

Original Article

Epidemiology and mortality in bacterial bloodstream infections in patients with hematologic malignancies

Duygu Mert¹, Sabahat Ceken¹, Gulsen Iskender¹, Dicle Iskender², Alparslan Merdin², Fazilet Duygu¹, Mustafa Ertek¹, Fevzi Altuntas²

¹ University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Infectious Diseases and Clinic Microbiology Clinic, Ankara, Turkey

² University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Hematology Clinic and Bone Marrow Transplantation Unit, Ankara, Turkey

Abstract

Introduction: Patients with hematological malignancies, who are in the high risk group for infectious complications and bacterial bloodstream infections. The aim of the study evaluated epidemiology and mortality in bacterial bloodstream infections in patients with hematologic malignancies. In addition to determine the risk factors, changes in the distribution and frequency of isolated bacteria.

Methodology: In this retrospective study. There were investigated data from 266 patients with hematological malignancies and bacterial bloodstream infections who were hospitalized between the dates 01/01/2012 and 12/31/2017.

Results: There were 305 blood and catheter cultures in febrile neutropenia attacks in total. In these total attacks, primary bloodstream infections were 166 and catheter-related bloodstream infections were 139. In blood cultures; *Escherichia coli* and *Klebsiella pneumoniae* bacteria were detected in 58,0% and 22,9% of the samples, respectively. 52,4% of the cultured Gram-negative bacteria were extended spectrum beta-lactamase (ESBL). Carbapenemase positive culture rate was 17,2% in Gram-negative bacteria cultures. *Staphylococcus epidermidis* was found in 38,4% of the Gram-positive bacteria cultures. In Gram-positive bacteria; methicillin resistance were detected in 82,2% of the samples. There was a statistically significant relationship between bloodstream infection and disease status. 60 patients with primary bloodstream infections were newly diagnosed.

Conclusions: In patients with hematological malignancies, certain factors in the bloodstream infections increase the mortality rate. With the correction of these factors, the mortality rate in these patients can be reduced. The classification of such risk factors may be an important strategy to improve clinical decision making in high-risk patients, such as patients with hematological malignancies.

Key words: Hematological cancers; bacterial bloodstream infections; mortality.

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Introduction

Patients with hematological malignancies are in the high risk group for infectious complications. Bacterial bloodstream infections are frequently seen in these patients. In a recent study, in patients with newly diagnosed hematological malignancies, microbiologically documented bacterial infection rate was found as 9,4% and bacterial bloodstream infection rate was found as 85,1% [1]. These infections could cause serious morbidity and mortality when they are not treated quickly and effectively [2]. Usually, the bacterial agent is unknown at the beginning of the infection. It is of great importance to know the frequency of the microbial agents in these patients [3].

Recently, some studies have reported that Gram-negative bacteria are the most common cause of bacterial bloodstream infections in patients with

hematological malignancies [4]. In addition, especially in these patients with infections caused by Gram-negative bacteria, antimicrobial resistance rates of bacteria were found to be increased [4].

The aim of this study is to determine whether there is a difference between primary bacteremia and catheter-related bacteremia for mortality in patients with hematological malignancies. In addition to determine the clinical and epidemiological characteristics, risk factors, changes in the distribution and frequency of isolated bacteria, and to evaluate the mortality rates of these infections in order to review the antimicrobial resistance status of the bacteria.

Methodology

The study was planned as a retrospective study. University of Health Sciences Dr. Abdurrahman

Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee approval was obtained (Approval date: 07/04/2018 and decision no: 2018-07/83).

The data of 266 patients who were followed up and treated with the diagnosis of hematological malignancies and who were found to have bacterial bloodstream infections were analyzed during the period from 01/01/2012 to 12/31/2017. When fever was $\geq 38,3^{\circ}\text{C}$ in patients with hematological malignancies, at least 2 vials of blood cultures were drawn from each patient at 30 minutes' intervals. Blood cultures were obtained from different peripheral veins of patients with central venous catheter (CVC), including one from the catheter. Automated BacT / ALERT 3D (bioMerieux, Marcy-l'Etoile, France) system, that detect growth of blood cultures by signal, was used. Antibiotic susceptibility tests of factors were performed according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). According to the Center for Disease Control and Prevention (CDC) definitions; the patients were divided into two groups as primary bloodstream infections and catheter-related bloodstream infections. A total of 305 positive cultures were detected.

Results of the patients were recorded electronically from the health records. The demographic data of the patients and their other informations at the time of cultures were recorded in a pre-prepared form. Patients with microbial growth in their blood and/or catheter cultures were included in the study.

18 years and older patients with hematologic malignancies, and who had clinical, laboratory and microbiological bacteremia diagnosis were included in the study. Patients who were under 18 years old, pregnant patients and without hematological malignancies were excluded from the study.

The following information were recorded: Age, sex, type of disease, date of hospitalization and discharge, date of bacterial bloodstream infection, name of active Gram-negative infection, culture status of expanded spectrum beta lactamase, carbapenemase culture status, quinolone resistance, aminoglycoside resistance, name of active Gram-positive infection, methicillin resistance, vancomycin resistance, infection type (primary or catheter-related bloodstream infection), disease status (newly diagnosed, remission, refractory, relapse, stable, not evaluated group), neutrophil count, duration of neutropenia, name of the given chemotherapy regimen (induction, consolidation, salvage regimen, other chemotherapies, no chemotherapy), antibiotics used in the last three

months, hospitalization status in the last three months, other bloodstream infections in the last three months, additional diseases (Diabetes mellitus, chronic obstructive pulmonary disease, hypertension, coronary artery disease, chronic renal failure, serobrovascular disease, chronic hepatitis B infection, chronic hepatitis C infection, human immune deficiency infection, solid organ cancer, other diseases), initial antibiotic therapy (cefoperazone-sulbactam, piperacillin-tazobactam, meropenem, cefoperazon-sulbactam and vancomycin, piperacillin-tazobactam and teicoplanin, meropenem and daptomycin, linezolid, colistin, meropenem and teicoplanin), antibiotic starting day, catheter status (presence of central and urinary catheter), intensive care unit stay, steroid use, clinical complication (septic shock, organ failure, etc.), total hospitalization day, discharge and mortality status.

Statistical analysis

SPSS (IBM SPSS Statistics 24) program was used in the comparison of statistical data. The data were entered into statistical software program and analyzed by using the same computer software program. In order to interpret the findings, frequency tables and descriptive statistics were used.

The categorical descriptive data were presented as frequency distribution and percentages (%) and the measurable descriptive data were presented as mean \pm standard deviation (SD) and median (the largest, the smallest values).

The " χ^2 -cross tables" were used to examine the relationship between two qualitative variables. "Mann-Whitney U" test (Z-table value) statistics were used to compare the two non-normally distributed independent groups. $P < 0,05$ was considered statistically significant.

Results

Data of 266 patients with hematological malignancies and/or bacterial bloodstream infections, who were hospitalized between the dates 01/01/2012 and 12/31/2017, were analyzed. Total of 305 blood and catheter culture positive infections occurred in febrile neutropenia attacks of these patients.

155 (58,3%) of the patients were male and 111 (41,7%) of the patients were female. The mean age of the patients was $45,02 \pm 16,47$ years.

124 (46,5%) of the patients had myeloid leukemia (AML) and 58 (21,8%) of the patients had non Hodgkin lymphoma (NHL) (Table 1).

Total number of positive cultures in blood and/or catheter cultures were 305. 142 (46,5%) of the patients were diagnosed with AML (Table 2).

Table 1. Basic findings of the patients.

Variable (N = 266)	n	%
Gender		
Female	111	41,7
Male	155	58,3
Age		
60 years and under	213	80,1
Over 60	53	19,9
Diagnosis of disease		
Acute myeloid leukemia	124	46,5
Acute lymphoblastic leukemia	62	23,3
Chronic myeloid leukemia	2	0,8
Chronic lymphoblastic leukemia	2	0,8
Hairy cell leukemia	1	0,4
Multiple myeloma	12	4,5
Multiple dysplastic syndrome	5	1,9
Non-Hodgkin's lymphoma	58	21,8

Table 2. Findings of patients in total attacks

Variable	N	%	Mean ± S.D.	Median (min-max)
Diagnosis of disease				
Acute myeloid leukemia	142	46,5		
Acute lymphoblastic leukemia	75	24,6		
Chronic myeloid leukemia	2	0,7		
Chronic lymphoblastic leukemia	2	0,7		
Hairy cell leukemia	1	0,3		
Multiple myeloma	13	4,3		
Multiple dysplastic syndrome	5	1,6		
Non-Hodgkin's lymphoma	65	21,3		
Length of stay (days)			34,59 ± 16,89	30,0 (6,0-101,0)
Alive-stay time (days)			34,52 ± 16,32	29,5(7,0-101,0)
Duration of neutropenia			15,72 ± 13,04	12,0 (0,0-76,0)
Infection type				
Primary	166	54,4		
Catheter	139	45,6		
Antibiotic use in the last three months	127	41,6		
Initial antibiotic				
Cefoperazone sulbactam	93	30,6		
Piperacillin tazobactam	88	28,8		
Meropenem	86	28,2		
Cefoperazone sulbactam + vancomycin	22	7,2		
Piperacillin tazobactam + teicoplanin	7	2,3		
Meropenem + daptomycin	3	1,0		
Linezolid	1	0,3		
Colistin	3	1,0		
Meropenem + teicoplanin	2	0,6		
Central catheter use	227	74,4		
Urinary catheter use	41	13,5		
Steroids use	83	27,2		
Stay in intensive care	72	23,6		
Mortality				
Alive	234	76,7		
Exit	71	23,3		

The mean duration of hospital stay of patients was $34,59 \pm 16,89$ (days) during the total attacks. The mean duration of neutropenia of the patients was $15,72 \pm 13,04$ (days) in total attacks (Table 2).

Primary bloodstream infection number in total attacks was 166 (54,4%) and catheter-related bloodstream infection number was 139 (45,6%) (Table 2).

Initial antibiotic therapy was cefoperazone-sulbactam for 93 (30,6%) of primary and/or catheter-related bloodstream infections (Table 2).

There were 227 (74,4%) patients with central catheter, 41 (13,5%) patients with urinary catheter and 83 (27,2%) patients with steroid history (Table 2). 72 (23,6%) of the patients were hospitalized in the intensive care unit. In the study; 234 (76,7%) of the patients were alive and 71 (23,3%) of the patients were dead (Table 2).

Antibiotic use was also evaluated; 127 (41,6%) of the patients with bloodstream infections had used antibiotics in the last three months (Table 2).

In blood cultures, *Escherichia coli* and *Klebsiella pneumoniae* bacteria were detected in 134 (58,0%) of the samples and 53 (22,9%) of the samples, respectively (Table 3). 122 (52,4%) of the cultured Gram-negative bacteria were extended spectrum beta-lactamase (ESBL). In 40 (17,2%) of the cultured Gram-negative bacteria, carbapenemase resistance were found.

Staphylococcus epidermidis was found in 28 (38,4%) of the cultured Gram-positive bacteria samples (Table 3). In the Gram-positive bacteria; methicillin resistance were detected in 60 (82,2%) of the samples and vancomycin resistance was detected in only 1 (1,4%) of the samples.

A statistically significant relationship between bloodstream infections and disease status was found ($p = 0,018$). 60 (36,2%) patients with bloodstream infections were newly diagnosed and 11 (6,6%) patients had stable disease (Table 4).

37 (26,7%) patients with catheter-related bloodstream infections were newly diagnosed and 1 (0,7%) patient with catheter-related bloodstream infection was in the undiagnosed group (Table 4).

The highest rate of primary and/or catheter-related bloodstream infections was in the newly diagnosed group of patients. Data from 266 patients with hematological malignancies and/or bacterial bloodstream infections who were hospitalized between the dates 01/01/2012 and 12/31/2017 were analyzed. Relationship between bloodstream infections and chemotherapy regimen were also seen ($p > 0,05$) (Table 4).

There were statistically significant relationships between bacteremia and presence of other bloodstream infections, central catheter use, quinolone prophylaxis, steroid usage in the last three months ($p = 0,005$, $p = 0,000$, $p = 0,009$ and $p = 0,011$, respectively) (Table 4).

There was a statistically significant difference according to the number of neutrophil counts during the bloodstream infections with respect to being primary or catheter-related ($p = 0,003$). Neutrophil counts were significantly higher in patients with catheter-related bacteremia than those with primary bacteremia (Table 5). However, there was no statistically significant difference in duration of neutropenia (days) ($p > 0,05$). In addition, there was no statistically significant relationship between bacteremia and total length of stay in hospital (Table 5).

There was a statistically significant relationship between mortality and disease status ($\chi^2 = 23,829$; $p = 0,000$). 71 (30,4%) alive patients were newly diagnosed and 28 (39,4%) dead patients were relapsed patients (Table 6).

A statistically significant relationship between mortality and chemotherapy regimen ($\chi^2 = 27,738$; $p = 0,000$) was observed. 77 (33,0%) alive patients received consolidation chemotherapy regimens and 34 (47,9%) dead patients received salvage chemotherapy regimens (Table 6).

There were statistically significant correlations between mortality and antibiotic use in the last three months and duration of hospitalization ($p = 0,019$ and $p = 0,040$) (Table 6).

The correlations between mortality and urinary catheter use, intensive care stay, steroid use, clinical complications were statistically significant ($p = 0,000$, $p = 0,000$, $p = 0,019$ and $p = 0,000$, respectively) (Table 6).

There was no statistically significant relationship between mortality and central catheter use ($p > 0,05$) (Table 6).

In addition, there was a statistically significant difference between mortality and the duration of hospitalization (days) before infection ($p = 0,001$) (Table 7).

There was no statistically significant difference between mortality and neutrophil count, duration of neutropenia (days), appropriate antibiotic initiation day, total length of hospitalization (days) ($p > 0,05$) (Table 7).

In terms of mortality, there was no statistically significant difference between patients with primary bloodstream infections and patients with catheter related bloodstream infections ($p = 0,712$) (Table 4).

Table 3. Bacteria isolated from blood and catheter cultures

	n	%
Gram-negative bacteria		
<i>Escherichia coli</i>	134	58,0
<i>Klebsiella pneumoniae</i>	53	22,9
<i>Pseudomonas aeruginosa</i>	17	7,4
<i>Enterobacter cloacae</i>	7	3,0
<i>Acinetobacter baumannii</i>	9	3,9
<i>Aeromonas hydrophila/caviae</i>	2	0,8
<i>Pseudomonas spp</i>	4	1,6
<i>Sphingomonas paucimobilis</i>	1	0,4
<i>Klebsiella oxytoca</i>	1	0,4
<i>Stenotrophomonas maltophilia</i>	2	0,8
<i>Acinetobacter lwoffii</i>	1	0,4
<i>Proteus mirabilis</i>	1	0,4
Gram-positive bacteria		
<i>Staphylococcus haemolyticus</i>	11	15,1
<i>Corynebacterium spp</i>	2	2,6
<i>Staphylococcus epidermidis</i>	28	38,4
<i>Enterococcus faecium</i>	8	11,0
<i>Streptococcus mitis</i>	2	2,7
<i>Staphylococcus hominis</i>	17	23,3
<i>Staphylococcus aureus</i>	2	2,7
<i>Staphylococcus warneri</i>	1	1,4
<i>Kocuriakristinae</i>	1	1,4
<i>Staphylococcus spp</i>	1	1,4

Table 4. The relationship between hematologic malignancy and bacteremia.

Variable	Bacteremia		Statistical analysis* Possibility
	Primary (n, %)	Catheter (n, %)	
Status of the disease			
Newly diagnosed	60 (36,2%)	37 (26,7%)	p = 0,018
Remission	39 (23,5%)	33 (23,7%)	
Refractor	17 (10,2%)	28 (20,1%)	
Relapse	39 (23,5%)	38 (27,4%)	
Stable disease	11 (6,6%)	2 (1,4%)	
No evaluation group	-	1 (0,7%)	
Chemotherapy regimen			
Induction	59 (35,5%)	36 (26,1%)	p = 0,090
Consolidation	47 (28,3%)	34 (24,6%)	
Salvage	49 (29,5)	61(44,2)	
Other chemotherapy	4 (2,4%)	4 (2,9%)	
No chemotherapy	7 (4,3%)	3 (2,2%)	
Antibiotic use in the last three months	69 (41,6%)	58 (41,7%)	p = 0,977
Hospitalization in the last three months	92 (55,4%)	82 (59,0%)	p = 0,530
Another bloodstream infection in the last three months	22 (13,3%)	36 (25,9%)	p = 0,005
Additional disease	48 (28,9%)	46 (33,1%)	p = 0,431
Initial antibiotic compliance	104 (62,7%)	85 (61,6%)	p = 0,850
Central catheter use	90 (54,2%)	137 (98,6%)	p = 0,000
Urinary catheter use	27 (16,3%)	14 (10,1%)	p = 0,120
Quinolone prophylaxis	71 (47,7%)	55 (65,5%)	p = 0,009
Steroids use	55 (33,1%)	28 (20,1%)	p = 0,011
Stay in intensive care	42 (25,3%)	30 (21,6%)	p = 0,446
Mortality			
Alive	126 (75,9%)	108 (77,7%)	p = 0,712
Exit	40 (24,1%)	31 (22,3%)	

*The “ χ^2 —cross tables” were used to investigate the relationship between two qualitative variables.

Table 5. Comparison of neutrophil count and duration according to bacteremia status.

Variable	Bacteremia		Statistical analysis* possibility
	Primer Median (Min-Max)	Catheter Median (Min-Max)	
Neutrophil count	30,0 (0,0-9080,0)	50,0 (0,0-7620,0)	p = 0,003
Duration of neutrophil (days)	13,0 (0,0-76,0)	12,0 (0,0-59,0)	p = 0,512
Total length of stay in hospital	28,0 (6,0-101,0)	30,0 (7,0-98,0)	p = 0,315
Stay in hospital before infection	15,0 (0,0-62,0)	15,0 (1,0-93,0)	p = 0,586

*"Mann-Whitney U" test (Z-table value) statistics were used to compare the two non-normally distributed independent groups.

Table 6. Relationship between some features of the patient and mortality.

Variable	Mortality		Statistical analysis* Possibility	
	Alive (n,%)	Exit (n,%)		
Status of the Disease				
Newly diagnosed	71 (30,4%)	26 (36,7%)	$\chi^2 = 23,829$ p = 0,000	
Remission	69 (29,5%)	3 (4,2%)		
Refractor	33 (14,1%)	12 (16,9%)		
Relapse	49 (20,9%)	28 (39,4%)		
Stable disease	11 (4,7%)	2 (2,8%)		
No evaluation group	1 (0,4%)	-		
Diagnosis of the Disease				
Acute myeloid leukemia	110 (47,0%)	32 (45,1%)	$\chi^2 = 9,590$ p=0,283	
Acute lymphoblastic leukemia	57 (24,4%)	18 (25,4%)		
Chronic myeloid leukemia	1 (0,4%)	1 (1,4%)		
Chronic lymphoblastic leukemia	-	2 (2,8%)		
Hairy cell leukemia	1 (0,4%)	-		
Multiple myeloma	9 (3,8%)	4 (5,6%)		
Multiple dysplastic syndrome	4 (1,6%)	1 (1,4%)		
Non-Hodgkin's lymphoma	52 (22,4%)	13 (18,3%)		
Chemotherapy regimen				
Induction	69 (29,6%)	26 (36,6%)		$\chi^2 = 27,738$ p = 0,000
Consolidation	77 (33,0%)	4 (5,6%)		
Salvage	76 (32,6%)	34 (47,9%)		
Other chemotherapy	7 (3,0%)	1 (1,4%)		
No chemotherapy	4 (1,8%)	6 (8,5%)		
Quinolone prophylaxis	88 (50,3%)	38 (65,5%)	$\chi^2 = 4,070$ p = 0,044	
Antibiotic use in the last three months	106 (45,3%)	21 (29,6%)	$\chi^2 = 5,540$ p = 0,019	
Hospitalization in the last three months	141 (60,3%)	33 (46,5%)	$\chi^2 = 4,220$ p = 0,040	
Another bloodstream infection in the last three months	45 (19,2%)	13 (18,3%)	$\chi^2 = 0,030$ p = 0,862	
Central catheter use	173 (73,9%)	54 (76,1%)	$\chi^2 = 0,129$ p = 0,719	
Urinary catheter use	13 (5,6%)	28 (39,4%)	$\chi^2 = 53,463$ p = 0,000	
Hospitalization in intensive care	3 (3,0%)	65 (91,5%)	$\chi^2 = 236,886$ p = 0,000	
Steroids use	56 (23,9%)	27 (38,0%)	$\chi^2 = 5,465$ p = 0,019	
Clinical complications	5 (2,1%)	66 (93,0%)	$\chi^2 = 251,578$ p = 0,000	
Initial antibiotic compliance	148 (63,5%)	41 (57,7%)	$\chi^2 = 0,771$ p = 0,380	
Appropriate antibiotic start day				
0-1	139 (59,4%)	45 (64,3%)	$\chi^2 = 2,548$ p = 0,467	
2.	30 (12,8%)	10 (14,3%)		
3.	42 (17,9%)	7 (10,0%)		
4 and above	23 (9,9%)	8 (11,4%)		

*The " χ^2 -cross tables" were used to investigate the relationship between two qualitative variables.

Table 7. Comparison of some parameters according to mortality.

Variable	Mortality		Statistical analysis* Possibility
	Alive Median (min-max)	Exit Median (min-max)	
Neutrophil count	30,0 (0,0-9080,0)	30,0 (0,0-4910,0)	Z = -0,261 p = 0,794
Duration of Neutrophil(days)	12,0 (0,0-76,0)	15,0 (0,0-59,0)	Z = -1,504 p = 0,133
Appropriate antibiotic start day	1,0 (1,0-8,0)	1,0 (0,0-7,0)	Z = -0,877 p = 0,381
Duration of hospitalization (days) before infection	14,0 (1,0-64,0)	18,5 (0,0-93,0)	Z = -3,460 p = 0,001
Total length of stay in hospital (day)	30,0 (7,0-101,0)	29,0 (6,0-98,0)	Z = -0,251 p = 0,802

*“Mann-Whitney U” test (Z-table value) statistics were used to compare the two non-normally distributed independent groups.

Discussion

The infections are major cause of morbidity and mortality in cancer patients [5]. Neutropenia is the most important factor leading to infection development in patients with hematological malignancies. When the absolute neutrophil count is below 500 mm³, the rate of infection increases and when this count is between 0-100 mm³, the incidence of bacteremia and serious infection increases [6].

In this study, the mean neutrophil count was 30 /mm³ in patients with primary bloodstream infections and it was 50 /mm³ in patients with catheter-related bloodstream infections. There was a statistically significant relationship between bacteremia and neutrophil count (p = 0,003). In newly diagnosed patients, the incidence of primary and/or catheter-related bloodstream infections was found to be increased.

In a study of Jacob *et al.* the most common hematological malignancy was AML in febrile neutropenic patients [7]. Also, the most common hematologic malignancy was AML (46,5%) in this study.

Most of the infections of neutropenic patients are formed by bacteria. In recent studies, it has been reported that there is an increase in Gram-positive bacteria as a cause of severe bacterial infection in cancer patients [4,8].

In a study of Trearichi *et al.*, Gram-negative bacteria were isolated as the most common cause of bloodstream infections in patients with hematological malignancies. In their study; the most frequently isolated Gram-negative bacteria were *E. coli* and *K. pneumoniae* [9].

In a study of Kara *et al.* Gram-negative bacteria were the most frequently isolated (52,6%) in bloodstream infections of patients with hematologic malignancies. *E. coli* (17,3%) and *Klebsiella* spp.

(11,0%) were the most frequently isolated Gram-negative bacteria. Coagulase negative staphylococcus (10,4%) and *Corynebacterium* spp. (6,3%) were the most frequently isolated Gram-positive bacteria (35,8%) [10]. In a study by Marin *et al.*, they found that in patients with hematological malignancies extended spectrum beta-lactamase (ESBL) negative Gram-negative bacteria was the most frequently agent as cause of bloodstream infections [11].

This study also supports these findings; Gram-negative bacteria were isolated more frequently as both primary and/or catheter-related bloodstream infections. And *E. coli* was the most common isolated bacteria among these bacteria. In Gram-negative bacteria, ESBL positivity was found as 52,4% and carbapenamase positivity was found as 17,2%.

According to the other studies, methicillin-resistant isolates of *Staphylococcus aureus* (MRSA) were low and all staphylococcal and enterococcal isolates were susceptible to vancomycin, teicoplanin and linezolid [12,13].

In this study, the most frequently isolated Gram-positive bacteria were coagulase-negative *Staphylococcus*. Methicillin resistance was 82,2%.

The studies have shown that invasive procedures and aggressive chemotherapy increase the risk of infection [12].

According to the Infectious Diseases Society of America (IDSA) guidelines, two different risk classifications have been proposed for high risk patients. First, high risk patients having long term (7-days duration) and deep neutropenia (ANC, 100 cells /mm³ following cytotoxic chemotherapy) and/or presence of significant medical comorbidities. The second classification risk is Multinational Association for Supportive Care in Cancer (MASCC) risk index scoring system [13].

Marin *et al.* reported that in patients with advanced hematologic malignancies bloodstream infection mortality rate was increased [11].

In this study, a statistically significant relation was found between mortality and disease status in patients with hematological malignancies and bloodstream infections ($p = 0,000$). In patients with progression, death due to bloodstream infections was also found to be higher.

There was a statistically significant correlation between chemotherapy regimen and mortality ($p = 0,000$). Mortality was higher in patients who were receiving salvage chemotherapy.

The consensus based National Comprehensive Cancer Network (NCCN) guidelines recommend consideration of fluoroquinolone prophylaxis in high risk patients as: primarily, allogeneic hematopoietic cell transplantation (HCT) patients, neutropenic patients receiving induction chemotherapy for acute leukemia and the patients with expected duration of neutropenia >10 days [14].

In this study, significant correlation was found between mortality and quinolone prophylaxis receiving patients, antibiotic use in the last three months, hospitalization in the last three months ($p = 0,044$, $p = 0,019$ and $p = 0,040$, respectively).

In their study, Marin *et al.* reported that the mortality rate due to bloodstream infections were higher in corticosteroid receiving patients with hematological malignancies [11]. The corticosteroids play a decisive role in immune function as well as systemic cytokine release. The use of steroids in the treatment causes adrenal atrophy and causes an inadequate adrenal response to control the inflammatory condition [15].

In the other studies, the risk factors for mortality in adult and pediatric patients with hematological malignancies were found as febrile neutropenia or hospitalization in the intensive care unit [16-19].

In a study conducted by Tumberello *et al.*, a significant relationship was found between the presence of permanent urinary catheter and mortality [20].

In this study, there was a statistically significant relationship between mortality and urinary catheter use, intensive care stays, steroid use, clinical complications, and the duration of hospitalization (days) before infection.

Despite appropriate antibiotic treatment, bloodstream infections in neutropenic patients continue to be significant mortality cause [21]. Immediate initiation of empirical antibiotic therapy reduces mortality in febrile neutropenic patients [22].

In this study, there was no statistically significant relationship between baseline antibiotic suitability and appropriate antibiotic onset day and mortality. This was thought to be caused by the primary disease of the patients.

Conclusion

The bloodstream infections are common and the number of drug-resistant agents also increase in patients with hematological malignancies. Therefore, it should be diagnosed early and treated with adequate antibacterial treatment. In these patients, certain factors in the bloodstream infections might increase the mortality rate. These factors could help in identifying patients with higher mortality rates. Therefore, the mortality rate might be reduced with the correction of these factors in these patients. This study showed that the classification of such risk factors might be an important strategy to improve the clinical decision to make high risk patients.

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Author's contributions

Duygu Mert was the designer, coordinator, data collector and corresponding author. Sabahat Ceken was the author, data collector and planner of study. The other authors were data collectors and author.

Ethics approval and consent to participate

Ethical approval was obtained from Clinical Research Ethics Committee of University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Training and Research Hospital. (Approval date: 07/04/2018 and decision no: 2018-07 / 83).

References

- Pagano L, Caira M, Rossi G, Tumberello M, Fanci R, Garzia MG, Vianelli N, Filardi N, De Fabritiis P, Beltrame A, Musso M, Piccin A, Cuneo A, Cattaneo C, Aloisi T, Riva M, Rossi G, Salvadori U, Brugiattelli M, Sannicolò S, Morselli M, Bonini A, Viale P, Nosari A, Aversa F; Hema e-Chart Group, Italy (2012) A prospective survey of febrile events in hematological malignancies. *Ann Hematol* 91: 767-774.
- Ozturk A, Gunay A, Uskent N (1997) Febrile neutropenia treatment approach: Evaluation of 53 cases. *Klinik Journal* 10: 30-32.

3. Sigurdardottir K, Digranes A, Harthug S, Nesthus I, Tangen JM, Dybdahl B, Meyer P, Hopen G, Løkeland T, Grøttum K, Vie W, Langeland N (2005) A multicentre prospective study of febrile neutropenia in Norway: Microbiological findings and antimicrobial susceptibility. *Scand J Infect Dis* 37: 455-464.
4. Trecarichi EM, Tumbarello M (2014) Antimicrobial-resistant Gram-negative bacteria in febrile neutropenic patients with cancer: Current epidemiology and clinical impact. *Curr Opin Infect Dis* 27: 200-210.
5. Viscoli C, Castagnola E (1998) Planned progressive antimicrobial therapy in neutropenic patients. *Br J Haematol* 102: 879-888.
6. Akova M (2003) Nosocomial infections in cancer patients and transplant patients. In Doganay M, Unal S, editors. *Hospital infections*. Ankara: Ankara Scientific Medical Publishing House. 749-65.
7. Jacob LA, Lakshmaiah KC, Govindbabu K, Suresh TM, Lokanatha D, Sinha M, Vijaykumar BR, Sumathi BG, Jayashree RS (2014) Clinical and microbiological profile of febrile neutropenia in solid tumors and hematological malignancies at a tertiary cancer care center in South India. *Indian J Cancer* 51: 464-468.
8. Montassier E, Batard E, Gastinne T, Potel G, de la Cochetiere MF (2013) Recent changes in bacteremia in patients with cancer: A systematic review of epidemiology and antibiotic resistance. *Eur J Clin Microbiol Infect Dis* 32: 841-850.
9. Trecarichi EM, Pagano L, Candoni A, Pastore D, Cattaneo C, Fanci R, Nosari A, Caira M, Spadea A, Busca A, Vianelli N, Tumbarello M, HeMABIS Registry—SEIFEM Group, Italy (2015) Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: An Italian multicentre prospective survey. *Clin Microbiol Infect* 21: 337-343.
10. Kara O, Zarakolu P, Ascioğlu S, Eteğül S, Uz B, Buyukasik Y, Akova M (2015) Epidemiology and emerging resistance in bacterial bloodstream infections in patients with hematologic malignancies. *Infect Dis* 47: 686-693.
11. Marín M, Gudiol C, Ardanuy C, Garcia-Vidal C, Jimenez L, Domingo-Domenech E, Pérez FJ, Carratalà J (2015) Factors influencing mortality in neutropenic patients with hematologic malignancies or solid tumors with bloodstream infection. *Clin Microbiol Infect* 21: 583-590.
12. Antoniadou A, Giamarellou H (2007) Fever of unknown origin in febrile leukopenia. *Infect Dis Clin North Am* 21: 1055-1090.
13. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 52: 427-431.
14. National Comprehensive Cancer Network (NCCN) (2014) *Clinical Practice Guidelines in Oncology. Prevention and Treatment of Cancer-Related Infections*. Version 2.2014. Available: <http://www.nccn.org> Accessed: 06 November 2014.
15. Cooper M, Stewart P (2003) Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 348: 727-734.
16. Hampshire PA, Welch CA, McCrossan LA, Francis K, Harrison DA (2009) Admission factors associated with hospital mortality in patients with haematological malignancy admitted to UK adult, general critical care units: A secondary analysis of the ICNARC case mix programme database. *Crit Care* 13: R137.
17. Soares M, Silva UV, Teles JM, Silva E, Caruso P, Lobo SM, Dal Pizzol F, Azevedo LP, de Carvalho FB, Salluh JI (2010) Validation of four prognostic scores in patients with cancer admitted to Brazilian intensive care units: Results from a prospective multicenter study. *Intensive Care Med* 36: 1188-1195.
18. Paganini HR, Aguirre C, Puppa G, Garbini C, Javier RG, Ensinnck G, Vrátnica C, Flynn L, Iacono M, Zubizarreta P, for the Febrile Neutropenia Study Group (2007). A prospective, multicentric scoring system to predict mortality in febrile neutropenic children with cancer. *Cancer* 109: 2572-2579.
19. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting, Feld R, Gallagher J, Herrstedt J, Rapoport B, Rolston K, Talcott J (2000) The multinational association for supportive care in cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 18: 3038-3051.
20. Tumbarello M, Trecarichi EM, Caira M, Candoni A, Pastore D, Cattaneo C, Fanci R, Nosari A, Spadea A, Busca A, Vianelli N, Spanu T, Pagano L (2012) Derivation and validation of a scoring system to identify patients with bacteremia and hematological malignancies at higher risk for mortality. *PLoS ONE* 7: e51612.
21. Schelenz S, Nwaka D, Hunter PR (2013) Longitudinal surveillance of bacteraemia in hematology and oncology patients at a UK cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. *J Antimicrob Chemother* 68: 1431-1438.
22. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L (2010) Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother* 54: 4851-4863.

Corresponding author

Duygu Mert, MD
 University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara
 Oncology Training and Research Hospital, Infectious Diseases and
 Clinic Microbiology Clinic. Mehmet Akif Ersoy mah., Vatan cad.,
 No:91, 06300, Yenimahalle/Ankara, Turkey.
 Tel: +90 5066486279
 Fax: +90 3123466747
 E-mail: drduygumert@hotmail.com

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