Original Article

GMSMJ

Greater Mekong Subregion Medical Journal

Epidemiology and Antimicrobial Susceptibility of Bloodstream Infections among Febrile Neutropenic Patients at a Thai University Hospital

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Received 19 February 2025 • Revised 21 March 2025 • Accepted 24 March 2025 • Published online 1 May 2025

Abstract:

Background: Febrile neutropenia is a frequent and serious complication in patients undergoing chemotherapy for malignancies, often resulting in significant morbidity and mortality. Understanding local epidemiology and antimicrobial resistance patterns is critical to optimizing empirical therapy for bloodstream infections in this population.

Objective: This study aimed to evaluate the current microbiological profile and antimicrobial susceptibility patterns of bloodstream infections (BSIs) in neutropenic patients at Phramongkutklao Hospital. Additionally, the study sought to identify factors associated with drug-resistant infections and determine their impact on patient mortality.

Materials and Method: This retrospective analytical study reviewed the medical records of febrile neutropenic patients with bloodstream infections at Phramongkutklao Hospital between January 1, 2017, and December 31, 2021. The study aimed to describe the epidemiological trends and antimicrobial susceptibility patterns in febrile neutropenic patients with bacteremia.

Results: A total of 151 febrile neutropenic patients with bloodstream infections were included, with a mean age of 43.42 years. Males constituted 57.6% of the cohort. The most common underlying conditions were acute myeloid leukemia (60.9%), acute lymphoblastic leukemia (25.2%), and multiple myeloma (10.6%). Gram-negative bacteria were the most frequently isolated pathogens (73.5%), primarily *Escherichia coli* (33.7%), *Klebsiella pneumoniae* (19.9%), and *Pseudomonas aeruginosa* (10.6%). Gram-positive bacteria accounted for 19.9% of cases, and fungi 6.6%. Significant associations were observed between urinary catheter use and infections caused by carbapenem-resistant Enterobacterales (CRE) and vancomycin-resistant Enterococci (VRE) ($p < 0.05$), while parenteral nutrition use was linked to methicillin-resistant *Staphylococcus aureus* (MRSA) infections ($p = 0.02$). The overall 14-day mortality rate was 16.6%, with CRE and VRE infections contributing

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significantly to mortality ($p < 0.01$). A Pitt bacteremia score greater than 3 was also identified as a significant predictor of mortality.

Conclusion: Gram-negative bacteria remain the predominant pathogens in febrile neutropenic patients with bloodstream infections. Their prevalence and evolving antimicrobial resistance patterns are critical considerations in guiding empirical therapy at Phramongkutklao Hospital.

Keyword: Febrile neutropenia, Bloodstream infections, Antimicrobial resistance

Introduction

Chemotherapy-induced neutropenia is associated with fever in approximately 10-50% of patients with solid tumors and more than 80% of patients with hematologic malignancies. This fever is primarily attributed to underlying infections.[1] Given the critical nature of this condition, the administration of broad-spectrum antimicrobial therapy, aligned with established clinical guidelines, is imperative.[1-3] Delayed or insufficient initial antimicrobial therapy, especially in septic or septic shock conditions, significantly increases mortality risk.[4] Prompt and appropriate antimicrobial intervention has been shown to reduce morbidity and mortality rates among these patients.

The epithelial barrier serves as the body's primary defense mechanism against microbial invasion. However, chemotherapy disrupts not only cancer cells but also the epithelial lining of organs such as the digestive tract and oral cavity, enabling normal microbial flora to translocate into tissues and the bloodstream.[2,5] Additionally, chemotherapy-induced neutropenia diminishes both the quantity and functionality of neutrophils, the immune system's first responders to infections. As a result, patients undergoing chemotherapy face a heightened susceptibility to infections.[6] Notably, infection-related symptoms in neutropenic patients are often subtle or even asymptomatic, with fever being one of the few common indicators.[7] Thus, managing fever in these patients can be particularly challenging.

Severe complications arising from febrile neutropenia, including septic shock, acute renal failure, respiratory failure, and heart failure, occur in 25-30% of cases, with an associated mortality rate of approximately 11%. In cases involving severe infections, this rate can increase by up to 50%.[3] Mortality is influenced by factors such as comorbidities, the severity and duration of neutropenia, and the presence of bacteremia.[8] Mortality rates differ based on the causative pathogen, standing at 18% for gram-negative bacterial infections and 5% for gram-positive infections. Previous research suggests that gram-negative infections are more prevalent, accounting for 60–70% of cases.[9-13]

Antibiotic resistance poses a significant challenge to treatment outcomes in both the general population and patients with febrile neutropenia.[14,15] Therefore, maintaining up-to-date epidemiological data on pathogens within individual healthcare institutions is essential for optimizing the selection of broad-spectrum antimicrobials. Such data can contribute to lowering the rates of severe complications, morbidity, and mortality. This study aims to examine the epidemiology and antimicrobial susceptibility patterns of bloodstream

infections in febrile neutropenic patients at Phramongkutklao Hospital. Additionally, it seeks to identify factors associated with antimicrobial resistance and mortality in this patient population.

Materials and Method

Ethical considerations

The study received ethical approval from the Institutional Review Board of the Royal Thai Army Medical Department, Bangkok, Thailand (Approval number: IRBRTA 0805/2023). All procedures adhered to the Declaration of Helsinki and complied with the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Study design and participants

This retrospective cohort study was conducted at Phramongkutklao Hospital in Bangkok, Thailand, over a five-year period from January 2017 to December 2021. The study population included patients admitted to the Department of Medicine with febrile neutropenia and confirmed bloodstream infections, based on laboratory findings.

Febrile neutropenia was defined as either a single axillary temperature of ≥ 38.3°C or a sustained temperature of ≥ 38°C for over one hour. Neutropenia was characterized as an absolute neutrophil count (ANC) of < 1,000 cells/mm^3 or < 1,500 cells/mm^3 with a predicted decline to < 500 cells/mm^3 within 48 hours, following the Infectious Disease Society of America (IDSA) guidelines.[16] Patients were excluded if they had known HIV infection, pathogen contamination, infections occurring after the diagnosis of febrile neutropenia, or infections with identifiable causes, such as pneumonia or urinary tract infections.

Procedures

Data were retrospectively extracted from inpatient medical records, including demographic information such as age, gender, comorbidities, underlying malignancy, chemotherapy regimen, and catheter use. Data on causative pathogens and antimicrobial susceptibility in bloodstream infections among neutropenic patients were also reviewed. The clinical presentation at the time of febrile neutropenia diagnosis and subsequent outcomes were documented using standardized case report forms.

Standard laboratory procedures were followed for blood cultures as part of routine clinical practice. Pathogen identification was performed using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibility testing was conducted through automated broth microdilution (Sensititre, Thermo Fisher, Cleveland, OH, USA), with minimum inhibitory concentration (MIC) values determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[17]

Outcomes

The primary outcomes included microbiological isolates and antimicrobial susceptibility patterns. Clinical outcomes were evaluated based on the use of mechanical ventilation, ICU length of stay, incidence of organ failure, and mortality rates. Additionally, the Pitt bacteremia score was analyzed as a prognostic indicator for mortality.[18, 19]

Statistical analysis

The sample size was calculated using data from C. Gudio, et al.[9], which reported a 49% prevalence of bloodstream infections

with isolated cultures. To achieve statistical significance ($p < 0.05$) with 90% power, a minimum of 145 participants was required. Descriptive statistics were reported as means or medians for continuous variables and as frequencies and percentages for categorical variables. Comparisons of categorical variables were performed using the Chi-square test, while continuous variables were analyzed using the independent T-test or Mann-Whitney U test, as appropriate. Statistical analyses were conducted using STATA software, Version 14.0 (StataCorp, College Station, TX, USA). A p-value of < 0.05 was considered statistically significant

Results

Participants were recruited for the study between January 2017 and December 2021. Initially, 253 individuals diagnosed with febrile neutropenia were screened. Of these, 39 participants were excluded due to negative blood cultures, resulting in 214 eligible participants with positive blood cultures. Among these, 58 participants met exclusion criteria, and an additional 5 were excluded due to receiving palliative care or missing data. Consequently, 151 participants were included in the final analysis (Figure 1).

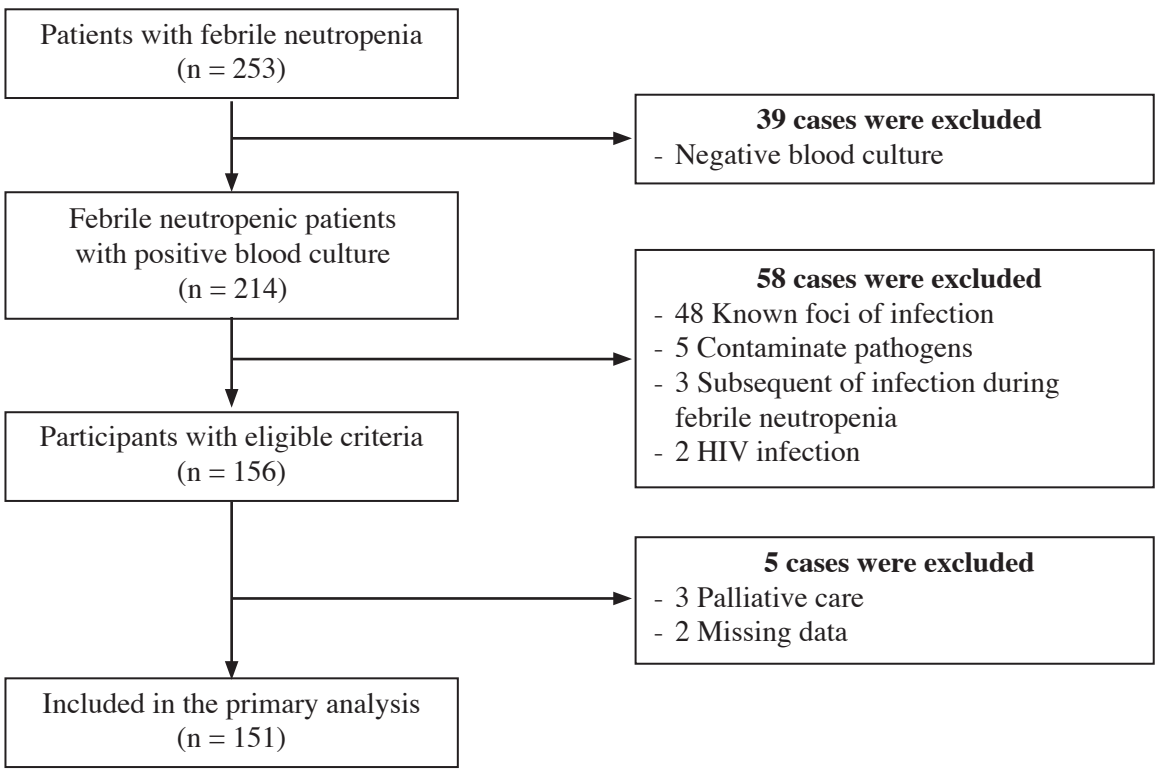

Figure 1 Patient enrollment and the flow of study

Baseline demographic and clinical characteristics are detailed in Table 1. The cohort comprised predominantly male participants (87/151; 57.6%), with a mean age of 43.42 ± 17.04 years. Hypertension was the most prevalent comorbidity, followed by chronic kidney disease and diabetes mellitus.

Hematologic malignancies were the most common underlying conditions (99.3%), with only 0.7% of cases attributed to solid malignancies. Acute myeloid

leukemia (AML) was the most frequent primary diagnosis (60.9%), followed by acute lymphoblastic leukemia (ALL) (25.2%) and multiple myeloma (10.6%). Chemotherapy regimens included FLAG-IDA (20.5%), Hyper-CAVD (17.9%), Int-DAC (13.2%), 7+3 (7.9%), and Hi-DAC (7.9%) (Table 1).

Table 1 Baseline demographic data of 151 participants with febrile neutropenia

Patient characteristics	**Number (%)**
Age, years (mean ± SD)	43.42 ± 17.04
Male sex	87 (57.6%)
Underlying disease	
Hypertension	36 (23.8)
Chronic kidney disease	14 (9.3)
Diabetes mellitus	11 (7.3)
Ischemic heart disease	10 (6.6)
Chronic lung disease	7 (4.6)
Cirrhosis	4 (2.6)
Underlying malignancy	
Acute myeloid leukemia	92 (60.9)
Acute lymphocytic leukemia	38 (25.2)
Multiple myeloma	16 (10.6)
Non-Hodgkin lymphoma	2 (1.3)
Chronic myeloid leukemia	2 (1.3)
Colonic cancer	1 (0.7)
Chemotherapy regimen	
FLAG-IDA regimen	31 (20.5)
Hyper-CVAD regimen	27 (17.9)
Int-DAC regimen	20 (13.2)
7+3 (cytarabie + anthracycline) regimen	12 (7.9)
Hi-DAC regimen	12 (7.9)
Concurrent corticosteroid therapy	50 (33.1)
Previous hospitalization (within 3 months)	139 (92.1)
Previous antimicrobial therapy (within 3 months)	126 (83.4)
Central venous catheter or PICC insertion	132 (87.4)
Urinary catheter insertion	40 (26.5)
Parenteral nutrition	7 (4.6)

Primary outcome

Among the 151 blood culture isolates, Gram-negative bacteria accounted for the majority (73.5%), followed by Gram-positive bacteria (19.9%) and fungi (6.6%). The most common Gram-negative pathogens were *Escherichia coli* (33.7%), *Klebsiella pneumoniae* (19.9%), *Pseudomonas aeruginosa* (10.6%), and *Acinetobacter baumannii* (3.9%). For Gram-positive isolates, *Corynebacterium* species (4.6%), *Enterococcus faecium* (4.6%), and *Staphylococcus aureus* (4.1%) were prevalent. Fungal isolates primarily included *Candida* species (5.2%) (Table 2).

Table 2 Causative organisms of 151 episodes of febrile neutropenia with positive blood culture

Isolated organisms	Number (%)	Isolated organisms	Number (%)
Gram-negative bacteria	**111 (73.5)**	**Gram-positive bacteria**	**30 (19.9)**
Escherichia coli	51 (33.7)	*Corynebacterium* spp.	7 (4.6)
Klebsiella pneumoniae	30 (19.9)	*Enterococcus faecium*	7 (4.6)
Pseudomonas aeruginosa	16 (10.6)	*Staphylococcus aureus*	6 (4.1)
Acinetobacter baumannii	6 (3.9)	Viridans group streptococci	5 (3.3)
Acinetobacter spp.	3 (2.0)	Coagulase-negative staphylococci	5 (3.3)
Aeromonas spp.	3 (2.0)	**Fungi**	**10 (6.6)**
Salmonella spp.	1 (0.7)	*Candida* spp.	8 (5.2)
Stenotrophomonas maltophilia	1 (0.7)	*Trichosporon asahii*	1 (0.7)
		Fusarium spp.	1 (0.7)

Antimicrobial susceptibility analyses revealed that 47.1% of *E. coli* and 43.3% of *Klebsiella pneumoniae* isolates were susceptible to ceftriaxone. Imipenem susceptibility varied across pathogens, with rates of 94.1% for *Escherichia coli*, 73.3% for *Klebsiella pneumoniae*, 81.3% for *Pseudomonas aeruginosa*, and 16.7% for *Acinetobacter baumannii*. Colistin susceptibility was high for *Pseudomonas aeruginosa* (100%) and *Escherichia coli* (90.2%) but lower for *Klebsiella pneumoniae* (56.7%) and *Acinetobacter baumannii* (83.3%). Amikacin exhibited strong activity against *Escherichia coli* (100%), *Klebsiella pneumoniae* (96.7%), and *Pseudomonas aeruginosa* (87.5%), though activity against *Acinetobacter baumannii* was limited (33.3%).

Among Gram-positive bacteremia cases (19.9%), methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in 50%, while coagulase-negative staphylococci (CoNS) were entirely resistant to methicillin (MRCoNS). All strains of MRSA, MSSA, and CoNS were susceptible to vancomycin. Conversely, *Enterococcus faecium* exhibited 100% resistance to vancomycin, qualifying as vancomycin-resistant enterococci (VRE). Viridans group streptococci remained susceptible to ceftriaxone and vancomycin. Detailed susceptibility patterns are presented in Figures 2 and 3.

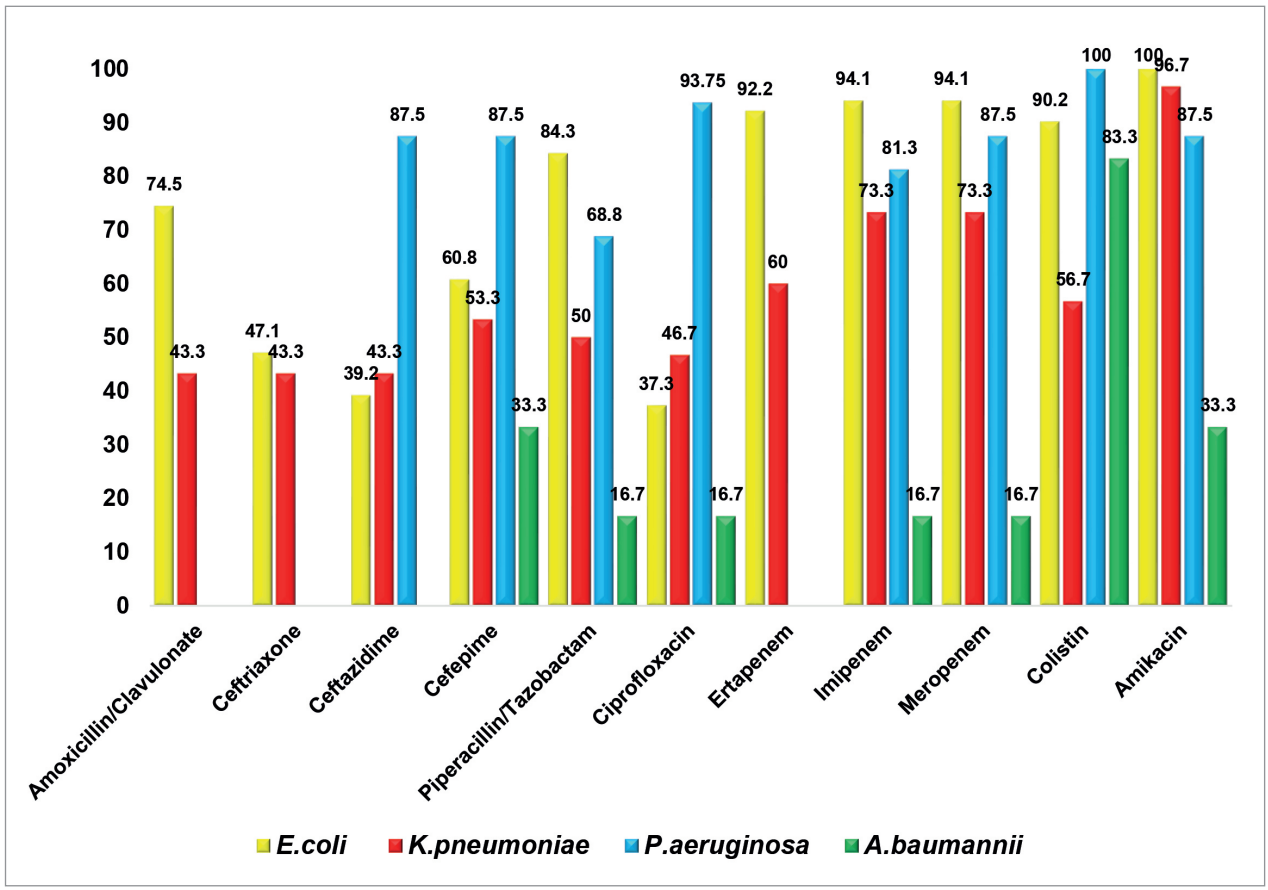

Figure 2 Antimicrobial susceptibility pattern of Gram-negative bacteria

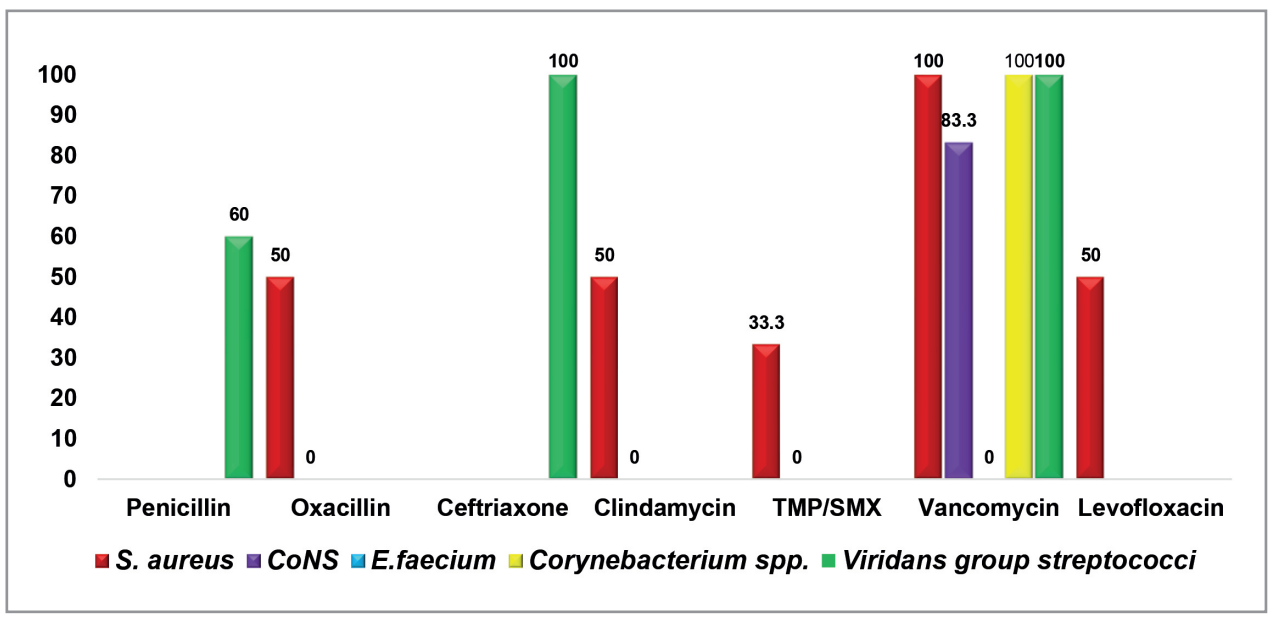

Figure 3 Antimicrobial susceptibility pattern of Gram-positive bacteria

Secondary outcomes

At diagnosis, 61.6% of patients presented with fever without localized symptoms, while 13.9% reported perianal pain, and 12.6% showed signs of thrombophlebitis. Laboratory findings revealed a mean absolute neutrophil count (ANC) of 172.48 ± 394.28 cells/mm^3, with an average neutropenia duration of 17.05 ± 11.92 days.

Complications included respiratory failure requiring mechanical ventilation in 14.6% of patients, critical illness necessitating ICU transfer in 13.9%, and a 14-day mortality rate of 16.6% (Table 3).

Table 3 Clinical presentation and outcomes in patients with febrile neutropenia

Clinical presentation and outcome	**Total episode (n = 151)**
Clinical presentation at diagnosis, n (%)	
Fever	93 (61.6)
Perianal pain	21 (13.9)
Thrombophlebitis	19 (12.6)
Gastrointestinal tract symptoms	6 (4.0)
Respiratory tract symptom	6 (4.0)
Pitt bacteremic score at diagnosis (mean ± SD)	1.78 ± 2.11
Absolute neutrophil count at diagnosis (cell/mm^3; mean ± SD)	172.48 ± 394.28
Duration of neutropenia (days; mean ± SD)	17.05 ± 11.92
Duration of hospitalization (days; mean ± SD)	34.02 ± 16.79
Clinical complication, n (%)	
Mechanical ventilation use	22 (14.6)
Intensive care unit transfer	21 (13.9)
Organ failure*	49 (32.5)
14-day mortality	25 (16.6)

*Organ failure: acute respiratory failure that needs O_2 therapy, acute heart failure, acute kidney injury defined by AKIN criteria, acute hepatocellular injury that AST/ALT elevated > 3UNL.

Subgroup analysis showed that patients with multidrug-resistant (MDR) organism infections had a higher 14-day mortality rate compared to those without MDR infections (50% vs 28.67%, p = 0.06). Specifically, bloodstream infections caused by carbapenem-resistant Enterobacterales (CRE) significantly increased the risk of 14-day mortality (HR 6.1; 95% CI 1.5–24.95; p = 0.01). (Table 4)

Table 4 Fourteen-day mortality rate in subgroup analysis of patients with multidrug resistance organisms infection

Mortality rate	With drug resistance, frequency (%)	Without drug resistance, frequency (%)	HR (95% CI)	p-value
Any MDROs	10 (50)	43 (28.67)	2.49 (0.97-6.40)	0.06
3GCephRE	2 (33)	27 (44.26)	0.63 (0.11-3.70)	0.61
CRE	5 (50)	10 (14.08)	6.1 (1.50-24.95)	0.01
MDR *P. aeruginosa*	0 (0)	5 (33.33)	0.64 (0.02-18.37)	0.79
CRAB	3 (100)	1 (33.33)	11.67 (0.32-422.17)	0.18

Abbreviations: MDROs, Multidrug resistant organisms; 3GCephRE, 3rd generation cephalosporin resistant Enterobacterales; CRE, Carbapenems resistant Enterobacterales; MDR, Multidrug resistant; CRAB, Carbapenems resistant *A. baumannii*

Risk factors for drug resistance included Foley catheter use and mechanical ventilation. Foley catheter insertion was associated with an elevated risk of CRE infection (HR 3.64; 95% CI 1.16-11.44; p = 0.03) and VRE infection (HR 7.79; 95% CI 1.45-41.92; p = 0.02). Similarly, mechanical ventilation significantly increased the likelihood of CRE infection (HR 5.45; 95% CI 1.35-22.04; p = 0.02) (Table 5).

Table 5 Factor associated drug resistance organisms

Factors associated with 3GCephRE	**HR (95% CI)**	**p-value**
• Present of Foley's catheter	0.39 (0.10-1.39)	0.15
• Mechanical ventilator use	0.49 (0.09-2.72)	0.41
• Previous antibiotic use within 3 months	0.58 (0.16-2.13)	0.41
• Previous hospitalization within 3 months	1.59 (0.27-9.33)	0.61
Factors associated with CRE	**HR (95% CI)**	**p-value**
• Present of Foley's catheter	3.64 (1.16-11.44)	0.03
• Mechanical ventilator use	5.45 (1.35-22.04)	0.02
• Previous antibiotic use within 3 months	2.80 (0.33-23.55)	0.34
• Previous hospitalization within 3 months	3.33 (0.18-62.38)	0.42

ROC analysis identified a Pitt bacteremia score of >3 as the optimal cut-off for predicting mortality in bloodstream infections. This score demonstrated a sensitivity of 88%, specificity of 91.3%, a positive predictive value of 66.7%, and a negative predictive value of 97.5% (Figure 4).

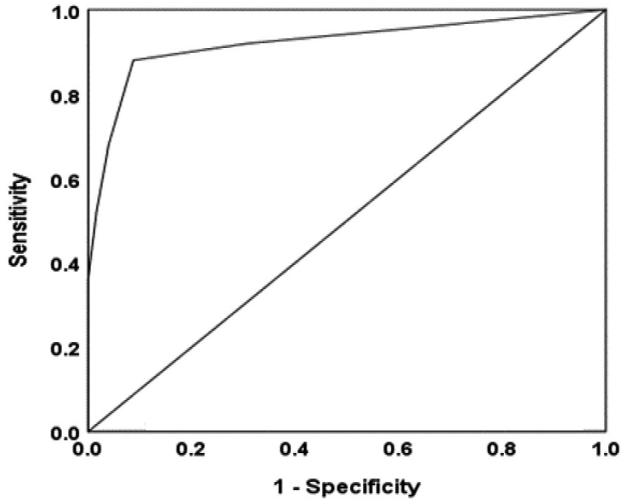

Figure 4 AUROC curve analysis Pitt bacteremic score to predictors of mortality in BSI

Discussion

Febrile neutropenia is a frequent and serious complication among patients with hematologic malignancies undergoing chemotherapy. Consistent with findings from previous studies[1], hematologic malignancies were identified as the predominant underlying cause of febrile neutropenia at Phramongkutklao Hospital. Acute myeloid leukemia, acute lymphoblastic leukemia, and multiple myeloma were the most commonly observed conditions, consistent with findings reported in similar research.[13]

This study reaffirms that Gram-negative bacteria (73.5%) remain the predominant causative agents in febrile neutropenic patients, followed by Gram-positive bacteria (19.9%) and fungi (6.6%). The variability in the incidence of Gram-positive infections compared to previous studies may reflect differences in geographic regions, hospital protocols, and time periods, with reported rates of 29.9%[11], 62%[20], and 67%.[9] While prior institutional data highlighted a higher prevalence of Gram-positive infections, our findings align with international reports identifying Enterobacteriaceae, specifically *Escherichia coli* (33.7%) and *Klebsiella pneumoniae* (19.9%), as the most isolated Gram-negative pathogens.[9, 11, 12, 20] The detection of *Pseudomonas aeruginosa* in 10.6% of cases reinforces its importance as a pathogen requiring coverage in empirical antibiotic regimens for febrile neutropenic patients, as evidenced by incidence rates of 7%[9], 14%.[12] Notably, this study identified an increased incidence of candidemia (5.2%), compared to previous studies reporting 1.5%.[9] which may be linked to the rising use of central venous catheters, peripherally inserted central catheters (PICC), and parenteral nutrition. Clinicians should consider fungal infections, such as candidemia, in patients who do not respond to antibiotic therapy, even though these infections occur less frequently than bacterial ones. Delayed recognition of fungal infections can lead to worse outcomes, so early consideration is crucial, especially in immunocompromised individuals or those with prolonged hospital stays.

The escalating prevalence of antimicrobial resistance remains a major global challenge in managing bloodstream infections. According to the World Health Organization (WHO) 2024 Bacterial Priority Pathogens List (BPPL), Gram-negative bacterial pathogens continue to be classified as critical threats, particularly carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Enterobacterales* (CRE), and third-generation cephalosporin-

resistant *Enterobacterales* (3GCRE).[21, 22] This study identified a higher resistance rate of Enterobacterales to ceftazidime (58.75%) and fluoroquinolones (58%) compared to previous reports.[23] Additionally, this study found an increased resistance to fluoroquinolones, with a resistance rate of 58%, compared to 38.2%[12] and 26%.[24] However, susceptibility to piperacillin-tazobactam (67.2%) compare with previous studies have reported varying levels of sensitivity, ranging from 53.2%[12], 87.5%[23], to 95%.[24] This trend aligns with the increasing burden of CRE and 3GCRE, which are ranked among the highest-priority pathogens due to their widespread prevalence, resistance mechanisms, and limited treatment options. The carbapenems remains relatively high, underscoring their role in the empirical treatment of resistant Gram-negative infections, According to the current IDSA guidance[25] for the treatment of third-generation cephalosporin resistance, carbapenems are recommended for treating infections caused by these organisms. Nevertheless, the development of carbapenem resistance, as observed in 7.8% of Enterobacterales isolates, similar to previous studies that reported 7.1%.[23] The biofilm-associated resistance increases the persistence of *Klebsiella pneumoniae* in hospital environments, emphasizing the necessity of stringent infection control measures, particularly in immunocompromised populations like febrile neutropenic patients especially those with indwelling catheters.[26] Furthermore, resistance to tigecycline among CRKP strains has been reported in Thailand indicating the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Klebsiella pneumoniae strains. The present further treatment limitations, necessitating the careful selection of combination therapies to optimize patient outcomes.[27]

Given the rising prevalence of drug-resistant Gram-negative infections, healthcare providers must continuously adapt treatment strategies based on local epidemiology. Strengthening antimicrobial stewardship, optimizing infection control, and developing novel therapies are crucial to mitigating multidrug-resistant infections. The persistence of CRAB, CRE, and 3GCRE as WHO critical-priority pathogens highlights the need for a global AMR response. Effective catheter care, environmental disinfection, and targeted antibiotic strategies can prevent recurrent bloodstream infections, particularly those caused by *Pseudomonas aeruginosa*, while enhanced surveillance and antibiotic restrictions help reduce resistance and improve outcomes.

Bloodstream infections are a significant cause of morbidity and mortality in cancer patients with febrile neutropenia.[20] These infections can be reduced by prescribing appropriate empirical antibiotics based on the local antibiotic resistance patterns in hospitals.[4] The 14-day mortality rate of 16.6% is consistent with earlier studies from Thailand, with similar patient characteristics contributing to comparable outcomes 19.2%[11], 19%[28], and 19.7%[23], respectively. The similar mortality rates may be attributed to the comparable age and underlying comorbidities of the patient groups. Drug-resistant infections, particularly CRE infections, emerged as significant contributors to mortality, alongside elevated Pitt bacteremia scores. These findings emphasize the importance of identifying high-risk patients and tailoring treatment strategies accordingly. This finding aligns with studies on drug-resistant infections in the general patient population, not just those with neutropenia.[15]

This study highlights the evolving epidemiology of pathogens and resistance patterns in febrile neutropenic patients.

Ongoing surveillance of local pathogens and their susceptibility is essential to inform empirical antibiotic policies. Additionally, the increasing incidence of candidemia necessitates greater awareness and consideration in treatment protocols.

This study has several limitations. As a single-center study, the findings may not represent the broader population across Thailand. The retrospective design relied on medical records, leading to potential missing data and confounding variables that may affect the analysis of drug resistance. Future research should expand to multicenter studies across hospitals of varying levels—primary, secondary, and tertiary care to identify additional risk factors for drug-resistant infections in febrile neutropenic patients. Such studies will enhance the generalizability of findings and provide a more comprehensive understanding of this critical issue.

Conclusion

Gram-negative bacteria continue to pose significant challenges in managing febrile neutropenic patients with bloodstream infections. Infections caused by multidrug-resistant Gram-negative organisms are associated with increased morbidity and mortality, highlighting the need for appropriate empirical antimicrobial therapy guided by local resistance patterns. Continuous surveillance of antimicrobial resistance trends is imperative to optimize treatment strategies, prevent complications, and improve outcomes in this vulnerable population.

Conflict of Interest

Role of the funding source

The authors have no financial disclosures. The researchers had full and unrestricted access to all study data and maintained sole responsibility for the decision to submit this manuscript for publication.

Acknowledgements

This research would not have been possible without the exceptional dedication and support of the nurses and healthcare personnel at the Department of Medicine, Phramongkutklao Hospital, who provided invaluable assistance in patient care and data collection. The authors also extend their gratitude to Miss Dollapas Punpanich, statistician, for her expert guidance and support in analyzing the collected data.

ICMJE Statement

Chutchawan Ungthammakhun contributed to the conception and design of the work. Nalinporn Deechat was responsible for the acquisition of data. Both Chutchawan Ungthammakhun and Nalinporn Deechat contributed to the analysis and interpretation of the data. Nalinporn Deechat drafted the manuscript, and the manuscript was revised collaboratively by the authors. Both authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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