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Research Article

The Effect of Bacterial Pathogens Isolated from Blood Cultures on Prognosis in Febrile Neutropenia in Hematological Malignancies

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Abstract

Objectives: In patients with hematological malignancies infections are among important causes of mortality. Our aim in this study is to investigate the factors affecting morbidity and mortality in our patients hospitalized for hematological malignancies who developed febrile neutropenia and were diagnosed with bloodstream infection.

Methods: This retrospective study was conducted using the data of 95 febrile neutropenic cases with hematological malignancies and bloodstream infections who were hospitalized in the hematology clinic between 2015 and 2020. The growth of bacterial agents in the blood cultures of febrile neutropenic patients, the susceptibility of these agents and the effects of susceptibility on the prognosis were investigated.

Results: 50.5% (n=48) of the patients were female and 49.5% (n=47) were male; the mean age was 61.5±13.2 years. In blood cultures, E. coli was observed in 25 patients (26.3%), *K.pneumoniae* in 18(18.9%), Coagulase-negative staphylococci in 14 (14.7%), P.aeruginosa in 9 (9.4%) and S.aureus in 7 (7,4%) patients. A significant correlation was found between using antibiotics for a shorter time and the risk of mortality (p=0.001). It was determined that the decrease in the neutrophil count increased the mortality risk (p<0.001) and the increase in the CRP level on the day of recovery from neutropenia increased the mortality risk (p<0.001).

Conclusion: Early diagnosis and treatment of infections that cause significant morbidity and mortality are important. Therefore, in order to achieve better results in the management of febrile neutropenia, each center should closely monitor the causes of infection and establish treatment protocols.

Keywords: Antimicrobial susceptibility, febrile neutropenia, blood culture, hematological malignancy, prognosis

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Infection is an important cause of morbidity and mortality in patients with hematological malignancies (HM).[1,2] The most important side effect of chemotherapy in HM is febrile neutropenia (FN) and tendency to infections in these patients is multifactorial. Factors such as severe neutropenia (neutrophil count, <100/mm^3), rapid decrease in neutrophil count, and prolonged neutropenia for more than 10 days increase the risk of infection.[3,4] Studies have shown that the cause of death in 50-80% of patients with acute leukemia and 50% of patients with lymphoma and solid organ tumors is infections.[5,6] Our aim is to investigate the factors affecting morbidity and mortality in our patients

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who were hospitalized for HM who developed febrile neutropenia and were diagnosed with bloodstream infection.

Methods

In this study, the data obtained from the medical charts of 95 patients with HM who were diagnosed and hospitalized in the Adult Hematology Clinic Medicine between January 1, 2015 and December 31, 2020 were evaluated retrospectively. This study obtained the approval from the ethics committee (Approval Date: 09.06.2021; Reference Number / Protocol No: 2021/11) and was done in accordance with the Declaration of Helsinki.

HM diagnosis was based on evaluation of clinical findings and the results of complete blood count, peripheral smear, bone marrow aspiration and biopsy, histochemical staining, flow cytometry and cytogenetic evaluation. The diagnosis of FN was defined as a single-measurement of body temperature as ≥38.3°C without any environmental factor, or a body temperature of 38.0-38.2°C for more than one hour, and the peripheral blood absolute neutrophil count below 500/mm3 or 500-1000/ mm3 but decreased to below 500/mm3 in 48 hours. Complete blood count and C-reactive protein (CRP) was studied. (The upper reference limit of serum CRP to a healthy reference population is 8 mg/L). The blood culture bottles taken from the patients were incubated in the BacT/Alert 3D Blood Culture Systems (bioMérieux, France). Only skin contaminants cultured from two or more blood cultures within 48 h where patients had one of the following signs or symptoms including fever, chills, rigors or hypotension were included. Clinical and epidemiological data including patient demographics, underlying disease, date of positive blood culture, and organism/s isolated, were collected when the patient's first positive blood culture was identified. The identifications and susceptibilities of all isolates were tested by Microscan Walkaway 96 Plus (Beckman Coulter, USA). Etest strips (bioMérieux, France) were also used to determine the minimum inhibitory concentration of carbapenem-resistant microorganisms. Susceptibility testing was interpreted using EUCAST Clinical Breakpoints.[7] All of the isolated microorganisms were classified according to the general bacterial name and general antimicrobial resistance mechanism. In the general causative agent definition Staphylococci, enterococci and Listeria spp were included in the Gram-positive bacteria group, streptococci were evaluated separately; *Escherichia coli (E.coli), Klebsiella spp, Enterobacter spp, Salmonella spp and Proteus spp* were included in the Gram-negative enteric bacteria group; *Pseudomonas spp and Acinetobacter spp* were included in the non-fermentative bacteria group. *Extended spectrum beta-lactamase producing (ESBL) Gram-negative enteric bacteria, carbapenem-resistant Gram-negative bacteria, methicillin-resistant staphylococci, vancomycin-resistant enterococci* were included in the definition of general antimicrobial resistance. The records obtained from the medical charts of the study patients were examined retrospectively and it was recorded whether piperacillin/tazobactam, ceftriaxone, moxifloxacin, ampicillin/sulbactam was given as the initial empirical treatment, whether empirical antifungal was added in case of persistent fever, and whether there was a switch to directed antimicrobial treatment in case of blood culture positivity. Demographic characteristics, 30-day follow-up period, neutrophil count, neutropenia duration, CRP level and comorbidities of the patients were analyzed. All findings were recorded in the statistical analysis program for analysis. FN-related mortality rates and their relationship with other parameters were analyzed based on the recorded data.

Statistical Analysis

Statistical analyses of collected data were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Determination of the normally distributed data was conducted using the Kolmogorov-Smirnov test. Numerical variables that had normal distribution were expressed as the mean±standard deviation.Non-normal distribution were expressed as the median (min-max). The categorical variables were expressed as numbers and percentages. ANOVA test (posthoc:bonferroni test) or Kruskall Wallis H posthoc: Dunn's test) tests were used to compare numeric variables between three groups. The Chi square and the Fisher exact chi square tests were used in the comparison of the categorical variables. Cox regression analyses were conducted to establish any possible independent predictors of mortality. $P<0.05$ was taken as statistical significance.

Results

Ninety-five patients were included in the study and consisted of 47 acute leukemia (42 AML, 5 ALL), 21 lymphoproliferative diseases (12 non Hodgkin lymphoma, 1 Hodgkin lymphoma, 8 CLL), 17 multiple myeloma and 10 bone marrow failure (9 myelodysplastic syndrome, 1 aplastic anemia) cases. 50.5% (n=48) of the patients were female, 49.5% (n=47) were male, and the number of attacks was 1 in 83.2% (n=79) of all patients. Age distribution by disease groups have revealed that mean age was 58.2±13.2 years in patients with acute leukemia; 61.6±13.4 years in the lymphoproliferative disease group; 69.4±13.1 years in patients with bone marrow failure and 65.6±10.3 years in multiple myeloma patients. After one-month follow-

up 33.7% (n=32) of the patients have died. There was no relationship between other demographic characteristics and mortality (Table 1). In blood cultures *E.coli* was isolated from 25 patients(26.3%) and *K.pneumoniae* from 18 (18.9%), *Coagulase-negative staphylococci (CoNS)* from 14 (14.7%), *Pseudomonas aeruginosa (P.aeruginosa)* from 9 (9.4%), *Staphylococcus aureus (S.aureus)* from 7 (7.4%) and other Gram-positive and negative bacteria from 28 of them. The distribution and resistance rates of the bacterial growth are shown in Table 2. Such a significant association between the causative agents and antimicrobial resistance and mortality wasn't found. It was determined that a 100-unit decrease in the neutrophil count increased the mortality risk 1.06 times (HR:0.94; p<0.001) and a 1-unit increase in the CRP level on the day of recovery from neutropenia increased the mortality risk 1.06 times (HR:1.06; p<0.001). Mortality risk was found to be lower in patients with ≥1000 neutrophil count compared to those with 0-500 neutrophil count (HR:0.37; p=0.044). This was similar for the neutrophil count just after recovery from neutropenia. However, in those with neutropenia count between 500-1000, the mortality risk did not differ significantly compared to those with a neutropenia count between 0-500, but, those with neutrophil count between 500-1000 just after recovery from neutropenia recovery had a lower mortality risk compared to those with a neutropenia count between 0-500 (HR:0.22; p=0.014) (Table 3). No significant relationship was found

Table 1. The relationship between demographic characteristics of patients and mortality

Variables	All population n=95	Survival		Univariable Cox Regression		
		Alive n=63	Exitus n=32	HR	95% CI	p
Age, years	61.5±13.2	62.1±13.3	60.1±13.0	0.99	0.97-1.02	0.464
Sex, n (%)						
Female	48 (50.5)	30(47.6)	18 (56.3)	ref		
Male	47 (49.5)	33 (52.4)	14 (43.8)	0.76	0.38-1.54	0.450
Disease diagnosis,n (%)						
Acute leukemia	47 (49.5)	31 (49.2)	16 (50.0)	ref		
Lymphoproliferative	21 (22.1)	15 (23.8)	6 (18.8)	0.81	0.32-2.06	0.652
BF	10 (10.5)	9 (14.3)	1 (3.1)	0.26	0.04-1.99	0.195
MM	17 (17.9)	8 (12.7)	9 (28.1)	2.01	0.89-4.56	0.094
Attack number, n (%)						
1	79 (83.2)	51 (81.0)	28 (87.5)	ref		
2 or more	16 (16.9)	12 (19.1)	4 (12.5)	0.66	0.23-1.87	0.432
Underlying disease n(%)						
Diabetes mellitus	26 (27.4)	18 (28.6)	8 (25.0)	0.91	0.41-2.03	0.824
Hypertension	51 (53.7)	33 (52.4)	18 (56.3)	1.18	0.58-2.36	0.651
CAD	12 (12.6)	7 (11.1)	5 (15.6)	1.44	0.55-3.73	0.457
COPD	11 (11.6)	10 (15.9)	1 (3.1)	0.22	0.03-1.59	0.133
Hepatitis B	5 (5.3)	3 (4.8)	2 (6.3)	1.10	0.26-4.62	0.893
Rectum CA	3 (3.2)	3 (4.8)	0	0.05	0.01-148.90	0.457
Scleroderma	2 (2.1)	0	2 (6.3)	4.46	1.06-18.85	0.042*
Autoimmune hepatitis	1 (1.1)	0	1 (3.1)	3.42	0.46-25.32	0.228
RA	1 (1.1)	1 (1.6)	-	0.05	0.01-50750.5	0.669
Chemotherapy, n(%)						
1st Stage	31 (32.6)	21 (33.3)	10 (31.3)	ref		
2nd Stage	4 (4.2)	2 (3.2)	2 (6.3)	1.80	0.39-8.23	0.450
3rd Stage	2 (2.1)	1 (1.6)	1 (3.1)	2.41	0.31-18.80	0.403
Supportive	9 (9.5)	6 (9.5)	3 (9.4)	1.11	0.31-4.04	0.873
Induction	41 (43.2)	28 (44.4)	13 (40.6)	0.99	0.44-2.26	0.984
Recovery	8 (8.4)	5 (7.9)	3 (9.4)	1.23	0.34-4.46	0.756

Numerical variables were expressed as mean±standard deviation or median (min-max). Categorical variables were shown as numbers(%). *p<0,05 shows statistical significance. CA: cancer; CAD: coronary artery disease; BF: bone marrow failure; COPD: Chronic obstructive pulmonary disease; MM: multiple myeloma; RA: rheumatoid arthritis; HR: Hazard ratio; CI: confidence interval; ref: referance.

Table 2. Distribution of microorganisms grown in blood culture and antibiotic resistance

Microorganisms	Number	Percentage of AB resistant mo*(%)
Escherichia coli	25 (26.3%)	
ESBL-positive	8	32
Carbapenem-resistant	2	8
Klebsiella pneumoniae	18 (18.9%)	
ESBL-positive	7	38.8
Carbapenem-resistant	5	27.7
Coagulase-negative staphylococci	14 (14.7%)	
Methicillin-resistant	9	64.2
Pseudomonas aeruginosa	9 (9.4%)	
Carbapenem-resistant	1	11.1
Staphylococcus aureus	7 (7.4%)	
Methicillin-resistant	1	14.2
Enterococcus faecium	6 (6.3%)	
Vancomycin-resistant	2	33.3
Enterococcus faecalis	4 (4.1%)	
Acinetobacter baumannii	2 (2.1%)	
Carbapenem-resistant	1	50
Enterobacter cloacae	2 (2.1%)	
Salmonella spp	2 (2.1%)	
Enterobacter aerogenes	1 (1.1%)	
Group G β-hemolytic streptococci	1 (1.1%)	
Listeria monocytogenes	1 (1.1%)	
Proteus mirabilis	1 (1.1%)	
Streptococcus agalactiae	1 (1.1%)	
Streptococcus pneumoniae	1 (1.1%)	
TOTAL	95	

* AB resistant mo: Antibiotic resistant microorganisms. ESBL, Extended spectrum beta-lactamase producing.

between Gram-negative and Gram-positive bacteria species and mortality (Table 4). Diabetes mellitus rate was lower in patients with acute leukemia compared to other diagnostic groups, and distribution of other comorbidities were similar between diagnostic groups. The growth rate of Gram-negative enteric bacteria and Gram-positive bacteria in blood culture was higher and the growth rate of Gram-negative non-fermentative bacteria was lower in the acute leukemia group compared to other diagnoses. General antimicrobial resistance distribution did not differ significantly between the diagnostic groups. Median absolute neutrophil count and neutrophil count after recovery from neutropenia were found to be lower in the acute leukemia group compared to other diagnoses (Table 5).

Gram-negative non-fermentative bacteria group was found to be higher in patients with diabetes mellitus, no relationship was found between bacterial species and other demographic characteristics (Table 6). Shorter duration of antibiotic treatment was associated with a 1.09 (HR:0.92; p=0.001) fold increase in the risk of mortality. It was determined that the median duration of antibiotic use in 26 patients with FN who died was 5 days (1-30 days) and that taking antibiotics for a shorter period of time was associated with an increased risk of mortality (Table 7).

Discussion

In this study, 95 patients diagnosed with bloodstream infection (BSI) among patients with HM developed FN were evaluated. It was observed that the most common HM in patients with BSI was acute leukemia. The mortality rate was found to be 33.6% in patients with BSI, however, the mortality rate was 50% in acute leukemia. Çalık et al.[2] reported the mortality rate of BSI at Day 7 and Day 21 21.6% and 35.4% respectively. The mortality rate in our study was similar to these studies and it's assumed that high mortality rate in our study is related to the greater depth and longer duration of neutropenia. FN is frequently encountered in acute myeloid leukemia, and this is supposedly due to the use of intensive chemotherapy causing prolonged and deep neutropenia, which increases the risk of infection.[8-10] Most of the patients in our study were diagnosed with acute leukemia and most of them were receiving induction therapy (83%). Infectious complications in patients with HMs most commonly occur due to cytopenia depends on intensive chemotherapy.[11] The risk of infection increases with the depth and duration of neutropenia. This occurs mostly after induction chemotherapy for acute leukemia.[11] Neutrophil levels were low in most of our patients due to the diagnosis of acute leukemia and induction therapy that they were receiving. The depth of neutropenia was more effective on higher rate of mortality than the duration of neutropenia. Moreover, Gram-negative enteric bacteria were isolated from 28 (53.8%) of 52 patients with a neutrophil count below 500, while Gram-negative non-fermentative bacteria were isolated from four of these patients. Gram-positive bacteria (staphylococci and enterococci) were isolated from 16 (30.7%) of 52 patients with a neutrophil count below 500. Among our patients in those with diabetes which is known to cause neutrophil dysfunction, Gram-negative non-fermentative bacteria was more frequently isolated. It was assumed that this was not only due to neutrophil dysfunction, but also due to low neutrophil count, since 17 (65.4%) of 26 patients with diabetes had an absolute neutrophil count of 1000 or less. Early diagnosis, blood cultures, and prompt initiation of appropriate intravenous antibiotics are important in the treatment of FN.[12] In our clinic when FN was suspected in hospitalized patients,

Table 3. Association between laboratory findings and mortality

Variables	All population n=95	Survival		Univariable Cox Regression		
		Alive n=63	Exitus n=32	HR	95% CI	p
The general causative agent, n (%)						
Gram-negative enteric bacteria group	49 (51.6)	32 (50.8)	17 (53.1)	ref		
Gram-positive bacteria group	32 (33.7)	23 (36.5)	9 (28.1)	0.79	0.35-1.77	0.567
Non-fermentative bacteria group	11 (11.6)	6 (9.5)	5 (15.6)	1.614	0.60-4.38	0.347
Streptococci	3 (3.2)	2 (3.2)	1 (3.1)	0.825	0.11-6.21	0.852
The general antimicrobial resistance, n (%)						
ESBL-negative Gram-negative enteric bacteria	28 (29.5)	19 (30.2)	9 (28.1)	ref		
ESBL-positive Gram-negative enteric bacteria	15 (15.8)	8 (12.7)	7 (21.9)	1.617	0.60-4.34	0.340
Carbapenem sensitive non-fermenter bacteria	9 (9.5)	6 (9.5)	3 (9.4)	1.199	0.32-4.43	0.786
methicillin-resistant staphylococci	10 (10.5)	9 (14.3)	1 (3.1)	0.278	0.04-2.20	0.225
methicillin-susceptible staphylococci	11 (11.6)	9 (14.3)	2 (6.3)	0.514	0.11-2.34	0.395
Vancomycin susceptible enterococci	8 (8.4)	4 (6.3)	4 (12.5)	1.864	0.57-6.06	0.300
Others	14 (14.7)	8 (12.7)	6 (18.8)	1.416	0.50-3.98	0.510
Absolute neutrophil count, $x10^2$	1 (0-167)	4 (0-167)	1 (0-79)	0.98	0.97-1.00	0.172
0-500	56 (58.9)	34 (54.0)	22 (68.8)	ref		
500-1000	9 (9.5)	4 (6.3)	5 (15.6)	1.87	0.71-4.93	0.210
≥1000	30 (31.6)	25 (39.7)	5 (15.6)	0.37	0.14-0.97	0.044*
Duration of neutropenia, days	10 (0-31)	12 (3-31)	5.5 (0-21)	0.83	0.75-0.91	<0.001*
Neutrophil count on the day of recovery from neutropenia, $x10^2$	24 (0-198)	2650 (0-198)	0 (0-92)	0.94	0.91-0.97	<0.001*
0-500	31 (32.6)	6 (9.5)	25 (78.1)	ref		
500-1000	10 (10.5)	7 (11.1)	3 (9.4)	0.22	0.07-0.73	0.014*
≥1000	54 (56.8)	50 (79.4)	4 (12.5)	0.05	0.02-0.14	<0.001*
CRP count	177 (3-470)	181 (3-470)	163.5 (5-463)	0.99	0.98-1.00	0.313
CRP count on the day of recovery from neutropenia	64 (3-541)	47 (3-541)	236.5 (17-459)	1.06	1.04-1.08	<0.001*

Numerical variables were expressed as mean±standard deviation or median (min-max). Categorical variables were shown as numbers (%). *p<0,05 shows statistical significance. Abbreviations: ESBL, Extended-spectrum beta-lactamase, CRP, C-reaktif protein, HR: Hazard ratio, CI: confidence interval, ref: referance.

Table 4. Relationship between bacteria and mortality

Bacteria	Univariable Cox Regression		
	HR	95% CI	p
Gram-negative enteric bacteria	ref		
Escherichia coli	2.122	0.26-16.96	0.478
Klebsiella pneumoniae	3.154	0.39-25.23	0.279
Gram-positive bacteria			
Enterococcus faecalis	3.122	0.35-27.95	0.309
Methicilline-resistant CoNS	0.656	0.04-10.48	0.765
Methicilline-susceptible CoNS	1.145	0.07-18.31	0.924
S.aureus	0.01	0.01-98521.2	0.983
Other Gram-positive bacteria	5.944	0.62-57.32	0.123
P.aeruginosa	3.66	0.41-32.77	0.246
A.baumannii	4.271	0.27-68.41	0.305
Streptococci	1.914	0.12-30.61	0.646

Categorical variables shown as numbers (%). Abbreviations: HR: Hazard ratio, CI: confidence interval, ref: referanc.

empirical antibiotic treatment was started quickly after blood and other cultures were taken. Eighty (84.2%) of our patients were receiving empirical or directed antibiotic treatment. The mortality rate on Day 30th was 33.6%, there were 15 (15.8%) patients who did not receive antibiotics, and 7 (21.9%) of them died. In addition, antibiotic use less than five days was found to be associated with mortality. The widespread occurrence of MDR (Multi drug-resistant) bacteria has increased the burden of morbidity and mortality among cancer patients.[13] Appropriate empirical antimicrobial therapy has a significant impact on survival.[14,15] In our study, no significant relationship was found between Gram-negative and Gram-positive bacteria and mortality and this is assumed to be related with early antibiotic treatment. It is also suggested that the prompt and appropriate switch of antibiotics according to the results of the microbiologic culture was also effective. Chen et al.[1] have reported Gram-negative bacteria as the most commonly encountered causative pathogens (G-; 64.7%);

Table 5. Distribution of laboratory findings according to diagnosis groups

Variables	Acute leukemia n=47	Lymphoproliferative n=38	Bone marrow failure n=10	p
The general causative agent, n(%)				
Gram-negative enteric bacteria group	28 (59.6)	18 (47.4)	3 (30.0)	0.050*
Gram-positive bacteria group	17 (36.2)	12 (31.6)	3 (30.0)	
Non-fermentative bacteria group	2 (4.3)	6 (15.8)	3 (30.0)	
Streptococci	0	2 (5.3)	1 (10.0)	
The general antimicrobial resistance, n (%)				
ESBL-negative Gram-negative enteric bacteria	16 (34.0)	11 (28.9)	1 (10.0)	0.616
ESBL-positive Gram-negative enteric bacteria	8 (17.0)	5 (13.2)	2 (20.0)	
Carbapenem sensitive non-fermenter bacteria	2 (4.3)	4 (10.5)	3 (30.0)	
Methicillin-resistant staphylococci	5 (10.6)	3 (7.9)	2 (20.0)	
Methicillin-susceptible staphylococci	6 (12.8)	4 (10.5)	1 (10.0)	
Vancomycin susceptible enterococci	4 (8.5)	4 (10.5)	0	
Others	6 (12.8)	7 (18.4)	1 (10.0)	
Absolute neutrophil count, $x10^2$	0 (0-6500)	900 (0-9900)	750 (100-16700)	<0.001*
Duration of neutropenia, days	11 (0-31)	8 (0-25)	10 (5-30)	0.215
Neutrophil count on the day of recovery from neutropenia, $x10^2$	1200 (0-10200)	2600 (0-17000)	3400 (0-19800)	0.041*
CRP count	169 (5-463)	182.5 (3-438)	306 (25-470)	0.696
CRP count on the day of recovery from neutropenia	86 (5-541)	64 (3-362)	43 (7-257)	0.393

Numerical variables were expressed as mean±standard deviation or median (min-max). Categorical variables were shown as numbers(%). *p<0.05 shows statistical significance. CRP: C-reaktif protein. ESBL: Extended-spectrum beta-lactamase.

Vahedian-Ardakani et al.[16] have also reported Gram-negative pathogens as common agents.[17,18] In our study, *E.coli* (26.3%), K. pneumoniae (18.9%) and CoNS (14.7%) were the first three infectious agents. Compared to other diagnoses, the rate of Gram-negative enteric bacteria and Gram-positive bacteria was higher in the acute leukemia group, but the rate of Gram-negative non-fermentative bacteria was lower. This is assumed to be due to the lower median neutrophil count in acute leukemia group compared to patients having other diagnoses. The 30-day mortality is higher in patients with Gram-negative MDR bacteria in whom this high rate is closely related to initiation of inappropriate antimicrobial therapy in the first 24 hours.[18] In our study, methicillin-resistance was present in 10 of 21 patients who are Staphylococci positive (47.6%), and 2 of 11 patients who are non-fermentative Gram-negative bacteria positive (18.1%) were resistant to carbapenems. Presence of antibiotic resistance may indicate probable difficulties regarding decision-making for antibiotic treatment choice in FN management. However, in our study, no significant relationship was found between the causative agents in general and general antimicrobial resistance and mortality. CRP is a marker of inflammatory activity; higher values have been associated with an increased risk of mortality.[19,20] The increase in CRP level on the day recovery of patients from neutropenia have also increased the risk of mortality and this may point out to the importance of monitoring CRP levels in addition to neutrophil count. The limitation of this study is that it is being retrospective and not all patients with HM, but only patients with BSI were included in the study.

To conclude, Gram-negative bacilli were found to be the most frequently grown microorganisms in the blood culture of patients with HM during a FN attack. Since Gram-negative and Gram-positive bacteria are found to be resistant to many antibiotics, it is predicted that there will be difficulties in the antibiotics stewardship in febrile neutropenia. In the follow-up of these patients, close monitoring of neutropenia duration, neutrophil count and CRP values seems to be important in terms of early diagnosis and early switching to appropriate antibiotics, in terms of reducing mortality and morbidity.

Disclosures

Ethics Committee Approval: This study was approved by the ethics committee of Zonguldak Bülent Ecevit University for the use of patient data for publication purposes (Approval Date: 09.06.2021; Reference Number / Protocol No: 2021/11).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.A.A., D.H.; Design – M.A.A., D.H.; Supervision – M.A.A., D.H.; Materials – M.A.A., D.H.;

Table 6. The relationship between demographic characteristics and bacteria

Variables	Gram-negative enteric bacteria group n=49	Gram-positive bacteria group n=32	Non-fermentative bacteria group n=11
Age, years	62.5±12.2	57.7±14.1	64.9±13.0
Sex, n(%)			
Female	25 (51.0)	16 (50.0)	6 (54.5)
Male	24 (49.0)	16 (50.0)	5 (45.5)
Attack number, n (%)			
1	42 (85.7)	26 (81.3)	8 (72.7)
2 or more	7 (14.3)	6 (18.8)	3 (27.3)
Underlying disease, n (%)			
Diabetes mellitus	8 (16.3)	10 (31.3)	7 (63.6)
Hypertension	27 (55.1)	14 (43.8)	8 (72.7)
CAD	6 (12.2)	4 (12.5)	2 (18.2)
COPD	3 (6.1)	5 (15.6)	3 (27.3)
Hepatitis B	2 (4.1)	1 (3.1)	2 (18.2)
Rectum CA	1 (2.0)	2 (6.3)	0
Scleroderma	0	1 (3.1)	1 (9.1)
Autoimmune hepatitis	1 (2.0)	0	0
RA	1 (2.0)	0	0
Chemotherapy, n (%)			
1st Stage	16 (32.7)	8 (25.0)	6 (54.5)
2nd Stage	1 (2.0)	2 (6.3)	1 (9.1)
3rd Stage	0	0	1 (9.1)
Supportive	3 (6.1)	4 (12.5)	1 (9.1)
Induction	24 (49.0)	15 (46.9)	2 (18.2)
Recovery	5 (10.2)	3 (9.4)	0

Numerical variables were expressed as mean±standard deviation or median (min-max). Categorical variables were shown as numbers(%). *p<0,05 shows statistical significance. CAD, coronary artery disease; COPD, Chronic obstructive pulmonary disease; RA, rheumatoid arthritis.

Table 7. Characteristics of antibiotic use and its relationship with mortality

Variables	All population n=95	Survival		Univariable Cox Regression		
		Alive n=63	Exitus n=32	HR	95% CI	p
AB treatment, n(%)						
No	15 (15,8)	8(12,7)	7(21,9)	ref		
Yes	80 (84,2)	55(87,3)	25(78,1)	0,60	0,26-1,38	0,225
AB treatment duration, days	11 (0-30)	14(0-30)	4(0-30)	0,92	0,87-0,96	0,001*
Follow-up, days	30 (1-30)	30(30-30)	5,5(1-30)	-	-	-

Numerical variables were expressed as mean±standard deviation or median (min-max). Categorical variables were shown as numbers(%). *p<0,05 shows statistical significance. Abbreviations: AB: Antibiotic, HR: Hazard ratio, CI: confidence interval, ref: referance.

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