Prospective analysis of febrile neutropenia patients with bacteraemia: the results of an international ID–IRI study

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ARTICLE INFO

ABSTRACT

Objectives: Bacteraemia during the course of neutropenia is often fatal. We aimed to identify factors predicting mortality to have an insight into better clinical management.

Methods: The study has a prospective, observational design using pooled data from febrile neutropenia patients with bacteraemia in 41 centres in 16 countries. Polymicrobial bacteraemias were excluded. It was performed through the Infectious Diseases–International Research Initiative platform between 17 March 2021 and June 2021. Univariate analysis followed by a multivariate binary logistic regression model was used to determine independent predictors of 30-d in-hospital mortality (sensitivity, 81.2%; specificity, 65%).

Results: A total of 431 patients were enrolled, and 85 (19.7%) died. Haematological malignancies were detected in 361 (83.7%) patients. *Escherichia coli* (n = 117, 27.1%), Klebsiellae (n = 95, 22% %), Pseudomonadaceae (n = 63, 14.6%), Coagulase-negative Staphylococci (n = 57, 13.2%), *Staphylococcus aureus* (n = 30, 7%), and Enterococci (n = 21, 4.9%) were the common pathogens. Meropenem and piperacillin-tazobactam susceptibility, among the isolated pathogens, were only 66.1% and 53.6%, respectively. Pulse rate (odds ratio [OR], 1.018; 95% confidence interval [CI], 1.002–1.034), quick SOFA score (OR, 2.857; 95% CI, 2.120–3.851), inappropriate antimicrobial treatment (OR, 1.774; 95% CI, 1.011–3.851), Gram-negative bacteraemia (OR, 2.894; 95% CI, 1.437–5.825), bacteraemia of non-urinary origin (OR, 11.262; 95% CI, 1.368–92.720), and advancing age (OR, 1.017; 95% CI, 1.001–1.034) were independent predictors of mortality. Bacteraemia in our neutropenic patient population had distinctive characteristics. The severity of infection and the way to control it with appropriate antimicrobials, and local epidemiological data, came forward.

Conclusions: Local antibiotic susceptibility profiles should be integrated into therapeutic recommendations, and infection control and prevention measures should be prioritised in this era of rapidly increasing antibiotic resistance.

1. Introduction

Neutropenic patients cannot mount normal immune responses, and disseminated infection like bacteraemia can arise without obvious symptoms and clinical findings, but the fever solely. Bacteraemia during neutropenia is significantly more often fatal compared with non-neutropenic patients [1]. In addition, increasing multi-drug resistant microorganisms causing bacteraemia has become a serious challenge for clinicians [2].

Although current guidelines commonly used in the antimicrobial management of febrile neutropenia [3–6] are generated in countries with sufficient laboratory and antibiotic resources where antibiotic resistance is relatively low [7], the guidelines emphasise using local antibacterial resistance patterns in determining empirical therapeutic strategies. Thus, the selection of empirical antimicrobial therapy in febrile neutropenia is both of the utmost importance and a major challenge.

In this study, we aimed to identify the factors predicting 30-d in-hospital mortality, provide epidemiological data regarding antimicrobial resistance, and illustrate the importance of antibiotic stewardship policies.

2. Methods

2.1. Study design

Febrile neutropenia patients with bacteraemia were included in this study. The study has a prospective and observational design. Inpatients followed between 17 March 2021 and 17 June 2021 were enrolled into the study, which was performed through the Infectious Diseases–International Research Initiative [ID-IRI]; https://infectdisiri.com/). ID-IRI has members worldwide as clinical researchers, and they voluntarily join ID-IRI research projects.

2.2. Setting

In this study, 41 well-known referral centres from 16 countries (Türkiye, the United Arab Emirates, Spain, Romania, Pakistan, Oman, Kazakhstan, Italy, Iran, Hungary, Egypt, Czech Republic, Croatia, Bulgaria, Bangladesh, and Bahrain) submitted clinical and laboratory data from febrile neutropenia patients with bacteraemia.

2.3. Data Collection

The data were collected through a web-based case report format. The following parameters were recorded: demographic, clinical and laboratory parameters; underlying haematological and/or oncological diseases; bacteraemia organisms and their susceptibility profiles; prior prophylaxis and current antibiotic treatments; and 30-d mortality data.

2.4. Ethical consent

The ethical consent of the study was approved/registered by the Istanbul Medeniyet University, School of Medicine on 24 February 2021 (2021/0112).

2.5. Case definition of neutropenic fever

Febrile neutropenia is defined as a single oral temperature greater than or equal to 38.3 °C, or a temperature greater than or equal to 38 °C for at least an hour, plus an absolute neutrophilic count (ANC) of less than 500 cells/mL or ANC < 1000 per mL, which is expected to decrease below 500 cells/mL in the next 48 h [8].

2.6. Inclusion criteria

(1) Patients with neutropenic fever;
(2) Bacteraemia;
(3) >16 y of age;
(4) Initial blood stream infection after hospital admission; and
(5) Use of either Clinical & Laboratory Standards Institute (CLSI) [9] or European Committee on Antimicrobial Susceptibility Testing (EUCAST) [10] guidelines for antibiotic susceptibility tests (AST) in the microbiology laboratory of the participating hospital.

2.7. Exclusion criteria

1. Patients with polymicrobial growth in the blood cultures;
2. Patients with blood culture positivity other than the initial isolate in the subsequent blood cultures within 30 d of hospitalisation;
3. Patients with fungal blood culture positivity; or
4. Patients with any confirmed fungal infection, according to European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium definitions [11].

2.8. Definitions

(a) **Prolonged neutropenia:** Neutropenia longer than 7 d [4].
(b) **Deep neutropenia:** ANC lower than 100 cells/mL [4].
(c) **Bacteraemia:** Association of at least one positive blood culture and a prescription of a systemic antibiotic treatment to treat bacteraemia. Common skin contaminants like coagulase negative staphylococci (CoNS) were considered to be significant when they grew in at least two blood cultures within 48 h [12,13].

(d) **Severity index:** We did not use the MASCC score, which assesses the severity of the cases to decide on site of care, as our patients were already admitted to hospitals, nor did we use septic shock category because of inconsistent approaches in starting vasopressors and because febrile neutropenic (FN) patients with septic shock represent a minority among FN patients. Instead, the quick SOFA (qSOFA) score was used to delineate the severity status of the FN patients.
(e) **Sepsis:** A qSOFA score of ≥2 [14].
(f) **Central line–associated blood stream infection (CLABSI):** Standard definition for CLABSI was adopted [15].
(g) **Hypotension**: Mean arterial pressure <65 mmHg [16].
(h) **Mainstay of antimicrobial treatment:** Extended spectrum beta-lactams were considered as the mainstay of treatment in patients with febrile, if the microbiological data were not available; these were anti-pseudomonal cephalosporins such as ceftazidime or cefepime, carbapenems such as imipenem and meropenem, and piperacillin–tazobactam [3–6].
(i) **Type of therapy:** Combination therapy was defined as the empirical administration of more than one antibiotic; monotherapy was defined as administration of a single antibacterial agent.
(j) **Appropriate empirical treatment:** Regimen including at least one antibiotic with in vitro activity against the isolated multi-drug resistant pathogen, according to the AST. All the co-investigators confirmed that they have provided appropriate doses, timing, and routes for the antimicrobial drugs.

2.9. Bacterial identification and susceptibility

Microbial identification was performed using commercially available panels (e.g., Vitek II; Biomerieux, Paris, France) and standard biochemical and/or enzymatic tests.

2.10. Interpretation of AST

All the laboratories of the participant referral hospitals used CLSI or EUCAST recommendations. When the AST guideline, either CLSI [9] or EUCAST [10], did not provide any breakpoints for a certain microorganism, then the breakpoints of the other guideline was used, and the susceptibility data of the microorganism were included in the database. Otherwise, AST result was recorded as non-applicable. Multi-drug resistance was as defined elsewhere [17]. Automated systems and disc diffusion methods were used as per these standard official published guidelines. Colistin and vancomycin testing results were included in the analysis if microdilution method was used. When the microorganisms were not tested for a given antibiotic, non-tested isolates were excluded from the denominator in calculating the susceptibility rate. During the data analysis, (i) cefoxitin-resistant Staphylococci were coded resistant to all beta-lactams; (ii) Enterococci were recorded as resistant to all cephalosporins; and (iii) All Gram-positive bacteria were recorded colistin-resistant.

2.11. Outcome

The primary outcome was defined as 30-d all-cause mortality.

2.12. Statistical analysis

Pearson chi-square, Fisher-Freeman-Halton exact test, and Mann-Whitney U test were used for obtaining unadjusted effects on mortality. According to the results of these tests, the factors with *P* value less than 0.10 were considered candidates for the
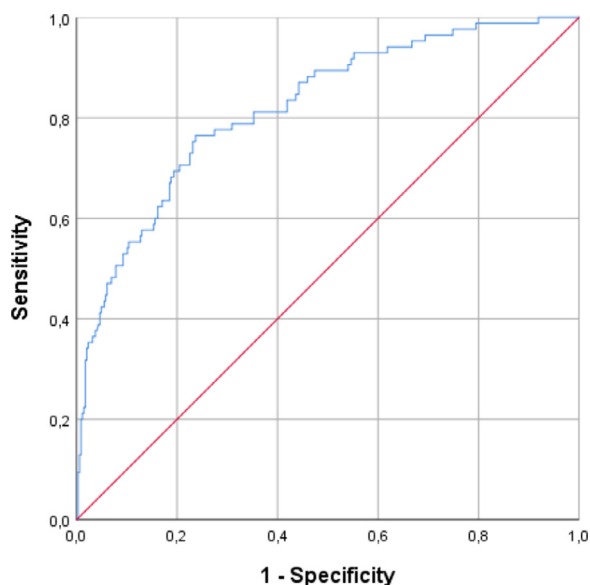
Figure 1. The distribution of blood borne pathogens.

multivariate model, and adjusted effects of the variables were calculated for each variable. These effects were assessed using the stepwise variable selection method through the multivariate binary logistic regression model. $P < 0.05$ was accepted as statistically significant. The performance and the internal validity of the model were evaluated with the receiver operating characteristic curve (Fig. 1), sensitivity, specificity, and the model's quality index. Moreover, a nomogram was provided for the easy interpretation of

the model's predictions (Fig. 2). SPSS (ver. 23) and Stata (ver. 14.0) programs were used for statistical calculations.

3. Results

In this study, 461 patients were submitted by the participant centres. However, 16 patients were excluded from the study because of missing data, and 14 patients were ineligible because of polymicrobial growth in the blood cultures. Hence, 431 neutropenic fever patients with bacteraemia were included in this study. The mean number of the cases submitted from the participating centres was 10.51 ± 8.62.

Ultimately, 85 (19.7%) patients died within 30 d of the bacteraemia diagnosis. A total of 187 (43.4%) of patients were females. The mean age of the patients was 47.02 ± 17.86 y. The means of qSOFA score and ANC were 1.08 ± 0.99 and $175.18 \pm 199.03/\mu L$, respectively. A total of 140 (32.5%) patients were defined to have sepsis when positive blood culture was taken. The means of neutropenia duration, and duration between the positive blood culture and normalization of body temperature, were 16.06 ± 21.49 and 6.7 ± 12.62 d. Overall, 77 (17.9%) patients had longer duration of neutropenia than 30 d. The mean values of highest body temperature, pulse rate, and respiratory rate at the time of positive blood cultures were 38.71 ± 0.54, 107.74 ± 19.25, and 22.4 ± 9.79, respectively.

3.1. Primary diagnoses

Haematological malignancies were diagnosed in 361 patients, and solid tumours were identified in 81 patients. Eleven patients had co-existent solid tumours and haematological malignancies. All patients in this study who received active chemotherapy had a per-
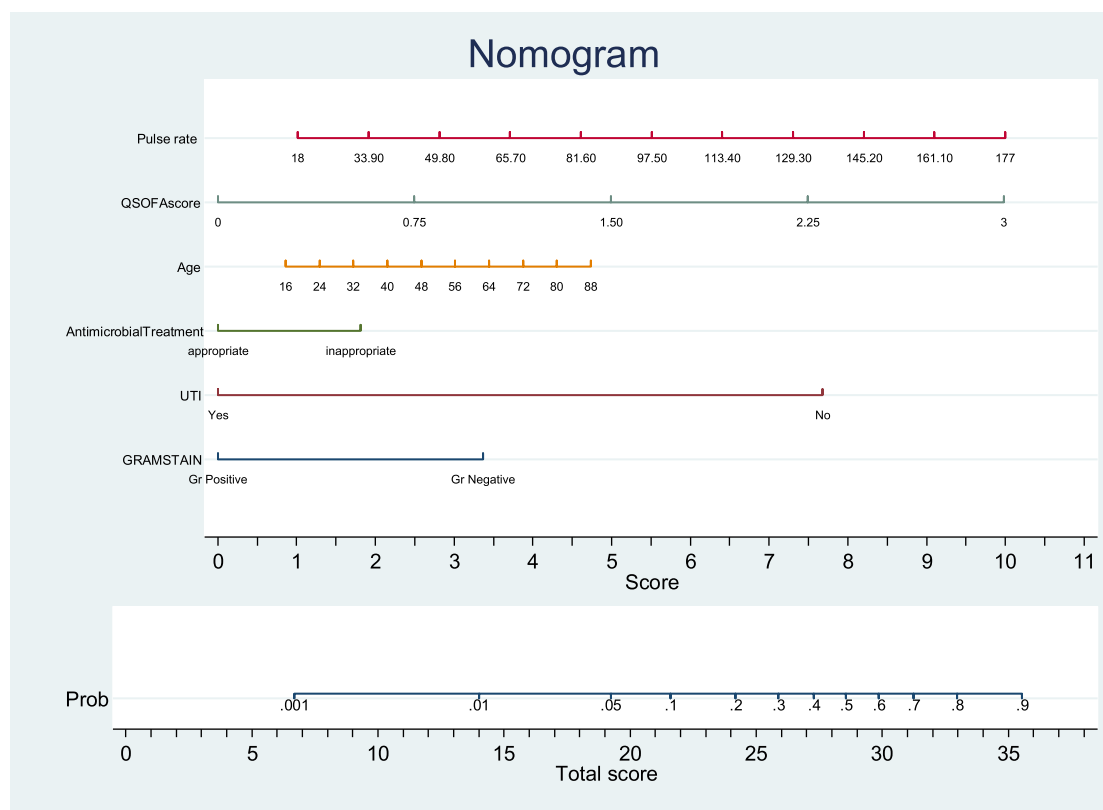

Figure 2. Nomogram of the final model. qSOFA, quick SOFA; UTI, urinary tract infection.
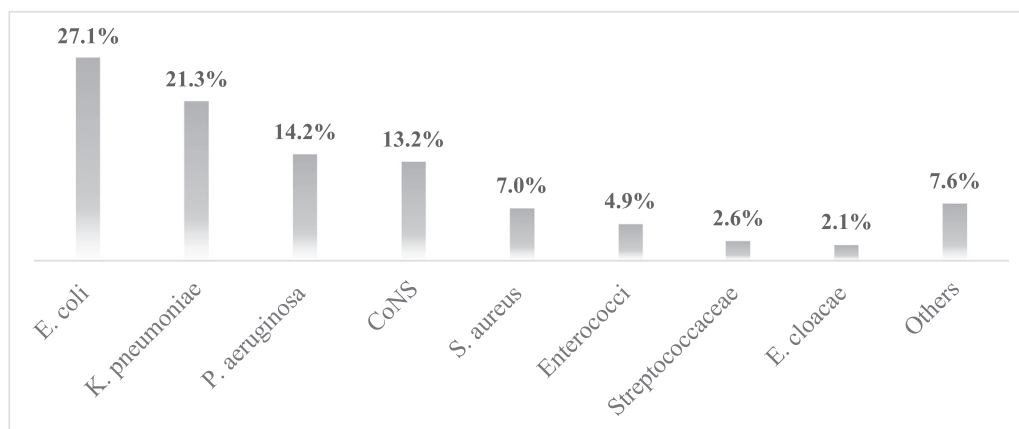
Figure 3. Bloodborne pathogens in the study. CoNS, coagulase negative staphylococci.

formance status of Eastern Cooperative Oncology Group score between 0 and 2.

(a) **Haematological diagnoses:** acute myelogenous leukaemia (n = 134), acute lymphocytic leukaemia (n = 81), lymphomas (n = 57; non-Hodgkin lymphoma [n = 45], Hodgkin's lymphoma [n = 12]), multiple myeloma (n = 40), myelodysplastic syndromes (n = 20), chronic leukaemias (n = 18; chronic lymphocytic leukaemia [n = 13], chronic myeloid leukaemia [n = 5]), other haematological disorders (n = 10; aplastic anaemia [n = 3], hairy-cell leukaemia [n = 2], amyloidosis [n = 2], histiocytic sarcoma [n = 1], mycosis fungoides [n = 1], hemophagocytic syndrome [n = 1]).

(b) **Oncological diagnoses:** lung cancer (n = 18), colorectal cancer (n = 10), ovarian cancer (n = 7), breast cancer (n = 7), pancreas cancer (n = 6), gastric cancer (n = 6), gallbladder cancer (n = 5), endometrial cancer (n = 3), Ewing's sarcoma (n = 2), urinary bladder carcinoma (n = 2), cervix cancer (n = 1), cholangiocarcinoma (n = 1), choriocarcinoma (n = 2), liver cancer (n = 1), mediastinal sarcoma (n = 1), head and neck squamous cell carcinoma (n = 2), osteosarcoma (n = 1), prostate cancer (n = 1), neuroectodermal tumour (n = 1), renal malignancy (n = 1), spindle-cell carcinoma (n = 1), rhabdomyosarcoma (n = 1), thymoma (n = 1).

3.2. Infectious diagnoses

Overall, 150 infectious diagnoses were detected in 146 (33.8%) patients as follows: CLABSI (n = 39, 9%), pneumonia (n = 41, 9.2%), urinary tract infection (n = 24, 5.6%), skin and soft tissue infection (n = 20, 4.6%), abdominal infections (n = 12; 2.8%; peritonitis [n = 2, 0.5%]; enterocolitis [n = 3, 0.7%]; proctitis [n = 1, 0.2%]), mucositis (n = 2; 0.5%), and abscess formation (n = 12; 2.8%; perianal abscess [n = 6, 1.4%]; soft tissue abscess [n = 2, 0.5%]; gluteal abscess [n = 2, 0.5%]; perirectal abscess [n = 1, 0.2%]; inguinal abscess [n = 1, 0.2%]).

3.3. Distribution of blood-borne pathogens

(a) **Gram-negatives (n = 310, 71.9%):** *E. coli* (n = 120, 27.1%), Klebsiellae (n = 98, 22.7%; *Klebsiella pneumoniae* [n = 92]; *Klebsiella aerogenes* [n = 3]; *Klebsiella oxytoca* [n = 2]; *Klebsiella variicola* [n = 1]), Pseudomonadaceae (n = 63, 14.6%; *Pseudomonas aeruginosa* [n = 61]; *Pseudomonas mendocina* [n = 1]; *Pseudomonas stutzeri* [n = 1]), Acinetobacter Spp. (n = 12, 2.8%; *Acinetobacter baumannii* [n = 10]; *Acinetobacter haemolyticus* [n = 1]; *Acinetobacter junii* [n = 1]),

Enterobacter cloacae (n = 9, 2.1%), others (n =11, 2.6%; *Stenotrophomonas maltophilia* [n = 3]; *Ralstonia mannitolilytica* [n = 3]; *Burkholderia cepacia* [n = 1]; *Aeromonas veronii* [n = 1]; *Delftia acidovorans* [n = 1]; *Proteus mirabilis* [n = 1]; *Sphingomonas paucimobilis* [n = 1]).

(b) **Gram-positives (n = 121, 28.1%):** CoNS (n = 57, 13.2%; *Staphylococcus epidermidis* [n = 34]; *Staphylococcus hominis* [n = 7],;*Staphylococcus haemolyticus* [n = 4]; *Staphylococcus lentus* [n = 1]; *Staphylococcus lugdunensis* [n = 1]; Untyped CoNS [n = 10]), *Staphylococcus aureus* (n = 30, 7%), Enterococci (n = 21, 4.9%; *Enterococcus faecium* [n = 14]; *Enterococcus faecalis* [n = 7]), Streptococcaceae (n = 11, 2.6%; *S. pneumoniae* [n = 4]; *S. mitis* [n = 3]; *S. pyogenes* [n = 1]; *S. oralis* [n = 1]; *S. intermedius* [n = 1]; S. *viridans* untyped [n = 1]), Listeria monocytogenes (n = 1, 0.2%), Corynebacterium striatum (n = 1, 0.2%) (Fig. 3).

3.4. Antibiotic susceptibility

AST results of the infecting pathogens are presented in Table 1. Common resistance profiles were as follows:

(a) Methicillin resistance among *S. aureus* (n = 30) and CoNS (n = 57) were 43.3% and 80.7%, respectively.
(b) Vancomycin resistance was seen in 2 (9.5%) *Enterococcus faecium* strains out of 21 Enterococcal isolates.
(c) Meropenem resistance in certain Gram-negatives were as follows: *Acinetobacter baumannii* (8 of 10; 80%), *K. pneumoniae* (26 of 92; 28.3%), *P. aeruginosa* (5 of 61; 8.2%), and *E. coli* (9 of 117; 7.7%).

3.5. Antimicrobial therapy

Monotherapy was given in 274 (63.5%) patients while combined therapy was started in 157 (36.4%) patients.

(a) **Mainstay of treatment:** Piperacillin-tazobactam (n = 237, 55%), carbapenems (meropenem/imipenem [n = 145, 33.6%]), cefepime (n = 33, 7.7%), cefotaxime/ceftriaxone (n = 6, 1.4%), ceftazidime (n = 4, 0.9%), levofloxacin (n = 3, 0.7%), and vancomycin (n = 3, 0.7%) were used as the mainstays of treatment. None of our patients received colistin, aminoglycosides, or tigecycline as the mainstay of treatment. Rather they were used as part of combination regimens.
(b) **Combined antibiotics:** Vancomycin (n = 60, 13.9%), amikacin/gentamicin (n = 17, 3.9%), teicoplanin (n = 19,

Table 1
Antibiotic susceptibility patterns of the common antibiotics used in patients with febrile neutropenia.

Entire cohort (n = 431)[a]	MER	P-Tz	CEP	CAZ	FOS	TYG	COL	AK	LEV
Susceptible	285	231	173	113	52	161	197	219	141
	66.1%	53.6%	41.7%	27.5%	24.6%	56.7%	54.4%	59.3%	35.5%
Intermediate	6	5	15	20	(–)	(–)	4	24	57
	1.4%	1.2%	3.6%	4.9%	(–)	(–)	1.1%	6.5%	14.4%
Resistant	108	183	216	172	13	21	140	103	171
	25%	42.5%	52%	41.8%	6.2%	7.4%	39.9%	27.9%	43.1%
Not applicable	32	12	11	106	152	102	10	23	28
	7.4%	2.8%	2.7%	25.8%	72%	35.9%	2.8%	6.2%	7.1%
Non-tested isolates	(–)	(–)	16	20	220	147	80	62	34
Gram negatives	**MER**	**P-Tz**	**CEP**	**CAZ**	**FOS**	**TYG**	**COL**	**AK**	**LEV**
A. baumannii (n = 10)	2	2	1	2	NA	NA	6/9[b]	2	1
	20%	20%	10%	20%	NA	NA	66.7%	20%	10%
E. coli (n = 117)	107	84	52/109	55/107	20/24	57/68	67/71	101	58/114
	91.5%	71.8%	47.7%	51.4%	83.3%	83.8%	94.4%	86.3%	50.9%
E. cloacae (n = 9)	9	6	6	4	1/1	4/5	4/4	7	5
	100%	66.7%	66.7%	44.4%	100%	80%	100%	77.8%	55.6%
K. pneumoniae (n = 92)	66	43	32/86	25/85	15/18	34/37	64/72	45	25
	71.7%	46.7%	37.2%	29.4%	83.3%	91.9%	88.9%	48.9%	27.2%
P. aeruginosa (n = 61)	51	44	35/59	19/58	NA	NA	48/54	34/60	17/54
	83.6%	72.1%	59.3%	32.8%	NA	NA	88.9%	56.7%	31.5%
Gram positives	**MER**	**P-Tz**	**CEP**	**DPT**	**FOS**	**TYG**	**SXT**	**AK**	**LEV**
E. faecium (n = 14)	NA	3	0	NA	NA	9/10	0/4	1/9	NA
	NA	21.4%	0	NA	NA	90%	0%	11.1%	NA
CoNS (n = 57)	11	11	11	16/16	7/11	33/35	18/37	8/18	19/45
	19.3%	19.3%	19.3%	100%	63.6%	94.3%	48.6%	44.4%	42.'%
S. aureus (n = 30)	17	17	17	6/7	9/10	18/19	6/14	10/14	14/24
	56.7%	56.7%	56.7%	85.7%	90%	94.7%	42.9%	71.4%	58.3&
Streptococci (n = 11)	11	11	11	NA	NA	–	0/2	NA	3/6
	100%	100%	100%	NA	NA	NA	0%	NA	50%

AK, amikacin; CAZ, ceftazidime; CEP, cefepime; COL, colistin; FOS, fosfomycin; LEV, levofloxacin, DPT: daptomycin; MER, meropenem; NA, not applicable; P-Tz, piperacillin-tazobactam; SXT, trimethoprim sulfamethoxazole; TYG, tigecycline.
[a] Antibiotic susceptibility percentage was calculated by excluding the non-tested isolates from the denominator.
[b] Referred to gentamicin susceptibility.

4.4%), colistin (n = 8, 1.9%), tigecycline (n = 3, 0.7%), levofloxacin (n = 5, 1.2%), ceftriaxone (n = 1, 0.2%), linezolid (n = 2, 0.5%), and metronidazole (n = 1, 0.2%) were given as parts of combination therapy.

3.6. Empiric antifungal use

Antifungals were given as part of initial empirical regimen in 8 (1.7%) patients: fluconazole (n = 6), caspofungin (n = 1), and amphotericin-B (n = 1).

3.7. Empirical anti-Gram-positive coverage

Provided in 87 (20.2%) patients: vancomycin (n = 63, 14.6%), teicoplanin (n = 19, 4.4%), tigecycline (n = 3, 0.7%), and linezolid (n = 2, 0.5%). In 17 (19.5%) of 87 patients, methicillin-resistant Staphylococcus aureus was ultimately recovered from the blood. Accordingly, methicillin-resistant Staphylococcus aureus was isolated in 12 (30.7%) of 39 patients with central line associated blood stream infection, 1 (50%) of 2 with mucositis, 1 (4.6%) of 22 who were hypotensive, 6 (14.6%) of 41 with pneumonia, and 4 (20%) of 20 with skin and soft-tissue infection.

3.8. Appropriateness of the antimicrobial treatment

Initial treatment was appropriate in 275 (63.8%) patients, inappropriate in 141 (32.7%) patients, and not applicable (see definitions) in 15 (3.4%) patients. In 136 patients with inappropriate antimicrobial treatment, antibiotics were modified according to the culture and AST data. The remaining five patients had died before the modification of treatment. Distribution of blood-borne pathogens in the study are presented in Fig. 1.

3.9. Mortality risk

Quantitative and qualitative variables affecting mortality and their unadjusted effects according to the univariate analysis are presented in Tables 2 and 3, respectively. The multivariate model was established with the help of the information obtained from the univariate evaluation. This final model showing the risk factors affecting mortality and their adjusted effects is found in Table 4. Ultimately, pulse rate (odds ratio [OR], 1.018; 95% confidence interval [CI], 1.002–1.034), qSOFA score (OR, 2.857; 95% CI, 2.120–3.851), inappropriate antimicrobial treatment (OR, 1.774; 95% CI, 1.011–3.851), Gram-negative bacteraemia (OR, 2.894; 95% CI, 1.437–5.825), bacteraemia of non-urinary origin (OR, 11.262; 95% CI, 1.368–92.720), and age (OR, 1.017; 95% CI, 1.001–1.034) were found to be six significant risk factors of mortality. When the cut-off value of 0.135 is taken for the predicted risk probabilities from the final model containing these six variables, and those with a probability higher than this value are accepted as 'death', the sensitivity and specificity of the model were 81.2% and 65%, respectively. The area under the receiver operating characteristic curve of the predicted risk probabilities was found to be 0.821 ± 0.026 (P < 0.001). Moreover, the index for the model quality was 0.77 (Fig. 2).

4. Discussion

In this prospective, observational study, one-third of our patients had focal infection. We did not find that the following factors facilitating the development of infection among neutropenic patients with malignancies [3–6,18] contributed significantly to 30-d in-hospital mortality when bacteraemia occurred. These are type of underlying haemato-oncological malignancy, underlying comorbid conditions including diabetes, levels of inflammatory markers,

Table 2
Quantitative variables affecting mortality and their unadjusted effects.

| | Outcome | n | Mean | SD | Min | Max | Percentiles | | | P^a |
							25th	Median	75th	
Age	Died	85	52.6	17.5	16	86	39.5	55.0	66.5	**0.001**
	Survived	346	45.6	17.7	16	88	31.0	46.0	59.3	
Neutropenia duration	Died	59	13.1	12.0	1	60	6.0	10.0	16.0	0.408
	Survived	341	16.6	22.7	1	277	6.0	10.0	19.0	
Duration between	Died	85	24.4	45.3	0	275	2.0	11.0	21.0	0.236
admission and culture	Survived	346	14.9	23.2	0	245	2.0	10.0	17.0	
Duration between culture	Died	85	5.2	5.1	0	30	2.0	3.0	6.0	0.250
and being afebrile	Survived	346	7.1	13.8	0	190	2.0	4.0	7.0	
Highest body temperature	Died	85	38.7	0.7	36.10	40.00	38.3	38.7	39.0	0.838
	Survived	346	38.7	0.5	37.00	40.20	38.3	38.7	39.0	
Pulse rate	Died	85	113.8	16.7	80	174	103.5	112.0	124.5	**< 0.001**
	Survived	346	106.3	19.6	18	177	96.0	105.0	116.0	
Respiratory rate	Died	85	24.1	5.8	13	41	20.0	24.0	26.0	**< 0.001**
	Survived	346	22.0	10.5	12	105	18.0	20.0	23.0	
Systolic	Died	85	98.4	19.1	56	165	86.5	100.0	100.0	**< 0.001**
	Survived	346	109.5	16.4	64	176	100.0	110.0	120.0	
Diastolic	Died	85	60.3	13.5	25	94	50.0	60.0	70.0	**< 0.001**
	Survived	346	68.0	11.0	35	100	60.0	70.0	79.0	
qSOFA score	Died	85	1.9	1.0	0	3	1.0	2.0	3.0	**< 0.001**
	Survived	346	.9	0.9	0	3	.0	1.0	1.0	
WBC (/μL)	Died	85	1549.3	5073.5	0	32 940	100.0	340.0	860.0	0.072
	Survived	346	1157.5	6872.6	0	126 700	200.0	500.0	1000.0	
ANC (/μL)	Died	85	146.7	176.0	0	690	0.0	100.0	275.0	0.202
	Survived	346	182.2	203.9	0	980	0.0	100.0	310.0	
Hb (g/dL)	Died	85	8.26	1.57	7.30	8.00	9.30	85	8.26	0.941
	Survived	346	8.28	1.54	7.30	8.20	9.13	346	8.28	
Platelet count (/μL)	Died	80	28 059.5	70 727.2	1.0	596 000.0	47.8	10 000.0	33 750.0	0.198
	Survived	333	31 343.8	44 769.3	1.0	298 000.0	54.5	15 000.0	40 000.0	
CRP level (mg/dL)	Died	72	157.94	505.14	14.30	36.30	197.00	72	157.94	0.055
	Survived	317	437.43	6120.27	11.17	25.10	98.00	317	437.43	
Procalcitonin (ng/mL)	Died	46	7724.8	35 925.2	.00	177 025.00	1.3	9.5	62.5	**0.011**
	Survived	215	36.6	141.8	.00	1165.00	.7	4.0	8.0	
ESR (mm/h)	Died	19	62.8	28.6	26	120	36.0	62.0	85.0	0.814
	Survived	122	64.00	29.200	6	140	43.0	60.5	86.0	

ANC, absolute neutrophilic count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; qSOFA, quick SOFA score; SD, standard deviation; WBC, white blood cells.

[a] Mann-Whitney U test or independent samples t-test.

blood parameters (haemoglobin, platelet, ANC), neutropenia duration, deep neutropenia, previous antimicrobial prophylaxis, and hematopoietic stem cell transplantation type if it was done. In addition, underlying infection-related parameters like the infectious foci, the type of infecting pathogen, the duration of hospital stay before the detection of bacteraemia, empirical use of anti-Gram-positive agents, range of fever, and the duration for normalisation of body temperature did not affect the outcome.

However, we did find that inappropriate antimicrobial treatment, Gram-negative bacteraemia, and the bacteraemia of non-urinary origin significantly decreased survival. At the same time, qSOFA score (2.857-fold for each unit increase), pulse rate (1.018-fold for each increasing digit), and advancing age (1.017-fold rising risk yearly) contributed to mortality as reflected in the nomogram in Fig. 2. Consequently, when bloodstream infection develops in a neutropenic patient, the clinical picture had distinctive characteristics dominating underlying malignancy and infection-related parameters. The pulse rate and qSOFA score reflect the severity of infection, along with local epidemiological data indicating the prevalence of Gram-negative pathogens, known for their more severe outcomes [19], Additionally, mortality is influenced by the management of infection, especially in cases involving drug-resistant pathogens, where appropriate antimicrobial treatment plays a crucial role.

In addition, because endogenous flora is known to be significantly more susceptible to antimicrobial drugs [20], bacteraemia originating from urinary tract infection was likely to be coming from the endogenous flora and have a relatively benign course. Moreover, we have shown that younger patients were more likely to survive compared with elderly patients who are more prone to bloodstream infections [21] due to immunosenescence.

E. coli, Klebsiella, *P. aeruginosa*, Enterobacter, Serratia, Acinetobacter, *S. aureus*, CoNS, Enterococci, and alpha-haemolytic streptococci are known as the top ten bacterial pathogens in haematology-oncology centres [22]. Over the last two decades, there was a significant incline in favour of Gram-negatives [23]. Accordingly, *E. coli, K. pneumoniae, P. aeruginosa*, CoNS, *S. aureus, E. faecium*, Streptococci, *A. baumannii*, and *E. cloacae* were the common pathogens in descending order (Fig. 3). More than two-thirds of the patients had bloodstream infections due to Gram negatives in this study. According to our data, methicillin resistance among *S. aureus* and CoNS, vancomycin resistance in *Enterococcus faecium*, carbapenem resistance among Gram-negatives, *Acinetobacter baumannii*, and *K. pneumoniae* in particular were the noteworthy challenges to the treating clinicians. In actuality, the antibiotic resistance profiles of bloodborne isolates were lower in the studies published one to two decades ago [23–25]. There are reports indicating that the hospital-acquired isolates are causing infections in FN patients [4,26]. According to our data, the infecting blood-borne pathogens were exceedingly resistant and could be comparable with hospital-acquired isolates [7]. Although most haemato-oncology patients are treated as outpatients during their long-lasting chemotherapy or they were hospitalised in specialized centres for clinical stabilization, it appears that they acquire extensively resistant microbes during their contacts in the hospitals. The inappropriate use of broad-spectrum antibiotics is another cause [27]. Thus, infection control measures for this subgroup of patients are crucial and high priorities.

Table 3

Qualitative variables affecting mortality and their unadjusted effects.

		Died		Survived		P[a]
		n	%	n	%	
Gender	F	35	18.7	152	81.3	0.646
	M	50	20.5	194	79.5	
CRF	No	76	18.8	328	81.2	0.066
	Yes	9	33.3	18	66.7	
DM	No	60	17.1	290	82.9	**0.005**
	Yes	25	30.9	56	69.1	
CVD	No	75	19.9	302	80.1	0.812
	Yes	10	18.5	44	81.5	
Rheumatological comorbidity	No	82	19.4	340	80.6	0.300
	Yes	3	33.3	6	66.7	
Endocrinological comorbidity	No	84	19.8	340	80.2	0.716
	Yes	1	14.3	6	85.7	
COPD	No	81	19.9	327	80.1	0.773
	Yes	4	17.4	19	82.6	
Other	No	85	20.1	337	79.9	0.215
	Yes	0	0.0	9	100.0	
Primary Disease	ALL	14	17.3	67	82.7	0.507
	AML	24	17.9	110	82.1	
	MDS	3	15.0	17	85.0	
	Chronic leukemias	3	16.7	15	83.3	
	Lymphoma	11	19.3	46	80.7	
	Multiple myeloma	6	15.0	34	85.0	
	Other hematological disorders	3	30.0	7	70.0	
	Solid tumors	21	29.6	50	70.4	
HSCT	None	77	21.9	275	78.1	**0.035**
	Allogeneic	6	13.6	38	86.4	
	Autologous	2	5.7	33	94.3	
Prolonged Neutropenia	No	23	16.4	117	83.6	0.235
	Yes	62	21.3	229	78.7	
Antimicrobial prophylaxis used before bacteremia	No	46	22.0	163	78.0	0.247
	Yes	39	17.6	183	82.4	
Empiric therapy	Mono therapy	42	15.3	232	84.7	**0.002**
	Combined regimen	43	27.4	114	72.6	
Antimicrobial Treatment	Inappropriate	37	26.2	104	73.8	**0.022**
	Appropriate	46	16.7	229	83.3	
Use of anti-Gram-positive agents	No	61	17.7	283	82.3	**0.039**
	Yes	24	27.6	63	72.4	
Colonization with MDR bacteria	No	70	18.3	312	81.7	**0.042**
	Yes	15	30.6	34	69.4	
Hypotension	No	73	17.8	336	82.2	**<0.001**
	Yes	12	54.5	10	45.5	
Confirmed abdominal infection	No	84	20.0	335	80.0	0.315
	Yes	1	8.3	11	91.7	
CLABSI	No	80	20.4	312	79.6	0.256
	Yes	5	12.8	34	87.2	
Mucositis	No	85	19.8	344	80.2	0.644
	Yes	0	0.0	2	100.0	
Pneumonia	No	73	18.7	317	81.3	0.100
	Yes	12	29.3	29	70.7	
Skin and soft tissue infections	No	81	19.7	330	80.3	0.974
	Yes	4	20.0	16	80.0	
Urinary tract infection	No	84	20.6	323	79.4	**0.049**
	Yes	1	4.2	23	95.8	
Abscess formation	No	82	19.6	337	80.4	0.711
	Yes	3	25.0	9	75.0	
Deep Neutropenia	No	44	18.1	199	81.9	0.338
	Yes	41	21.8	147	78.2	
Pathogen Grouping	Acinetobacter spp.	7	58.3[a]	5	41.7	**0.001**
	E. coli	22	18.8[b]	95	81.2	
	Enterobacter spp.	4	33.3[ab]	8	66.7	
	Klebsiella spp.	23	24.2[ab]	72	75.8	
	Enterococci	6	28.6[ab]	15	71.4	
	Pseudomonas spp.	14	22.2[ab]	49	77.8	
	Staphylococci	6	6.9[c]	81	93.1	
	Streptococci	0	0.0[c]	11	100.0	
	Others	3	23.1[ab]	10	76.9	
Gram Stain	Gr Negative	72	23.2	238	76.8	**0.003**
	Gr Positive	13	10.7	108	89.3	

CRF: Chronic renal failure, DM: Diabetes mellitus, CVD: Cardiovascular disease, COPD: Chronic obstructive pulmonary disease, HSCT: Hematopoietic stem cell transplantation, MDR: Multi-drug resistant, CLABSI: Central line associated blood stream infection, ALL: Acute lymphocytic leukemia, AML: Acute myelogenous leukemia, MDS: Myelodysplastic syndromes.

[a] Pearson chi-square test or Fisher-Freeman-Halton exact test.

When the P value was found to be statistically significant for multiple categories of parameters more than two, letters were placed next to the % values. If these letters are completely different from each other (i.e. if one is a, the other is b), the respective % values also differ statistically significantly from each other.

Table 4
Risk factors affecting mortality and their adjusted effects.

Risk factors	OR	95% CI for OR		
		Lower	Upper	P^a
Pulse rate	1.018	1.002	1.034	0.025
qSOFA score	2.857	2.120	3.851	< 0.001
Inappropriate antimicrobial treatment	1.774	1.011	3.111	0.046
Non-urinary source bacteraemia	11.262	1.368	92.720	0.024
Gram-negative bacteraemia	2.894	1.437	5.825	0.003
Age	1.017	1.001	1.034	0.039
Constant	0.000			< 0.001

CI, confidence interval; OR, odds ratio; qSOFA, quick SOFA score.
[a] Multiple binary logistic regression model by stepwise variable selection method.

The essential step is to apply all available microbiological diagnostic methods to identify the infecting pathogen and its antibiotic susceptibility profile, to provide targeted therapy. Although microbiological improvements have reduced blood culture recovery time, leading to positivity within the first 24 h in over 90% of FN patients [28], inappropriate treatment and prolonged time to initiation of adequate antibiotic treatment have been related to increased mortality in this population [29]. Our data emphasise the same issues. Even for meropenem, which has long been accepted as the most reliable antimicrobial in the management of FN patients, only two-third of the blood-borne pathogens were fully susceptible. When it comes to piperacillin-tazobactam, the other reliable option used in the management of FN, full susceptibility was seen in only half of the isolates. Therefore, exceedingly high resistance profiles in the participating centres impose a significant dilemma on how to manage antibacterial resistance. This is clinically reflected with the duration of normalisation of body temperature in the study. Although a mean of one week was required for stabilization, a wide heterogeneity existed in our cohort. Although the urgent need to adapt guidelines to current epidemiology has been noted [30], the solution to this problem is challenging.

One of the key findings of our study is that severely ill patients will face therapeutic failure if administered inappropriate antibiotics for what turns out to be highly resistant bacterial pathogen while neutropenic. Hence, using well-established clinical severity scores or the nomogram (Fig. 2) would be better surrogate markers of critical status in FN patients. Consequently, we believe that antimicrobial treatment based on local epidemiology should be prioritised particularly in critical patients who may need combination regimens to overcome bacterial resistance. In this regard, antimicrobial stewardship programs are the key strategies in hospitals where high resistance profiles are common. Colistin, aminoglycosides, and fosfomycin can be the part of combination treatment with broad spectrum beta-lactams, to overcome the risk of inappropriate empirical antibacterial treatment in FN patients with severe sepsis based on the local epidemiological findings. De-escalation policies should be in place after the reports of the blood cultures become available.

One of the strengths of this study was including all bacterial bloodstream organisms, not just Gram-negative or Gram-positive bacteria. Moreover, the study had a prospective design, whereas most studies are retrospective. Our study also excluded polymicrobial bacteraemias on admission and within 30 d of hospitalization. Thus, the effects of bloodstream infections due to a single blood-borne pathogen were analysed through a robust mathematical model (Fig. 1).

There are several potential limitations of this study. First, heterogeneity may have existed between the hospitals in the selection of antimicrobials in patients with FN. Second, there may be unmeasured differences that may affect both the prognosis and treatment choices, such as the presence of mucositis [31] or undetected invasive fungal infections [32]. Third, the diversity of underlying comorbid conditions may be a confounding factor that could affect the progression of the disease. Finally, the status of the primary diseases, such as whether it is a new diagnosis, in remission, or a relapsing primary disease, was not captured in our database.

Consequently, in the era of rapidly evolving antibacterial resistance, local epidemiological data and antibiotic susceptibility profiles should be integrated into therapeutic recommendations in the management of critical FN patients [33] along with well-established infection control and prevention policies as guided by international guidelines.

Competing interests: None declared.

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