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# The role of blood culture in the management of febrile neutropenia in patients with hematological malignancies at Hiwa Hospital in Iraq

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## Abstract:

**BACKGROUND:** We have some serious complications during the treatment of hematological malignancies that adversely affect the outcome. Febrile neutropenia (FN) is one of the most common serious complications that carry a mortality rate of 10%–34%. Conventional microbiological cultures are still routinely investigated to identify the offending microorganisms causing this condition, then to treat according to the results of sensitivity testing. At the same time, factors affecting this outcome need to be explored to lower this high mortality rate.

**OBJECTIVES:** To evaluate the usefulness of blood culture (BC) in determining the antibacterial management plan in immunocompromised adult and pediatric patients being admitted with FN to Hiwa hospital in Sulaymaniyah.

**MATERIALS AND METHODS:** A descriptive retrospective study done at Hiwa Hospital in Sulaymaniyah, Kurdistan region of Iraq on 402 FN episodes admitted to the hospital over 18 months studied. Several variables were taken within the patients through their electronic records being reviewed thoroughly.

**RESULTS:** The positive cultures showed 6 (1.5%) sample fungal, 26 (6.5%) samples Gram-positive bacteria, and 34 (8.5%) sample Gram-negative bacteria. Age (odds ratio [OR] = 1.027) ( $P \leq 0.001$ , confidence interval [CI]: 95%: 1.01–1.042), duration of neutropenia (OR = 1.020) ( $P \leq 0.001$ , CI: 95%: 1.02–1.032), and hospital stay before BC (OR = 1.020) ( $P \leq 0.001$ , CI: 95%: 0.010–0.035) were the predictors of death in patients.

**CONCLUSIONS:** The findings reveal that BC is still a useful intervention in the treatment of FN. Age, the duration of neutropenia, and length of stay in a hospital are the predictive factors of mortality.

## Keywords:

Blood culture, febrile neutropenia, hematological malignancies

## Introduction

Febrile neutropenia (FN) is one of the most serious hematological emergencies that carries elevated risk of morbidity and mortality, in addition to increased cost of treatment and unnecessary interruption in chemotherapy administration.<sup>[1,2]</sup> Hence, early intervention with broad-spectrum

antibiotics is crucial. On the other hand, we need to limit antibiotic exposure to avoid the development of multidrug-resistant bacteria. There is a wide range of variation among different hospitals in the choosing antibiotic protocols to treat those patients, according to the pathogenic bacterial mapping of the area.<sup>[2,3]</sup> Cancer patients are at an increased risk of infection because of the nature of their disease, myelosuppression, defective mucosal barriers caused by chemotherapy and/or immunotherapy, poor nutritional

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status, and prolonged hospitalization, an addition to advanced age.<sup>[4,5]</sup> FN can be prevented in many cancer patients after receiving chemotherapy through using granulocyte colony-stimulating factors (G-CSFs), leading to decreased hospital stay and lowered all-cause mortality, although it is less evident. On the other hand, the use of G-CSF is associated with bone ache and local injection site unpleasant effect.<sup>[6,7]</sup>

FN is defined as an absolute neutrophil count (ANC) ( $\leq 500$  per  $\mu\text{L}$ ) (or  $\leq 1000$  per  $\mu\text{L}$  with a predicted decline to  $\leq 500$  per  $\mu\text{L}$  over the next 48 h) with a coexisting once oral body temperature of more than or equal to  $38.3^\circ$  (orally) or more than  $38.0^\circ$  Celsius maintained over 1 hour.<sup>[8]</sup>

Blood culture (BC) is still the gold standard test to guide further management of this fatal condition. Nevertheless, there are several drawbacks in managing FN driven by BC, such as the intricate and extended growth period of bacteria, running of antibiotics before taking blood samples, false alarm rate from skin contamination, or insufficient sample size. On average, to obtain a positive conventional BC result, 6–24 h are needed, then 18–24 h for the susceptibility pattern.<sup>[2]</sup> BC yields a positive result in 10%–25% of samples taken, which is relatively low. Even though FN is caused by bacteria most of the time.<sup>[9,10]</sup>

We conducted this study to evaluate the usefulness of BC in determining the antibacterial management plan in immunocompromised adult and pediatric patients diagnosed with hematological malignancies being admitted with FN to Hiwa hospital in Sulaymaniyah, Iraq, over 18 months.

## Materials and Methods

This descriptive and retrospective study was conducted at Hiwa Hospital in Sulaymaniyah, Kurdistan region of Iraq, a 250-bed teaching tertiary healthcare facility delivers all hemto-oncology services to a population of more than 3,000,000 people. We included all FN episodes in adults and pediatric patients with hematologic malignancies such as acute lymphoblastic leukemia, acute myeloblastic leukemia, myelodysplastic syndrome, nonHodgkin lymphoma, Hodgkin lymphoma, aplastic anemia (AA), multiple myeloma, plasma cell leukemia, hematopoietic stem cell transplantation for various indications, AA, and Fanconi anemias, admitted to the hospital from December 2023 till June 2025. High-quality data on demographic characteristics, microbiological results, prophylactic antibiotics, and outcomes were collected directly from the electronic medical records. We excluded those patients without accurate data such as

temperature records missing or insufficient BC due to small sample size. The scientific committee board of Hiwa hospital approved the study. Informed consent was not required due to the study's retrospective nature. We did not exclude patients on prophylactic or therapeutic antibiotics as per our institutions' regulations, neutropenic patients should be on prophylactic antibiotics, and in FN patients should be started on preemptive broad-spectrum antibiotics as soon as possible and BC is mandatory as a standard of care. The presence of fever may indicate insufficient antimicrobial coverage that BC may be positive in spite of antibiotic usage.

Four hundred and two patients admitted to the hospital with FN were included in the study. The febrile neutropenic episode was defined according to the guidelines mentioned elsewhere. The clinical samples collected from blood at FN onset as per the hospital rules and the on-call doctor. The samples were either taken from peripheral blood or both peripheral blood and central venous (CV) line if the patient was having a CV line, then it was transferred to the microbiology unit of the laboratory using BD BACTEC ped plus/F culture vials. Samples were incubated at  $35^\circ\text{C}$  in the Bactec FX system, Becton, Dickinson, and Company, USA, an automatic device flags microbial development by detecting  $\text{CO}_2$  production. On having a positive sample, a Gram stain was then carried out to categorize the bacteria as either Gram-positive or Gram-negative culture. Positive cultures were subcultured onto blood and MacConkey agar plates and incubated at  $37^\circ\text{C}$  under both aerobic and anaerobic conditions for 24–48 h. Additional biochemical tests were conducted when needed to refine identification. Antibiotic susceptibility testing was performed using the BD Phoenix™ M50 Automated Microbiology System, Becton, Dickinson, and Company, USA, an automated machine that gives minimum inhibitory concentration figures and interpretive classes. Cultures were considered negative if no growth was sensed after 5 days of incubation, even though certain circumstances, it was given more time.

## Statistical analysis

Assessment of the usefulness of BC and factors affecting the outcome of FN management analyzed by SPSS v27, (IBM, New York, USA). With  $P \leq 0.05$  was considered statistically significant,  $P$  value based on the Chi-square and fisher exact tests.

## Ethical approval

This study was approved by the research ethics committee at Hiwa hospital, by document no. 336 on April 15, 2025. Informed patient consent waived by the ethical committee because of the nature of the study.

## Results

A total of 402 FN episodes included in this retrospective study. The positive cultures showed 6 (1.5%) sample fungal, 26 (6.5%) samples Gram-positive bacteria, and 34 (8.5%) sample Gram-negative bacteria. Age (odds ratio [OR] =1.027) ( $P \leq 0.001$ , confidence interval [CI]: 95%: 1.011–1.042), duration of neutropenia (OR = 1.020) ( $P \leq 0.001$ , CI: 95%: 1.02–1.032), and hospital stay before BC (OR = 1.020) ( $P \leq 0.001$ , CI: 95%: 0.010–0.035) were the predictors of death in patients.

Table 1 gives the demographic data of febrile neutropenic patients with hematological malignancies. The age of the cohort had a mean  $\pm$  standard deviation (SD)  $32.59 \pm 23.840$  years. The highest percentages were noted as in the following age groups, in descending fashion, 111 (27.6%), 102 (25.4%), and 58 (14.4%) patients were having in 50 years and above, 1–9 years, and 30 years and 39 years each. The sex showed 206 (51.2) female patients and 196 (48.8) men. Patients were mainly inhabitants of urban areas, where 188 (46.8%) were staying in the urban regions. The specimens of BC were obtained by sampling the patients, from late 2023 till early 2025, but majority were in 2024 and comprised 364 (90.5%) samples. The mean of hematological parameters for BC positive versus negative were as follows: White blood cell count was 757/738 per mL, ANC 232/237 per mL, hemoglobin 8.8/8.9 g/dL, and platelet count of 50.7/49 per mL.

Three most common comorbidities observed in the study population were hypertension, diabetes mellitus, and hypothyroidism with hypertension, were shown in 35 (8.7%), 14 (3.5%), and 8 (2%) patients, respectively. It is noteworthy that 328 (81.6%) patients did not have a preexisting systemic pathology. The most common chemotherapy regimen that was used includes United Kingdom National Randomised Trial For Children and Young Adults with Acute Lymphoblastic Leukaemia and Lymphoma (UKALL) 13 150 (37.2%) patients, carmustine, etoposide, cytarabine, melphalan (BEAM) 80 (19.9%), fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA) 60 (14.9%), 3+7 50 (12.7%), and decitabine 40 (9.9%). Table 2 has more details.

The mean  $\pm$  SD duration of neutropenia before culture in all patients was  $11.68 \pm 16.573$  days. The longest durations of neutropenia were observed, in the descending order, in the following intervals: 0–9 days, 10–19 days, and 20–29 days, occurring in 247 (61.4%), 89 (22.1%), and 43 (10.7%) patients, respectively.

The mean  $\pm$  SD length of hospital stay prior to BC was  $10.60 \pm 16.754$  days. Among the patients, 244 (60.7%) were hospitalized for 0–10 days before culture, 152 (37.8%)

were hospitalized for 11–49 days, and 6 (1.5%) had been hospitalized for  $\geq 60$  days prior to culture.

Regarding the type of intravenous access used, 126 (31.3%) patients received peripheral venous lines, while 276 (68.7%) patients had central venous lines in place.

The number of BC orders per patient was as follows: 352 (87.6%) patients had one order, 30 (7.5%) had two orders, 11 (2.7%) had three orders, 7 (1.7%) had four orders, and 2 (0.5%) patients had five orders [Table 3].

**Table 1: Demographic information of patients with hematological malignancies with febrile neutropenia**

| Characteristics     |           | Frequency (Percent) |
|---------------------|-----------|---------------------|
| Age (year)          |           | 32.59 $\pm$ 23.840  |
| Age category (year) | 1-9       | 102 (25.4%)         |
|                     | 10-19     | 50 (12.4%)          |
|                     | 20-29     | 37 (9.2%)           |
|                     | 30-39     | 58 (14.4%)          |
|                     | 40-49     | 44 (10.9%)          |
|                     | $\geq 50$ | 111 (27.6%)         |
| Sex                 | Female    | 206 (51.2%)         |
|                     | Male      | 196 (48.8%)         |
| Living area         | Rural     | 110 (27.4%)         |
|                     | Sub rural | 104 (25.9%)         |
|                     | Urban     | 188 (46.8%)         |
| Date the culture    | 2023      | 13 (3.2%)           |
|                     | 2024      | 364 (90.5%)         |
|                     | 2025      | 25 (6.2%)           |

**Table 2: Comorbidities and Type of chemotherapy information of patients with hematological malignancies with FN**

| Characteristics      |                                                           | Frequency (Percent) |
|----------------------|-----------------------------------------------------------|---------------------|
| Comorbidities        | No pre-existing condition                                 | 328 (81.6%)         |
|                      | Cerebrovascular accident, Hypertension                    | 2 (0.5%)            |
|                      | Diabate Mellitus I                                        | 4 (1%)              |
|                      | Diabate mellitus I, Hypertension                          | 13 (3.2%)           |
|                      | Heart Failure                                             | 1 (0.2%)            |
|                      | Hypertension                                              | 35 (8.7%)           |
|                      | Hypertension, Diabate Mellitus I, Ischemic Heart diseases | 1 (0.2%)            |
|                      | Hypertension, Hypothyroidy                                | 7 (1.7%)            |
|                      | Hyperthyroid                                              | 2 (0.5%)            |
|                      | Hypothyroidy                                              | 2 (0.5%)            |
|                      | Ischemic Heart diseases, Hypertension                     | 3 (0.7%)            |
|                      | Diabate Mellitus II                                       | 3 (0.7%)            |
|                      | Diabate Mellitus II, Hypertension                         | 1 (0.2%)            |
| Type of chemotherapy | UKALL                                                     | 150 (37.2%)         |
|                      | BEAM                                                      | 80 (19.9%)          |
|                      | FLAG-IDA                                                  | 60 (14.9%)          |
|                      | 3+7 (Cytarabine Daunorubicin)                             | 50 (12.7%)          |
|                      | DECITABINE                                                | 40 (9.9%)           |
|                      | OTHER                                                     | 23 (5.7%)           |

An evaluation into the history of consuming antibiotics among the study population demonstrated that 107 (26.6%) individuals had no previous consuming. Among those prescribed antibiotics, the most prescribed agent was levofloxacin 55 (13.7%) and ciprofloxacin 25 (6.2%), while 179 (45%) of the patients were on broad-spectrum antibiotics before the BC was taken. All

**Table 3: Duration of neutropenia, Hospital in days and BC order of patients with hematological malignancies with FN**

| Characteristics                                           | Frequency (Percent) |
|-----------------------------------------------------------|---------------------|
| Duration of neutropenia till the culture was taking       | 11.68±16.573        |
| Hospital in days before the culture                       | 10.60±16.754        |
| Duration of neutropenia till the culture was taking (day) |                     |
| 0-9                                                       | 247 (61.4%)         |
| 10-19                                                     | 89 (22.1%)          |
| 20-29                                                     | 43 (10.7%)          |
| 30-39                                                     | 5 (1.2%)            |
| 40-49                                                     | 5 (1.2%)            |
| 50-59                                                     | 5 (1.2%)            |
| ≥60                                                       | 8 (2%)              |
| Type of IV access                                         |                     |
| Peripheral Venous Lines (PVL)                             | 126 (31.3%)         |
| Central Venous Lines (CVL)                                | 276 (68.7%)         |
| Hospital in days before the culture                       |                     |
| 0-10                                                      | 244 (60.7%)         |
| 11-49                                                     | 152 (37.8%)         |
| ≥60                                                       | 6 (1.5%)            |
| Blood culture order                                       |                     |
| 1                                                         | 352 (87.6%)         |
| 2                                                         | 30 (7.5%)           |
| 3                                                         | 11 (2.7%)           |
| 4                                                         | 7 (1.7%)            |
| 5                                                         | 2 (0.5%)            |

**Table 4: Prior antibiotic consumption of patients with hematological malignancies with FN**

| Prior antibiotic use        | Frequency(percentage) |
|-----------------------------|-----------------------|
| Non                         | 107 (26.6%)           |
| Levofloxacin                | 55(13.7%)             |
| Ciprofloxacin               | 25(6.2)               |
| Amoxicillin-clavulanic acid | 10 (2.5%)             |
| Amoxicillin                 | 9 (2.2%)              |
| Metronidazole               | 8 (1.9%)              |
| Amoxicillin/Azithromycin    | 2 (0.5%)              |
| Azithromycin                | 2 (0.5%)              |
| Cefixime                    | 2 (0.5%)              |
| Ciprofloxacin/Azithromycin  | 1 (0.2%)              |
| Metronidazole               |                       |
| Amoxicillin/Ciprofloxacin   | 1 (0.2%)              |
| Broad spectrum antibiotics  | 179 (45%)             |

**Table 5: Microbial culture result of patients with hematological malignancies with FN**

| Characteristics        | Frequency (Percent) |
|------------------------|---------------------|
| Blood Culture          |                     |
| Negative               | 336 (83.6%)         |
| Fungal                 | 6 (1.5%)            |
| Gram-positive bacteria | 26 (6.5%)           |
| Gram-negative bacteria | 34 (8.5%)           |

the other information about the use of antibiotics before is presented in Table 4.

BC results are summarized in Table 5. The culture results of 6 (1.5%) samples were fungal, 26 (6.5%) sample were Gram-positive bacteria, and 34 (8.5%) sample were Gram-negative bacteria. The culture results were negative in 336 (83.5%) patients.

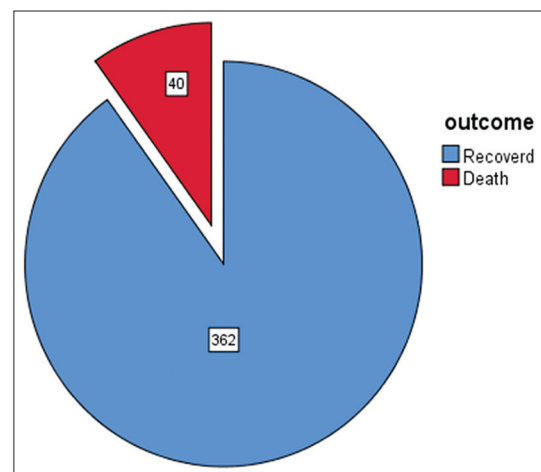
Table 6 presents the distribution of microorganisms which were detected in the BC in hospitalized patients.

All the samples showing fungal growth were positive for candida. Among the BCs that were Gram-positive, alpha hemolytic MRS positive *Streptococcus* in 5 samples (19%), *Staphylococcus aureus* in 4 samples (15%), and *Streptococcus pneumoniae* in 3 samples (11.5).

Within the BCs that were Gram-negative, carbapenemase positive *Escherichia coli* in 7 occasions (21%), *E. coli* in 5 samples (15%), extended-spectrum beta-lactamase (ESBL) positive *E. coli* in 4 (12%) samples, and 3 (8.9%) tests in this group were positive for ESBL positive *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* each.

The susceptibility summary of the isolated microorganisms is given in Table 7.

In the sample studied, sixty BCs were positive for bacterial growth. Majority of them were susceptible to four antibiotics or more 43 (72%). Three isolates showed resistance to all antibiotics (*P. Aeruginosa* carbapenemase positive, *A. Bauminni* carbapenemase positive, and *K. pneumoniae* ESBL positive extensively drug-resistant), while another nine (15%) were sensitive to three antibiotics only. Other isolates showed various responses to different antibiotics, as detailed in Table 7.



**Figure 1: Disease outcome in patients with hematological malignancies and febrile neutropenia**



**Table 6: Microbes identified among patients based on the type of positive blood culture results in patients with hematological malignancies and febrile neutropenia**

| Blood culture          | Microbe                                               | Frequency (%) |
|------------------------|-------------------------------------------------------|---------------|
| Fungal                 | <i>Candida</i>                                        | 6 (100)       |
| Gram-positive bacteria | <i>Streptococcus</i> alpha hemolyticus                | 5 (19)        |
|                        | MRS positive                                          |               |
|                        | <i>Corynebacterium</i>                                | 1 (3.8)       |
|                        | <i>C. amycolatum/C. striatum</i>                      | 1 (3.8)       |
|                        | <i>Enterococcus</i>                                   | 1 (3.8)       |
|                        | <i>S. hominis</i> MRS positive                        | 2 (7.7)       |
|                        | <i>M. luteus</i>                                      | 1 (3.8)       |
|                        | <i>S. hemolyticus</i> MRS and MLSb and betalactamase  | 1 (3.8)       |
|                        | <i>S. sciuri</i> MRS positive                         | 1 (3.8)       |
|                        | <i>S. aureus</i>                                      | 4 (15)        |
|                        | <i>S. epidermidis</i>                                 | 2 (7.7)       |
|                        | <i>S. epidermidis</i> beta lactamase MRS MLAb subtype | 1 (3.8)       |
|                        | <i>S. viridans</i> alpha hemolytic                    | 1 (3.8)       |
|                        | <i>M. luteus</i>                                      | 1 (3.8)       |
|                        | <i>S. pneumoniae</i>                                  | 3 (11.5)      |
|                        | <i>S. viridans</i> alpha hemolytic                    | 1 (3.8)       |
| Gram-negative bacteria | <i>A. Baumannii</i>                                   | 1 (3)         |
|                        | <i>E. coli</i> carbapenemase positive                 | 7 (21)        |
|                        | <i>K. pneumoniae</i> carbapenemase positive           | 2 (5.9)       |
|                        | <i>E. coli</i> carbapenemase and ESBL positive        | 1 (3)         |
|                        | <i>E. coli</i>                                        | 5 (15)        |
|                        | <i>E. coli</i> ESBL positive                          | 4 (12)        |
|                        | <i>E. cloacae</i> ESBL positive                       | 1 (3)         |
|                        | <i>K. pneumoniae</i> ESBL positive                    | 3 (8.9)       |
|                        | <i>E. cloacae</i> carbapenemase positive              | 1 (3)         |
|                        | <i>P. multocida</i>                                   | 1 (3)         |
|                        | <i>S. marcescens</i>                                  | 1 (3)         |
|                        | <i>K. oxytoca</i>                                     | 1 (3)         |
|                        | <i>K. pneumoniae</i>                                  | 1 (3)         |
|                        | <i>K. pneumoniae</i> ESBL-positive XDR                | 1 (3)         |
|                        | <i>P. aeruginosa</i>                                  | 3 (8.9)       |
|                        | <i>P. aeruginosa</i> carbapenemase positive           | 1 (3)         |

*P. aeruginosa*=*Pseudomonas aeruginosa*, *K. pneumonia*=*Klebsiella pneumoniae*, *K. oxytoca*=*Klebsiella oxytoca*, *S. marcescens*=*Serratia marcescens*, *P. multocida*=*Pasteurella multocida*, *E. cloacae*=*Enterobacter cloacae*, *E. coli*=*Escherichia coli*, *A. Baumannii*=*Acinetobacter baumannii*, *S. viridans*=*Viridans streptococci*, *S. pneumonia*=*Streptococcus pneumoniae*, *M. luteus*=*Micrococcus luteus*, *S. epidermidis*=*Staphylococcus epidermidis*, *S. aureus*=*Staphylococcus aureus*, *S. haemolyticus*=*Staphylococcus haemolyticus*, ESBL=Extended-spectrum beta-lactamases, MRS=Methicillin-Resistant *Staphylococci*, *C. amycolatum*=*Corynebacterium amycolatum*, *C. striatum*=*Corynebacterium striatum*, *S. hominis*=*Staphylococcus hominis*, *S. sciuri*=*Staphylococcus sciuri*, XDR=Extensively drug-resistant

The most effective antibiotic in treating Gram-positive bacteria in patients with FN: Vancomycin and linezolid both were able to inhibit bacterial growth in 23 out of the 26 g positive BCs. While amikacin was the best in showing activity against Gram-negative BC bacterial growth in 32 out of 34 g negative labeled BCs. Both

**Table 7: Antibiotics effective against microbes identified in patients with hematological malignancies and febrile neutropenia with positive bacterial blood cultures**

| Number of effective antibiotics | Frequency (%) |
|---------------------------------|---------------|
| Non                             | 3 (5)         |
| 1                               | 2 (3.3)       |
| 2                               | 2 (3.3)       |
| 3                               | 9 (15)        |
| 4 or more                       | 43 (72)       |

levofloxacin and ciprofloxacin showed equal activity to each other on 12/26 and 7/34 to both Gram-positive and Gram-negative bacteria, respectively.

The clinical outcome was favorable in 362 (90%) patients, who showed signs of recovery, whereas 40 (10%) patients ultimately succumbed to their illness [Figure 1].

There was no statistically significant difference in patient outcomes between genders. Among male patients, 21 (10.2%) died, while 19 (9.7%) female patients died.

However, the patient outcome did show a statistically significant association with age group ( $P \leq 0.001$ ). In the 1–9 years' age group, 7 (6.9%) patients died; in the 30–39 years age group, 5 (8.6%) patients died; in the 40–49 years age group, 3 (6.8%) patients died; and in the  $\geq 50$  years age group, 23 (20.7%) patients died. In addition, one death was observed in each of the 10–19 and 20–29 years' age groups. These findings indicate that the highest mortality rate was observed in patients younger than 10 years and older than 50 years.

Outcome was also statistically associated with the duration of neutropenia before BC ( $P \leq 0.005$ ). Among patients with neutropenia lasting 0–9 days, 19 (7.7%) died; among those with 10–19 days of neutropenia, 11 (12.4%) died; in those with 20–29 days, 5 (11.6%) died; among patients with 50–59 days of neutropenia, 2 (40%) died; and among those with  $\geq 60$  days of neutropenia, 3 (37.5%) died.

Furthermore, patient outcome was significantly related to the length of hospital stay before BC ( $P \leq 0.001$ ). Of the patients hospitalized for 0–10 days, 17 (7.0%) died; among those hospitalized for 11–49 days, 20 (13.2%) died; and among those hospitalized for  $\geq 60$  days, 3 (50.0%) died [Table 8].

As per the logistic regression model, age of the patients proved to be a very important indicator in predicting mortality with OR (1.027) ( $P \leq 0.001$ , CI: 95%: 1.011–1.042); hence, the risk of mortality was higher as the age of the patients increased.

The duration of neutropenia was also found to be a factor of importance that was a predictor to death with

**Table 8: Comparison of disease outcome based on gender, age group, duration of neutropenia, and length of hospital stay before culture in patients with hematological malignancies and febrile neutropenia**

| Characteristics                                           | Clinical outcome |              | P*    |
|-----------------------------------------------------------|------------------|--------------|-------|
|                                                           | Recovered, n (%) | Death, n (%) |       |
| Gender                                                    |                  |              |       |
| Female                                                    | 185 (89.8)       | 21 (10.2)    | 0.867 |
| Male                                                      | 177 (90.3)       | 19 (9.7)     |       |
| Age category (year)                                       |                  |              |       |
| 1–9                                                       | 95 (93.1)        | 7 (6.9)      | 0.001 |
| 10–19                                                     | 49 (98)          | 1 (2)        |       |
| 20–29                                                     | 36 (97.3)        | 1 (2.7)      |       |
| 30–39                                                     | 53 (91.4)        | 5 (8.6)      |       |
| 40–49                                                     | 41 (93.2)        | 3 (6.8)      |       |
| ≥ 50                                                      | 88 (79.3)        | 23 (20.7)    |       |
| Duration of neutropenia till the culture was taking (day) |                  |              |       |
| 0–9                                                       | 228 (92.3)       | 19 (7.7)     | 0.005 |
| 10–19                                                     | 78 (87.6)        | 11 (12.4)    |       |
| 20–29                                                     | 38 (88.4)        | 5 (11.6)     |       |
| 30–39                                                     | 5 (100)          | 0            |       |
| 40–49                                                     | 5 (100)          | 0            |       |
| 50–59                                                     | 3 (60)           | 2 (40)       |       |
| ≥ 60                                                      | 5 (62.5)         | 3 (37.5)     |       |
| Hospital in days before the culture                       |                  |              |       |
| 0–10                                                      | 227 (93)         | 17 (7)       | 0.001 |
| 11–49                                                     | 132 (86.8)       | 20 (13.2)    |       |
| ≥ 60                                                      | 3 (50)           | 3 (50)       |       |

\*P-value based on Chi-square and Fisher's exact tests

**Table 9: Predictors variable of death in patients with hematological malignancies and febrile neutropenia**

| Variable                            | OR    | P* (CI: 95%)          |
|-------------------------------------|-------|-----------------------|
| Age                                 | 1.027 | ≤ 0.001 (1.011–1.042) |
| Gender                              |       |                       |
| Female                              | 1.070 | ≤ 0.850 (0.532–2.153) |
| Male                                | 1     |                       |
| Duration of neutropenia             | 1.010 | ≤ 0.001 (1.02–1.032)  |
| Hospital in days before the culture | 1.020 | ≤ 0.001 (1.010–1.035) |

\*P-value based on logistics regression. CI=Confidence interval, OR=Odds ratio

an (OR = 1.020) ( $P \leq 0.001$ , CI: 95%: 1.02–1.032) implying that the longer the neutropenia lasted; the greater was the possibility of death.

In addition, hospital stay before BC was identified as strong prognostic factor (OR = 1.020) ( $P \leq 0.001$ , CI: 95%: 1.010–1.035), which means that the longer hospital stays the higher the possibility to die [Table 9].

## Discussion

FN is considered as a medical emergency for the patients of oncology who, without timely treatment, have high chances of developing complications and mortality.<sup>[11]</sup> BC is a central diagnostic test because it offers vital information on the choice of proper antibiotic treatment.<sup>[12]</sup> We have assessed its use in the management of FN in patients with hematologic malignancies in the

current study. Despite the large percentage of cultures being negative, clinically relevant pathogens were found in a subgroup of patients, fungi in 6 samples (1.5%), Gram positive bacteria in 26 samples (6.5%), and Gram-negative bacteria in 34 samples (8.5%). Notably, the identification of multidrug resistant (MDR) pathogens, including carbapenemase-producing *E. coli*, ESBL-producing *K. pneumoniae*, and methicillin-resistant *Staphylococcus haemolyticus*, highlights the current issue of antimicrobial resistance within this susceptible group. Clinically, the 10 percent mortality rate in this cohort underscores the severity of FN and statistically, advanced age, prolonged neutropenia, and long hospital stay before BC was significantly related to increased risk of mortality.

The age distribution showed that the proportion of children or elderly patients was high, which indicates the wide and heterogeneous character of the study population. Such diversity can affect the overall risk profile, comorbidities prevalence, and the type of hematologic malignancies, and, ultimately, clinical outcomes. Other studies have a higher mean age than the current cohort,<sup>[12]</sup> there are some studies that have targeted the younger population, like pediatric patient.<sup>[12]</sup>

Hypertension, type I diabetes, and hypothyroidism were the most frequent comorbidities. EF Azerefege *et al.*<sup>[13]</sup> reported an almost 10% rate of major underlying conditions, and JC Alvarez-Payares *et al.*<sup>[12]</sup> found the

rate of comorbidity of hypertension to be 24.02% and diabetes of 11.04%. Comorbidities are known risk factors that can aggravate the severity of the diseases, raise the rate of complications, and lead to worse mortality among patients with FN.<sup>[14]</sup>

UKALL, BEAM, FLAG-IDA, and Decitabine were the most common chemotherapy regimens used. Certain chemotherapy regimens are highly related to the type of cancer and may affect the extent, depth, and the length of neutropenia.<sup>[15]</sup> Since prolonged neutropenia (>7 days) is associated with elevated morbidity and mortality,<sup>[10]</sup> according to the result, a large percentage of patients had short-term neutropenia is at least somewhat reassuring.

Increased mortality was related to longer hospital stay, especially in older patients, showing more complex disease and the necessity to provide longer supportive care.<sup>[16]</sup> This finding is like earlier studies,<sup>[17,18]</sup> which showed that a long hospital stay is associated with increased patient mortality.

Based on the results, the BC positivity rate was about 16.7%, which included Gram-negative, Gram-positive bacteria, and fungi. This positivity rate is consistent with previous studies; Wang<sup>[19]</sup> report the overall BC and patient episode of FN positivity rates of 8.16 and 13.35, respectively. A higher proportion of positive cultures was reported in another study by A. Talukdar *et al.*<sup>[20]</sup> than the current results.

Of positive cultures (excluding likely contaminants), Gram-negative bacteria were somewhat more common than Gram-positive organisms and fungal growth was observed in 1.5% of positive cultures. This finding is consistent with epidemiological trends and indicates an increased prevalence of Gram-negative pathogens in bloodstream infections in febrile neutropenic patients.<sup>[21]</sup>

*Candida* species were the only fungal isolates in the positive cultures. *E. coli* carbapenemase-producing and ESBL-producing *K. pneumoniae* were among the most important pathogens found among Gram-negative bacteria. These results are in line with Zhang *et al.*<sup>[22]</sup> study indicating that *E. coli* and *K. pneumoniae* are the most common Gram-negative pathogens in febrile neutropenic patients.

The most often found Gram-positive organisms were *S. haemolyticus* methicillin-resistant (MRSA +) and *Streptococcus* species, these results are consistent with Mišura Jakobac *et al.* study<sup>[23]</sup> on the prevalence of *S. aureus* (including MRSA) and other Gram-positive cocci. The existence of MDR pathogens such as positive carbapenemase *E. coli*, positive carbapenemase *P. aeruginosa*, *K. pneumoniae* ESBL positive, and positive

*S. haemolyticus* MRSA is an indicator of increasing antimicrobial resistance.<sup>[24]</sup>

The results of antibiotic sensitivity patterns revealed that the greatest number of isolates were sensitive to tigecycline, gentamicin, and amikacin. These results regarding the sensitivity of the isolated bacteria to antibiotics in the present study are consistent with the results of other studies, such that in the study of Musbau *et al.*<sup>[25]</sup> Gram-negative bacteria were sensitive to beta-lactam antibiotics and gentamicin, while Gram-positive organisms showed high sensitivity to vancomycin and linezolid. Moreover, *E. coli* was sensitive to first- and second-line antibiotics.

In the current study, 10% of the patients died, which is like the reports in the world, which are usually between 9.5% and 34.4%.<sup>[11]</sup> The observed mortality in this cohort is within an acceptable range, particularly in view of the patient's profile, which had a relatively lower burden of comorbidities.

Age group was statistically significant in relation to patient outcome. Patients over 50 years and children of 1–9 years were recorded to have the highest mortality levels. These results support the use of age as one of the predictors of mortality, as depicted by other studies.<sup>[26]</sup> The interval of neutropenia before the collection of BCs also had a significant correlation with outcome. The duration of neutropenia was a predictor of death whereby the longer the neutropenia, the higher the risk of death, which was also confirmed in other literature.<sup>[11]</sup> Furthermore, duration of hospital stay before culture collection was found to have a significant correlation with patient outcome as was mentioned above.

### Strength and limitation

One of the main strengths of this study was the relatively large sample size for a single center study. Advanced statistical methods, including logistic regression, facilitated identification of predictors independently associated with mortality. Furthermore, obtaining detailed demographic, clinical, and microbiological data enabled a rigorous multivariable analysis.

However, there are some limitations that need to be addressed. The retrospective nature limited the ability to control all potential confounders, especially history of antibiotic use before admission. Comparative insights were also limited due to the lack of a group (e.g., patients with hematologic malignancy without FN) with a “competing” cause for FN. Furthermore, the absence of some details about clinical characteristics (i.e., ANC) limited the possibility to comprehensively investigate the association between severity of neutropenia and clinical outcome.

## Conclusions

The findings of this study reveal that BC continues to be an important diagnostic modality in monitoring the course of FN in patients with hematologic malignancies, helping to detect the causative resistant pathogens and adjust the treatment method. Nevertheless, the low proportion of positive culture justifies the need for additional diagnostic tools. Predictive factors for age and duration of neutropenia and poor prognosis for length of hospitalization, highlighting the necessity for early treatment to decrease mortality. It is suggested that prophylactic therapies and new diagnostic approaches are to be targeted for the improvement in these patients in such clinical context.

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## Conflicts of interest

There are no conflicts of interest.

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