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Evaluation of prognostic factors in febrile neutropenic patients with hematological malignancies

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ABSTRACT

Objectives: Hematological malignancies presenting with febrile neutropenia constitute an important health issue all over the globe. In this study we aimed to elucidate the prognostic factors of febrile neutropenic patients with hematological malignancies and to investigate the causes of mortality.

Method: This research had a retrospective nature. A total of 174 febrile neutropenia patients ≥ 18 years of age hospitalized has been enrolled in the study. Patients enrolled in the analy-sis were determined according to American Society for Infectious Diseases 2010 Febrile Neutro-penia Diagnosis and Treatment Guidelines. Accordingly, neutropenia was defined as an expected decrease in the absolute neutrophil count (ANS) to < 500 cells/mm³ or < 500 cells/mm³ over the next 48 hours and body temperature over ≥ 38°C.

Results: A total of 174 patients has been included in the analysis and 32 (18.5%) died while 142 (81.5%) did not develop mortality. When the statistically significant results are evaluated according to multivariate analysis; Age, Crp, MASCC, acute renal failure, hypotension were similar in both groups. On the other hand, when univariate statistically highly significant results are evaluated ac-cording to multivariate analysis; Presence of urinary catheter, diagnosis of bacterial pneumonia and ANS not increasing after 1 week were found to be statistically significant in the mortality group.

Conclusion: The results of the study showed that in febrile neutropenic patients, mortality was increased by 6.7 times by a diagnosis of bacterial pneumonia, 245.6 times by the absence of ANS elevation, and 13.9 times by urinary catheterization.

Keywords: Febrile neutropenia, hematological malignancy, mortality

Hematological malignancies presenting with febrile neutropenia constitute an important health issue all over the globe. There has been an increase in the treatment success of patients with hematologi-cal malignancies in recent years with developments in cytotoxic agents. However these molecules have also raised the risk of opportunistic infections. Fever seen in patients with neutropenia after chemotherapy may be the first and often the only symptom of infection. On the contrary, fever may not be observed in the elderly and patients receiving corticosteroid therapy. In such cases, hypoten-sion or clinical deterioration may also be significant in revealing infections.

Nevertheless, non-infectious causes of fever, such as tumor necrosis, bleeding, and drugs with a pyrogen effect should not be overlooked. In neutropenic patients, signs of inflammation may be subtle. Therefore, taking cultures from possible foci of infection in neutropenic patients is very important in

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obtaining evidence of infection and guiding treatment. In the presence of prolonged neutropenia and deep neutropenia, the risk of infection increases. Bacterial infection is inevitable in almost all cases with deep neutropenia lasting longer than three weeks. [1]

Severe mucosal damage, especially in the gastrointestinal tract is the most important focus of infec-tion following chemotherapy. The genitourinary system, skin and soft tissue, and respiratory tract are other foci of infection. Bacteremia and invasive fungal infections are common in neutropenic patients whose mucosal barrier has been destroyed, but only 10-25% of these cases can be docu-mented. Approximately 80% of infections identified in many patients are caused by endogenous flora bacteria. [2] However, a significant portion of hospitalized patients are colonized with microor-ganisms in the hospital flora within weeks following their hospitalization. This further increases the possibility of resistant microorganisms in infections that develop during hospitalized care.

Despite all developments up to date, infections remain the most common cause of death in patients with hematological malignancies. [3] While the mortality rate associated with febrile neutropenia was reported to be 30% in the 1970s, it has decreased to 2-10% with advances in antibiotic therapy and early antimicrobial therapy. [4] In the United States, approximately 1 patient dies from hematological malignancy in every nine minutes. Such high mortality rates show the importance of a preemptive approach to these patients. International guidelines recommend taking blood cultures from patients presenting with neutropenic fever and initiating antimicrobial therapy within 60 minutes. [5] Howev-er, some researchers suggest that treatment should be started within 30 minutes. [6] During septic shock, survival is reduced by 8% for each hour of delay in the initiation of therapy. [7] The aim of this study was to determine factors of poor prognosis in patients with febrile neutropenia.

Study Hypothesis

In this study we aimed to elucidate the prognostic factors of febrile neutropenic patients with hema-tological malignancies and to investigate the causes of mortality.

METHODS

This research had a retrospective nature. Febrile neutropenia patients ≥ 18 years of age hospitalized has been enrolled in the study. A total 174 patients diagnosed with hematological malignancies, who received inpatient treatment at the Adult Hematology Clinic of Eskişehir Osmangazi Universi-ty Medical Faculty Hospital between January 2016 and August 2018 has been enrolled in this study. Ethics committee approval has been granted at 18.09.2018 with protocol number 11-09/2018. The study was conducted according to the Declaration of Helsinki clinical research prin-ciples and informed consent form was obtained from all participants.

Patients enrolled in the analysis were determined according to American Society for Infectious Diseases 2010 Febrile Neutropenia Diagnosis and Treatment Guidelines. Accordingly, neutropenia was defined as an expected decrease in the absolute neutrophil count (ANS) to < 500 cells/mm³ or < 500 cells/mm³ over the next 48 hours. Fever was defined as the single oral measurement of body temperature being ≥ 38.3 °C (101 °*F*) or a persistent level of ≥ 38 °C (100.4 °*F*) over a one-hour period.

Febrile neutropenia attack, which occurred between the day of hospitalization and discharge, was evaluated once. The daily peak fever, number of days to fever response, and blood values of white blood cell count, ANS, C-reactive protein (CRP) and procalcitonin (PCT) were recorded. The state of consciousness, hypotension, total parenteral nutrition support, and development of mucositis were also noted from the daily follow-up notes. Patients with underlying diseases were examined in terms of mortality.

The patients who were administered granulocyte-colony-stimulating factor (G-CSF) on the day they became febrile neutropenic were noted. The ANS value not exceeding 500 cells/mm³ within one week was considered as the absence of ANS elevation. The number of chemotherapy days was evaluated for the patients that received chemotherapy within the last three months. In addition, the patients that underwent chemotherapy at any time from the onset of febrile neutropenia were noted. The day when the patients became febrile neutropenic, and any invasive attempt were also recorded.

The infection foci of the patients were evaluated as one or more foci. The category of unexplained fever was used for the cases in which no focus was detected.

Multinational Association for Supportive Care in Cancer (MASCC) scores were calculated on the day that the patients met the criteria for febrile neutropenia. The patients who had a fever response with the initial

treatment of febrile neutropenia but whose body temperature increased again at least 48 hours after this response were considered to have secondary fever.

Statistical Analysis

In this study, the Shapiro-Wilk test of normality was used for continuous variables. The Mann-Whitney U test was conducted for the variables that were not normally distributed. Descriptive statistics were presented as median (25%-75%) and mean ± standard deviation values. The chi-square test was performed for categorical variables, and the data were shown as frequency and percentages. The binary logistic regression analysis was conducted to determine the probability of occurrence of the disease according to risk factors. The goodness-of-fit of the model was evaluated according to the Hosmer Lemeshow test. IBM SPSS Statistics v. 20.0 *(SPSS Inc., Chicago, Illi-nois)* was used for statistical calculations. The statistical significance was taken as $p < 0.05$

RESULTS

A total of 174 patients has been included in the analysis and 32 (18.5%) died while 142 (81.5%) did not develop mortality. The comparison of the demographic characteristics and p values of the mortality and non-mortality groups was denoted in Table 1.

The mean age was 63.8 ± 13.1 years in the mortality group and 52.5 ± 16.4 in the non-mortality group, indicating no significant difference. There was also no significant difference in mortality according to gender. The mean fever response time was found to be 5.5 ± 3.9 days in the mortality group ($p = 0.008$). Chronic diseases were similar in the two groups, with no statistically significant difference. In the mortality group, 19.5% of the patients died on the day of hospitalization, with no statistically significant difference compared to the other group. In the same group, the rate of con-fusion was 21.8%, hypotension 31.2%, acute renal failure 37.5%, mucositis 50%, central venous catheter 25%, and urinary catheter 18.7%, and these were statistically significant (Table 2.).

In the mortality group, the median C-reactive protein value was 136.5 mg/L, and the median pro-

Table 1. Comparison of Demographic Characteristics between the Mortality and Non-mortality Groups of Febrile Neutropenia

Demographic characteristic	Mortality group n = 32 (%)	Non-mortality group n = 142 (%)	*P* value
Age (years)**	63.8 ± 13.1	52.5 ± 16.4	**< 0.001**
Gender			
Male	15 (46.8%)	71 (50%)	0.902
Female	17 (53.2%)	71 (50%)	
Fever*	38.4 °C (38.1-38.6 °C)	38.3 °C (38.2-38.6 °C)	0.600
Fever response time (days)**	5.5 ± 3.9	3.3 ± 2.3	**0.008**
Chronic disease			
Diabetes mellitus	8 (25%)	28 (19.7%)	0.505
Hypertension	8 (25%)	38 (26.7%)	0.838
Chronic renal failure	1 (3.1%)	12 (8.4%)	0.301
COPD	3 (9.3%)	5 (3.5%)	0.153
Chronic hepatitis B carrier	2 (6.2%)	9 (28.1%)	0.985
Coronary artery disease	5 (15.6%)	3 (2.1%)	0.153
Chemotherapy during treatment	11 (34.3%)	44 (30.9%)	0.710
Post-chemotherapy days*	11 (4-19)	8 (5-10.2)	0.366
Length of hospitalization (days)*	19.5 (7-26.7)	14 (10-19.2)	0.223

COPD, chronic obstructive pulmonary disease

*median (quartiles), **mean ± standard deviation

Table 2. Comparison of Clinical Characteristics between the Mortality and Non-mortality Groups of Febrile Neutropenia

Clinical characteristic	Mortality group n = 32 (%)	Non-mortality group n = 142 (%)	*P* value
Clouding of consciousness	7 (21.8%)	2 (1.4%)	**< 0.001**
Hypotension	10 (31.2%)	10 (7%)	**< 0.001**
Acute renal failure	12 (37.5%)	6 (4.2%)	**< 0.001**
Total parenteral nutrition	4 (12.5%)	5 (3.5%)	0.061
Mucositis	16 (50%)	40 (28.1%)	**0.029**
Central venous catheter	8 (25%)	11 (7.7%)	**0.010**
Jugular	4 (12.5%)	5 (3.5%)	
Port	4 (12.5%)	3 (2.1%)	
Subclavian	0 (0%)	2 (1.4%)	
Femoral	0 (0%)	1 (0.7%)	
Urinary catheter	6 (18.7%)	2 (1.4%)	**< 0.001**

calcitonin value was 0.72 ng/mL, and this was statistically significant compared to the non-mortality group. Mortality was not related to hematological malignancy type, but 40.6% of the pa-tients that died had an acute myeloid leukemia diagnosis. While the rate of patients with a clinically or microbiologically proven infection diagnosis was 90.6%, the rate of fever of unknown origin was 9.3% in those who developed mortality. İt was statistically significant. Among these diagno-ses, pneumonia and bacteremia were prominent (Table 3.). Mortality was found to be significantly higher among the patients with secondary fever which is given in Table 4. (59.3%)

In the mortality group, there was no absolute neutrophil count (ANS) elevation (42.3%) even after one week. The rate of those who did not receive G-CSF in the mortality group was %73.7. The rate of patients whose MASCC score resulted as high risk among those who developed mortality was %59.3 and it was statistically significant. While galactomannan positivity was present in 5 patients (%15.6) in mortality group, it was found positive in 6 patients (%54.2) in those without mortality and a statistically significant. In univariate analysis the patients with a clinical or

Table 3. Comparison of Infection Foci between the Mortality and Non-Mortality Groups

Infection foci	Mortality group		Non-mortality group		*P* value
	n = 50	(%)	n = 112	(%)	
Urinary system infection	7	14	26	23.2	0.624
Primary bacteremia	13	26	22	19.6	**0.003**
Bacteremia secondary to urinary system infection	5	10	6	5.3	**0.031**
Bacterial pneumonia	9	18	10	8.9	**0.002**
Fungal pneumonia	8	16	8	7.2	**0.003**
Bacterial and fungal pneumonia	2	4	4	3.6	0.305
Soft tissue infection	2	4	9	8	1.000
Catheter infection	2	4	6	5.3	0.641
Anal abscess/infection	2	4	8	7.2	1.000
Other diagnoses	0	0	13	11.6	
Note: Both groups included patients with more than one diagnosis					

Table 4. **Relationship between Secondary Febrile Neutropenia Attack and Mortality**

Secondary febrile neutropenia attack	Mortality group		Non-mortality group		*P* value
	n = 32	(%)	n = 142	(%)	
Secondary fever	19	59.3	43	30.2	**0.004**
Blood culture growth in secondary fever	8	25	2	1.4	**< 0.001**
Urinary culture growth in secondary fever	4	12.5	3	2.1	0.186

Table 5. **Univariate and Multivariate Logistic Regression Analysis Results (number of independent variables in the model = 1)**

Clinical and laboratory data	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	OR 95% CI	*P* value	OR	OR 95% CI	*P* value
Age	1.053	1.022-1.084	**0.001**	1.007	0.956-1.062	0.758
C-reactive protein	1.010	1.005-1.015	**< 0.001**	1.002	0.994-1.010	0.571
Procalcitonin	1.048	1.007-1.090	**0.020**			
Secondary fever	3.365	1.526-7.422	**0.003**			
Secondary fever duration	1.089	0.986-1.201	0.091			
MASCC score	0.736	0.650-0.833	**< 0.001**	0.766	0.586-1.001	0.051
Acute renal failure	13.600	4.588-40.313	**< 0.001**	6.897	0.852-55.819	0.070
Clouding of consciousness	19.600	3.848-99.843	**< 0.001**	0.480	0.026-8.846	0.621
Hypotension	6.000	2.239-16.081	**< 0.001**	0.428	0.035-5.287	0.509
Mucositis	2.550	1.165-5.582	**0.019**			
Galactomannan positiveness	6.786	1.831-25.154	**0.004**			
Central venous catheter	3.970	1.447-10.892	**0.007**			
Urinary catheter	16.154	3.090-84.461	**0.001**	13.920	1.305-148.487	**0.029**
Diabetes mellitus	1.357	0.551-3.340	0.501			
Fungal pneumonia	5.583	1.911-16.309	**0.002**			
Bacterial pneumonia	5.165	1.893-14.090	**0.001**	6.760	1.263-36.191	**0.026**
Bacteremia	3.732	1.612-8.638	**0.002**			
Bacteremia secondary to urinary system infection	4.198	1.195-14.748	**0.025**			
Absence of ANS elevation	103.400	12.471-857.305	**< 0.001**	245.697	20.613-2928.594	**< 0.001**
Granulocyte-colony stimulating factor_not applied	3.516	1.174-10.531	**0.025**			
Clinically or microbiologically proven infection	8.160	2.376-28.020	**0.001**	2.516	0.351-18.023	0.358

OR: Odds ratio
CI: Confidence interval
MASCC: The Multinational Association for Supportive Care in Cancer
ANS: Absolute neutrophil count

micro-biological diagnosis had 8.1 times greater mortality rate compared to those without foci. It was also observed that the mortality rate was increased by 3.3 times among the patients with secondary fever. However, the presence of underlying chronic diseases or hematological malignancy did not increase mortality (Table 5.).

When the highly significant risk factors of mortality were further evaluated with the multivariate analysis, it was determined that mortality was increased by 6.7 times by bacterial pneumonia, 13.9 times by urinary catheterization, and 245.6 times by the absence of ANS elevation after one week (Table 5.).

Table 5 shows the distribution of prognostic factors affecting mortality in patients with febrile neutropenia attacks according to the univariate logistic regression analysis and the rates of factors with a highly significant difference ($p \leq 0.001$).

DISCUSSION

Rosa *et al*. concluded that each one-hour delay increased mortality by 18% and emphasized the need to start empirical treatment within 30 minutes. [1] In our study, 174 febrile neutropenia attacks were followed up, and the mortality rate was found to be 18.2%.

In the current study, the mortality and non-mortality groups were compared, and the mean age was found to be higher in the former ($p < 0.001$). In a multicenter study conducted in Korea by Kim *et al*., it was concluded that patients over 50 years of age had a poor prognosis. [3] In the literature, attention has been drawn to the increasing mortality with age, which has been attributed to the ef-fect of decreased immunity.

In a study investigating mortality among patients with hematological malignancies and bloodstream infections, Mario *et al*. reported that approximately 40% of the patients that died had acute myeloid leukemia (AML), 25% had non-Hodgkin lymphoma, and 13.6% had multiple myeloma. 4 In our study, of the patients in the mortality group, 40.6% were diagnosed with AML, 21.8% non-Hodgkin lymphoma, 15.5% myelodysplastic syndrome, 5% acute lymphoblastic leukemia, and 9.4% multiple myeloma.

In our study, we observed no statistically significant difference in comorbidities between the mor-tality and non-mortality groups. This was a favorable aspect of our study since similar initial comorbidities of the patients allowed identifying the main significant factors affecting mortality.

In this study, the median value of fever was found to be 38.4 °C in the mortality group, and there was no significant difference compared to the non-mortality group. Our clinical observations indi-cated that the highest fever peak could not be expected, especially in patients aged ≥ 65 years or those with cardiopulmonary comorbidities due to the deterioration of vital signs and changes in the mental status. It was determined that after these patients that met the fever criteria were treated with antipyretics, their fever was reduced. In a study by Mukoyama *et al*. evaluating the response of febrile neutropenic patients with AML to initial antibiotic therapy after chemotherapy, the median fever response time was calculated as 7 days. [5] In our study, the mean fever response time was 5.5 ± 3.9 days in the mortality group and 3.3 ± 2.3 days in the non-mortality group, and there was a statistically significant difference. We also examined the relationship between chemotherapy and febrile neutropenia and determined that the median duration of post-chemotherapy was 11 days in the mortality group, with no statistically significant difference compared to the non-mortality group.

Horasan *et al*. investigated the mortality factors of febrile neutropenic patients with bacteremia at Mersin University, Turkey and reported the mean length of hospital stay as 27.4 days. [6] In our study, it was observed that the length of hospitalization was higher than the literature data. This was because it was time for the next chemotherapy cycle for 55 patients receiving treatment for febrile neutropenia, and a total of 62 patients developed secondary fever.

In another study from Turkey evaluating prognostic factors in febrile neutropenic patients, Gencer *et al*. reported that the rate of hypotension was 44% in the mortality group. [7] In our study, hypo-tension was observed at a rate of 50% in the mortality group, and it increased mortality by six times. In another study of prognostic factors in febrile neutropenic patients, Tumberello *et al*. ob-served that although a central venous catheter was required in 54% of the patients in the mortality group, there was no statistically significant difference compared to the surviving group. In addition, the rate of acute renal failure was calculated as 29.5% for the mortality group, and that of hypoten-sion was 9%, with statistically significant differences between the two groups. [4] Kanafani *et al*. evaluated febrile neutropenic patients with bacteremia and concluded that the development of cloud-ing of consciousness increased mortality by 21.2 times. [8] In the current study, clouding of consciousness, hypotension, and renal failure were found to be associated with mortality at the time of initial

evaluation, and these factors increased mortality by 19.6, six and 13.6 times, respectively.

In a study conducted in Turkey, Demiraslan *et al*. investigated the effect of Stenotrophomonas maltophilia infections on mortality and determined no significant relationship between mucositis and mortality despite the rate of mucositis being 36% among the patients that died. [9] In the current study, the rate of mucositis was found to be 28.6% in the mortality group, and this condition was observed to increase mortality by 2.5 times. In addition, central venous catheter placement in-creased mortality by 3.9 times, while urinary catheter placement increased mortality by 13.9 times.

The skin and mucosa are the first and greatest defense lines of the human body, and the disappear-ance or the weakening of these barriers and defense systems because of invasive procedures are factors that facilitate the entry of microorganisms. In neutropenic patients, both the qualitative and quantitative insufficiency of leukocytes makes bacteremia inevitable. Therefore, every invasive pro-cedure to be performed on neutropenic patients should be well considered by calculating the bene-fit-harm ratio, and foreign bodies should be removed from the body as soon as possible when there is no longer an indication for an invasive intervention. In our sample, only eight patients had a uri-nary catheter at the time of the febrile neutropenia diagnosis, and due to this limited number, we thought it would be controversial to consider urinary catheterization as a risk factor.

Hii *et al*., who evaluated risk factors in 209 patients diagnosed with candidemia in Taiwan, showed that the mortality rate increased by 3.5 times in patients who had received total parenteral nutrition. [10] In contrast, in our study, the rate of total parenteral nutrition as found to be 12.5% in the mor-tality group and 3.5% in the non-mortality group, indicating no statistically significant difference.

When laboratory values are examined, Massaro *et al*. reported that the initial CRP value of the mor-tality group was 132 mg/L, which statistically significantly differed from the survivor group, while the PCT value was 0.77 ng/mL in the mortality group, with no significant difference. [11] We found similar results in our study. The CRP value was 136 mg/L and the PCT value was 0.72 ng/mL in the mortality group, and there was a statistically significant difference between the two groups in relation to both CRP and PCT elevations. However, the lack of an analysis of CRP and PCT val-ues according to infection foci, localized or systemic infection can be considered as a limitation of our study. In another study, Osmani *et al*. found the mean ANS value to be 127/mm³ in the mor-tality group and reported a statistically significant relationship between ANS and mortality. [12] Our findings contradict those reported in the literature. We observed no statistically significant differ-ence in the median ANS values of the mortality and non-mortality groups (85/mm³ and 100/mm³, respectively).

Similarly, the median number of leukocyte counts did not significantly differ between the two groups. It is possible to explain these results based on the non-homogeneous distribution of labora-tory data. We consider that this result was obtained because the number of patients with an initial ANS value of 500/mm³ and above was relatively higher compared to the literature. High BK counts, especially in patients with chronic myeloid leukemia and chronic lymphocytic leukemia diagnoses can explain the absence of a statistically significant difference in leukocyte.

In a mortality study of febrile neutropenic patients conducted in Turkey, Calik Basaran *et al*. report-ed that the rate of unexplained fever was 34% in the mortality group, and this rate reached 66% among the patients with clinically or microbiologically proven foci. It was observed that mortality was increased by 6.1 times in patients who developed bacteremia. [13] In our study, the rate of clini-cally or microbiologically proven infection foci was found to be 54.2%, this factor increased mor-tality by 8.1 times. Furthermore, we determined that mortality was increased by 3.7 times by bacte-remia, 4.1 times by bacteremia secondary to urinary tract infection, 6.7 times by bacterial pneumo-nia, and 5.5 times by fungal pneumonia. However, urinary tract infection was not significantly re-lated to mortality in our study.

Study Limitations

The limited aspects of our study; small number of patients and their retrospective nature can be counted.

CONCLUSION

The results of the study showed that in febrile neutropenic patients, mortality was increased by 6.7 times by a diagnosis of bacterial pneumonia, 245.6 times by the absence of ANS elevation, and 13.9 times by urinary catheterization. The small number of patients with urinary catheters was ob-served as a disadvantage of our study. It was concluded that in

febrile neutropenic patients, espe-cially if the ANS was not >500 even after more than 1 week, mortality increased 245. It was thought that this issue should be examined with more detailed studies on ANS.

Authors' Contribution

Study Conception: AG, NE,; Study Design: AG, NE, GO, GU,; Supervision: NE, GU, EG,; Ma-terials: AG, EG, GU,; Data Collection and/or Processing: AG, NE,; Statistical Analysis and/or Data Interpretation: AG, NE, GU, EG,; Literature Review: NE, GU, EG,; Manuscript Preparation: AG and Critical Review: NE, GU, EG.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

AML: acute myeloid leukemia
ANS: absolute neutrophil count
CRP: C-reactive protein
FN: Febrile Neutropenia
G – CSF: granulocyte colony stimulating factor
MASCC: Multinational Association for Supportive Care in Cancer
PCT: procalcitonin
SPSS: Statistics Package for Social Sciences

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