



ORIGINAL PAPER

Comparison of clinical profile and outcomes in patients with carbapenem resistant and carbapenem sensitive gram-negative bacteraemia

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ABSTRACT

Introduction and aim. Carbapenem-resistant Gram-negative bacteraemia (CR-GNB), an emerging public health concern due to limited treatment options and high mortality rates. Carbapenems, face reduced efficacy against resistant strains, posing a significant challenge. The aim was to compare clinical profiles and outcomes between CR-GNB and carbapenem-sensitive (CS-GNB) and to identify factors influencing mortality among these patients.

Material and methods. This prospective study was conducted at the tertiary care teaching hospital, enrolling 115 patients with GNB (55 CR-GNB and 60 CS-GNB). Following institutional approval and informed consent, patients underwent standardized testing (blood culture and susceptibility testing) with the VITEK method.

Results. CR-GNB patients had significantly longer hospital stays (12.88 vs. 8.87 days, $p=0.001$), higher ICU admissions (90% vs 49.3%), and prolonged antibiotic use (8.7 vs 6.04 days, $p=0.001$). Pneumonia was more prevalent in CR-GNB (42.5%) while UTIs dominated in CS-GNB cases (64%). Kaplan-Meier analysis showed increased mortality risk in CR-GNB, with hazard ratios of 1.82 (day-14) and 2.12 (day-28).

Conclusion. Thus, in our study CR-GNB posed a significant hazard for mortality risk. Thus, early identification, stringent infection control measures, and antimicrobial stewardship are crucial and to develop effective treatment strategies tailored to high-risk populations can enhance patient survival and limit the resistance.

Keywords. antimicrobial stewardship, beta-lactam antibiotics, carbapenem, gram-negative bacteraemia

Introduction

Gram-negative bacteraemia (GNB) is a formidable clinical challenge, often associated with severe systemic infections requiring prompt intervention due to the inherent risks of elevated mortality and morbidity.¹ Recently, there has been a discernible shift in the bloodstream infections epidemiology, with GN bacteria, particularly *Enterobacteriaceae* family, eclipsing

Gram-positive (GP) counterparts.¹⁻³ This transition coincides with an alarming rise in multidrug-resistant (MDR) GN infections, posing a global health threat.²⁻⁴

Carbapenems, a key class of beta-lactam antibiotics, have long been regarded as the cornerstone of treatment for a diverse spectrum of GNB infections.⁵ These antibiotics are classified into group-1 (ertapenem) which exhibits limited activity against non-fermentative

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GNB (NF-GNB), and group-2 (imipenem, meropenem, doripenem) were active against NF-GNB, particularly in nosocomial infections.⁵⁻⁷ Due to their broad-spectrum activity against both GP and GN bacteria, they are last-resort agents for MDR infections.⁸⁻¹⁰ However, rising incidence of carbapenem resistance (CR), mediated by the intricate web of mechanisms by carbapenemases enzymes such as KPC, NDM-1, and OXA48, as well as efflux pump mechanisms, has significantly compromised their clinical utility.^{11,12}

Among CR-GNB particularly *Enterobacteriaceae* (CRE), *Pseudomonas aeruginosa* (CRPA), and *Acinetobacter baumannii* (CRAB), which evolved into a critical concern, in nosocomial bloodstream infections.¹³ The increasing prevalence of CR-GNB isolates has prompted global authoritative bodies including the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), emphasizing the imperative need for surveillance, antimicrobial stewardship, and novel therapeutic approaches.⁹ Thus, responding to the global escalation of MDR among GN bacilli, there exists an urgent need for meticulous examination of in-vitro susceptibilities to carbapenems.^{1,3,14} Given the geographic variability in CR rates, disparities observed between Western and Asian countries, including India, emphasizing the need for region-specific investigations for effective containment strategies.^{3,14,15}

Despite ongoing advancement in antimicrobial therapy, the clinical management of CR-GNB infections remains challenging. Understanding the clinical characteristics and outcomes of patients with CR-GNB is essential to guiding treatment decisions and optimizing therapeutic strategies on a global scale.^{2,11,16,17} However, exciting literature on the clinical profiles and treatment outcomes of patients with CR-GNB remains limited, despite its critical relevance to patient care, and understanding it can contribute nuanced insights that extend beyond the healthcare setting.^{2,11,18} In essence, this will seek to illuminate not only the immediate clinical challenges posed by CR but also to contribute to the broader discourse on global antimicrobial resistance strategies.⁶

The rising incidence of CR-GNB underscores the need for further research to bridge current knowledge gaps and develop effective treatment algorithms.^{3,9,14} With this background, the present study aims to compare clinical profiles, microbiological spectrum, treatment approaches, and outcome of patients with CR-GNB and carbapenem sensitive (CS-GNB). Additionally, this study seeks to identify factors influencing mortality among these patients. With the WHO designating CRAB, CRPA, and CRE as critical priority pathogens,^{3,19} this study aligns with global efforts to combat antimicrobial resistance. Furthermore, it evaluates group-2 carbapenems' efficacy against *Enterobacteriaceae* resistant to group-1 agents.

Aim

To compare clinical profiles, microbiological spectrum, treatment approaches, and outcome of patients with CR-GNB and CS-GNB.

Material and methods

It was a hospital-based prospective analytical cross-sectional study was conducted by General Medicine department at tertiary-care teaching hospital, in Puducherry from the period of 2022 to 2024. Following Institutional Human Ethics Committee (IHEC) approval (MG-MCRI/Res/01/2021/38/IHEC/78), patients admitted to various departments including wards, intensive and cardiac care units (ICU and CCU), and cardio-thoracic vascular surgery units (CTVS), with positive blood cultures presented with CR-GNB and CS-GNB were considered for the study.

Eligibility criteria for the study participants include patients aged more than 18 years diagnosed with suspected sepsis confirmed by positive blood cultures with CR-GNB and CS-GNB by antibiotic susceptibility testing and who completed at least seven days of treatment from day one of the admission. Pregnant women, those diagnosed with polymicrobial bacteraemia, and cases deemed contaminants were excluded from the study.

Considering the prevalence of the CR-GNB especially *Enterobacteriaceae* was 18.5% in a study done by Thomas et al, in India.²⁰ Taking the confidence level at 95%, power at 80%, and 7 as precision, the sample size was calculated to be 115. Using the formula,

$$n = \frac{Z_{\alpha/2}^2 * p (1-p)}{d^2} = \frac{1.96^2 \times 0.18 (1-0.18)}{0.07^2} = 113.4$$

(rounded to the nearest higher figure of 115) ($Z_{\alpha/2}$ – 1.96; prevalence (p) – 0.18; precision (d)) – 0.07) the sample size calculated. Consecutive sampling technique was used to include all patients with inclusion criteria until the desired sample size was achieved.

Data were collected using a semi-structured proforma which included demographic details along with relevant clinical and laboratory data. Patients admitted with suspected sepsis underwent routine investigations including blood culture and antibiotic susceptibility testing (AST). Initial treatment for suspected sepsis was empirical, with definitive treatment based on blood culture results with either CR-GNB and CS-GNB.

Blood samples were collected aseptically from patients with suspected sepsis and inoculated into standard aerobic and anaerobic blood culture bottles, which were then incubated in an automated system (BacT/ALERT) for continuous monitoring. Once the cultures flagged positive, samples were sub-cultured onto appropriate solid media (MacConkey agar) for isolation. Following isolation, bacterial identification and AST

were performed using the VITEK 2 compact system (bioMérieux, France). Identification of GNB was done using GN-ID cards and AST was conducted using AST-GN cards (GN83) according to Clinical and Laboratory Standards Institute (CLSI) guidelines.²¹

Data analysis

The collected data were entered in Microsoft Excel and analyzed using Epi-info (ver. 7.2.2.6; Centers for Disease Control and Prevention, Atlanta, GA, USA, and World Health Organization) and IBM Statistical Package for Social Sciences for Windows (SPSS Inc. version 23.0, Chicago, IL, USA). Normality of the variables were measured using Shapiro-Wilk test and Q-Q plot. The data was presented in the form of numbers and percentages for qualitative variables and mean \pm standard deviation (SD)/median with interquartile range (IQR) for quantitative variables. Appropriate tests of significance i.e., Chi-square test or Fisher exact test, and Student t-test was used to test the significance. Values of $p < 0.05$ was statistically significance. Kaplan-Meier survival analysis was used to evaluate the mortality outcomes.

Results

In this study, among 115 patients, 40 (34.8%) were diagnosed with CR-GNB, while 75 (65.2%) had CS-GNB. The demographic details and comorbidity status of the study participants were presented in

Table 1. The odds of developing CR-GNB among the patients with diabetes and hypertension were 1.0 and 2.24 times higher when compared to the patients with no comorbidity*

Variables	CR-GNB (n=40)	CS-GNB (n=75)	p
Age (in years)	57.45 \pm 17.26	56.43 \pm 11.65	0.730 ^a
Gender			0.080 ^b
Female	11 (27.5)	33 (44.0)	
Male	29 (72.5)	42 (56.0)	
Diabetes mellitus	Present	24 (60.0)	1.000 ^b
Absent	16 (40.0)	30 (40.0)	
Hypertension	Present	15 (37.5)	0.043 ^b
Absent	25 (62.5)	32 (42.7)	
CVA	Present	9 (22.5)	0.980 ^b
Absent	31 (77.5)	58 (77.3)	
CKD	Present	7 (17.5)	0.690 ^b
Absent	33 (82.5)	64 (85.3)	
Other comorbidities	Present	7 (17.5)	0.200 ^b
Absent	33 (82.5)	68 (90.7)	

*^a – independent t-test; ^b – Pearson's Chi-square test, categorical variables were presented in number (percentage); while continuous variables were presented in mean \pm SD, CS – carbapenem sensitive, CR – carbapenem resistant, GNB – gram negative bacterium, CVA – cerebro-vascular accident, CKD – chronic kidney disease

The mean SOFA score was significantly elevated in the CR-GNB group (8.1 ± 2.4) when compared to CS-

GNB group (6.5 ± 2.0), indicating greater severity in CR-GNB cases. The outcome of the patients admitted in ICU and ward were presented in Table 2. The odds of admitting the patients in ICU with CR-GNB was 9.24 times higher than the CS-GNB in our study.

Table 2. Outcomes of the patients admitted in the hospital (n=115)*

Variables	CR-GNB (n=40)	CS-GNB (n=75)	p
Admission	ICU	36 (90.0)	<0.01
	Ward	4 (10.0)	
Indwelling catheter	No	8 (20.0)	<0.01
	Yes	32 (80.0)	
Mortality in 14 days	Alive	21 (52.5)	<0.01
	Death	19 (47.5)	
Mortality in 28 days	Alive	9 (22.5)	<0.01
	Death	31 (77.5)	

* Pearson's Chi-square test, CS – carbapenem sensitive; CR – carbapenem resistant; GNB – gram negative bacterium; ICU – intensive care units

Table 3. Disease distribution in patients with CR- and CS-GNB (n=115)

Disease	CR-GNB (n=40) n (%)	CS-GNB (n=75) n (%)
Abdominal wall cellulitis	1 (2.5)	0 (0)
Catheter related blood stream infection (CRBSI)	2 (5.0)	3 (4.0)
Cellulitis	4 (10.0)	1 (1.3)
Cholecystitis	0 (0)	1 (1.3)
Cholelithiasis	0 (0)	1 (1.3)
Colangitis	0 (0)	1 (1.3)
Corrosive Poisoning	0 (0)	1 (1.3)
Diabetic foot ulcer	1 (2.5)	0 (0)
Infective endocarditis (IE)	1 (2.5)	0 (0)
Melioidosis	1 (2.5)	1 (1.3)
Necrotizing fascitis	2 (5.0)	2 (2.7)
Peritonitis	4 (10.0)	0 (0)
Pneumonia	17 (42.5)	11 (14.7)
Spontaneous bacterial peritonitis (SBP)	1 (2.5)	1 (1.3)
Typhoid	0 (0)	3 (4.0)
Urinary tract infection (UTI)	6 (15.0)	48 (64.0)
UTI+ pneumonia	0 (0)	1 (1.3)

In Table 3, distribution of the disease for both CR- and CS-GNB were presented, where 42.5% and 15% of the patients in CR-GNB and 14.7% and 64% of patients in CS-GNB were presented with pneumonia and urinary tract infection (UTI). *Klebsiella* (37.5%), and *E. coli* (25%) were the most common pathogens presented in CR-GNB group, while in CS-GNB *E. coli* (56%) was most common followed by *Pseudomonas* (14.7%) (Fig. 1). In CS-GNB group the duration of antibiotics was 6.04 ± 2.57 days while in CR-GNB group it was 8.7 ± 4.28 days and found to be statistically significant. Similarly, the duration of hospital stay was found to be 8.87 ± 2.29 days and 12.88 ± 5.67 days in CS-GNB and CR-GNB and

were statistically significant ($p = 0.001$) shows that patients with CR-GNB higher hospital stay when compared to CS-GNB patients. The type of antibiotics used were presented in Table 4.

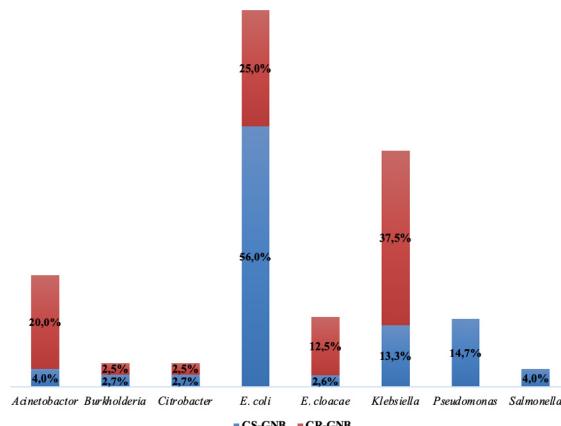


Fig. 1. Distribution of pathogens in patients with CR-GNB and CS-GNB

Table 4. Antibiotics used in patients with CR- and CS-GNB after the culture report (n=115)

Antibiotics	CR-GNB (n=40) n (%)	CS-GNB (n=75) n (%)
Cefoperazone sulbactam and vancomycin	1 (2.5)	0 (0)
Meropenem	1 (2.5)	22
Amikacin	1 (2.5)	0 (0)
Cefixime	0 (0)	1 (1.3)
Cefoperazone sulbactam	0 (0)	15 (20.0)
Ceftaxime	0 (0)	1 (1.3)
Ceftazidime	0 (0)	1 (1.3)
Ceftazidime avibactam	6 (15.0)	1 (1.3)
Ceftazidime avibactam, aztreonam	1 (2.5)	0 (0)
Ceftazidime avibactam polymyxin B	1 (2.5)	0 (0)
Ceftriaxone	0 (0)	11 (14.7)
Ciprofloxacin	0 (0)	2 (2.7)
Colistin meropenem	1 (2.5)	1 (1.3)
Colistin teicoplanin	1 (2.5)	0 (0)
Cotrimoxazole	0 (0)	1 (1.3)
Norfloxacin	0 (0)	3 (4.0)
Piperacillin tazobactam	2 (5.0)	15 (20.0)
Polymyxin B	17 (42.5)	0 (0)
Polymyxin B teicoplanin	5 (12.5)	0 (0)
Polymyxin B tigecycline	1 (2.5)	0 (0)
Teicoplanin	1 (2.5)	1 (1.3)
Teicoplanin linezolid	1 (2.5)	0 (0)

Survival of the patients on day 14 (Fig. 2) and day 28 (Fig. 3) were plotted using the Kaplan-Meier curve among CR-GNB and CS-GNB. It showed a clear trend of poorer survival outcomes among patients with CR-GNB compared to CS-GNB. On day 14, hazard ratio (HR) was 1.82 (0.85–3.91, $p=0.122$) indicating that CR-GNB patients had an 82% higher risk of mortality at any given

time compared to CS-GNB patients, though this was not statistically significant. By day 28, the HR increased to 2.12 (0.35–12.93, $p=0.416$) for CR-GNB group indicating 2.12 times the risk of mortality compared to CS-GNB patients, but due to the wide confidence interval suggests variability in outcomes (Table 5).

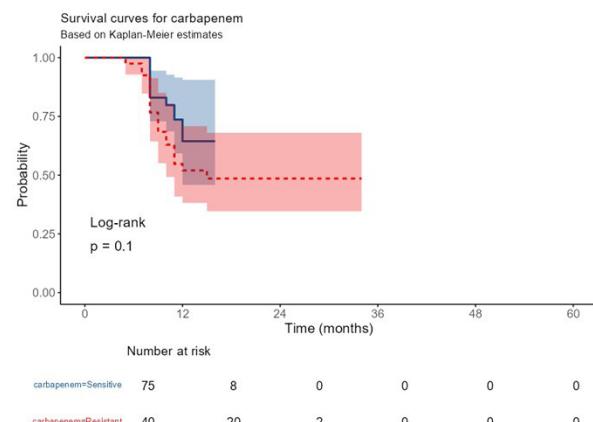


Fig. 2. Kaplan-Meier curve for the survival of the patients (day 14)

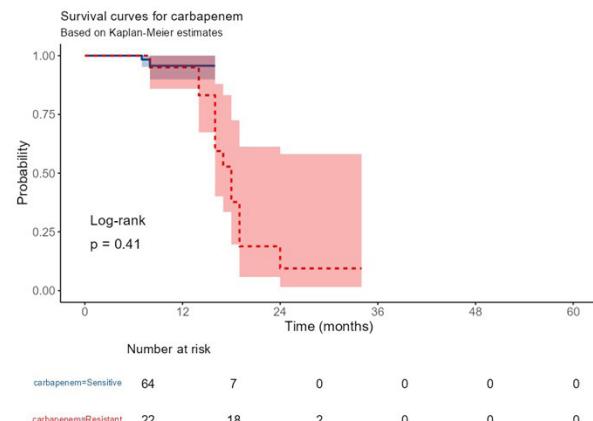


Fig. 3. Kaplan-Meier curve for the survival of the patients (day 28)

Table 5. Hazard ratio of the carbapenem*

Carbapenem	n (%)	HR (95% CI); p
Day 14		
Sensitive (ref)	75 (65.2)	1.82 (0.85–3.91); 0.122
Resistant	40 (34.8)	
Day 28		
Sensitive (ref)	64 (74.4)	2.12 (0.35–12.93); 0.416
Resistant	22 (25.6)	

* Cox-regression analysis, ref – reference group, HR – hazard ratio, CI – confidence interval, a HR greater than 1 indicates increased risk, while less than 1 indicates decreased risk compared to the reference group

Discussion

This hospital-based prospective study which was conducted by General Medicine department at tertiary-care teaching hospital, in Puducherry which aimed to compare the clinical profile and outcomes of the patients with CR-GNB and CS-GNB. Our findings indicate that CR-GNB infections are associated with greater disease severity, a higher likelihood of ICU admission, and an increased mortality risk, particularly in high-risk populations with underlying comorbidities.

The gender distribution in our study revealed that a higher percentage of male patients were present in the CR-GNB (72.5%) compared to the CS-GNB group (56%). Conversely, the percentage of female patients was higher in the CS-GNB group (44%) than in the CR-GNB group (27.5%). Research by Doi et al., highlighted similar trends, where male patients were more frequently observed with CR-GNB infections due higher exposure rates to healthcare settings and invasive procedures, increasing their risk for resistant infection.¹⁸

Additionally, diabetes was equally prevalent in both groups (60%), reinforcing the findings by Cruz-López et al., indication that diabetes acts as a well-known risk factor for infections due to weekend immune dysfunction.²² Study by Aon et al., showed that 30-day hospital mortality was significantly higher among the diabetes group when compared to non-diabetic patients (48.9% and 28.2%, respectively) demonstrated that there is an association between the diabetes and CR among the patients.²³ Similarly, another study by Ghareeb et al., also resulted that patient with diabetes had increased CR when compared to non-diabetes patients.²⁴ On the other hand, hypertension was significantly more common in CS-GNB group (57.3%) compared to CR-GNB (37.5%) group, a trend was also observed in studies by Tängdén et al., and Paul et al. suggested that while comorbidities predispose patients to infections, they do not necessarily correlate directly with resistance patterns.^{16,25} As for the patients with CKD, is common in CR-GNB patients in our study (17.5%), aligns with the study by Theuretz-bacher et al. noted that CKD patients, often requiring dialysis, have higher exposure to invasive procedures, increasing the risk of multidrug-resistant infections.¹⁷

A higher percentage of CR-GNB patients were admitted to the ICU (90%) compared to the CS-GNB group (49.3%). Study by Tängdén et al., and Muteeb et al. reported that CR-GNB infections are more severe and require more intensive management.^{16,26} This shows that increased severity is attributed to the limited treatment options and the high virulence of the pathogens involved, necessitating critical care interventions.^{10,11,16,26} Similarly, the prolonged hospital stay was associated with CR-GNB (mean 12.88 days) ally with the study done by Doi et al. who attributed that extended hospitalization to treatment failure and higher rates of complication.¹⁸ Hassoun-Kheir

et al. conducted the study resulted that *CR-Enterobacteriales* (CRE) colonized patients among the 1-year survivor had increased length of hospital stay than the controls (odds ratio (OR) 1.52; $p < 0.001$).²⁷ Likewise, study by Sharma et al. resulted that the median hospital stay was 17 days in CRE patients than non-CRE patients and another study by Priyendu et al. had the median days of 12 in *CR-Klebsiella pneumonia* (CRKp) patients, align with our study results where the patients with CR-GNB had the median days of 12 than CS-GNB patients.^{27,29} These indicated that CR colonization had longer hospital stay than CS-GNB patients.

As for the antibiotic duration we found that it was significantly longer in CR-GNB patients (8.7 vs 6.04 days, $p=0.001$) reflecting that the difficulty in achieving successful treatment outcomes. As per Infectious Disease Society of America (IDSA) 2024 guideline for the treatment of antimicrobial resistant GNB,³⁰ showed that treatment duration varies as per the type of antibiotic and the patient's status. Studies by Paul et al.,²⁵ highlighted that prolonged antibiotic therapy is both a cause and a consequence of antibiotic resistant, as patients with resistant infections often require multiple treatment modifications. Study by Soto et al.,³¹ showed that CRE patients required prolonged courses of active therapy of about 14 days while the short course required 9 days which was similar to our study findings. Similarly, the guideline by Park et al.,³² also implied that CRE required longer duration of treatment when compared to CS patients.

A study by Paul et al.,²⁵ highlighted that the use of indwelling catheters is a significant risk factor for acquiring CR-GNB. The study found that patients with such devices are more likely to develop severe infections, which often require more intensive and prolonged treatment, further increasing the risk of antibiotic resistance.²⁵ Our study's findings align with these observations, demonstrating a significantly higher prevalence of indwelling catheters in patients with CR-GNB infections.

Disease distribution varied significantly between the two groups. The most common disease in the CR-GNB group was pneumonia (42.5%), followed by urinary tract infections (UTIs) (15%) and cellulitis (10%). In contrast, the CS-GNB group showed a different pattern. UTIs were the most prevalent disease in this group (64.0%), followed by pneumonia (14.7%) and typhoid (4.0%). According to Cruz-López et al. CR-GNB infections are frequently linked to pneumonia, particularly ventilator-associated pneumonia (VAP), due to the critical nature of the patients, frequent use of invasive devices and prolonged hospital stays.²² This is consistent with our finding that pneumonia is the most common disease in the CR-GNB group.

Klebsiella pneumoniae (37.5%) and *E. coli* (25%) were the most common pathogens in CR-GNB cases, whereas in CS-GNB, *E. coli* was the predominant isolate

(56%). This pattern is in consistent with the global surveillance studies by Nordmann and Poirel also reported that *K. pneumoniae* and *E. coli* are among the leading the CR pathogens worldwide.³³ While study by Afify et al. also found that *K. pneumoniae* were resistant to colistin similar to our study findings.³⁴ This explains the increased rate of pneumonia in patients with CR-GNB where *K. pneumoniae* plays a major role in causation of CR in the patients.

Polymyxin B (42.5%) was the most frequently used antibiotic in CR-GNB group, followed by the ceftazidime-avibactam (15%). In contrast, meropenem was the primary agent in CS-GNB cases (28%). The increased use of combination therapies such as polymyxins with other agents reflects current treatment guidelines that emphasize the synergy for overcoming resistant, as suggested by IDS guidelines, and Doi et al.^{18,30} Another study by Nordmann and Poirel showed that use of ceftazidime-avibactam had gained traction as an alternative in treating CRE.³²

Survival analysis showed an increased risk of mortality in the CR-GNB group. The HR on day 14 was 1.82 (p 0.122) while on day 28 it was 2.12 (p 0.416), suggesting a trend towards higher mortality in CR-GNB patients, although statistical significance was not reached. Studies by Tsachouridou et al. and Kitaya et al. reported similar findings, indicating that CR-GNB infections significantly impact patient survival, especially in critically ill individuals.^{1,2} Study by Cienfuegos-Gallet et al. showed that CRKp had lower survival time when compared to CSKp patients (relative time is 0.44).³⁵ Similarly, study by Kulkova et al. also provided that significant difference in 28-days survival in patients with CR-GNB and CS-GNB (log rank p=0.033) which was similar to our findings but found to be significant.³⁶ Thus, high mortality rates were found to be occurred in patient with CR-GNB than CS-GNB. Although these results in our study did not reach statistically significant, likely due to the sample size, they reflect a clinically meaningful trend, as patients with CR-GNB infections experience prolonged illness and a higher likelihood of mortality over time. These findings align with global data, emphasizing the urgent need for early intervention, aggressive infection control, and targeted antimicrobial therapy to mitigate the impact of CR-GNB on patient survival.

Conclusion

This study highlights the substantial healthcare burden of CR-GNB infections, which lead to longer hospital stays, extended antibiotic treatment, higher ICU admissions, and increased mortality. Key strategies include early identification, optimized empirical therapy, and strong infection control to improve outcomes. Antimicrobial stewardship is critical in managing antibiotic use and curbing resistance spread, especially given

the link between comorbidities (like hypertension, diabetes, and CKD) and CR-GNB. The frequent use of indwelling catheters in resistant cases underscores the need for strict infection control. Global surveillance, targeted interventions for high-risk groups, and continued research are essential for combating antimicrobial resistance effectively.

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Declarations

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Author contributions

Conceptualization, V.R. and K.S.C.; Methodology, V.R. and S.S.; Software, A.K.; Validation, V.R. and S.S.; Formal Analysis, A.K.; Investigation, AK; Resources, AK; Data Curation, AK; Writing – Original Draft Preparation, A.K. and V.R.; Writing – Review & Editing, S.S. and K.S.C.; Visualization, SS; Supervision, K.S.C.; Project Administration, V.R. and S.S.

Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

All data generated or analyzed in this study are included in this published article.

Ethics approval

The Institutional Ethical Committee (MGMCR/Res/01/2021/38/IHEC/78) approved this study.

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