

# Intersection of Cancer and Sepsis: Molecular Characterization of Bacterial Pathogens and Antimicrobial Resistance in Hematological Patients from Erbil, Iraq

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## ABSTRACT

**Background and Objective:** Sepsis remains a leading cause of mortality in patients with hematological malignancies, particularly in settings with escalating antimicrobial resistance (AMR). This study characterized bloodstream pathogens, resistance phenotypes, and genetic determinants among septic hematological cancer patients in Erbil, Iraq.

**Methods:** A nine-month observational study (September 2024–March 2025) enrolled 80 patients (40 septic, 40 non-septic controls). Blood cultures were processed using the BacT/ALERT system. Antimicrobial susceptibility testing was performed using VITEK 2 Compact and Kirby–Bauer methods. Resistance genes were detected using the BioFire FilmArray BCID panel. Statistical analysis was conducted using SPSS v25 ( $p < 0.05$ ).

**Results:** Septic patients were significantly older than controls ( $49.2 \pm 21.5$  vs.  $32.8 \pm 21.2$  years;  $p = 0.0009$ ). Gram-negative pathogens predominated (55%). *Escherichia coli* (22.5%) was the most frequent isolate, followed by *Staphylococcus hominis* (15%). Gram-positive isolates exhibited universal resistance to ceftazidime and penicillin (100%) and high resistance to oxacillin and erythromycin (88.9%), while linezolid retained 83.3% activity. Gram-negative isolates demonstrated marked resistance to cefotaxime (90.9%), ampicillin (81.8%), and imipenem (63.6%). The most prevalent resistance genes were blaCTX-M (22.7%) and NDM (9.1%) among Gram-negative isolates and mecA/mecC (11.1% each) among Gram-positive isolates.

**Conclusion:** The high prevalence of multidrug-resistant pathogens, including carbapenem-resistant strains, underscores the urgent need for molecular surveillance and region-specific antimicrobial stewardship in hematological oncology settings.

**Keywords:** hematological malignancy, Iraq, bloodstream infection, antimicrobial resistance genes

## Article Information

Submission Date: 22/7/2025  
Revision date: 28/7/2025  
Acceptance date: 7/9/2025  
Publishing date: June 2026

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## INTRODUCTION

Currently, cancer has emerged as a prevalent disease in the world. It is considered the second leading cause of mortality within developed countries.<sup>1</sup> Cancer patients have impaired immune systems, either due to the malignancy itself or due to chemotherapy and radiation therapy administration, that lead to susceptibility to infection, including bacterial sepsis.<sup>2</sup> Sepsis has become one of the most common causes of death in non-cardiac intensive care units across many countries.<sup>3</sup> Sepsis is a life-threatening condition that occurs when the body's response to infection causes widespread inflammation, leading to tissue damage, organ failure, and potentially death. It is particularly dangerous in immuno-compromised individuals, such as cancer patients.<sup>4,5</sup>

Sepsis is one of several critical factors that were independently linked with increased mortality rates among cancer patients.<sup>6</sup> Cancer patients, who are often found in a state of severe immunosuppression, cause a significant risk of experiencing serious infections that can ultimately lead to life-threatening sepsis.<sup>7</sup> Challenge for the global healthcare system, facing many countries. However, new antibiotics are being used, and antibiotic resistance has emerged. Consequently, the issue elevated significantly, which leads to difficulties in the treatment of bacterial infections.<sup>8</sup> Cancer patients are experiencing severe bacterial infections because of impairment of their immune systems for a prolong time resulting in high rates of morbidity and mortality. They are also most susceptible to the consequences of AMR due to inappropriate use of broad-spectrum antibiotics. This current crisis imposes immediate global action to combat bacterial infection, antibiotic resistant bacteria and sepsis.<sup>9,10</sup> This study aims to investigate the bacterial isolates, antibiotic sensitivity patterns, and antibiotic resistance genes in cancer patients with and without sepsis, aiming to enhance the understanding of bacterial infections and resistance mechanisms in this vulnerable population. Molecular data on bloodstream pathogens and resistance determinants in haematological malignancy patients from Iraq are limited, despite the growing global burden of sepsis and antimicrobial resistance (AMR) among cancer patient.<sup>12</sup> We therefore hypothesized that septic hematological cancer patients in Erbil have a high prevalence of multi-drug-resistant pathogens driven by clinically significant resistance genes, necessitating region-

specific surveillance and antimicrobial stewardship strategies.

## METHODS

### Study design and sample collection

This observational study was conducted over nine months (September 2024-March 2025) at Nanakali Hospital in Erbil, Iraq. Eighty hematological cancer patients were enrolled: 40 cancer and sepsis-positive while 40 had cancer but without sepsis (control group), The sample size (n=80) was determined based on the number of eligible patients admitted during the study period and feasibility considerations. comparing 50 males and 30 females. Inclusion criteria included patients diagnosed with hematological malignancies, admitted to Nanakali Hospital, with a confirmed bloodstream infection or clinical suspicion of sepsis. Blood samples (5-10 mL) were collected aseptically for culture and biomarker analysis.

### Microbiological identification and susceptibility testing

Microbiological identification and susceptibility testing blood cultures were incubated using the BacT/ALERT automated system. Positive cultures were subculture for bacterial isolation and identification. Antimicrobial susceptibility testing (AST) was performed using the VITEK 2 COMPACT SYSTEM (bioMérieux, France), employing GN and GP cards tailored to organism type.

### Molecular Detection of Resistance Genes

Resistance genes were identified using the BioFire BCID Panel, which amplifies and detects nucleic acids from multiple bloodstream pathogens in a single test.

### Statistical Analysis

Data were analyzed using SPSS v25. Continuous variables were reported as mean  $\pm$  SD and compared using unpaired t-tests; categorical variables were analyzed using Chi-square tests. A p-value  $< 0.05$  was considered statistically significant.

### Ethical approval

Ethical approval was obtained from the Research Ethics Committee of Hawler Medical University, College of Dentistry (reference no: HMU/2425196), and written informed consent was obtained from all participants.

## RESULTS

### Patient Demographics

The study included 80 hematological cancer pa-

tients (40 with sepsis and 40 controls), with sepsis cases being significantly older ( $p=0.0009$ ), while

no significant difference was observed in chemotherapy cycles or gender distribution (Table 1).

**Table 1.** Baseline Characteristics by Case and Control

Characteristics	Case (n=40)	Control (n=40)	P value
Age (Years) Mean $\pm$ SD	49.2 $\pm$ 21.5	32.8 $\pm$ 21.2	0.0009
Chemotherapy cycles Mean $\pm$ SD	3.1 $\pm$ 1.7	2.8 $\pm$ 2.2	0.4970

Upon comparing baseline demographics by gender, no significant variations were observed in age or the number of chemotherapy cycles between males and females (Table 2).

**Gender-Based Comparison of Serum Procalcitonin and WBC Levels**

No significant differences were observed between males and females for procalcitonin, WBC, or CRP levels in this cohort (Table 2)

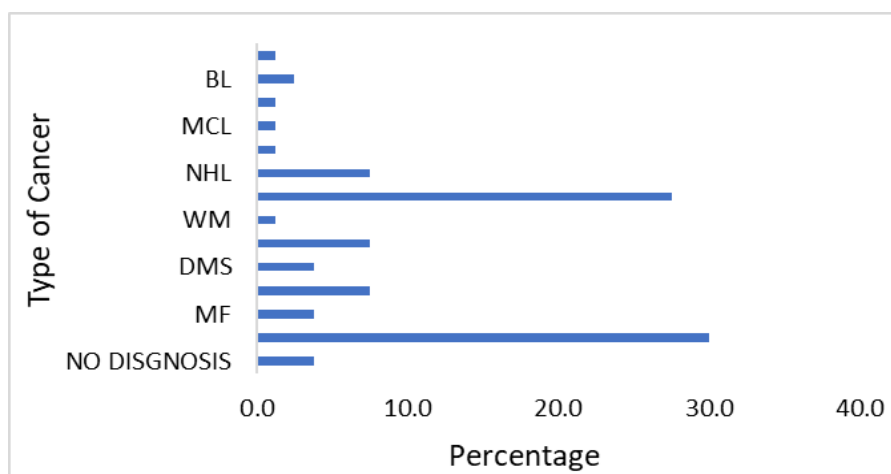
**Table 2.** Sepsis Markers Among Target Population

Characteristics	Male (n=50)	Female (n=30)	P value
Procalcitonin Mean $\pm$ SD (ng/mL)	8.3 $\pm$ 16.4	5.8 $\pm$ 9	0.4453
WBC Mean $\pm$ SD (cells/ $\mu$ L)	13.4 * 10 <sup>3</sup> $\pm$ 39.5 * 10 <sup>3</sup>	3.9 * 10 <sup>3</sup> $\pm$ 7.3 * 10 <sup>3</sup>	0.1971
CRP Mean $\pm$ SD (mg/L)	84.7 $\pm$ 74.1	73.9 $\pm$ 89.5	0.5614

**Distribution of Hematologic Malignancies**

Acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) were the most prevalent haematologic cancers in this group. Lympho-

mas also emerged, albeit with a relatively lower incidence. Infrequent occurrences of rare subtypes, such as Waldenström’s macroglobulinemia and mantle cell lymphoma, were observed.

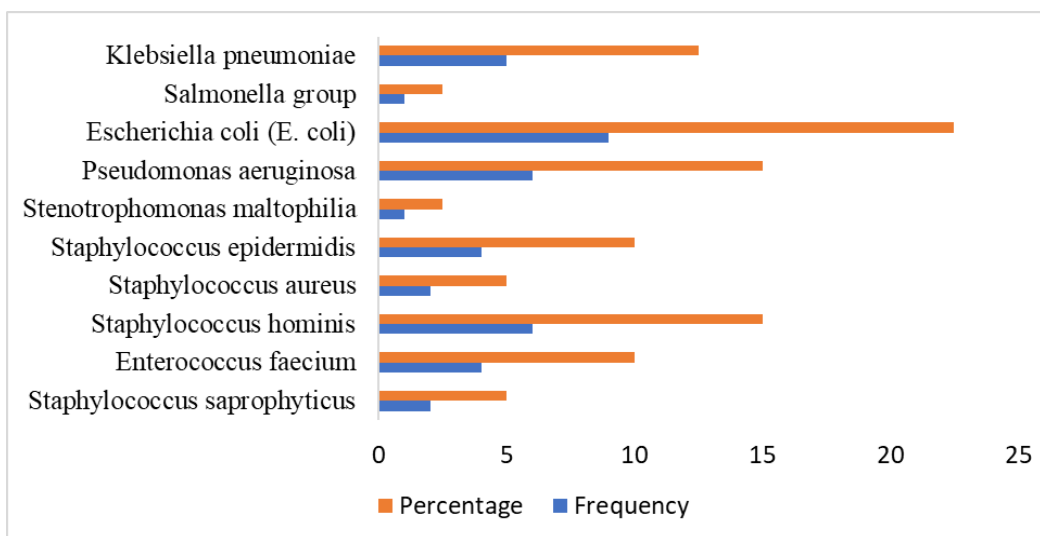


**Figure 1:** The frequency and distribution of cancer types among the patients

**Distribution of Gram-negative and Gram-positive microorganisms**

Gram-negative bacteria accounted for a modest majority at 55%, compared to 45% for gram-

positive strains. Notably, E. coli emerged as the most frequently isolated pathogen, identified in 22.5% of cases.



**Figure 2.** Distribution of microorganisms isolated from hematological cancer patients

### Antibiotic Resistance Profile of Gram-Positive Microorganisms

Gram-positive isolates exhibited complete resistance to both cefoxitin and penicillin. High levels of resistance were also noted against oxacillin,

erythromycin, and fusidic acid. In contrast, linezolid, nitrofurantoin, and tigecycline remained highly effective. Notably, vancomycin resistance was observed in approximately 39% of isolates (Table 3).

**Table 3.** Antibiotic Resistance and Sensitivity Profile of Gram-Positive Microorganisms

Antibiotic Class	Antibiotic	Resistance (%)	Sensitive (%)	Intermediate (%)
Beta-lactams	Cefoxitin	18 (100)	-	-
	Penicillin	18 (100)	-	-
	Oxacillin	16 (88.9)	2 (11.1)	-
Aminoglycosides	Gentamicin	9 (50)	9 (50)	-
	Tobramycin	12 (66.7)	6 (33.3)	-
Fluoroquinolones	Levofloxacin	9 (50)	8 (44.4)	1 (5.6)
	Moxifloxacin	7 (38.9)	7 (38.9)	4 (22.2)
Macrolides	Erythromycin	16 (88.9)	2 (11.1)	-
Lincosamides	Clindamycin	12 (66.7)	6 (33.3)	-
Oxazolidinones	Linezolid	3 (16.7)	15 (83.3)	-
Glycopeptides	Teicoplanin	4 (22.2)	13 (72.2)	1 (5.6)
	Vancomycin	7 (38.9)	11 (61.1)	-
Tetracyclines	Tetracycline	11 (61.1)	7 (38.9)	-
Glycylcycline	Tigecycline	4 (22.2)	14 (77.8)	-
Phosphonic acid derivative	Fosfomicin	6 (33.3)	11 (61.1)	1 (5.6)
Nitrofuran	Nitrofurantoin	2 (11.1)	16 (88.9)	-
Steroid Antibiotics	Fusidic acid	14 (77.8)	4 (22.2)	-
Rifamycins	Rifampicin	8 (44.4)	10 (55.6)	-

### Antibiotic Resistance Profile of Gram-Negative Microorganisms

Gram-negative isolates demonstrated significant resistance to ampicillin, cefotaxime, and trimethoprim. Resistance to carbapenems is concerned,

with imipenem and meropenem exhibiting resistance rates of 63.6% and 54.5%, respectively. Conversely, the greatest sensitivity was noted with colistin, tigecycline, and aminoglycosides, including amikacin and gentamicin (Table 4).

**Table 4.** Antibiotic Resistance and Sensitivity Profile of Gram-Negative Microorganisms

Antibiotic Class	Antibiotic	Resistance (%)	Sensitive (%)	Intermediate (%)
Beta-lactams	Ampicillin	18 (81.8)	3 (13.6)	1 (4.5)
	Tazobactam	16 (72.7)	6 (27.3)	-
	Cefotaxime	20 (90.9)	1 (4.5)	1 (4.5)
	Ceftazidime	15 (68.2)	4 (18.2)	3 (13.6)
	Ceftolozane	13 (59.1)	9 (40.9)	-
	Cefepime	16 (72.7)	6 (27.3)	-
	Imipenem	14 (63.6)	6 (27.3)	2 (9.1)
Aminoglycosides	Amikacin	10 (45.5)	12 (54.5)	-
	Gentamicin	7 (31.8)	15 (68.2)	-
Fluoroquinolones	Ciprofloxacin	15 (68.2)	4 (18.2)	3 (13.6)
Glycylcycline	Tigecycline	6 (27.3)	15 (68.2)	1 (4.5)
Polymyxins	Colistin	6 (27.3)	16 (72.7)	-
Sulfonamides	Trimethoprim	18 (81.8)	4 (18.2)	-

### Genetic Determinants of Antibiotic Resistance in Gram-Positive Microorganisms

Among the Gram-positive isolates, 11.1% possessed the *mecA* gene, whereas an additional 11.1% had *mecC*. Several also possessed *vanA* or *vanB* genes. Notably, 44.4% of the isolates exhibited no identifiable resistance genes; yet, the existence of vancomycin resistance markers is concerning (Table 5).

**Table 5.** Antibiotic Resistance Gene Profile in Gram-Positive Microorganisms

Resistance Gene	Frequency (%)
Absence	44.4
MecA	11.1
MecA/C	5.6
VanA	5.6
VanB	5.6
Merj	11.1
MecC	11.1
MecA and VanA	5.6
Total	100.0

### Genetic Determinants of Antibiotic Resistance in Gram-Negative Microorganisms

The predominant resistance gene detected among the Gram-negative isolates was *blaCTX-M*, found in roughly 23% of samples, with numerous variations of NDM. Remarkably, almost 41% of isolates had no identifiable resistance genes, underscoring significant variability in resistance patterns (Table 6).

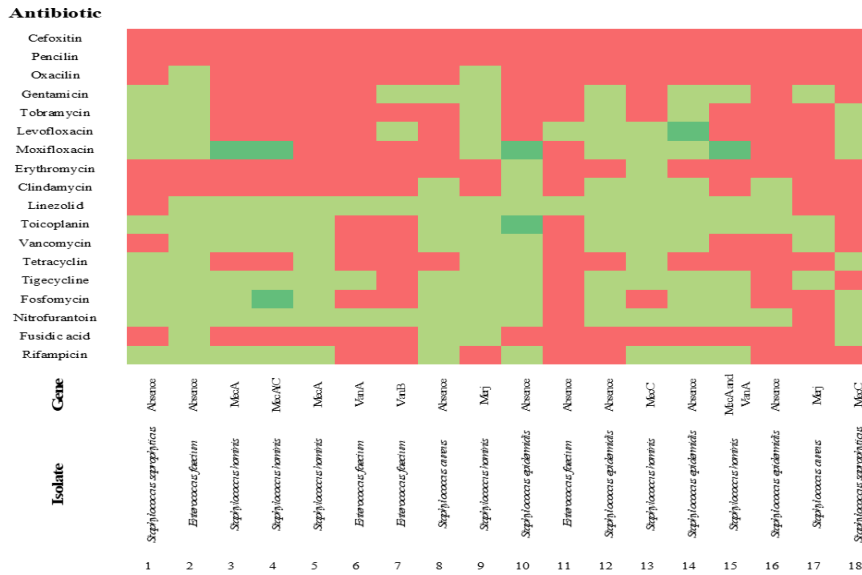
**Table 6.** Antibiotic Resistance Gene Profile in Gram-Negative Microorganisms

Resistance Gene	Frequency (%)
Absence	40.9
IMP	4.5
NDM	9.1
BlaCTX-M	22.7
VIM	4.5
CTXM	4.5
NDM and OX48LIKE	4.5
NDM and CTX	4.5
NDM and BlaCTX-m	4.5
Total	100.0

### Heat map data analysis for Gram-positive

The analysis revealed consistent resistance to both cefoxitin and penicillin among all isolates. Methicillin and vancomycin resistance varied, corresponding primarily to the presence of *mecA/C* and *vanA/B* genes. Notably, there was widespread re-

sistance to fusidic acid, even in the absence of detectable *fusB* genes. Sensitivity to linezolid, aminoglycosides, fluoroquinolones, tetracycline, fosfomycin, and rifampicin ranged considerably, reflecting a heterogeneous resistance profile among the Gram-positive isolates.

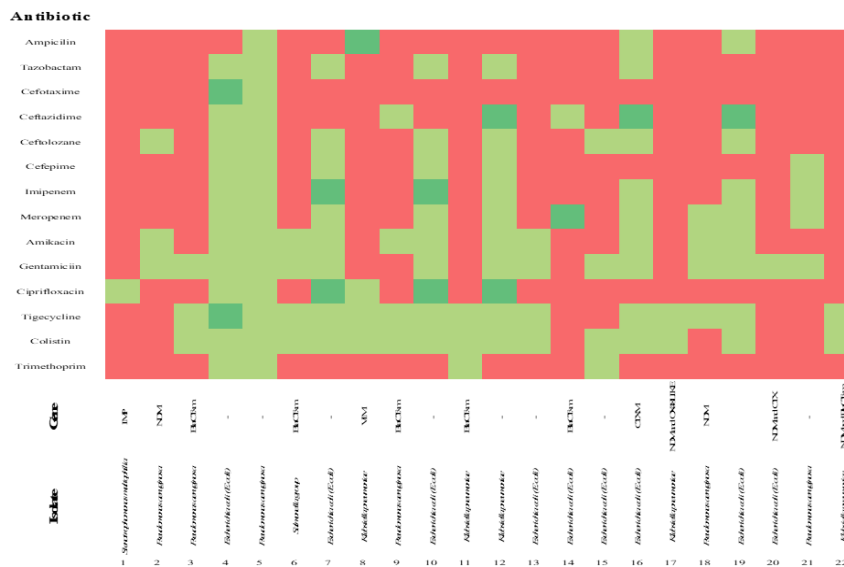


**Figure 3.** Antibiotic resistance profiles across Gram-positive and associated resistance genes: red (resistance), green (sensitivity), blue (not tested), TB tools

### Heat map data analysis for Gram-negative

The heat map clearly demonstrated widespread resistance to  $\beta$ -lactams and carbapenems, primarily linked to the presence of *bla*CTX-M and carbapenemase genes. In contrast, colistin and tigecycline generally remained effective against most

isolates. Interestingly, approximately 41% of isolates did not harbor the expected resistance genes, indicating that alternative, possibly uncharacterized, mechanisms may also play a significant role in mediating resistance.



**Figure 4.** Antibiotic resistance profiles across Gram-negative and associated resistance genes: red (resistance), green (sensitivity), blue (not tested), TB tools

## DISCUSSION

Sepsis, a life-threatening condition, drives high mortality and morbidity in hospitalized patients, and sepsis during neutropenia is a major cause of mortality in hematological cancer patients.<sup>13,14</sup>

Therefore, this study provides critical insights into the sociodemographic, microbiological profiles, antibiotic resistance patterns, and genetic determinants of resistance among hematological cancer patients with sepsis, a population at high risk of life-threatening infections due to immunosuppression from both malignancy and chemotherapy. The findings highlight the urgent need for customized antimicrobial strategies in this vulnerable cohort.

According to the results of microbiological analysis, Gram-negative was observed in 55% (n=22) blood samples while Gram-positive was observed in 45% (n=18) blood samples. Similarly, Gram-negative bacteria were the predominant microorganisms (84.9%) among cancer patients with febrile neutropenia in Iran (aged:  $43.5 \pm 24.98$  years old).<sup>15</sup>

According to the results, microbiological analysis identified a diverse spectrum of pathogens across the 40 positive samples (Figure 2). Gram-negative bacteria were more prevalent (55%, n = 22) than Gram-positive bacteria (45%, n = 18). *Escherichia coli* (22.5%, n = 9) was the most frequently isolated pathogen, followed by *Staphylococcus hominis* (15%, n = 6). *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were also predominant (12.5% each, n = 5), while *Staphylococcus epidermidis* and *Enterococcus faecium* each accounted for 10% of cases (n = 4). Less common isolates included *Staphylococcus saprophyticus* and *Staphylococcus aureus* (5% each, n = 2). Cumulatively, *E. coli* and *S. hominis* were the two most prevalent pathogens. The rising number of cases identifying *Staphylococcus hominis novobiosepticus* in biological specimens highlights its potential virulence and clinical significance.<sup>16</sup>

In this study, universal resistance (100%) was observed for cefoxitin and penicillin among Gram-positive pathogens, while oxacillin (88.9%), erythromycin (88.9%), and fusidic acid (77.8%) also showed high resistance rates. Linezolid (83.3% sensitive) and nitrofurantoin (88.9% sensitive) demonstrated strong efficacy. Notably, vancomycin resistance was observed in 38.9% of isolates, with 61.1% remaining sensitive. These results showed significant resistance to first-line antibiotics (beta-lactams, macrolides) among Gram-

positive microorganisms, while linezolid, nitrofurantoin, and tigecycline (77.8% sensitive) showed high sensitivity.

Similarly, while our Gram-negative isolates exhibited substantial resistance to carbapenems (63.6% to imipenem, 54.5% to meropenem), the Jordanian study documented full carbapenem susceptibility among ESBL-producing organisms and *Enterobacter* species, with 83.4% sensitivity in *Pseudomonas aeruginosa*.

The high resistance to  $\beta$ -lactams and carbapenems observed in this study may be mechanistically linked to the dissemination of extended-spectrum  $\beta$ -lactamases (ESBLs) and carbapenemase-producing genes such as blaCTX-M and NDM. These enzymes hydrolyze broad-spectrum cephalosporins and carbapenems, significantly limiting therapeutic efficacy. In addition, selective antibiotic pressure in immunocompromised hematological patients, frequent hospitalization, and repeated exposure to broad-spectrum agents may accelerate horizontal gene transfer and clonal expansion of multidrug-resistant strains.

The observed distribution of antibiotic resistance genes among Gram-positive and Gram-negative microorganisms in our study aligns with global patterns of resistance. In our study, the most frequently detected resistance genes were *mecA* (11.1%, n = 2) and *mecC* (11.1%, n = 2), followed by *merJ* (11.1%, n = 2). The *mecA/C* combination was identified in 5.6% of isolates (n = 1), while *vanA* and *vanB* were each detected in 5.6% of isolates (n = 1). Notably, 44.4% of isolates (n = 8) showed no detectable resistance genes. Among gram-negative isolates, the most prevalent resistance gene was blaCTX-M (22.7%, n = 5), followed by NDM (9.1%, n = 2). Other detected genes included IMP (4.5%, n = 1), VIM (4.5%, n = 1), CTX-M (4.5%, n = 1), and combinations of NDM + OXA-48-like (4.5%, n = 1), NDM + CTX-M (4.5%, n = 1), and NDM + blaCTX-M (4.5%, n = 1). Notably, 40.9% (n = 9) of isolates harbored no detectable resistance genes. Notably, a considerable proportion of phenotypically resistant isolates lacked detectable resistance genes. This phenotypic-genotypic discrepancy may be explained by alternative resistance mechanisms not covered by the molecular panel, including efflux pump overexpression, porin channel mutations reducing antibiotic permeability, chromosomal mutations affecting target sites, biofilm-associated resistance, or the presence of uncharacterized resistance

genes. These findings underscore the complexity of antimicrobial resistance and highlight the limitations of targeted molecular diagnostics when used in isolation. Multiple resistance mechanisms were observed, with blaCTX-M being the dominant gene in the studied cohort. In this study the prevalence rate of vanA/B gene was (21.4%), this finding can be considered as a study reported that the sensitivity and specificity of Film Array blood culture identification panel was 100%.<sup>17</sup> This study has certain limitations, including the relatively small sample size and the use of a targeted molecular panel that may not detect all resistance determinants. Future studies incorporating whole-genome sequencing and larger multicenter cohorts are warranted to provide a more comprehensive understanding of resistance mechanisms in this population.

### Recommendations

- Enhance Antimicrobial Stewardship: Implement robust programs based on local surveillance data to guide appropriate antibiotic use and preserve the efficacy of last-resort agents.
- Integrate Rapid Molecular Diagnostics: Utilize tools like the BioFire panel for rapid pathogen and resistance gene identification to enable timely, targeted therapy over broad empirical treatment.
- Prioritize Effective Agents: Consider linezolid and tigecycline in empirical regimens for high-risk septic patients at Nanakali Hospital, pending susceptibility results.
- Conduct Further Research: Investigate the underlying mechanisms (e.g., efflux pumps, porin loss) in phenotypically resistant isolates that lack common resistance genes to fully understand the local resistome.
- Strengthen Infection Control: Reinforce infection prevention and control measures to limit the transmission of MDR organisms within the hospital environment.

### CONCLUSION

This study concludes that multidrug-resistant bacterial infections are highly prevalent among septic hematological cancer patients in Erbil. The microbiological landscape is dominated by Gram-negative pathogens like *E. coli* and resistant Gram-positive organisms such as *S. hominis*.

- Extensive resistance to first-line antibiotics, including  $\beta$ -lactams and carbapenems, severely

limits empirical treatment options.

- The presence of critical resistance genes (blaCTX-M, NDM, mecA) confirms a high-risk molecular epidemiology
- A notable percentage of resistant isolates lacked identifiable genes on the tested panel, highlighting the complexity of resistance and the need for broader diagnostic approaches.
- Linezolid and tigecycline demonstrated preserved efficacy, positioning them as crucial therapeutic alternatives in this high-risk patient group.

### Acknowledgments

The authors would like to sincerely thank the staff of Nanakali Hospital for their valuable cooperation and support during data collection and sample acquisition. Their assistance was essential for the completion of this study.

### Conflict of Interest

The authors declare no conflicts of interest.

### Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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