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Short Communication

Predictors and outcomes of multi-drug–resistant gram-negative bacteremia in patients with cancer: A retrospective cohort study at a tertiary cancer center in Oman

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ABSTRACT

Objectives: This study aimed to delineate the characteristics and outcomes of gram-negative bacteremia (GNB) in oncology patients; analyze the risk factors for multi-drug–resistant (MDR) GNB; and assess its impact on the recurrence of bloodstream infection (BSI), hospital stay, and 30-day mortality.

Methods: Data, including demographics, clinical features, common cancers, and microbiologic findings, were collected retrospectively from electronic medical records of patients admitted with solid tumors and BSI episodes between January and December 2022. Fisher's exact tests were used to determine the effect of MDR-GNB on 30-day mortality and BSI recurrence. The Wilcoxon rank-sum test assessed the differences in the length of hospital stay. Logistic regression models identified the risk factors for MDR-GNB.

Results: Among 1074 patients, 77 episodes of GNB bacteremia occurred in 59 individuals (47% male, median age 57.4 years). Of these, 37 (48%) were MDR-GNB. Carbapenem resistance was noted in 9.1% of GNB episodes. Previous antibiotic use was significantly associated with MDR-GNB (odds ratio 7.82; 95% confidence interval 2.52-24). MDR-GNB was linked to longer hospital stays (median 23 vs 10.5 days, $P = 0.003$) and higher recurrence rates than non-MDR-GNB (35.13% vs 5.0%, $P < 0.001$). However, 30-day mortality did not significantly differ between the groups (35.14% vs 32.5%, $P = 0.81$).

Conclusion: Previous antibiotic use predicted MDR-GNB in patients with solid tumor. MDR-GNB bacteremia increased the length of hospital stay and risk of recurrence compared with non-MDR-GNB bacteremia.

Introduction

Oncology patients are highly susceptible to infections, including bloodstream infections (BSIs), that can lead to severe consequences, such as prolonged hospitalization, increased healthcare costs, and elevated mortality rates [1–3]. The etiology of BSI in patients with cancer has shifted, with gram-negative organisms, such as *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, emerging as the primary culprits [4,5]. The rise of multi-drug–resistant (MDR) strains poses a significant challenge owing to limited treatment options and increased risk of treatment failure [6]. Despite advancements in medical care and infection control, data on BSI in patients with solid tumor remain scarce. This retrospective cohort study aimed to examine the predictors and outcomes of MDR gram-negative bacteremia (GNB) in oncology patients at a tertiary cancer center, identifying risk factors for multi-drug resistance and assessing its impact on BSI recurrence, hospital stay duration, and 30-day mortality.

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Table 1
Clinical characteristics of gram-negative bloodstream infections (MDR-GNB) in patients with solid tumors: difference between multi-drug–resistant and –susceptible organisms.

	MDR-GNB (N = 37)	Non MDR-GNB (N = 40)	Total (N = 77)
Age (years)	60 (16-86)	63.5 (17-86)	61 (16-86)
White cell count (×1000 per microliter)	11.5 (2-42)	10 (1-30)	10 (1-42)
C-reactive protein	140 (10-480)	140 (10-450)	140 (10-480)
Sex (female)	19 (51.35)	22 (55)	41 (53.25)
Tumor type			
Biliary	16 (43.24)	14 (35)	30 (38.96)
Gastrointestinal cancer	7 (18.92)	10 (25)	17 (22.08)
Breast cancer	4 (10.81)	4 (10)	8 (10.39)
Genitourinary cancer	4 (10.81)	4 (10)	8 (10.39)
Sarcomas	1 (2.7)	2 (5)	3 (3.9)
Head and neck tumors	1 (2.7)	1 (2.5)	2 (2.6)
Lung cancer	2 (5.41)	0 (0)	2 (2.6)
Gynecology tumors	0 (0)	1 (2.5)	1 (1.3)
Others	2 (5.4)	4 (10)	6 (7.8)
Comorbidities			
Diabetes mellitus	23 (62.16)	16 (40)	39 (50.65)
Neutropenia	0 (0)	3 (7.5)	3 (3.9)
Previous antibiotic therapy	32 (86.49)	18 (45)	50 (64.94)
Intravascular catheter	25 (67.57)	27 (67.5)	52 (67.53)
Previous surgical procedure	12 (32.43)	7 (17.5)	19 (24.68)
Prosthetic stents			
Biliary	11 (29.73)	10 (25)	21 (27.27)
Ureteric double j	4 (10.81)	3 (7.5)	7 (9.09)
Gastrointestinal	1 (2.7)	0 (0)	1 (1.3)
Source of bacteremia			
Biliary	14 (37.84)	12 (30)	26 (33.77)
Abdomen	11 (29.73)	5 (12.5)	16 (20.78)
Central line	6 (16.22)	10 (25)	16 (20.78)
Urinary tract infection	2 (5.41)	6 (15)	8 (10.39)
Pneumonia	1 (2.7)	1 (2.5)	2 (2.6)
Skin and soft tissue	0 (0)	1 (2.5)	1 (1.3)
Unknown	3 (8.11)	5 (12.5)	8 (10.39)
Microorganism			
Escherichia coli	21 (56.76)	16 (40)	37 (48.05)
Klebsiella pneumonia	11 (29.73)	13 (32.5)	24 (31.17)
Pseudomonas species	2 (5.41)	10 (25)	12 (15.58)
Acinetobacter species	3 (8.11)	1 (2.5)	4 (5.19)

MDR-GNB, multi-drug resistant gram-negative bacteremia.

Patients and methods

Study design and cohort information

We conducted a retrospective cohort study at a 100-bed tertiary cancer center in Muscat, Oman. All patients with cancer admitted from January and December 2022 with at least one episode of gram-negative bacilli bacteremia were included. Recurrent bacteremia within 7 days was excluded. Data extracted from electronic medical records included demographics, baseline characteristics, clinical features, comorbidities, microbiology data, infection source, and outcomes such as 30-day mortality, hospital stay duration, and bacteremia recurrence. The study, approved by the institutional review board and ethics committee of Sultan Qaboos Comprehensive Cancer Care and Research Centre (CCCRC - 37 - 2022) waived the need for informed consent due to its retrospective nature.

Variables

Febrile neutropenia was diagnosed with fever (oral temperature of 38.3˚C or two consecutive readings above 38˚C for at least 1 hour) and an absolute neutrophil count ≤500 neutrophils/μL or expected to drop below 500 neutrophils/μL within 48 hours. Central line–associated BSI were identified using the National Healthcare Safety Network definition. Previous antibiotic therapy referred to systemic antibiotic use 1 month before the BSI event, whereas previous surgical procedure referred to abdominal surgery within 1 month before BSI. MDR-GNB encompasses extended-spectrum β-lactamase (ESBL)–producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), and non-fermenting gram-negative bacteria resistant to at least one antibiotic in three or more classes. BSI recurrence was defined as the detection of the same bacterial species after 7 days of a previous event. The 30-day inpatient mortality was any cause of death within the first 30 days of bacteremia onset.

Microbiologic studies

Blood samples were incubated in BacT/ALERT culture media bottles (bioMérieux) for up to 5 days or until microbial growth. Bacteria were identified using matrix-assisted laser desorption/ionization-time of flight mass spectrometry with the VITEK MS system (bioMérieux), and antibiotic susceptibility was tested with the Vitek 2 System (bioMérieux), following Clinical and Laboratory Standards Institute guidelines. Carbapenem resistance was confirmed using Xpert Carba-R (Cepheid) for specific resistance genes (OXA-48, KPC, NDM, IMP, and VIM).

Statistical analysis

Continuous variables were summarized by medians and ranges, whereas categorical variables by frequencies and proportions. Fisher's exact test examined the associations between MDR-GNB bacteremia and bacteremia recurrence and 30-day mortality. The Wilcoxon rank-sum test assessed the association between MDR-GNB bacteremia and length of hospital stay. Logistic regression identified predictors of MDR-GNB

Table 2
Risk factors, outcomes, and odds ratios of multi-drug resistance gram-negative bacilli (MDR-GNB) bloodstream infections in the univariable and multivariable analyses.

	Univariable logistic regression Odds ratio (95% confidence interval)	*P*-value	Multivariable logistic regression Odds ratio (95% confidence interval)	*P*-value
Age (year)	1 (0.97-1.03)	0.89	0.99 (0.94-1.04)	0.69
White blood cells (×1000 per microliter)	1.04 (0.98-1.1)	0.19	1.02 (0.93-1.12)	0.67
C-reactive protein	1 (0.997-1.005)	0.59	1 (0.99-1.01)	0.79
Male gender	1.16 (0.47-2.84)	0.75	1.82 (0.42-7.83)	0.42
Diabetes	2.46 (0.99-6.17)	0.054	2.27 (0.54-9.58)	0.27
Previous antibiotics	7.8 (2.53-4.21)	0.0004	13.99 (2.37-82.82)	0.0036
Central line	1 (0.39-2.61)	0.995	0.77 (0.15-3.97)	0.76
Recent surgery	2.26 (0.78-6.58)	0.13	1.35 (0.26-6.99)	0.72
Stents				
None	1 (Reference)		1 (Reference)	
Biliary	1.41 (0.51-3.96)	0.51	1.45 (0.25-8.33)	0.68
Ureteric double J stent	1.71 (0.35-8.51)	0.51	0.84 (0.05-14.2)	0.9
Source				
Central line	1 (Reference)		1 (Reference)	
Intra-abdominal (abdomen, biliary)	2.45 (0.75-8.02)	0.14	0.34 (0.02-4.94)	0.43
Pneumonia	1.67 (0.09-31.87)	0.73	0.67 (0.02-27.35)	0.83
Primary/Unknown	1 (0.17-5.77)	1	0.06 (0/.002-2.04)	0.12
Other	0.48 (0.07-3.09)	0.44	0.09 (0.003-2.84)	0.17

Outcomes of GNB bacteremia	MDR-GNB bacteremia N = 37	Susceptible N = 40	*P*-value
Length of stay, median (range)	23 (0-204)	10.5 (0-95)	0.0048
Recurrent bacteremia, n (%)	13 (35.14%)	2 (5%)	0.0011
30-day mortality, n (%)	13 (35.14%)	13 (32.5%)	0.8148

MDR-GNB, multi-drug resistant gram-negative bacteremia.

bacteremia, presenting odds ratios and 95% confidence intervals. Statistical analysis used SAS software version 9.4 (SAS Institute, Cary, NC), with $P \leq 0.05$ considered significant.

Results

During the study period, among 1074 patients with solid tumors, 77 episodes of GNB bacteremia occurred in 59 admitted patients. The annual incidence rate was 32.1 cases per 1000 patient admissions. Nearly half (48%) of these episodes were attributed to MDR strains. The characteristics of patients in the two study groups (MDR-GNB and non-MDR-GNB) are detailed in Table 1. The median age of the cohort was 61 years (16-86 years). A total of 41 (53.25%) episodes occurred in females. The most prevalent type of cancer among patients with GNB BSI was pancreaticobiliary cancer (38.96%), followed by gastrointestinal (GI) cancer (22.08%). Only three patients exhibited neutropenia at the time of the BSI episode.

The causative organisms of the 77 episodes of GNB BSI were *E. coli* (37), *K. pneumoniae* (24), *Pseudomonas aeruginosa* (12), and *Acinetobacter baumannii* (4). A total of 37 of these episodes (60.6%) were caused by organisms resistant to multiple drugs. A total of 25 (40.98%) of the *Enterobacterales* group organisms were identified to be ESBL-producing strains, and seven (11.47%) were categorized as CRE. Metallo-β-lactamase (MBL) was detected in 75% of the CRE isolates, either alone or in combination with OXA-48. A total of 10 of 12 (83.3%) *Pseudomonas* species isolates were pan-susceptible, whereas three of four *A. baumannii isolates* were MDR.

The primary sources of bacteremia were biliary (33.77%), intra-abdominal (20.78%), and line-related (20.78%). The MDR-GNB group exhibited higher frequencies of diabetes mellitus, previous antimicrobial exposure, and recent surgical procedures. Patients with GI tumors and pancreaticobiliary tumors had higher rates of MDR-GNB, with 54.5% (six of 11) of patients with GI tumor and 53.3% (16 of 30) of patients with pancreaticobiliary tumor had MDR-GNB. In the univariate analysis, previous antimicrobial exposure was identified as a risk factor for MDR-GNB bacteremia (odds ratio 13.99, 95% confidence interval 2.37-82.82, $P = 0.0004$), which remained significant in the multivariable logistic regression model ($P = 0.00036$). Table 2 provides a summary of the results of the univariable and multivariable analyses assessing the factors potentially associated with MDR-GNB.

The MDR-GNB group was also associated with an increase in the length of hospital stay (median: 23 vs 10.5 days, $P = 0.0011$) and an elevated risk of recurrence (35.14% vs 5%, $P = 0.0048$). There was no statistically significant difference in the 30-day crude mortality between the two groups.

Discussion

This retrospective cohort study was conducted to shed light on the prevalence of GNB BSI, the risk factors for MDR, and the outcomes of BSI in patients with solid tumors. Our study found that the annual incidence of BSI was 32.1 cases per 1000 patient admissions of individuals with solid malignancies. This incidence is higher than the rates reported from developed countries [3,7]. However, our cohort of patients is unique because all had advanced solid malignancies. Consistent with previous research, our study found that BSI events occurred mostly in patients with hepato-biliary and GI malignancies [2,8].

Our study found that almost half of the GNB BSI episodes were caused by MDR strains, with biliary, intra-abdominal, and line-related infections being the primary sources of bacteremia. Previous antibiotic therapy was identified as a risk factor for MDR-GNB bacteremia among patients with cancer, which aligns with the widely acknowledged contribution of antibiotic exposure to bacterial resistance [9]. Multi-drug resistance was associated with prolonged hospital stay and an increased risk of recurrent bacteremia. However, there was no significant difference in 30-day crude mortality between the MDR-GNB and non-MDR-GNB groups, which is consistent with existing literature [2,3,8].

Our study concurred with the reported trend of predominant causes of GNB bacteremia: *E. coli* and *Klebsiella pneumoniae* were the most prevalent organisms involved in GNB BSI [5,6]. BSI caused by *Enterobacterales* showed 40.9% were ESBL-producing isolates and 11.4% were carbapenem-resistant, with 75% carrying the MBL gene. Although, the rate of CRE (11.47%) was lower than previously reported in Oman, it was consistent with similar distributions of causative organisms seen in other studies [10].

The limitations of the study include its monocentric nature, small sample size, and retrospective design. However, the findings contribute significantly to our understanding of GNB infections in patients with cancer with solid tumors in Oman. It showed that intra-abdominal infections were the most common source of infection and previous antibiotic was an independent risk factor for MDR. ESBL was the predominant pattern of resistance. CRE were lower than reported, with a predominance of MBL. The findings emphasized the importance of tailoring guidelines for managing infections and highlighted the need for further research and surveillance in such cohort of patients.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

Approved (CCCRC - 37 – 2022).

Authors' contributions

George M. Varghese: Contributed to study design, writing the manuscript, and final review of the manuscript. **Bassem Awada:** Contributed to data collection and writing the manuscript. **Athar Khirbash Al-Khirbash:** Contributed to data collection. **Sumbel Mumtaz:** Contributed to data collection. **Jorge Abarca:** Contributed to reviewing and writing the manuscript. **Hasan Al-Sayegh:** Contributed to conducting the data analysis and reviewing the manuscript. **Manyando Milupi:** Contributed to reviewing the manuscript. **Augustin Emilio Garcia:** Contributed to reviewing the manuscript. **Munjid Al Harthy:** Contributed to reviewing the manuscript. **Issa Al Qarshoubi:** Contributed to reviewing the manuscript. **Khalid Al Baimani:** Contributed to reviewing the manuscript.

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