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The Relationship Between Inflammatory Parameters and the Duration of Febrile Neutropenia in Children with Febrile Neutropenia

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ABSTRACT

Febrile neutropenia is the most common complication and emergency condition frequently seen in pediatric patients receiving cytotoxic chemotherapy. Indices calculated using various ratios of parameters in complete blood counts are important predictors of various outcomes in conditions where the inflammatory process is at the forefront. This study aimed to investigate whether Neutrophil-Lymphocyte, Platelet-Lymphocyte, Monocyte-Lymphocyte ratio,and Systemic Immuno-Inflammation Index, Systemic Inflammation Response Index are effective markers on the duration of febrile neutropenia in children diagnosed with febrile neutropenia.

This retrospective analysis involved 59 pediatric patients diagnosed with cancer-related febrile neutropenia. Among the participants, 52.5% (n=31) were classified in the short-duration febrile neutropenia category, comprising 51.6% (n=16) males and 48.4% (n=15) females. Conversely, 47.5% (n=28) were categorized in the long-duration febrile neutropenia group, which included 57.1% (n=16) males and 42.9% (n=12) females.

In the statistical analysis of the indices obtained from the ratios of complete blood count parameters measured on the first day of febrile neutropenia, there was a significant difference between the groups in terms of the Platelet/Lymphocyte ratio (p=0.045).

This study suggested that various inflammatory parameters do not have a significant predictive effect on the duration of febrile neutropenia in pediatric patients monitored for short-term and long-term neutropenic fever. In our research, the group with prolonged neutropenia exhibited a decrease in Platelet/Lymphocyte ratio, which contrasts with existing literature. This discrepancy may be attributed to the fact that a substantial portion of the pediatric patients diagnosed with febrile neutropenia had a primary diagnosis of leukemia

Keywords: Child, Febrile Neutropenia, Monocyte-Lymphocyte Ratio, Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, Systemic Immune Inflammation Index, Systemic Inflammation Response Index

Introduction

Febrile neutropenia (FN) is the most common complication and emergency condition in pediatric patients receiving cytotoxic chemotherapy, leading to the high morbidity and mortality (1).

It is estimated that 10% to 50% of patients with solid tumors, and over 80% of those with hematologic malignancies will develop a fever during at least one chemotherapy cycle associated with neutropenia. This is particularly concerning in patients who are expected to have profound neutropenia (ANC <100 cells/mm^3) and neutropenia lasting seven days or more, such as those undergoing induction chemotherapy for acute leukemia (2,3).

The mortality rate associated with febrile neutropenia is higher in patients who experience prolonged fever and extended duration of neutropenia, especially in those with high-risk or relapsed/refractory malignancies (4).

Identifying risk groups, especially high-risk groups, in critically ill patient populations is crucial. Various diagnostic tools have been

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developed over time for this purpose, ranging from simple biomarkers based on single measurements to complex indices that consider ratios and prediction models integrating multiple methods.

Changes in components of the complete blood count, such as neutrophils, lymphocytes, monocytes, and platelets, play a fundamental role in immune system responses affected by various factors and are critical in systemic inflammation, injury, and stress. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), Systemic Inflammation Response Index (SIRI), and indices calculated using various ratios of parameters in complete blood counts have been reported as important predictors of outcomes in conditions where the inflammatory process is prominent (5,6,7).

While risk groups for adults with FN are well-defined, there is insufficient information on this topic in children. Inflammatory indices may reflect the severity of serious diseases like cancer and therefore predict risk groups and/or mortality. Biomarkers or inflammatory indices for pediatric cases have not been clearly defined yet (8).

This study aims to investigate whether NLR, PLR, MLR, PLR, SII,and SIRI are effective markers for the duration of febrile neutropenia in children diagnosed with febrile neutropenia.

Material and Methods

Study Design: This retrospective single-center study was conducted in the Pediatric Hematology and Oncology Department at a tertiary care center from January 1, 2021, to August 1, 2023.

Ethics Statement: Approval was obtained from the local ethics committee for the study (No: 2023/410).

Inclusion and Exclusion Criteria: The study included 59 pediatric patients who were hospitalized and treated for cancer-related febrile neutropenia in our hospital's pediatric hematology and oncology services.

Inclusion criteria: Patients had to be between 29 days and 18 years of age, with their data on diagnosis and treatment processes accessible from the hospital registry system.

Exclusion criteria: Patient's outside the 29 days to 18 years age range, not followed by our hospital's pediatric hematology and oncology department, or with data not accessible from the hospital registry system were excluded.

Patients who met the inclusion criteria were followed up for the duration of febrile neutropenia as the primary outcome and mortality as the secondary outcome.

Data Collection and Variables: The patients' ages, genders, number of febrile neutropenia days, antimicrobial treatments received, treatment durations during the first febrile neutropenia attack within the study's date range and culture results from blood or other sites if detected were recorded. Additionally, the presence of temporary or permanent catheters, and other data related to mortality if it occurred were documented.

Level of urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), albumin, hemoglobin (Hb); white blood cell (WBC), platelet (PLT), lymphocyte, monocyte, and neutrophil counts were recorded from tests performed on the first day of hospitalization due to febrile neutropenia. NLR, PLR, MLR, SII, and SIRI ratios were calculated from complete blood count parameters. Microbiological data (isolated organisms) were monitored through the microbiological laboratory information system and any isolated microorganisms were recorded. Antimicrobial treatments given to the patients and the number of treatment days were also recorded.

Management of Febrile Neutropenia in Children

Febrile neutropenia was defined by the following criteria:

- A single body temperature ≥38.3ºC or temperature ≥38.0ºC sustained for >1 hour or that occurs twice within a 24-hour period.
- An ANC < 0.5 x10^9 /L or ANC < 1.0 x 10^9 /L expected to decrease to < 0.5 x 10^9 /L over the subsequent 48 hours (9,10).

Duration of febrile neutropenia was determined as the time from the onset of fever to the time when the neutrophil count reached 500 cells/mm^3 in neutropenic patients.

All neutropenic patients underwent examinations twice daily. Their vital signs, including heart rate, oxygen saturation, and blood pressure, were monitored every four hours, while urine output was assessed every 24 hours. Patients exhibiting hemodynamic instability were subjected to continuous monitoring.

The etiological investigation and microbiological monitoring were conducted in accordance with

the established protocol, which included the following procedures:

- In instances where a patient presented with a fever spike, multiple blood cultures were collected based on the patient's age. Samples were obtained from both the central catheter and the peripheral line. Furthermore, a urine culture and a chest X-ray were conducted.

- In the absence of microbiological evidence, a pair of blood cultures was performed on a daily basis.

- Upon microbiological identification, blood cultures were repeated every 48 hours until two consecutive negative results were achieved.

- Thoracic and sinus CT scans were routinely performed for cases of persistent fever occurring between days five and seven. An abdominopelvic CT scan could be added if there were clinical and/or biological indications of infection.

The initial phase of empirical antibiotic treatment involved the administration of intravenous broad-spectrum antipseudomonal antibiotics, primarily piperacillin-tazobactam. This empirical antibiotic therapy commenced immediately upon the onset of fever. An antibiotic effective against Gram-positive bacteria and methicillin-resistant Staphylococci was incorporated in cases of suspected skin infections, catheter-related infections, or mucosal lesions. In instances of severe illness, aminoglycosides were introduced. Additionally, an antifungal medication was included in the antibiotic protocol when there was a suspicion of invasive fungal disease (9).

Statistical Analysis: The normal distribution of numerical variables was tested with the Shapiro-Wilk test. The Mann Whitney U test was used to compare non normally distributed variables in two groups. The analyses were conducted using the SPSS 22.0 Windows version package program with $P< 0.05$ considered significant.

Results

A total of patients included across all groups had a median age of 65 months (range 47-125 months). Among these patients, 54.2% (n=32) were male, while 45.8% (n=27) were female. Within the cohort diagnosed with febrile neutropenia (FN), 69.5% (n=41) were identified as having acute lymphoblastic leukemia (ALL), 5.1% (n=3) had acute myeloid leukemia (AML), 1.7% (n=1) were diagnosed with Burkitt lymphoma, 11.9% (n=7) had Ewing sarcoma, 1.7% (n=1) presented with hemophagocytic lymphohistiocytosis (HLH), 3.4% (n=2) were diagnosed with Langerhans cell histiocytosis (LCH), 3.4% (n=2) had medulloblastoma (MBL), 1.7% (n=1) were identified as having neuroblastoma (NBL), and 1.7% (n=1) had aplastic anemia.

52.5% (31) of the patients were in the short-duration febrile neutropenia group, of whom 51.6% (n=16) were male and 48.4% (n=15) were female 47.5% (28) patients were in the long-duration febrile neutropenia group, of whom 57.1% (n=16) were male and 42.9% (n=12) female). A statistically significant difference was found between the two groups in terms of age, but the difference was not significant in terms of gender. ($p=0.043$, $p=0.670$).

All patients' cancer treatment had been continuing for at least three months. None of the patients had laboratory and/or clinical findings suggestive of relapse or treatment failure at post-treatment follow-up. The median number of neutropenia days in the short-duration neutropenia group was 5 (4-6) and in the long-duration neutropenia group was 10 (8.5-13) days. The statistical analysis revealed a significant difference between the groups regarding the duration of neutropenia ($p=0.001$). The laboratory parameters checked on the first day of the febrile neutropenia attack of the patients and the Neutrophil/Lymphocyte, Platelet/Lymphocyte, Monocyte/Lymphocyte ratios, systemic immune-inflammation index and Systemic Inflammation Response Index calculated from the complete blood count parameters are shown in Table 1.

16.9 % (10) of the patients were given monotherapy treatment while the other patients were given combined treatment. The first line of empirical antibiotic therapy started as soon as the fever began. The first line of empirical antibiotic therapy included mostly piperacillin-tazobactam (240-300 mg, divided into 3-4 doses) or cefoperazone-sulbactam (100 mg/kg/day divided into 2-3 doses). Carbapenem treatment was also given when necessary. For suspected skin, catheter infection, or mucosal lesion, vancomycin treatment was added for gram-positive and *methicillin-resistant Staphylococci*. All treatments received by the patients are shown in Table 1.

Microorganisms were isolated from 30.5% (18) of blood cultures; gram-positive bacteria were isolated from 83.3% (15) of positive blood cultures, and gram-negative bacteria were isolated from 16.7% (3) of cultures. The most common bacteria were *Staphylococcus epidermidis* (6.8%) from positive blood cultures, followed by *Staphylococcus hominis* (5.1%), *Staphylococcus haemolyticus* (1.7%),

Table 1: Laboratory and Clinical Data of the Groups

Variables	Short-Duration Febrile Neutropenia Group Median (%25-%75)	Long-Duration Febrile Neutropenia Group Median (%25-%75)	P
Age (Month)	88 (55 -148)	57,5 (38 -85,5)	0,043 *
Febrile Neutropenia Duration	5 (4-6)	10 (8.5-13)	0.001 *
Hb** (g/dL)	8 (7.2-10.6)	9.3 (7.35-9.8)	0.750
WBC** (/mm3)	360 (170-700)	480 (220-715)	0.475
PLT (/mm3)	31000 (16800-73000)	22500 (11000-43000)	0.104
Neutrophils** (/mm3)	120 (30-290)	120 (55-195)	0.779
Lymphocytes** (/mm3)	140 (60 -330)	195 (110 -385)	0.274
NLR	0,56 (0,16 -2,26)	0,38 (0,14 -1,2)	0,366
PLR	214,29 (62,79 -700)	91,74 (27,5 -230,11)	0,045 *
MLR	0,06 (0 -0,23)	0,09 (0,02 -0,24)	0,366
SII	24659,09 (6909,09 -60500)	8661,82 (1775 -26645,27)	0,050
SIRI	0 (0-0)	0 (0 -0)	0,717
Ure	20 (15 -28)	20,5 (16,5 -29)	0,698
Creatinin	0,23 (0,15 -0,31)	0,18 (0,15 -0,26)	0,147
Albumin	38 (31 -43)	37,5 (30,5 -41)	0,330
AST	28 (22 -42)	37,5 (27 -66)	0,106
ALT	52 (24 -110)	43,5 (23 -95,5)	0,539
Uric Acid	2,3 (1,7 -2,9)	2,15 (1,75 -2,7)	0,767

*mean± SD, **median (IQR), Mann Whitney U testi
WBC: White Blood Cell, Hb: Hemoglobin, PLT: Platelet Count, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), Aspartate Transaminase (AST), Alanine Transaminase (ALT).

Staphylococcus oralis (1.7%), *Staphylococcus aerius* (1.7%), *Staphylococcus capitis* (1.7%), *Corynebacterium species* (3.4%), *Escherichia coli* (3.4%) and *Klebsiella oxytoca* (1.7%).

Discussion

This study aimed to investigate, the predictive performance of NLR, PLR, MLR, SII, and SIRI on the duration of febrile neutropenia in children diagnosed with cancer-related febrile neutropenia. Recent studies on febrile neutropenic pediatric patients have reported mortality rates ranging from 0.5% to 6.6% (9,11,12,13).

In our study, none of our patients experienced mortality and all patients were able to continue with their planned treatments.

The rate of mortality and serious complications is higher in patients with prolonged fever and post-fever neutropenia as well as in patients with high-risk or relapsed/resistant malignancies (4).

In recent years, various risk stratifications have been utilized and short-term hospitalizations with close outpatient follow-up have been implemented, especially in adults for suitable patients. Despite several studies emphasizing the predictive of value of laboratory no study has utilized complete blood count parameters to estimate the prognosis of pediatric patients with FN (14,15).

Preoperative analysis of peripheral blood is a cost-effective and standard procedure. Recent studies suggest a strong link between inflammation and tumor formation and progression (16,17).

Neutrophils serve as precursors of the innate immune response by participating in phagocytosis and secreting cytokines and mediators (18). They act as master effectors in the early hyperdynamic phase of infection and contribute to adaptive immune regulation (19). Lymphocytopenia, a marked decrease in the number of circulating lymphocytes, is observed after malignancy, severe

trauma, major surgery, severe sepsis, and systemic inflammation (20,21).

NLR, which is the ratio of neutrophil and lymphocyte counts, has been proposed as a simple, reliable, and cost-effective severity parameter in critically ill patients such as severe sepsis and septic shock (7). The prognostic value of NLR has been investigated in patients with COVID-19, patients with Hodgkin lymphoma, and various solid tumors, especially gastrointestinal malignancies. It has been reported to be an independent prognostic marker that can be used to determine disease severity and mortality (22-25). In our study, we evaluated the effect of NLR on the duration of febrile neutropenia and prognosis. Although NLR increased in the group with long neutropenia duration, the difference between the groups was not statistically significant. (Table. 1)

Peripheral blood contains monocytes and lymphocytes, both of which are associated with inflammation. A higher preoperative MLR indicates an increase in the number of monocytes or a decrease in the number of lymphocytes. Monocytes in the bloodstream are attracted to the tumor microenvironment and contribute to tumor growth. Furthermore, monocytes within the tumor develop into macrophages that can inhibit the immune system, promote metastasis, and facilitate the development of new blood vessels. Conversely, a decrease in the number of lymphocytes is often associated with a weakened ability of T lymphocytes to fight tumors. A weakened immune system due to low lymphocyte levels may inhibit the body's ability to fight tumor growth and metastasis (26-28). Tao et al. showed that preoperative MLR is a good prognostic indicator in predicting overall survival and disease-free survival after curative hepatectomy (29). Cananzi et al. examined preoperative monocyte-lymphocyte ratios to predict recurrence of gastrointestinal stromal tumors (30).

In our study, we evaluated the effect of MLR on the duration of febrile neutropenia and prognosis. Although MLR increased in the group with long neutropenia duration, the difference between the groups was not statistically significant. (Table 1)

Thrombocytosis and lymphocytopenia are related to the degree of systemic inflammation, while PLR has begun to be used as a new marker combining both hematological parameters (31). In addition to neutrophilia and lymphopenia, platelet proliferation is induced by proinflammatory cytokines, especially in conditions with strong triggers of systemic inflammatory response such as sepsis, malignancy, rheumatological disorders and trauma (32,33). Thrombocytosis is associated with increased inflammatory responses and aggravates the general inflammatory reaction in the body. Platelets directly interact with tumor cells and contribute to tumor growth, invasion and angiogenesis (34). Studies have shown that PLR is independently associated with prognosis in many cancers such as colorectal cancer, breast cancer, gastric cancer and hepatocellular carcinoma, regardless of age, gender and tumor site (35-38). When the prognostic role of PLR was investigated in various cancers, it was stated that increased PLR significantly worsened overall survival (39).

In our study, we evaluated the effect of PLR on the duration of febrile neutropenia and prognosis. While it was expected that PLR would increase in the group with long neutropenia duration, in our study, contrary to the literature, the rate decreased. In the statistical evaluation made between the groups, the difference was significant (Table 1). When we look at the studies, while the primary diseases of the patients causing febrile neutropenia were solid tumors, in our study, the primary disease of the majority of our patients was acute leukemia. As a result, the bone marrow is suppressed due to the primary disease and thrombocytopenia is observed instead of thrombocytosis. This causes decreased PLR.

SII is a widely mentioned biomarker in the current literature and was first described by Hu et al. in 2014 (40). This index is important because neutrophils, lymphocytes, and platelets play important roles in numerous inflammatory processes and have a special relationship between these cells. Researchers have shown that high SII generally emerges as a useful marker for overall survival, progression-free survival, and response to immunotherapy among cancer patients (41,42). In our study, we evaluated the effect of SII on the duration of febrile neutropenia and prognosis. While SII was expected to increase in the group with long neutropenia duration, in our study, contrary to the literature, the rate decreased. However, the difference was not significant in the statistical evaluation. (Table. 1)

SIRI is an inflammatory biomarker first identified by Qi et al. in 2016 (43). Numerous studies have shown that the prognostic significance of various cancer types can be assessed through parameters such as white blood cell counts, consisting of neutrophils, lymphocytes, and monocytes, and acute phase proteins such as C-reactive protein, and that elevated SIRI is associated with survival

in the prognosis of malignant diseases (44,45). In our study, we evaluated the duration of febrile neutropenia and the effect of SIRI on prognosis. While SIRI was expected to increase in the group with long neutropenia duration, in our study, contrary to the literature, the rate decreased. However, the difference was not significant in the statistical evaluation. (Table 1)

This study aimed to determine a rapid and cost-effective prognostic parameter that can be used to determine the duration of febrile neutropenia. However, the study did not observe a significant predictive effect of the parameters examined on the duration of febrile neutropenia and prognosis. Prospective and multicenter studies with a larger number of patients are required to investigate the future usability of the parameters.

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Limitation: This study has some limitations. First, this study is retrospective. Second, for the sake of generalizability of the study, patients were enrolled from a single center, which may have affected the results. Third, we did not analyze the effect of different chemotherapy regimens and treatment intensity on the outcome, which may have affected our results. For all these reasons, further research is needed to determine the relationship between the parameters and prognostic performance.

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Conflicts of Interest: No conflict of interest was declared by the authors.

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