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Original Article

Assessment of factors affecting timing of discharge in pediatric cancer patients with febrile neutropenia

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ABSTRACT

Background. Febrile neutropenia is a common cause of hospital admissions among pediatric cancer patients. To optimize personalized approaches for hospitalization and antibiotic treatment, risk stratification has been proposed. This study aimed to explore the impact of clinical and laboratory parameters on risk stratification for patient discharge.

Methods. This prospective study included pediatric lymphoma and solid tumor patients who were hospitalized due to febrile neutropenia between June 2018 and June 2019. Patient characteristics, primary oncological diagnosis and disease status, comorbid conditions, time elapsed after the last course of chemotherapy, use of granulocyte-colony stimulating factor (G-CSF) prophylaxis, presence of port catheter, infection type, fever values/duration, physical examination findings, and duration of neutropenia were collected. Laboratory investigations including complete blood counts, acute phase reactants at the onset of the episode, culture results were also recorded.

Results. The study examined 142 febrile neutropenic episodes from 88 consecutive patients. The median age of the study group was 6.8 years, with 19.3% of cases being lymphoma and 80.7% having solid tumors. The median hospital stay was 7 days. Factors associated with longer hospitalization periods included a lymphoma diagnosis, presence of comorbid conditions, bone marrow involvement, and febrile neutropenic period during hospitalization. Patients presenting with fever ≥ 39 °C at admission, poor general appearance, hypotension, prolonged capillary filling time, and severe infection signs had longer hospital stays. In febrile neutropenic episodes, absolute monocyte count ≤ 100 cells/mm^3, platelet count ≤ 50,000/mm^3, and prolonged neutropenia delayed discharge time. Patients with microbiologically defined infections, especially those with positive catheter cultures, also had delayed discharge.

Conclusion. The diagnosis of lymphoma, poor general condition at admission, presence of microbiologically defined infection, thrombocytopenia, delayed recovery of absolute neutrophil counts, and prolonged fever duration were significant factors in determining the treatment duration and predicting discharge time.

Key words: febrile neutropenia, infections, pediatric oncology, quality of life, risk scoring, safe discharge.

Febrile neutropenia is a common complication in children receiving cancer chemotherapy. The immune system of these patients is compromised by both treatments and in some cases by the cancer itself. The type, duration, and intensity of cancer treatment are key risk factors for infections, often affecting various aspects of their immune defenses. Additional risk factors such as mucous membrane abnormalities, the presence of indwelling

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catheters, malnutrition, extensive antibiotic use, and frequent hospitalizations further elevate the risk of infection.[1]

The standard approach to febrile neutropenia management involves the initiation of empirical antibiotic therapy and close observation. However, challenges such as increasing antibiotic resistance, catheter-related complications and nosocomial infections reduce patients' quality of life and increase treatment costs, presenting significant problems. These issues become more pronounced with extended hospital stays.[2]

Therefore, it is crucial to identify patients who might be eligible for early discharge or outpatient treatment and to design their treatments accordingly. Several guidelines have been published based on the findings and outcomes of patient series[2-5], but most of these guidelines focus on adult patients. Studies involving children are scarce and often encompass smaller patient cohorts.[6,7] Consequently, there is a need for prospective studies that comprehensively cover all relevant variables in pediatric cases.

The aim of this study was to evaluate the impact of data obtained at admission and during follow-up on the discharge timing of pediatric cancer patients hospitalized with febrile neutropenia.

Methods

This prospective study aimed to investigate the characteristics of febrile neutropenic episodes in patients under 18 years of age with lymphoma and solid tumors, treated at our Pediatric Oncology inpatient unit between June 1, 2018, and June 1, 2019. Leukemia cases were excluded from the study as their follow-up and treatment were managed by a different department within the institution. Patients who had undergone hematopoietic stem cell transplantation were also excluded from the study.

Demographic information of the patients during febrile neutropenic episodes, the location where fever began (outpatient or hospital), primary oncological diagnosis, primary disease status (remission, recurrent/resistant), comorbid conditions, time elapsed since last chemotherapy course, use of Granulocyte-colony stimulating factor (G-CSF) prophylaxis, presence of a port catheter, infection type (fever of unknown origin [FUO], clinically or microbiologically defined infection), fever value at the onset of the episode, physical examination findings (general condition, presence of hypotension/shock, capillary refilling time, mucositis, anal ulceration), highest recorded fever value, number of febrile days, and duration of neutropenia were recorded. Patients presenting with signs such as pallor, lethargy, poor perfusion, altered mental status, respiratory distress or dehydration were considered to be in poor general condition. This assessment was based on physicians' clinical observations during physical examinations. Laboratory investigations, including hemoglobin, leukocyte, absolute neutrophil and monocyte counts, platelet count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) at the onset of the episode as well as blood, catheter, urine and respiratory tract culture results, were also recorded. In addition, the antibiotics used during the episodes, modification periods, and discharge times were documented. Throughout the study, the parameters in the patient follow-up form were recorded separately for each episode, even though multiple episodes could occur in the same patient.

Febrile neutropenia was defined as an absolute neutrophil count (ANC) below 500/mm^3 or between 500 and 1,000/mm^3 with an expected decrease to below 500/mm^3 within 48 hours, accompanied by an axillary body temperature of 38.3 °C or higher, or 38 °C sustained for more than one hour. The highest recorded fever value upon admission was documented as the body temperature measured at the time of diagnosing febrile neutropenia. In all patients presenting with a febrile neutropenic episode, at least one set of peripheral blood cultures and, if present, cultures from each lumen of the

central venous catheter were obtained promptly after the onset of fever. Following culture collection, broad-spectrum empirical antibiotic therapy (piperacillin-tazobactam, meropenem or cefepime) was initiated. In cases where fever persisted beyond 48–72 hours, or if there was clinical deterioration at the onset of the episode, suspicion of a resistant pathogen, or a possible catheter-related infection, the antibiotic regimen was modified accordingly. Cases defined solely by fever without demonstrable clinical and laboratory signs of infection were categorized FUO. A clinically defined infection referred to an infection clinically diagnosed when the microbiologically infectious agent could not be identified. Examples included pneumonia, mucositis, cellulitis, sinusitis, perianal infections, and neutropenic enterocolitis (typhlitis). A microbiologically defined infection was defined as either the presence of the infectious agent in the blood culture, without a defined clinical focus, or the identification of a microbiological agent at a clinical focus without corresponding growth in the blood culture. Serious infections included catheter infection, port pocket infection, pneumonia, meningitis, typhlitis, and sepsis.

Patients were categorized based on the chemotherapy regimens they received prior to the onset of febrile neutropenic episodes. The chemotherapy regimens included doxorubicin, alkylating agents, and platinum-based regimens. The onset of febrile neutropenia was recorded after administration of the final dose of chemotherapy. The duration between the last chemotherapy dose and the onset of the febrile neutropenia episode was documented.

Data on the duration of neutropenia for each febrile episode were also collected and defined as the number of consecutive days with ANC below 500/mm^3. Neutropenia duration was defined as the period from the onset of neutropenia (ANC < 500/mm^3) to the first recovery of ANC to > 500/mm^3. Prolonged neutropenia was defined as an ANC remaining below 500/mm^3 for more than 7 days, regardless of the underlying cause.

Discharge decisions were based on several criteria, including hemodynamic stability, being afebrile for at least 24–48 hours, control of the infectious focus, evidence of neutrophil recovery, and the availability of a safe and supportive home environment for continued monitoring. Early discharge was defined as the discontinuation of intravenous antibiotic therapy and hospital discharge in low-risk patients who had received at least 72 hours of intravenous antibiotics, remained afebrile for a minimum of 24 hours, and had no documented source of infection. This approach was considered appropriate irrespective of bone marrow recovery, provided that reliable outpatient monitoring could be ensured.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 26.0 (SPSS Inc, USA). Numerical variables were expressed as mean ± standard deviation or median (range of distribution), while qualitative variables were presented as numbers and percentages. The assumption of normality for quantitative variables was assessed using the Shapiro-Wilk test. If a normal distribution was confirmed by the Shapiro-Wilk test, comparisons between two groups were conducted using the Student's t-test. If the assumption of homogeneity of variances was met, the Student's t-test was used; otherwise, the Welch test was applied. If a normal distribution was not present, the Mann-Whitney U test was used. Results were presented as mean ± standard deviation for the Welch test and Student's t-test, and as median (minimum–maximum) for the Mann-Whitney U test. Due to the violation of the homogeneity of variances assumption in the comparison of infection types, Welch's ANOVA was employed. Pairwise comparisons between groups for type of infection were conducted using the Tamhane T2 post hoc test. To evaluate type of infections, two dummy variables were generated. A multiple linear regression model was constructed using the variables that were found to be statistically significant in univariate

analyses. The backward elimination method was applied to identify the most relevant predictors influencing discharge time. To assess multicollinearity among independent variables, Variance Inflation Factors (VIF) were calculated. All VIF values were below 5, indicating that multicollinearity was not a concern. The coefficient of determination (R^2) was reported to evaluate the explanatory power of the final model. The significance level was set at $p<0.05$ for all analyses.

This study received ethical approval from Hacettepe University Non-Interventional Clinical Research Ethics Committee (No: GO 18/445). Written informed consent was obtained from parents/legal guardians for all participants.

Results

During the 12-month follow-up period, a total of 142 febrile neutropenic episodes from 88 patients were included in the study. The median age of the patients was 6.8 years (range: 0.4-17.2 years), and the male-to-female ratio was 1.2:1. Solid tumors were more prevalent than lymphomas, accounting for 80.7% of cases compared to 19.3% for lymphomas. Among the lymphomas, non-Hodgkin lymphoma was the most frequent diagnosis, while neuroblastoma was the most common solid tumor type associated with febrile neutropenic episodes. Table I presents the characteristics of febrile neutropenic patients.

For patients experiencing febrile neutropenic episodes, the median white blood cell count at admission was 500/mm^3 (range: 0-6,000/mm^3), and the median ANC was 50/mm^3 (range: 0-900/mm^3), additional parameters are presented in Table II.

Regarding the febrile neutropenic episodes, the median duration of fever was 2 days (range: 1-16 days), and the median duration of neutropenia

Table I. Demographic characteristics of pediatric cancer patients with febrile neutropenia (N=88).

	n (%)
Female / male gender	40 (45.5) / 48 (54.5)
Diagnosis	
Lymphoma	17 (19.3)
Non-Hodgkin lymphoma	16 (18.1)
Hodgkin lymphoma	1 (1.1)
Solid tumor	71 (80.7)
Neuroblastoma	17 (19.3)
Rhabdomyosarcoma	14 (15.9)
Ewing sarcoma	9 (10.2)
Central nervous system tumor	8 (9)
Osteosarcoma	7 (7.9)
Others*	16 (18.1)
Comorbid condition	18 (20.5)
Nephrotoxicity	5
Hepatotoxicity	4
Respiratory failure	3
Coagulation disorder	3
Immunodeficiency	3
Illness status	
Remission	71 (80.7)
Recurrent / resistant disease	17 (19.3)
Bone marrow involvement	28 (20.5)

*Wilms tumor, germ cell tumor, hepatoblastoma, retinoblastoma.

Table II. Laboratory parameters at the time of admission

Parameter	Median (range)
Hb (gr/dL)	8.8 (6.3-13.5)
WBC (/mm^3)	500 (0-6,000)
ANC (/mm^3)	50 (0-900)
AMC (/mm^3)	0 (0-1,500)
Thrombocytes (/mm^3)	69,500 (3,000-623,000)
CRP (mg/dL)	4.05 (0.2-46.6)
ESR (mm/h)	22 (2-96)

AMC: absolute monocyte count, ANC: absolute neutrophil count, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, Hb: hemoglobin, WBC: white blood cell.

was 3 days (range: 1-12 days). Clinical features of the episodes are detailed in Table III. In 60 episodes (42.3%), the focus of fever could not be determined, while infection was identified in the remainder, as either clinical (40.1%) or microbiological (17.6%). In blood and catheter culture positive cases, the most common pathogen isolated was methicillin-resistant *Staphylococcus aureus* (MRSA). Other pathogens are detailed in Table IV. There was only one case (0.7%) in which mortality was attributed to *Candida*-related sepsis; no other infection-related deaths occurred.

The median duration from the last chemotherapy administration to the onset of febrile neutropenia was 7 days. A total of 44 patients (38%) had received regimens that included both doxorubicin and alkylating agents. During follow-up, the most frequently observed chemotherapy protocols preceding febrile neutropenic episodes were as follows: 22.5% of episodes were associated with regimens containing both platinum and alkylating agents, 10.4% with platinum-based regimens, 9.2% with alkylating agents alone, 6.3% with regimens including both doxorubicin and platinum, and 13.4% with other chemotherapeutic agents. A comparison of discharge times across the different chemotherapy regimen groups revealed no statistically significant difference ($p = 0.186$).

The median length of hospital stay for patients with febrile neutropenic was seven days (range: 3-25 days) with antibiotic treatment. Empirical antibiotic therapy was initiated with piperacillin-tazobactam in 87 episodes (61.3%) febrile neutropenic episodes, meropenem in 33 episodes (23.2%), and cefepime in 22 episodes (15.5%). In 67 episodes (47%), antibiotic modification was required due to persistent fever after 48–72 hours (n=26), hemodynamic instability (n=16), or positive culture results (n=25). Patients who required

Table III. Features of febrile neutropenic episodes (N=142).

	n (%)
Number of episodes per patient, median (range)	1 (1-5)
Status at the time of admission	
At hospital	31 (21.8)
Outpatient	111 (78.2)
Time since last chemotherapy, median (range)	7 (0-22)
Prophylactic use of G-CSF	60 (42)
Severity of neutropenia	
ANC < 100 /mm^3	102 (71.8)
ANC > 100 /mm^3	40 (28.2)
Monocyte level	
AMC < 100 /mm^3	100 (70.4)
AMC > 100 /mm^3	42 (29.6)
Thrombocytopenia (<50,000 /mm^3)	61 (43)
Fever above 39 °C at admission	45 (31.2)
Poor condition	31 (21.8)
Hypotension	16 (11.2)
Capillary refill time >2 sec	16 (11.2)
Oral mucositis	39 (27.4)
Anal ulceration	11 (7)
Serious infection	38 (26.7)
Catheter-related infection	18 (12.6)
Pneumonia	10 (7)
Sepsis	5 (3.5)
Port pocket infection	2 (1)
Typhlitis	2 (1)
Meningitis	1 (0.7)
Type of infection	
FUO	60 (42.3)
Clinically defined	57 (40.1)
Microbiologically defined	25 (17.6)
Positive peripheral blood culture	13 (9.1)
Positive central venous catheter culture	17 (11.9)

ANC: absolute neutrophil count, AMC: absolute monocyte count, FUO: fever unknown origin, G-CSF: granulocyte-colony stimulating factor.

Table IV. Microbiological characteristics of culture-positive rebrile neutropenia episodes

	Peripheral blood (n)	Central venous catheter (n)
Methicillin-resistant *S. aureus*	1	3
Methicillin-resistant *S. epidermidis*	4	6
Pseudomonas aeruginosa	2	1
Escherichia coli	1	0
Enterococcus faecalis	2	1
Enterocccus faecium	0	3
Acinetobacter pitti	1	0
Hesbaspirullum aquaticum	1	0
Klebsiella oxycota	1	1
Candida kefyr	0	2

antibiotic modification had a median discharge time of 10 days, compared to 5 days for those who did not require modification ($p < 0.001$, Table V). Although neutropenia (ANC < 500/mm^3) persisted in 8 episodes, patients were discharged early, after a median of 3 days once signs of bone marrow recovery were observed. Only one patient (0.7%) was re-hospitalized for recurrent fever within 48 hours after discharge and was successfully discharged again following treatment.

Lymphoma diagnosis, presence of comorbidities, presence of catheter, and antibiotic modification were all significantly associated with prolonged hospitalization (Table V). Although no statistically significant association was observed between the length of hospital stay and sex or disease status ($p = 0.652$ and $p = 0.095$, respectively), patients with relapsed or refractory disease tended to have longer hospitalizations compared to those in remission. Additionally, patients presenting with an absolute monocyte count (AMC) ≤ 100/mm^3 and a platelet count ≤ 50,000/mm^3 were more likely to experience prolonged hospital stays ($p < 0.001$ and $p = 0.04$, respectively). In contrast, no statistically significant association was found between hemoglobin levels ≤ 7 g/dL or severe neutropenia (ANC ≤ 100/mm^3) and time to discharge ($p = 0.12$ and $p = 0.81$, respectively). When the length of hospitalization was analyzed based on infection type during febrile neutropenic episodes, patients with microbiologically documented infections had significantly longer hospital stays compared to those with clinically or microbiologically documented infections ($p < 0.001$). Laboratory and microbiological parameters associated with prolonged hospitalization included prolonged neutropenia, prolonged fever and positive blood and/or catheter cultures ($p < 0.001$).

Multiple linear regression analysis identified several significant factors influencing discharge time (Table VI). Based on standardized regression coefficients (β), microbiologically defined infection was the strongest predictor of discharge timing, associated with a 2.8-day longer hospital stay compared with FUO ($p<0.001$, $\beta = 0.345$). Prolonged fever (>96 hours) and poor general condition were associated with 2.7- and 2.6-day longer stays, respectively ($p<0.001$, $\beta = 0.312$ and $\beta = 0.277$). Prolonged neutropenia (≥7 days) extended hospitalization by 2.9 days compared with neutropenia lasting <7 days ($p<0.001$, $\beta = 0.228$). Patients requiring antibiotic therapy modification stayed 1 day longer ($p=0.041$, $\beta = 0.123$), those with lymphoma had a 1.1-day longer stay than patients with solid tumors ($p=0.013$, $\beta = 0.117$), and thrombocytopenia added 0.9 days to hospitalization ($p=0.014$, $\beta = 0.113$). The model demonstrated strong explanatory power, with $R^2 = 0.737$ and adjusted $R^2 = 0.721$, indicating that approximately 72% of the variance in discharge timing was explained by these variables.

Table V. Simple linear regression analysis of variables affecting discharge duration.

Variables	Days to discharge*	*p-value*
Gender		
Female (n=70)	7.8 ± 4.0	0.652[a]
Male (n=72)	8.1 ± 4.2	
Diagnosis		
Lymphoma (n=30)	9.5 ± 4.5	0.017[a]
Solid tumor (n=112)	7.5 ± 0.3	
Illness status		
Recurrent/Resistant disease (n=32)	9.3 ± 5.4	0.095[b]
Remission (n=110)	7.5 ± 3.5	
Bone marrow involvement		
Lymphoma (n=30)	9.7 ± 5.5	0.03[b]
Solid tumor (n=112)	7.4 ± 3.4	
Comorbid condition		
Yes (n=30)	9.6 ± 4.6	0.013[a]
No (n=112)	7.5 ± 3.8	
Central venous catheter		
Yes (n=90)	8.6 ± 4.5	0.005[b]
No (n=52)	6.8 ± 2.9	
Antibiotic therapy modifications		
Yes (n=67)	10.5 ± 4.3	< 0.001[b]
No (n=75)	5.6 ± 1.9	
Fever at admission		
≥ 39 °C (n=45)	9.6 ± 4.2	< 0.001[a]
< 39 °C (n=97)	7.1 ± 3.7	
General condition		
Poor (n=31)	13.0 ± 4.2	< 0.001[b]
Good (n=111)	6.5 ± 2.6	
Hypotension		
Yes (n=16)	13.0 ± 4.8	< 0.001[a]
No (n=126)	7.3 ± 3.5	
Capillary refill time		
>2 sec (n=16)	13.0 ± 4.8	< 0.001[a]
≤2 sec (n=126)	7.3 ± 3.5	
Serious infection		
Yes (n=38)	12.4 ± 4.1	< 0.001[b]
No (n=104)	6.3 ± 2.5	
Hemoglobin level		
≤ 7 g/dL (n=14)	9 (4-25)	0.12[c]
> 7 g/dL (n=128)	7 (3-21)	
Seerity of neutropenia		
≤100 cells /mm^3 (n=102)	8.0 ± 3.9	0.81[a]
>100 cells /mm^3 (n=40)	7.8 ± 4.3	
Absolute monocyte count		
≤100 cells /mm^3 (n=100)	8.7 ± 4.2	< 0.001[b]
>100 cells /mm^3 (n=42)	6.1 ± 2.9	
Thrombocyte count		
≤ 50,000 /mm^3 (n=61)	8.7 ± 4.5	0.04[a]
> 50,000 /mm^3 (n=81)	7.3 ± 3.5	
Type of infection		
Fever of unknown origin (n=60)	5.6 ± 2.0[+]	< 0.001[d]
Clinically defined (n=57)	8.5 ± 4.1[*]	
Microbiologically defined (n=25)	12.2 ± 3.78[x]	
Peripheral blood culture		< 0.001[a]
Positive (n=13)	13.1 ± 4.0	
Negative (n=129)	7.4 ± 3.7	
Central venous catheter culture		< 0.001[a]
Positive (n=18)	12.5 ± 3.2	
Negative (n=69)	7.5 ± 4.3	
Prolonged neutropenia (≥ 7 days)		< 0.001[a]
Yes (n=15)	12.6 ± 5.1	
No (n=123)	7.3 ± 3.4	
Prolonged fever (> 96 hours)		< 0.001[b]
Yes (n=41)	12.0 ± 4.3	
No (n=101)	6.3 ± 2.5	

[a,b,c,d] p-values are obtained from Student t-test, Welch test, Mann-Whitney U test, and Welch ANOVA respectively.
*Expressed as mean ± standard deviation, or median (range)
P < 0.05 printed bold.

Table VI. Multiple linear regression analysis of variables affecting discharge duration.

Variables	B	95% CI	β	p
Constant	7.792	6.578-9.005	-	0.000
Presence of lymphoma	1.116	0.252-2.080	0.117	0.013
Antibiotic therapy modification	0.987	0.039-1.935	0.123	0.041
Poor condition	2.689	1.601-3.778	0.277	<0.001
Thrombocytopenia (< 50,000 /mm^3)	0.911	0.184-1.639	0.113	0.014
Prolonged neutropenia (≥ 7 days)	2.931	1.747-4.114	0.228	<0.001
Prolonged fever (>96 hours)	2.769	1.779-3.758	0.312	<0.001
FUO vs. microbiologically defined	-2.792	-3.997- (-1.587)	0.345	<0.001
Clinically vs. microbiologically defined	-1.425	-2.517- (-0.334)	0.175	0.011

B: unstandardized coefficients; β: standardized coefficients, CI: confidence interval, FUO: fever of unknown origin.
$R^2 = 0.737$, $R^2adj = 0.721$, $p<0.001$

Discussion

The prompt initiation of broad-spectrum antibiotic therapy for all hospitalized children with febrile neutropenia has significantly reduced mortality rates.[8-11] The risk stratification is crucial to avoid toxicity, prevent the resistance, improve patient quality of life, predict prognosis, shorten antibiotic courses, hospital stays and reduce costs. Treatment algorithms for adult patients have been established based on high and low-risk febrile neutropenic categories.[4,12-14] Nonetheless, studies on risk classification and treatment algorithms for pediatric patients continue to progress.

Factors such as a diagnosis of leukemia or lymphoma[15-17], progressive disease[15], bone marrow involvement[15,16], and the presence of a central venous catheter[18] have been identified in literature as poor prognostic indicators in the treatment of febrile neutropenia among pediatric cancer patients. As our clinic mainly accepts patients with solid tumors and lymphomas, we observed that patients with lymphoma diagnosis had the longest hospital stay in our study. This may be attributed to their intensive chemotherapeutic regimens.[19-21] A prospective cohort study supports this observation, indicating that patients with hematological malignancies carry a higher risk of serious infections compared to those with solid tumors, likely attributed to the intensity of chemotherapy.[22] Despite these observations, we did not find a significant relationship between chemotherapy regimens and febrile neutropenia prognosis or discharge time in our study group. This lack of correlation may be influenced by the relatively small sample size of our study.

Ammann et al. reported that bone marrow involvement increases the risk of serious infection in febrile neutropenic pediatric cancer patients.[23] Similarly, we considered patients with bone marrow involvement to be at higher risk, and they indeed experienced prolonged hospitalization. Recurrent or resistant disease did not show a significant difference in terms of hospitalization duration, likely because the majority of patients in our study were newly diagnosed and in remission (80.7%). The prolonged hospitalization in febrile neutropenic episodes among patients with comorbid conditions supports findings from similar studies in the literature.[4,24]

Physical examination findings upon admission during febrile neutropenic episodes offer valuable insights into patient prognosis and treatment outcomes. In our study, patients presenting with fever of ≥ 39 °C, poor general condition, hypotension, prolonged capillary refill time, and severe infection had a more challenging and prolonged course of fever, resulting in a longer duration of antibiotic

administration. Evidence from the literature also supports the importance of general appearance and vital sign stability as indicators of the lack of serious infection, whereas a fever exceeding 38.5 °C, prolonged capillary refill time, and severe tachypnea are associated with an increased risk of infection. These physical examination findings and the overall general condition are essential markers of disease severity not only in febrile neutropenic patients but also across all patient groups.[20,25,26] Nevertheless, it is crucial to identify which examination findings carry greater predictive value than others. In our study, poor general condition on physical examination and prolonged fever demonstrated higher predictive value for hospitalization duration.

Determining the predictive value of laboratory tests is an essential aspect of numerous studies, including ours.[27,28] Notably, the neutrophil count stands out as a key parameter in diagnosing febrile neutropenia. In our study, a significant proportion (71%) of patients experienced severe neutropenia (ANC ≤ 100/mm^3). We found that the depth of neutropenia did not negatively impact the patients' days of antibiotic treatment or discharge time. Although our study did not establish a specific cutoff value for ANC, we observed a significantly longer hospital stay in febrile neutropenic patients with AMC ≤ 100/mm^3. Additionally, a platelet count of ≤ 50,000/mm^3 was associated with prolonged hospitalization. Our findings align with Amman et al.'s study, who reported that a platelet count less than 50,000/mm^3 and AMC less than 100/mm^3 were linked to an increased risk of serious infection in febrile neutropenic patients.[23] Similarly, Rackoff et al. reported that an AMC higher than 100/mm^3 was associated with a low risk of bacteremia.[29] In another study, an AMC lower than 100/mm^3 and prolonged neutropenia were associated with clinically or microbiologically defined infection.[30] Lima et al., also emphasized that a platelet count below 50,000/mm^3 at the onset of fever is particularly important as it indicates a higher likelihood of infection.[31] Alali et al. reported that the median length of stay for febrile neutropenia was three days shorter when patients were discharged when AMC >100/mm^3, which was associated with fewer unfavorable outcomes, resulting in reduced hospital days, shorter antibiotic courses, and lower costs.[32] Nevertheless, it is essential to classify patients presenting with an AMC ≤ 100/mm^3 and a platelet count of ≤ 50,000/mm^3 as high-risk. Such patients require careful management and should not to be considered for early discharge.

Regarding Hb and CRP values, our study did not identify specific threshold values. However, patients with low Hb levels and elevated CRP levels experienced later discharge. Notably, Rondinelli's study identified an Hb level less than 7 g/dL as a high-risk factor for serious infection complications.[18] Similarly, Ammann et al.'s study revealed that a CRP level higher than 90 mg/L increased the risk of serious infection.[23] In another study, febrile neutropenic children with a CRP higher than 90 mg/L, platelet count lower than 20,000/mm^3, and albumin levels lower than 2.5 g/dL were considered high-risk for complications and mortality.[33] Similar to the study conducted by Secmeer et al., CRP and procalcitonin levels were found to be higher in patients with neutropenic fever.[34] Although our study did not determine a specific CRP threshold, elevated CRP levels at admission may serve as a laboratory marker to predict the severity of infection and discharge duration. When examining the prognosis and discharge duration in febrile neutropenic patients, it becomes apparent that multiple laboratory parameters and clinical findings complicate the prediction of outcomes in individual patients. This likely explains why existing literature often assigns threshold values to specific data rather than determining comprehensive thresholds for all parameters.

The duration of neutropenia plays a crucial role in the decision to discharge for febrile neutropenic children with cancer. In our study group, patients with shorter neutropenia duration were discharged earlier, leading to shorter hospital stays. A retrospective study by Delebarre et al.

similarly emphasized prolonged neutropenia as the most critical parameter in predicting severe infection.[20] Although no standard neutrophil value is specified for discharge decisions in febrile neutropenic pediatric patients, current guidelines recommend discontinuing empirical antibacterial therapy after 48 hours if there is evidence of marrow recovery and blood cultures remain negative. This applies to both high-risk and low-risk febrile neutropenia patients who have been clinically well and afebrile for at least 24 hours, in accordance with the 2017 and 2023 guidelines.[7,35] In our study, eight febrile neutropenic cases were discharged despite an ANC < 500/mm^3 after at least three days of antibiotic treatment and a median of two days without fever during follow-up. Only one patient required re-hospitalization due to recurrent fever, and their subsequent infection was successfully treated.[36] Additionally, in another retrospective study evaluating 84 febrile neutropenic episodes in 56 patients as FUO, patients were discharged after at least 24 hours of afebrile and 72 hours of intravenous antibiotic therapy, irrespective of ANC levels. No re-hospitalization, deaths, or major complications were observed.[36] Likewise, in another study from the literature, 37 out of 83 low-risk febrile neutropenia episodes recovered after 48 hours of intravenous antibiotic treatment.[13] To facilitate early discharge planning, maintaining effective communication with parents and ensuring patients can promptly seek medical attention are essential prerequisites. However, in cases of low-risk febrile neutropenia where these conditions cannot be met, implementing early discharge remains challenging. Jackson et al. demonstrated that the Australian-UK-Swiss (AUS) rule and homecare criteria can safely identify children who can be discharged on oral antibiotics with parental monitoring, and that low-risk febrile neutropenia episodes in selected children require less than 24 hours of inpatient care.[37] Givone et al. established a consensus on criteria for initiating evidence-based step-down treatment in children with febrile neutropenia and low-risk infections, though no agreement was reached regarding the specific antimicrobial regimen for step-down therapy.[38] These findings highlight the need for further studies to better understand hospitalization duration and treatment decisions in febrile neutropenic children. Future research will play a crucial role in optimizing treatment protocols and ensuring safer discharge processes for these patients.

Febrile neutropenic patients experience infections resulting from reduced neutrophil function and compromised mucosal barriers, classified into different categories. In many cases, the source of fever cannot be identified. Clinically diagnosed infections are seen in 20-30% of febrile neutropenic episodes, however the etiological agent can only be identified microbiologically in only 10-30% of all cases.[4,39] Our microbiological infection rate was similar to that in the literature. We found a higher proportion of clinically diagnosed infections (40.1%), which may be attributed to the prospective design of our study, ensuring reliable data records and detailed physical examinations.

Our study did not analyze the hospital costs for febrile neutropenic patients. A study by Mueller et al. revealed that 40% of febrile neutropenic patients had a short hospital stay, and severe infections were rare.[40] Therefore, various studies have explored early discharge in low-risk febrile neutropenic patients to reduce the financial burden.[10,13] However, it should be emphasized that risk classification scores must be evaluated specifically for each pediatric oncology center.[6,13] In the study by Vargas et al., it was stated that outpatient management of low-risk patients had the potential to reduce the hospital treatment costs of febrile neutropenia events. This suggests that managing low-risk cases on an outpatient basis could alleviate the financial burden on the healthcare system compared to inpatient care.[41] Socioeconomic level of patients, hospital transportation options, available resources, and limitations of the social security system may vary significantly between regions, and all these factors influence early discharge decisions. A recent study demonstrated that

although ANC is commonly included in risk stratification strategies for the management of febrile neutropenia, socioeconomic factors that may influence readmission rates should also be taken into account.[42] According to our evaluation, these variables significantly affect the decision-making process. While our study suggests that early discharge without waiting for neutropenia resolution is possible for low-risk febrile neutropenic patients in accordance with pediatric febrile neutropenia guidelines, we observed that only 8 out of 142 febrile neutropenic episodes met this criterion. This was primarily due to the majority of patients (60.2%) coming from rural areas with lower socioeconomic levels.

Many studies conducted in children rely on retrospective data, limiting their findings to the routine evaluation parameters of a single clinic and not encompassing the broader literature. Due to the retrospective nature of such studies, certain clinical examination findings may not have been recorded, resulting in an emphasis on analyzing laboratory values alone. One of the strengths of our study is its prospective design. The higher rate of clinically diagnosed infections in our study might be attributed to this prospective approach and comprehensive evaluation. However, the limitations of our study include its single-center design and relatively limited sample size.

Conclusion

We conclude that the diagnosis of lymphoma, presence of comorbid conditions, central catheter use, bone marrow involvement, and febrile neutropenic episodes occurring during hospitalization are indicative of high-risk group evaluation and delayed discharge. Patients with fever ≥ 39°C at the time of febrile neutropenic episodes, poor general condition, hypotension, prolonged capillary refill time, and severe infection findings also experienced prolonged hospital stays and antibiotic administration. Prolonged fever and neutropenia were further associated with extended hospitalization. These results suggest that it is possible to devise a treatment plan based on early risk group determination, allowing clinicians to predict appropriate discharge timing. Early discharge of low-risk patients not only reduces hospital costs but also significantly improves patient quality of life. Oral antibiotic therapy with close follow-up is yet to be standardized for low-risk febrile neutropenic patients across all centers. Our study reveals high-risk criteria in febrile neutropenic patients, thereby making it possible to identify low-risk patients. Discharging low-risk patients early or providing outpatient follow-up must be integrated in the care of the pediatric cancer patients.

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Ethical approval

The study was approved by Hacettepe University Non-Interventional Clinical Research Ethics Committee (date: May 3, 2018, number: GO 18/445).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: CÜ, BA, NK, BY, AV, TK; data collection: CÜ; analysis and interpretation of results: CÜ, BA, NK, BY, AV, TK; draft manuscript preparation: CÜ, BA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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