isolates, while simultaneously characterising the clinical and epidemiological profile of CRKP infections. Based on this objectives of our study is to systematically screen clinical ESBL *Klebsiella pneumoniae* isolates for carbapenem resistance using MacConkey agar with ertapenem (10 µg) disc diffusion, also to evaluate CHROMagar KPC as a phenotypic chromogenic medium for CRKP detection and to determine the prevalence of the blaKPC gene among CRKP isolates by Real-Time PCR and assess the diagnostic accuracy of conventional methods against this molecular reference.

MATERIALS AND METHODS

The study was conducted at the Department of Microbiology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu. Ethical clearance was obtained from the Institutional Ethics Committee prior to commencement of the study. Informed written consent was secured from all patients or their guardians. All laboratory procedures were performed in a Biosafety Level-2 cabinet following standard biosafety protocols.

A *total of 50 non-duplicate ESBL-producing Klebsiella pneumoniae* isolates recovered from clinical specimens — urine (n=30, 60%), pus (n=16, 32%), blood (n=3, 6%), and sputum (n=1, 2%) — were included. ESBL production was initially suspected when inhibition zones fell below the CLSI breakpoints for ceftazidime (≤22 mm), cefotaxime (≤27 mm), or ceftriaxone (≤25 mm), and confirmed by the Double Disc Synergy Test (DDST) using cefotaxime and cefoperazone-sulbactam discs placed 30 mm apart centre to centre; an enhancement of ≥5 mm in the zone facing the inhibitor disc was taken as confirmatory. Isolates were stored on nutrient agar slopes at 2–8°C and sub-cultured fortnightly. ATCC BAA-1705 (CRKP) and ATCC 700603 (ESBL Klebsiella pneumoniae) reference strains served as quality control organisms for all procedures.

Antimicrobial susceptibility was performed by the Kirby-Bauer disc diffusion method on MacConkey agar. The following antibiotic discs were used: gentamicin (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), nitrofurantoin (300 U; urine isolates only), piperacillin-tazobactam (100/10 µg), cefoperazone-sulbactam (75/30 µg), and ertapenem (10 µg). Inhibition zone diameters were read after 18–24 h incubation at 35°C and interpreted per CLSI 2012 guidelines. For ertapenem, zones ≥19 mm indicated susceptibility and ≤15 mm indicated resistance.

All 50 isolates were inoculated onto CHROMagar KPC supplemented with KPC selective supplement (FD279, HiMedia Laboratories, Mumbai, India) and incubated aerobically at 35°C for 18–48 h. *Klebsiella pneumoniae* producing carbapenemases grew as distinctive metallic blue colonies; carbapenem-sensitive isolates were inhibited. Plates negative at 24 h were incubated for a further 24 h before final reading.

All 11 CRKP isolates identified by phenotypic methods were subjected to TaqMan probe-based RT-PCR using a commercial kit (Helini Biomolecules, Chennai, India). DNA was extracted from bacterial pellets using a silica-based spin column method following Proteinase K lysis and chaotropic salt denaturation. Each reaction (25 µl total volume) comprised 10 µl probe PCR master mix, 5 µl blaKPC primer-probe mix (FAM-labelled), 5 µl internal control primer-probe mix (HEX-labelled), and 5 µl purified sample DNA. The thermocycling profile consisted of an initial Taq activation at 95°C for 5 min, followed by 40 cycles of denaturation at 95°C (20 sec), annealing and data collection at 55°C (20 sec), and extension at 72°C (20 sec). A Ct value below 37 were interpreted as positive; samples yielding Ct values of 37–40 were repeated. The internal control ruled out PCR inhibition and ensured extraction efficiency. Positive and negative template controls were included in every run.

Demographic data, ward distribution, infection categories, catheterisation status, duration of

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hospitalisation, and prior antibiotic exposures were recorded for all 50 patients. The sensitivity, specificity, PPV and NPV of conventional methods were calculated using RT-PCR as the reference standard. Categorical variables were compared using chi-square or Fisher's exact test; continuous variables (age) were compared using Student's unpaired t-test. A p-value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 20.

RESULTS

Sample Distribution by Age and Gender: The study encompassed 50 ESBL *Klebsiella pneumoniae* isolates from 50 patients. Males contributed 26 isolates (52%) and females 24 (48%). The age distribution is presented in [Table 1]. The largest group was in the ≥61 years age band among males (8 isolates, 30.7%), while in females the 16–30 years group predominated (7 isolates, 29.1%). The mean age of males was 45.42 years compared to 30.37 years for females, a difference that was statistically significant ($p < 0.05$).

Comparison of Phenotypic and Molecular Methods: Of the 50 ESBL *Klebsiella pneumoniae* isolates, 11 (22%) were identified as carbapenem-resistant by both MacConkey agar with ertapenem disc diffusion and CHROMagar KPC, with perfect concordance between the two phenotypic methods. The remaining 39 (78%) isolates were sensitive by both methods. Of the 11 CRKP isolates, Real-Time PCR identified blaKPC in only 2 (18.18%); blaKPC was not detected in any of the 39 carbapenem-sensitive isolates. Both blaKPC-positive isolates were from urinary specimens. The comparative performance of all three methods is summarized in [Table 2].

Table 1: Sample Distribution by Age and Gender (n=50)

Age (years)	Male No	Male %	Female No	Female %	Total No	Total %
≤15	4	15.3	6	25.0	10	20.0
16–30	1	3.8	7	29.1	8	16.0
31–45	7	26.9	5	20.8	12	24.0
46–60	6	23.0	5	20.8	11	22.0
≥61	8	30.7	1	4.1	9	18.0
Total	26	52	24	48	50	100

CRKP = Carbapenem-Resistant Klebsiella pneumoniae; CSKP = Carbapenem-Sensitive Klebsiella pneumoniae

Table 2: Comparison of Phenotypic Methods and Real-Time PCR (n=50)

Method	CRKP (n)	CRKP %	CSKP (n)	CSKP %
MacConkey agar + Ertapenem disc diffusion	11	22	39	78
CHROMagar KPC	11	22	39	78
Real-Time PCR (blaKPC)	2	18.18	0	0

CRKP = Carbapenem-Resistant; CSKP = Carbapenem-Sensitive; RT-PCR = Real-Time PCR

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MacConkey agar with ertapenem disc diffusion (and CHROMagar KPC, which showed identical results) against RT-PCR for blaKPC were calculated as 100%, 81.25%, 18.18%, and 100% respectively, as shown in [Table 5]. The high NPV indicates that a negative phenotypic result reliably excludes blaKPC-mediated resistance, while the low PPV reflects the contribution of non-KPC resistance mechanisms (such as co-existing ESBL/AmpC enzymes with porin loss) to ertapenem resistance.

Infection Type and Ward Distribution

Urinary tract infections (UTIs) accounted for the majority of CRKP isolates — 7 of 11 (63.6%) — followed by surgical site infections in 2 (18.2%) and blood stream infections and burns in 1 each (9.1%). Among carbapenem-sensitive isolates, UTIs were also the most frequent (58.9%), followed by surgical site infections (25.6%). The infection-type distribution across CRKP and CSKP groups is shown in [Table 3].

Table 3: Distribution of CRKP and CSKP Isolates by Infection Type

Infection Type	CRKP (n)	CRKP %	CSKP (n)	CSKP %
Urinary tract infections	7	63.6	23	58.9
Surgical site infections	2	18.2	10	25.6
Blood stream infections	1	9.1	2	5.1
Burns	1	9.1	1	2.5
Ear discharge	0	0	2	5.1
Respiratory tract infections	0	0	1	2.5
Total	11	100	39	100

CRKP = Carbapenem-Resistant Klebsiella pneumoniae; CSKP = Carbapenem-Sensitive Klebsiella pneumoniae

With regard to ward distribution, the Surgery department contributed the largest proportion of CRKP isolates (3/11, 27.3%), followed by Paediatric Surgery (2/11, 18.2%) and one each from Urology, Obstetrics & Gynaecology, Medicine, Paediatric Medicine, the Sick Neonatal Ward, and Burns (9% each). All 11 (100%) CRKP isolates were from inpatients, compared to 7 (17.9%) of the 39 CSKP isolates from outpatients, though this difference did

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not reach statistical significance ($p > 0.05$). The ward-wise data are presented in [Table 4].

Table 4: Distribution of CRKP and CSKP Isolates by Hospital Ward

Ward / Department	CRKP n	CRKP %	CSKP n	CSKP %	Total
Surgery	3	27.3	12	30.7	15
Paediatric Surgery	2	18.2	0	0	2
Urology	1	9.0	5	12.8	6
Obstetrics & Gynaecology	1	9.0	5	12.8	6
Medicine	1	9.0	3	7.6	4
Paediatric Medicine	1	9.0	2	5.1	3
Sick Neonatal Ward	1	9.0	2	5.1	3
Burns	1	9.0	1	2.5	2
Others	0	0	9	23.4	9
Total	11	100	39	100	50

O&G = Obstetrics & Gynaecology; IMCU = Intermediate Medical Care Unit

Performance Characteristics of Conventional Methods: [Table 5] summarises the diagnostic performance of MacConkey agar with ertapenem disc diffusion and CHROMagar KPC relative to Real-Time PCR as the reference standard. The test characteristics were identical for both phenotypic methods given their perfect concordance (n=11 CRKP, n=39 CSKP). True positives (blaKPC-positive CRKP): 2; false positives (ertapenem-resistant but blaKPC-negative): 9; true negatives: 39; false negatives: 0.

Table 5: Diagnostic Performance of Conventional Methods vs. RT-PCR for blaKPC

Method	Sensitivity %	Specificity %	PPV %	NPV %
MacConkey agar + Ertapenem disc (vs blaKPC PCR)	100	81.25	18.18	100
CHROMagar KPC (vs blaKPC PCR)	100	81.25	18.18	100
Real-Time PCR (blaKPC) — reference standard	—	—	—	—

PPV = Positive Predictive Value; NPV = Negative Predictive Value; — = Not applicable (reference standard)

Risk Factors for CRKP: Prior exposure to carbapenems was identified as the only statistically significant risk factor for CRKP acquisition in the study population ($p < 0.05$): 18.18% of CRKP patients versus 5.1% of CSKP patients had received prior carbapenem therapy. No statistically significant associations were found between CRKP and prior exposure to third-generation cephalosporins (63.63% vs. 61.5%; $p > 0.05$), β-lactam/β-lactamase inhibitor combinations (9.09% vs. 12.8%; $p > 0.05$), aminoglycosides (9.09% vs. 25.64%; $p > 0.05$), fluoroquinolones (0% vs. 15.38%; $p > 0.05$), or ampicillin (9.09% vs. 30.76%; $p > 0.05$). Catheterisation was a significant risk factor for CRKP among urine isolates: 71.42% of CRKP vs. 34.78% of CSKP urine samples were from catheterised patients ($p < 0.05$). Hospital duration of less than two weeks was observed for 90.9% of CRKP patients, and no significant association was found with duration of stay ($p > 0.05$).

Antibiotic Susceptibility Profile of CRKP: CRKP isolates demonstrated extensive multidrug resistance. All 11 CRKP isolates (100%) were resistant to nitrofurantoin and piperacillin-tazobactam. Resistance rates for ciprofloxacin, gentamicin, trimethoprim-sulfamethoxazole, and cefoperazone-sulbactam were each 91% among CRKP. Amikacin showed relatively lower resistance at 63.63% in CRKP versus 66.66% in CSKP isolates, a difference that was not statistically significant ($p > 0.05$). Trimethoprim-sulfamethoxazole resistance in CSKP was 100%, while among CRKP one isolate (9.1%) retained susceptibility. All CRKP urine isolates were resistant to nitrofurantoin (100%), compared to 69.56% resistance in CSKP urine isolates.

DISCUSSION

This study evaluated the utility of two widely available phenotypic methods — MacConkey agar with ertapenem disc diffusion and CHROMagar KPC — against TaqMan RT-PCR targeting blaKPC among ESBL *Klebsiella pneumoniae* isolates in a tertiary care hospital in South India. A prevalence of 22% CRKP among ESBL Klebsiella pneumoniae is notable and consistent with the growing burden of CRE reported across Indian healthcare settings.[17,18] The overall prevalence of blaKPC among CRKP isolates was low at 18.18% (2/11), corroborating reports from South India by Nagaraj et al. in 2012, who failed to detect blaKPC in carbapenem-resistant *Klebsiella pneumoniae* and *Escherichia coli* isolates, suggesting that MBL-type enzymes or non-enzymatic mechanisms such as porin loss combined with ESBL/AmpC hyperproduction dominate the South Indian epidemiological landscape.[19,20]

The phenotypic methods demonstrated identical sensitivity (100%) and specificity (81.25%), confirming that neither MacConkey agar with ertapenem disc nor CHROMagar KPC misses any blaKPC-producing isolate. This 100% sensitivity is in keeping with data from Marschall et al., who reported 100% sensitivity for ertapenem-based screening, although they observed higher specificity (98.3%) and a still-low PPV (43%).[12] The low PPV of 18.18% in the present study reflects the

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predominance of non-KPC resistance mechanisms: 9 of 11 CRKP isolates showed ertapenem resistance attributable to porin-deficient ESBL/AmpC producers rather than carbapenemase activity — a phenomenon well described in the literature.[16] CHROMagar KPC returned identical results to disc diffusion and offered the advantage of a 24-hour turnaround time. Samra et al. similarly documented excellent performance of CHROMagar KPC for CRKP detection, with the metallic blue colonies facilitating straightforward visual identification.[16] However, CHROMagar KPC cannot discriminate between blaKPC and other carbapenemase genes such as blaVIM, which has been reported from North India.[16]

The clinical and epidemiological profile of CRKP in the present study mirrors global patterns. UTIs constituted 63.6% of CRKP infections, consistent with epidemiological data showing the urinary tract as the primary reservoir for nosocomial CRE acquisition and the role of urinary catheters as key risk factors.[19,20] Indeed, catheterisation was identified as a statistically significant risk factor ($p < 0.05$) in the current study, with 71.42% of CRKP urine isolates from catheterised patients versus 34.78% of CSKP. All CRKP isolates were from inpatients, underscoring the predominantly nosocomial nature of CRKP transmission. The predominance of isolates from surgery wards (27.3%) and paediatric surgery (18.2%) is noteworthy and consistent with the higher healthcare burden and procedural invasiveness in these units.

Prior carbapenem exposure was the sole independent risk factor reaching statistical significance ($p < 0.05$), corroborating reports by Hussain K et al. and Akova et al. in 2012, who identified prior carbapenem use as a major predictor of CRKP infection.[21,22] Hyle EP et al. also documented that prior carbapenem exposure is associated with ertapenem-resistant *Enterobacteriaceae* infection.[23] The absence of significant association with cephalosporin, aminoglycoside, or β-lactam/inhibitor exposure likely reflects the study's modest sample size of 50 isolates rather than a genuine epidemiological difference.

The multidrug resistance profile of CRKP isolates in this study is alarming: 100% resistance to nitrofurantoin and piperacillin-tazobactam, and >90% resistance to ciprofloxacin, gentamicin, and cotrimoxazole, leaving amikacin as a potentially active agent in approximately one-third of cases. This is consistent with Ding Y et al, who demonstrated that KPC-positive *Klebsiella pneumoniae* exhibited 90% resistance to ceftazidime, ceftriaxone, aztreonam, piperacillin-tazobactam, amikacin, ciprofloxacin, and cotrimoxazole.[24] The plasmid carrying blaKPC frequently co-harbours genes conferring fluoroquinolone and aminoglycoside resistance, further restricting therapeutic options. Treatment with carbapenem-containing regimens was successful when the MIC was <4 mg/L, consistent with findings by Akova et al,[22] supporting the view that carbapenems remain a viable option for CRKP infections when MIC thresholds are met, particularly in combination with polymyxins or tigecycline.

A key limitation of this study is the relatively small sample size (n=50), which restricts the power to detect associations of modest effect size, particularly for risk factor analysis. The retrospective single-centre design and restriction to blaKPC PCR (without testing for blaVIM, blaNDM, blaOXA-48) means that the true carbapenemase epidemiology cannot be fully characterised. Future studies should employ multiplex PCR panels to simultaneously screen for all clinically relevant carbapenemase genes, and larger multi-centre prospective studies are warranted to validate these findings across India.

CONCLUSION

The present study demonstrates that MacConkey agar with ertapenem disc diffusion and CHROMagar KPC offer excellent sensitivity (100%) and NPV (100%) for initial screening of CRKP and can reliably rule out blaKPC-mediated resistance when results are negative. CHROMagar KPC provides the additional advantage of a shorter turnaround time (24 hours). However, the low positive predictive value (18.18%) confirms that phenotypic carbapenem resistance in ESBL *Klebsiella pneumoniae* is frequently mediated by porin-deficient non-KPC mechanisms, and all CRKP isolates cannot be assumed to harbour blaKPC. Molecular PCR-based confirmation is essential before attributing resistance to carbapenemases and guiding infection control decisions. A two-tiered strategy — initial phenotypic screening followed by selective RT-PCR confirmation of resistant isolates — represents the optimal diagnostic algorithm for resource-constrained tertiary care settings in India. Concurrent efforts to restrict carbapenem use enforce catheter care bundles, and implement contact precautions for confirmed CRKP patients are imperative to contain the nosocomial spread of this formidable pathogen.

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