

Co-occurrence of *bla*_{OXA-23} and *bla*_{NDM-1} Genes in Carbapenem-resistant *Acinetobacter baumannii* Isolated from Bloodstream Infections: A Cross-sectional Study

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ABSTRACT

Introduction: *Acinetobacter baumannii* is a clinically significant Multidrug-Resistant (MDR) pathogen and a organism recognised by the World Health Organisation (WHO) due to its remarkable capacity to survive in hospital environments and acquire resistance determinants, particularly against carbapenems.

Aim: To investigate the prevalence of *bla*_{OXA-23} and *bla*_{NDM-1} resistance determinants in carbapenem-resistant *A. baumannii* (CRAB) strains associated with Bloodstream Infections (BSIs) among Intensive Care Unit (ICU) patients.

Materials and Methods: This hospital-based cross-sectional study was conducted in the Department of Microbiology, Saveetha Medical College and Hospitals, Chennai Tamil Nadu, India, from March 2023 to January 2025. A total of 36 non duplicate *A. baumannii* isolates were recovered from ICU patients diagnosed with BSIs. Bacterial identification and antimicrobial susceptibility profiling were carried out using the VITEK[®] 2 automated system. Molecular detection of the *bla*_{OXA-23} and *bla*_{NDM-1} resistance genes was performed by Polymerase Chain Reaction (PCR), followed by confirmation through Sanger sequencing. Sequence homology was evaluated using BLASTn, and multiple sequence alignment was employed to examine

genetic variability among the isolates. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS), applying Fisher's exact test, with a p-value <0.05 considered statistically significant.

Results: All isolates exhibited high resistance to β-lactams, fluoroquinolones, carbapenems, and aminoglycosides, while complete susceptibility was observed to tigecycline and colistin. The *bla*_{OXA-23} gene was detected in 34 (94.4%) of isolates, and *bla*_{NDM-1} in 19 (53%), with both genes co-existing in 19 (53%) of strains. Sequence analysis of representative amplicons showed 100% identity with reference *bla*_{OXA-23} and *bla*_{NDM-1} genes in BLASTn analysis. A significant association between *bla*_{OXA-23} and *bla*_{NDM-1} was observed (p-value=0.018).

Conclusion: The study confirmed the presence of *bla*_{OXA-23} and *bla*_{NDM-1} genes among clinical isolates of *A. baumannii*, demonstrating their strong association with carbapenem resistance. Sequencing revealed minor allelic variations but high conservation, indicating genetic stability for these resistance determinants. The co-existence of both genes suggests synergistic mechanisms contributing to MDR, underscoring the importance of continuous molecular surveillance and effective antimicrobial stewardship strategies.

Keywords: Bacteraemia, Drug resistance, Intensive care units, Oxacillinase, Sequence analysis

INTRODUCTION

A. baumannii is an opportunistic Gram-negative coccobacillus that has become a significant public health issue, especially in ICUs. It is frequently associated with critically-ill and immunocompromised patients, causing severe infections that are often difficult to treat and linked with poor clinical outcomes and high mortality rates. The organism's exceptional ability to persist in diverse hospital environments and acquire resistance to multiple classes of antimicrobial agents contributes to its success as a nosocomial pathogen [1,2]. Clinically, *A. baumannii* is implicated in a wide range of healthcare-associated infections, including Ventilator-Associated Pneumonia (VAP), BSIs, Urinary Tract Infections (UTIs), and Surgical Site Infections (SSIs) [3]. Among these, BSIs are particularly concerning due to their association with high fatality rates, often exceeding 35%. Recent studies have indicated mortality rates between 42% and nearly 70% in patients with *A. baumannii* bacteraemia, highlighting its clinical importance and the pressing necessity for continuous molecular surveillance [4,5].

Antimicrobial resistance in *A. baumannii* predominantly develops through the horizontal transfer of resistance genes mediated by

Mobile Genetic Elements (MGEs), including plasmids, transposons, and integrons [6]. These genetic components promote the swift dissemination of multidrug and carbapenem resistance, allowing *A. baumannii* to adapt and endure in hospital settings. Several observational studies have examined the clinical and epidemiological factors contributing to CRAB infections, emphasising the growing threat these strains pose to healthcare systems worldwide [7,8]. Reflecting its critical clinical significance, the WHO has classified CRAB as a top-priority pathogen for the development of new antimicrobial therapies [9].

CRAB infections impose a substantial burden on healthcare systems, leading to prolonged hospital stays, higher mortality rates, increased ICU admissions, and frequent hospital readmissions, all of which contribute to escalating healthcare costs and resource strain [10]. The production of carbapenem-hydrolysing class D-lactamases (CHDLs), commonly known as oxacillinases (OXAs), is largely responsible for the emergence of CRAB. To date, five major CHDL subgroups have been identified in *A. baumannii*: the intrinsic chromosomal OXA-51-like group and the acquired OXA-23-like, OXA-24-like, OXA-58-like, and OXA-143-like enzymes. Among these, OXA-23-like enzymes are the most prevalent and widely

disseminated worldwide, representing the dominant mechanism underlying carbapenem resistance in clinical isolates [11].

Carbapenem resistance in *Acinetobacter* species may also arise through the production of metallo- β -lactamases (MBLs), although this mechanism is comparatively less frequent. The major MBLs implicated include imipenemase (IMP), Verona integron-encoded metallo- β -lactamase (VIM), and New Delhi metallo- β -lactamase (NDM). Among these, NDM-1 is most commonly detected in *Klebsiella pneumoniae* and *Escherichia coli*, while *Acinetobacter* species often act as intermediate reservoirs. Nevertheless, NDM-1-producing *Acinetobacter* strains have been increasingly reported across the globe, facilitated by the high horizontal transferability of plasmids harbouring the *bla*_{NDM-1} gene and other associated resistance determinants, which severely limit available therapeutic options [12]. Although uncommon, the co-production of *bla*_{OXA-23} and *bla*_{NDM-1} enzymes has been documented in both African [13] and Asian [14] regions, raising further concern regarding the global dissemination of highly resistant *A. baumannii* lineages. The co-existence of two distinct carbapenemase and MBL-encoding genes within a single *A. baumannii* isolate represents an alarming mechanism of antimicrobial resistance, as it often confers enhanced resistance to β -lactam antibiotics and is associated with increased mortality rates among the infected.

The present study aimed to investigate CRAB isolates recovered from BSIs in ICU patients and to characterise their resistance profile at the phenotypic and molecular levels and secondary objectives were to determine the prevalence of *bla*_{OXA-23} and *bla*_{NDM-1} genes, to assess the co-occurrence of these resistance determinants, and to confirm and analyse sequence variations of the target genes using Sanger sequencing.

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted in the Department of Microbiology, Saveetha Medical College and Hospitals, Chennai, Tamil Nadu, India, between March 2023 and January 2025, after obtaining approval from the Institutional Human Ethics Committee (Approval No: IHEC/SDC/DT/FACULTY/23/MICRO/198). All participants provided written informed consent before being included in the study.

This was the time bound study; non duplicate *A. baumannii* isolates causing BSIs and meeting the inclusion criteria during this period were included in the analysis.

Inclusion criteria: Adult patients aged ≥ 18 years admitted in ICUs with laboratory-confirmed BSIs, as evidenced by positive blood culture results, were included in the study. To avoid duplication, only one blood culture isolate per patient was considered.

Exclusion criteria: Patients with polymicrobial BSIs, were not admitted to ICUs, were paediatric (<18 years), or if multiple isolates were obtained from the same patient and also isolates recovered from non blood clinical specimens were excluded from the study.

Strain Identification

Blood cultures in the present study were collected according to standard clinical microbiology practices. Two blood culture sets were obtained from each patient using separate venipuncture sites. Growth in at least one blood culture bottle was considered significant, and only one non duplicate isolate per patient was included for further analysis. Positive blood culture samples were subcultured onto blood agar and MacConkey agar plates (HiMedia, Mumbai, India) and incubated at 37°C for 18–24 hours. On blood agar, the isolates produced smooth, opaque, non haemolytic colonies, while on MacConkey agar they appeared as non lactose-fermenting, pale colonies. Distinct colonies were further assessed by Gram staining, which revealed Gram-negative coccobacilli. Species-level identification of *A. baumannii* was

carried out using the VITEK® 2 Compact system (bioMérieux, Marcy-l'Étoile, France). All confirmed isolates were preserved as glycerol stocks and stored at –20°C for further molecular and phenotypic analyses.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility profiling of all *A. baumannii* isolates was carried out using the VITEK® 2 Compact automated system. The antimicrobial agents evaluated included piperacillin–tazobactam (10 μ g), ceftazidime (30 μ g), cefoperazone–sulbactam (30 μ g), cefepime (30 μ g), ceftriaxone (30 μ g), imipenem (10 μ g), meropenem (10 μ g), amikacin (30 μ g), ciprofloxacin (5 μ g), levofloxacin (5 μ g), tigecycline (15 μ g), colistin (10 μ g), and trimethoprim-sulfamethoxazole (25 μ g). Tigecycline testing was performed only using the VITEK® 2 automated system as per the manufacturer's instructions. No CLSI-based MIC determination and susceptibility categorisation was applied for tigecycline.

Extraction of DNA

Plasmid DNA was extracted from freshly cultured CRAB isolates grown on MacConkey agar plates and incubated at 37°C for 24 hours. The extraction was performed using the Qiagen Plasmid DNA Extraction Kit (Qiagen, Germany) according to the manufacturer's protocol [15]. The concentration and purity of the extracted DNA were measured using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). The purified plasmid DNA samples were stored at –20°C until further analysis [16].

Screening of Antibiotic Resistance Genes

Antibiotic resistance genes in *A. baumannii* isolates were detected by PCR targeting *bla*_{OXA-23} (class D carbapenemase) and *bla*_{NDM-1} (class B metallo- β -lactamase) using primers synthesised by Eurofins Genomics India Pvt. Ltd. (Bangalore, India). The PCR conditions are listed in [Table/Fig-1].

Resistance genes		Primer sequence (5' – 3')	Temp	Amplicon size (bp)
<i>bla</i> _{OXA-23}	F	GATCGGATTGGAGAACCAGA	52°C	501
	R	ATTTCTGACCGCATTTCCAT		
<i>bla</i> _{NDM-1}	F	GGTTTGGCGATCTGGTTTTTC	52°C	621
	R	CGGAATGGCTCATCACGATC		

[Table/Fig-1]: Primers used for detection of *bla*_{OXA-23} and *bla*_{NDM-1} genes in *A. baumannii*

Each 25 μ L PCR reaction contained 12.5 μ L Takara Master Mix (Takara Bio Inc., Tokyo, Japan), 6.5 μ L nuclease-free water, 2 μ L of each primer, and 2 μ L DNA template. The cycling conditions included an initial denaturation at 95°C for 5 mins, followed by 40 cycles of denaturation at 95°C for 30 s, annealing at gene-specific temperatures for 30 s, and extension at 72°C for 1 min, with a final extension at 72°C for 5 mins. Amplicons were visualised on a 1.5% agarose gel stained with ethidium bromide, using a 100 bp DNA ladder (Thermo Fisher Scientific, USA) as a molecular weight marker.

Confirmation of the *bla*_{OXA-23} and *bla*_{NDM-1} Amplicons by Sequencing

Bi-directional sequencing of *bla*_{OXA-23} and *bla*_{NDM-1} amplicons was performed using the BigDye™ Terminator v3.1 Cycle Sequencing Kit on an ABI 3730XL Genetic Analyser. Forward and reverse reads were assembled and edited using BioEdit v7.2.5, and sequence identity was confirmed by BLASTn (Basic Local Alignment Tool) analysis against NCBI GenBank. Multiple sequence alignment was carried out using ClustalW v1.83, employing *A. baumannii* reference sequences (CP175878.1, CP199308.1, CP048827.1, and CP175883.1), which were selected based on their complete genome availability, high annotation quality, and documented

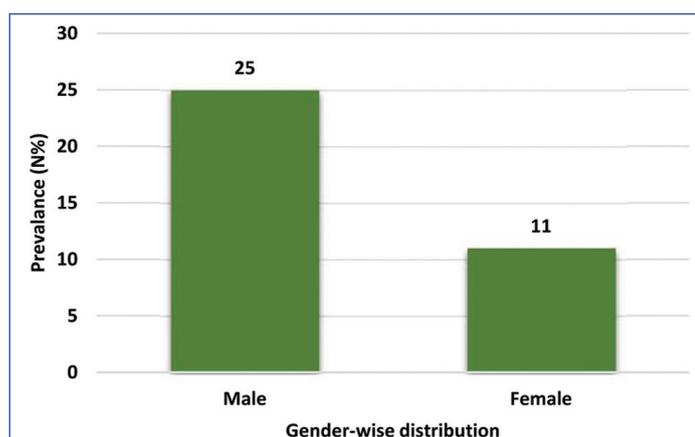
presence of the target resistance genes, to ensure accurate comparative alignment and sequence validation.

STATISTICAL ANALYSIS

Data were entered and analysed using SPSS version 25.0. Descriptive statistics were used to determine the frequency and percentage distribution of carbapenemase genes among the isolates. The association between the presence of *bla*_{OXA-23} and *bla*_{NDM-1} genes was analysed using Fisher's exact test, as the variables were categorical. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 136 non duplicate *A. baumannii* isolates were identified using the VITEK® 2 automated system. Gender distribution showed a higher number of isolates obtained from male patients compared to female patients [Table/Fig-2].



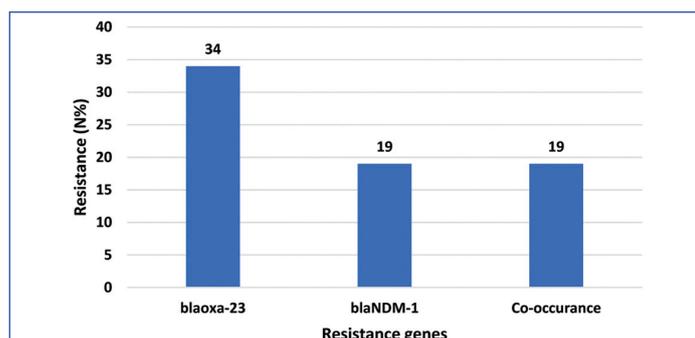
[Table/Fig-2]: Gender-wise distribution of *A. baumannii*.

Antimicrobial Susceptibility Pattern of *A. baumannii*

The antimicrobial susceptibility testing revealed that colistin and tigecycline were the only agents demonstrating complete sensitivity (100%) against all *A. baumannii* isolates. In contrast, all isolates exhibited complete resistance (100%) to a wide range of commonly used antibiotics, including piperacillin-tazobactam, cefoperazone/sulbactam, cefepime, ceftriaxone, ceftazidime, amikacin, ciprofloxacin, levofloxacin, imipenem, meropenem, and trimethoprim-sulfamethoxazole.

Frequency of *bla*_{OXA-23} and *bla*_{NDM-1} Genes among CRAB Isolates

All 36 CRAB isolates were screened for the presence of carbapenemase-encoding genes. Among these, 34 (94.4%) of isolates were positive for the *bla*_{OXA-23} gene, highlighting its predominant distribution among the tested isolates. The *bla*_{NDM-1} gene was detected in 19 (53%) of isolates, indicating a substantial prevalence of MBL producers within the collection [Table/Fig-3].



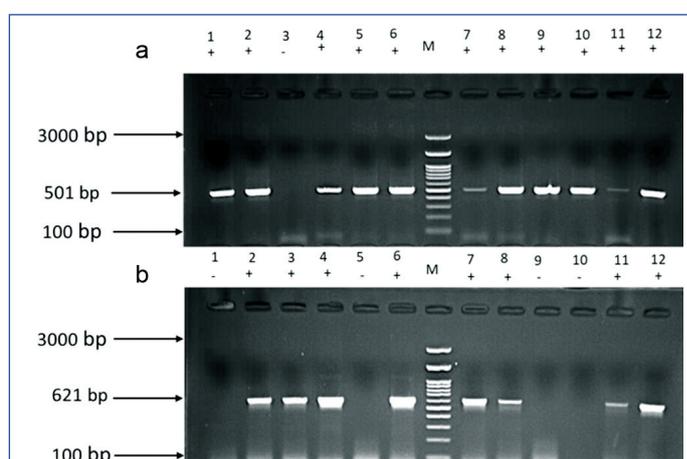
[Table/Fig-3]: Distribution of carbapenemase genes *bla*_{OXA-23} and *bla*_{NDM-1} and their co-occurrence among *A. baumannii* clinical isolates, indicating the prevalence of key resistance determinants.

Notably, all *bla*_{NDM-1}-positive isolates also carried *bla*_{OXA-23}, demonstrating the co-existence of class D and class B carbapenemase genes within the same strains. Fisher's exact test was performed on all CRAB isolates 36 (100%) and revealed a statistically significant association between the *bla*_{OXA-23} and *bla*_{NDM-1} genes (p-value=0.018). The strength of association was assessed using the phi (ϕ) coefficient, which is appropriate for 2x2 contingency tables with categorical variables and small sample sizes. A strong positive correlation ($\phi=0.53$) was observed, indicating frequent co-occurrence of these genes [Table/Fig-4].

Genes	Prevalence n (%)	Co-occurrence n (%)	Statistics
<i>bla</i> _{OXA-23}	34 (94.4)	19 (53)	Fisher's exact test, p-value= 0.018 Positive correlation ($\phi = 0.53$)
<i>bla</i> _{NDM-1}	19 (53)	19 (53)	

[Table/Fig-4]: Prevalence, co-occurrence, and statistical association of *bla*_{OXA-23} and *bla*_{NDM-1} genes in CRAB isolates.
 ϕ = phi coefficient

The remaining isolates, although negative for *bla*_{NDM-1}, consistently harboured *bla*_{OXA-23}, confirming it as the most frequently encountered carbapenemase determinant in this study. The PCR amplification profiles of the *bla*_{OXA-23} and *bla*_{NDM-1} genes are shown in [Table/Fig-5a,b], respectively.



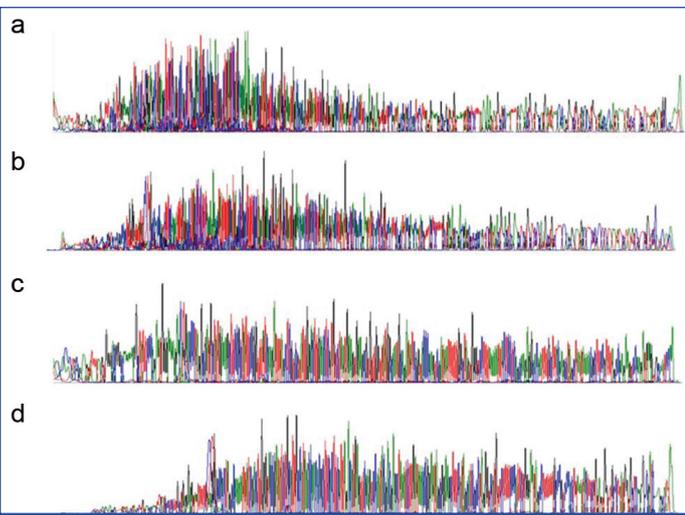
[Table/Fig-5]: Agarose gel electrophoresis showing PCR amplification of carbapenem-resistance genes in *A. baumannii* clinical isolates; a) Detection of the *bla*_{OXA-23} gene with an expected amplicon size of 501 bp; b) Detection of the *bla*_{NDM-1} gene with an expected amplicon size of 621 bp. M indicates 100 bp DNA ladder used as a molecular size marker.

Sequence Confirmation and Analysis of *bla*_{OXA-23} and *bla*_{NDM-1} Genes

Representative PCR amplicons of the *bla*_{OXA-23} and *bla*_{NDM-1} genes were subjected to Sanger sequencing to confirm their identity. The obtained sequences produced clear and well-resolved chromatogram peaks in both forward and reverse directions [Table/Fig-6a-d].

A BLASTn analysis of the sequences against the NCBI GenBank database confirmed 100% identity with *A. baumannii* *bla*_{OXA-23} and *bla*_{NDM-1} reference genes, validating the amplification specificity. Subsequent sequence alignment revealed notable genetic variations. The alignment of the *bla*_{OXA-23} sequence [Table/Fig-7a,b] revealed multiple nucleotide mismatches and partial deletions in both the upstream and downstream regions compared to the reference sequence. This indicates that there is genetic diversity among clinical isolates.

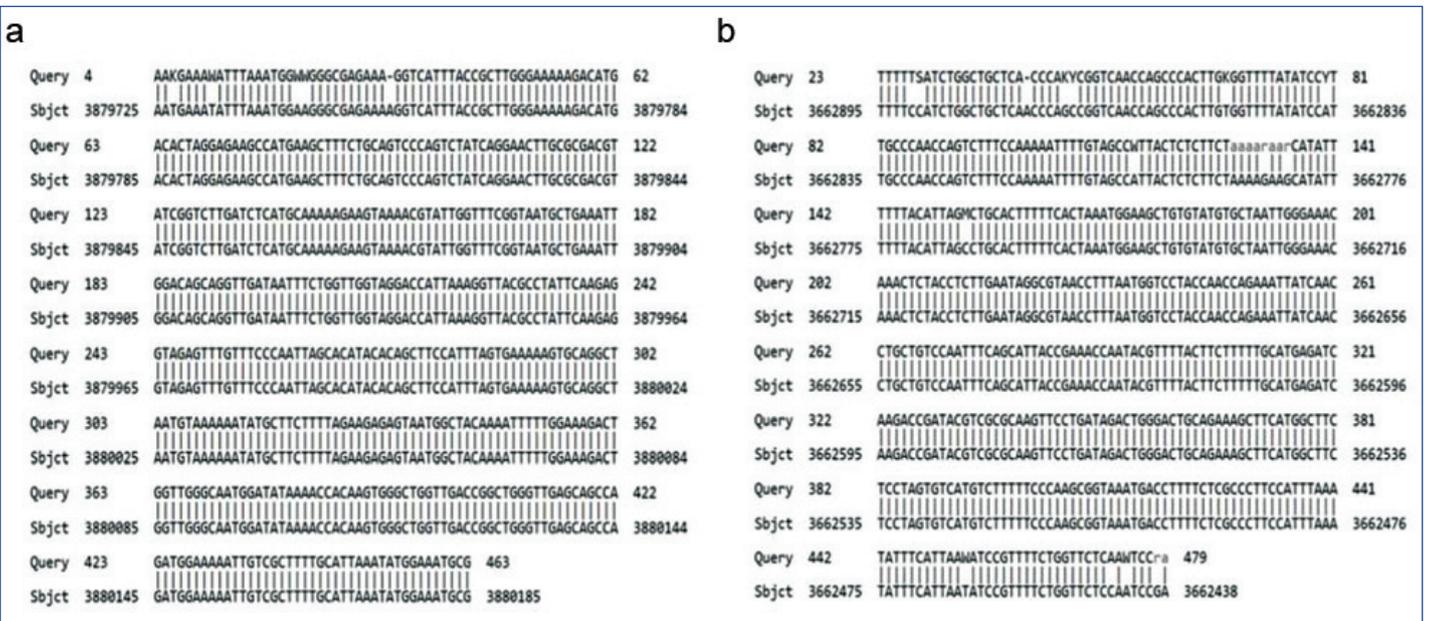
Similarly, alignment of the *bla*_{NDM-1} sequence [Table/Fig-8a,b] demonstrated minor base substitutions and few deletions across the amplified fragment, indicating sequence heterogeneity. Despite these variations, both gene sequences retained high similarity to their respective reference sequences, confirming accurate amplification and sequence authenticity.



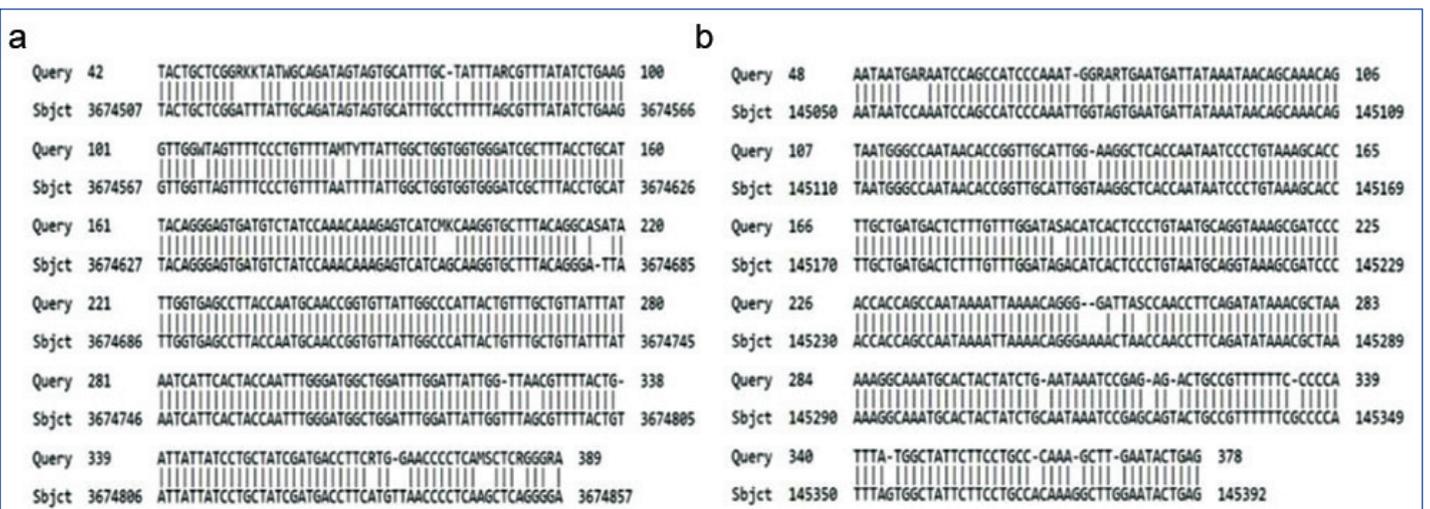
[Table/Fig-6]: Sanger sequencing chromatograms of carbapenemase genes; a) bla_{OXA-23} forward sequence; b) bla_{OXA-23} reverse sequence; c) bla_{NDM-1} forward sequence, and (d) bla_{NDM-1} reverse sequence showing clear nucleotide peak patterns confirming gene identity.

dissemination of mobile carbapenemase-encoding genes has substantially exacerbated this problem, positioning antimicrobial resistance in *A. baumannii* as a major challenge for hospital infection control programmes worldwide [17].

The increasing incidence of CRAB has significantly complicated clinical management, especially in ICUs, where therapeutic options are limited and associated with poor clinical outcomes. High morbidity and mortality rates linked to CRAB infections underscore the importance of understanding the molecular basis of resistance to inform effective control strategies [18]. In this context, the present study characterises the local distribution of key carbapenem resistance determinants among CRAB isolates recovered from BSIs in a tertiary care hospital in South India and highlights the need for sustained molecular surveillance and antimicrobial stewardship. Among the 36 non duplicate isolates analysed over a two-year period, infections were more frequently observed in male patients, consistent with earlier reports [19]. This trend may reflect longer ICU stays, increased exposure to invasive procedures, and a higher prevalence of underlying co-morbidities in this population.



[Table/Fig-7]: Sequence alignment of the bla_{OXA-23} gene showing nucleotide deletions and base mismatches between the query and subject sequences; a) Alignment depicting partial nucleotide deletions in the upstream region, and (b) Alignment showing internal mismatches and gaps in the downstream region of the amplified fragment.



[Table/Fig-8]: Sequence alignment of the bla_{NDM-1} gene showing nucleotide mismatches and minor deletions between the query and subject sequences. (a) Alignment representing variations observed in the upstream region, and (b) Alignment depicting sequence mismatches and deletions in the downstream region of the amplified fragment.

DISCUSSION

A. baumannii has emerged as a prominent nosocomial pathogen due to its remarkable ability to persist in hospital environments, survive under adverse conditions, and rapidly acquire resistance to multiple

antimicrobial agents. Although community-acquired infections have been reported sporadically, BSIs caused by *A. baumannii* predominantly occur in healthcare settings, particularly among critically-ill and immunocompromised patients. The widespread

The antimicrobial susceptibility profile of the isolates revealed resistance patterns across multiple antibiotic classes, including carbapenems. Although carbapenems were previously considered the mainstay for treating MDR *A. baumannii* infections, the emergence and global spread of CRAB have markedly reduced clinical utility. The clinical impact of CRAB infections is substantial, with reported mortality rates for hospital-acquired pneumonia and BSIs reaching up to 60% [20]. The study from India has similarly documented a high prevalence of CRAB among clinical isolates, reflecting the growing burden of resistance in the region [21]. Currently, therapeutic options are largely restricted to last-resort agents such as colistin and tigecycline; however, the emergence of resistance to these drugs has been increasingly reported, raising serious concerns regarding the sustainability of existing treatment regimens [22].

Molecular analysis in the present study revealed a high prevalence of *bla*_{OXA-23} detected in 94.4% CRAB isolates, underscoring its dominant role in mediating carbapenem resistance. In addition, *bla*_{NDM-1} was identified in 19 (53%) isolates, and notably, all *bla*_{NDM-1}-positive isolates also harboured *bla*_{OXA-23}, demonstrating the co-existence of multiple carbapenemase genes within the same strains. These findings align with existing evidence indicating that OXA-type carbapenemases and MBLs are the principal mechanisms of carbapenem resistance in *A. baumannii*, particularly in South and Southeast Asia [23]. Similar co-occurrence of *bla*_{OXA-23} and *bla*_{NDM-1} has been reported in clinical isolates from India, Nepal, and Northeast Algeria [24–26]. While MBLs are less commonly encountered in developed countries, their increasing prevalence in developing regions, often in combination with other carbapenemase genes and without apparent fitness cost, has been well documented [27]. Since its recent identification in India, *bla*_{NDM-1} has disseminated globally and remains the most prevalent NDM variant, with Asia accounting for a substantial proportion of reported cases [28].

Sequencing analysis of *bla*_{OXA-23} and *bla*_{NDM-1} in this study confirmed accurate gene amplification, with high-quality chromatograms and strong sequence identity validating primer specificity and assay reliability. Minor mismatches and partial deletions were observed, predominantly in non coding regions, indicating allelic variation among clinical isolates. Despite these variations, the overall high degree of sequence conservation suggests strong evolutionary pressure to maintain the functional integrity of these resistance determinants. Comparable levels of conservation, along with limited allelic diversity arising from horizontal gene transfer or adaptive mutations, have been reported in studies from other geographic regions [29,30]. These observations highlight the importance of continuous molecular surveillance to monitor emerging variants, trace the dissemination of resistant clones, and support targeted infection control interventions.

Overall, this study provides valuable insights into the molecular epidemiology and sequence diversity of *bla*_{OXA-23} and *bla*_{NDM-1} among CRAB isolates causing BSIs. The high prevalence and co-existence of these genes emphasise the growing complexity of antimicrobial resistance in *A. baumannii* and the associated clinical challenges. Integrating molecular surveillance with epidemiological data is essential to track resistant lineages and inform evidence-based infection control strategies. Future studies incorporating whole-genome sequencing would further elucidate the resistome and virulome of CRAB strains, assess the functional implications of allelic variations, and aid in identifying potential targets for novel therapeutic interventions.

Limitations(s)

It was conducted at a single centre, although representative *A. baumannii* isolates with confirmed carbapenem resistance were included. The genetic findings may not fully represent the nationwide molecular epidemiology; however, they align with previously reported

patterns of *bla*_{OXA-23} and *bla*_{NDM-1} dissemination. Furthermore, the work was confined to in-vitro molecular characterisation without correlating the genetic data to clinical outcomes and treatment responses. Nevertheless, the study provides important insights into the co-existence and sequence conservation of *bla*_{OXA-23} and *bla*_{NDM-1} genes and highlights their contribution to the growing burden of CRAB, emphasising the urgent need for continuous molecular surveillance and rational therapeutic strategies.

CONCLUSION(S)

The present study confirms the presence of the *bla*_{OXA-23} and *bla*_{NDM-1} genes among clinical CRAB isolates. Sequencing analysis revealed a high level of genetic conservation with only minor allelic variations, indicating the stability of these resistance determinants within the analysed strains. The co-existence of carbapenem and MBL resistance genes in the same isolates underscores the complexity of antimicrobial resistance in *A. baumannii* and the resulting limitations in available treatment options. Management of infections caused by such resistant strains relies primarily on last-resort antimicrobials, often administered based on antimicrobial susceptibility testing. These findings highlight the importance of continued molecular surveillance, strict infection control measures, and antimicrobial stewardship to control the spread of CRAB in clinical settings.

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