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# Significance of Interleukin-6 and C-Reactive Protein in Predicting Outcomes in Febrile Neutropenia in Children with Malignancy

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**Abstract**

**Background:** Febrile neutropenia (FN) is a common complication in children with cancer. We investigated the ability of interleukin-6 (IL-6) and C-reactive protein (CRP) to predict FN and fever in these patients.

**Methods:** In this cross-sectional analytical study, all eligible patients diagnosed with hematological and non-hematological cancers referred to hematology, oncology wards of Motahari Hospital in Urmia, from 2021 to 2022 were selected by convenience method. Demographic information, type of malignancy, stage of malignancy treatment, drugs receiving chemotherapy, accompanying symptoms, test results and paraclinical findings were collected. We predefined cutoff values at 30 pg/mL for IL-6 and 30 mg/dL for CRP.

**Results:** Of 30 pediatric cancer patients, 21 were male (70%) and nine were female (30%), with a mean age of 7.2 ± 3.46 years. The mean duration of fever and hospital stay was 3.14 ± 1.95 days and 7.85 ± 2.8 days, respectively, in the group with IL-6 levels exceeding 30 pg/mL. In contrast, for those with IL-6 levels below 30 pg/mL, the mean duration of fever and hospitalization stood at 6.0 ± 2.8 days and 10.6 ± 3.8 days, respectively. A significant association was noted between IL-6 levels and both hospital stay ($P = 0.034$) and fever duration ($P = 0.008$). Conversely, no notable correlation was evident between CRP levels and the duration of hospitalization or fever in the participants under investigation ($P \leq 0.79$).

**Conclusion:** Our findings suggest initial serum IL-6 levels may predict FN and fever in children with cancer. This makes IL-6 a potentially valuable tool for identifying low-risk patients.

**Keywords:** Metabolic disorders, Hematology, Oncology, Cancer

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## Introduction

Neutropenic sepsis, also known as febrile neutropenia (FN), continues to be a significant complication of childhood cancer therapy, with reported incidences of bacteraemia ranging from 11%-24%, PICU admissions ranging from 0.9-11%, and fatality rates ranging from 0.2%-3% (1-3). Consequently, children undergoing cancer treatment are often required to seek medical attention at the onset of a fever (4). Risk stratification models have been developed based on patient characteristics at the initiation of FN, allowing clinicians to categorize patients into low- or high-risk groups (5). Episodes of FN are considered severe if they persist for more than 7 days, progress to septic shock, or result in fatality; otherwise, they are classified as mild (6).

Fever occurring during FN represents a common and potentially life-threatening challenge in the management of pediatric cancer (7). Fortunately, advancements in supportive care have significantly decreased mortality rates attributed to infections (8). Current efforts are aimed at minimizing morbidity and healthcare expenses while enhancing the well-being of both the child and their family throughout these episodes (9). Specifically, there is a growing emphasis on establishing a clinical decision-making framework to identify children with FN who are at low risk of severe infections and medical issues, making them candidates for less aggressive treatment strategies (10).

A biomarker is broadly described as a measurable characteristic used to assess normal biological processes, disease-related mechanisms, or responses to treatment interventions (11). Levels of proinflammatory cytokines in the bloodstream can be influenced by microbial triggers, with interleukin-6 (IL-6) playing a crucial role in fever and inflammation (12). IL-6 serves as a versatile cytokine involved in regulating the functions of B and T cells as well as inducing acute-phase responses like the production of CRP, fibrinogen, and serum amyloid A protein (13). In

immunocompromised patients, CRP serves as a common marker for bacterial and fungal infections (14). Elevated CRP levels have been observed in febrile neutropenic patients with both diagnosed infections and cases of unidentified origin (15).

There have been conflicting findings regarding the significance of monitoring IL-6 levels and CRP in febrile neutropenic patients. While certain studies have demonstrated a relationship between plasma IL-6 levels and the clinical progression of FN in pediatric patients (16,17), there is inconsistency in the reported associations in adults with FN (18,19). The present research was undertaken to assess the predictive utility of IL-6 and CRP in anticipating FN and fever in children with cancer.

## Methods

In this cross-sectional analytical study, all eligible patients diagnosed with hematological and non-hematological cancers referred to the hematology and oncology wards of Motahari Hospital in Urmia, from 2021 to 2022 were selected by convenience method. Prior approval from the university ethics committee (Ethical code: IR.UMSU.REC.1400.337) was obtained and informed consent was taken from the parents or the patients.

The inclusion criteria encompassed children under the age of 14 years who experienced FN while undergoing cancer chemotherapy and presented for admission within 24 hours, excluding those with underlying conditions such as cardiovascular diseases, autoimmune diseases, and FMF. Fever was characterized as an axillary temperature exceeding > 38.5 °C on a single occasion or > 38.0 °C on two or more occasions within a 24-hour timeframe. Neutropenia was defined as a count of < 1000 neutrophils/mL upon admission. Our approach to managing FN aligned with the guidelines outlined by the International Antimicrobial Therapy Co-operative Group of the European Organization for Research and Treatment of Cancer (IATCGEORTC) (20).

### *Samples*

To assess the levels of IL-6 and CRP, blood samples were gathered on specific occasions: the onset of neutropenia, the onset of neutropenic fever, and the day the fever subsided. For those individuals experiencing neutropenia without fever incidents (n = 5), samples for IL-6 and CRP were taken upon reaching an absolute neutrophil count of 1000/μL. Before initiating intravenous (i.v.) antibiotic treatment, all patients underwent an initial assessment with blood and urine samples collected. Within 48 hours of admission, diagnostic evidence for documented infections such as pneumonia (n = 3), soft tissue infection (n = 2), and unexplained fever episodes (n = 12) was compiled. Daily differential blood counts were conducted. Participants were excluded from the study if they lacked sufficient plasma samples for IL-6 and PCT testing at specified time points (T0 and/or T1). Those who had been treated with non-standard antibiotic regimens or had undergone allogeneic stem cell transplantation within the previous month were precluded from participation in the study (21).

Data on variables such as gender and age, cancer type, cancer treatment stage, chemotherapy medications, concurrent symptoms, laboratory test outcomes, and additional clinical findings were gathered. This research examined the incidence of fever and neutropenia during various phases of cancer treatment, encompassing the initial phase, maintenance phase, remission phase, and cancer recurrence therapy.

### *Measurement of IL-6 level*

Plasma samples for IL-6 analysis were obtained by centrifuging EDTA-treated blood and then stored at -70 °C. The levels of IL-6 were determined using a commercially accessible ELISA kit (Dianova-Immunotech, Hamburg, Germany); the majority of individuals in good health exhibited IL-6 concentrations around 8 pg/mL.

### *Measurement of CRP level*

Serum CRP levels were assessed using a nephelometer in adherence to the manufacturer's guidelines from Behring, Marburg, Germany. According to the investigations by Karya et al (22) and Diepold et al (23), the designated thresholds for IL-6 and CRP were set at 30 pg/mL and 30 mg/dL, respectively.

### *Sample size calculation*

According to below formula and based on the study of Urbonas et al (24), an error level of 0.1 was accepted, and the power was calculated as 0.75%. The minimum required sample size was estimated to be 30 patients.

$$n = \frac{(Z_{1-a/2} + Z_{1-B})^2 \left[ P_1(1-P_1) + P_2(1-P_2) \right]}{(P_1 - P_2)^2}$$

### *Statistical analysis*

IL-6 and CRP data were summarized as medians and ranges. Initially, the normality of the data distribution was assessed utilizing the Kolmogorov-Smirnov test. If the data followed a normal distribution, a *t* test was employed to compare the means of quantitative data; alternatively, the Mann-Whitney U test was utilized for non-normally distributed data. The chi-square test was applied for analyzing categorical data. To compare these parameters across different groups, the Pearson correlation coefficient was examined to assess the relationships among variables. All statistical analyses were conducted at a significance level of 0.05 with a confidence level of 95% for all statistical tests.

## Results

This research involved 30 participants, consisting of

21 boys (70%) and nine girls (30%), with the mean age of 7.2 ± 3.46 years, ranging from 2 to 13 years. The distribution of age and demographic characteristics of the patients is illustrated in Table 1 using a frequency histogram. Over nine months, three patients experienced two instances of fever and neutropenia. Fortunately, there were no fatalities attributed to fever and neutropenia within the group.

Out of the total 30 patients, 19 were diagnosed with solid tumors, while 11 had hematologic malignancies. Among the solid tumors, Ewing sarcoma was the most prevalent at 21.05%, followed by Osteosarcoma at 15.5%. In the case of hematologic malignancies, acute lymphoblastic leukemia (ALL) accounted for the majority at 81.8%, with the Induction and Intensification subcategories showing considerable frequencies at 27.2%.

Based on the clinical manifestations observed, 7 patients (23.3%) exhibited respiratory failure, while 10 patients (33.3%) presented with gastrointestinal symptoms and mucocutaneous involvement, and 3 patients (10.0%) experienced renal failure. Fortunately, none of the patients succumbed to fever and neutropenia. In terms of culture findings, Gram-negative microorganisms were detected in 25 patients (83.33%). On the other hand, Gram-positive pathogens were isolated from 5 patients (16.6%), with *E. coli* (60.0%), *Acinetobacter* (20.0%), and *Enterobacter* (20.0%) being the predominant species identified (Table 1).

This study predominantly utilized ceftriaxone and amikacin as the initial antibiotic therapy in the majority of cases. The frequency distribution of primary and secondary antibiotic treatments is depicted in Figures 1 and 2, reflecting percentages. Among the patients receiving primary antibiotic treatment, 42% required a switch to a secondary drug. Notably, in the subgroup that commenced treatment with cefepime initially, the rate of antibiotic change stood at 33%. Conversely, in the cohort that was administered vancomycin in conjunction with the initial two antibiotics due to mucositis, the rate of antibiotic alteration was 29%. This can be attributed to vancomycin and cefepime being broader-spectrum agents providing coverage against both Gram-negative and positive organisms.

Out of the 30 patients included in the study, 16.6% (5 patients) necessitated antifungal therapy (such as bi-liposomal amphotericin) to alleviate fever. Among these patients, four fell into the severe fever and neutropenia category. The IL-6 levels in these individuals were recorded as follows: 39, 43, 98, and 90.4 pg/mL, with a group mean of 93.88 pg/mL, surpassing the established cutoff point. Nonetheless, due to the limited sample size, this observation could not be subjected to statistical analysis.

Given the limited quantity of blood culture samples collected from the subjects under investigation, despite clear clinical indications of bacteremia and sepsis, the disease severity was characterized by the presence of systemic inflammatory response syndrome (SIRS) symptoms (instability in hemodynamics) and admission to the intensive care unit. Out of the 30 patients, four individuals belonged to the severe fever and neutropenia subgroup, with the group's average IL-6 level of 56.2 pg/mL.

The mean fever duration in the group with an IL-6 level above 30 pg/mL was 3.14 ± 1.95 days, while the mean length of hospital stay was 7.85 ± 2.8 days. In contrast, the group with IL-6 levels below 30 pg/mL experienced a mean fever duration of 6.0 ± 2.8 days and an average hospitalization period of 10.6 ± 3.8 days. A significant association was found between IL-6 levels and both

**Table 1.** Frequency of studied variables of patients

| Variables | | | | No. (%) |
|---|---|---|---|---|
| Mean age (y) | 7.2 ± 3.46 | | | |
| Gender | | | | |
| Male | | | | 21 (70) |
| Female | | | | 9 (30) |
| Cancer types | Hematologic (n = 11, 36.66%) | ALL (n = 9, 81.8%) | Induction | 3 (27.2) |
| | | | Maintenance | 1 (9.09) |
| | | | Consolidation | 1 (9.09) |
| | | | Intensification | 3 (27.2) |
| | | | Interim | 1 (9.09) |
| | | AML (n = 2, 18.18%) | Maintenance | 1(9.09) |
| | | | MRC | 3(27.2) |
| | Solid (n = 19, 63.33%) | Hodgkin | | 1 (5.2) |
| | | PNET | | 2 (10.5) |
| | | Neuroblastoma | | 2 (10.5) |
| | | Metastatic Brain tumor | | 1 (5.2) |
| | | Ependymoma | | 1 (5.2) |
| | | Undifferentiated sarcoma | | 1 (5.2) |
| | | Osteosarcoma | | 3 (15.7) |
| | | Burkitt lymphoma | | 1 (5.2) |
| | | Medulloblastoma | | 2 (10.5) |
| | | Rhabdomyosarcoma | | 1 (5.2) |
| | | Ewing sarcoma | | 4 (21.05) |
| Disease symptoms | Pulmonary symptoms (upper and lower airways infection) | | | 7 (23.33) |
| | Gastrointestinal symptoms (with manifestations of typhoid and gastroenteritis) | | | 10 (33.3) |
| | Mucosal skin (oral and anal ulcers) | | | 10 (33.3) |
| | Kidney symptoms (urinary tract infection) | | | 3 (10.0) |
| Culture results | Negative (n = 25, 83.33%) | | | |
| | Positive (n = 5, 16.6%) | *E. coli* | | 3 (60.0) |
| | | *Acinetobacter* | | 1 (20.0) |
| | | *Enterobacter* | | 1 (20.0) |

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia.
Chi-square test.

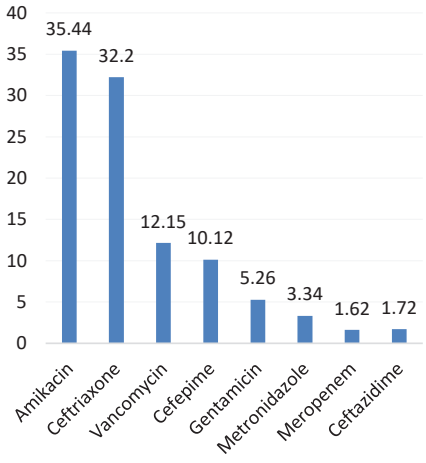


**Figure 1.** Primary antibiotic treatment

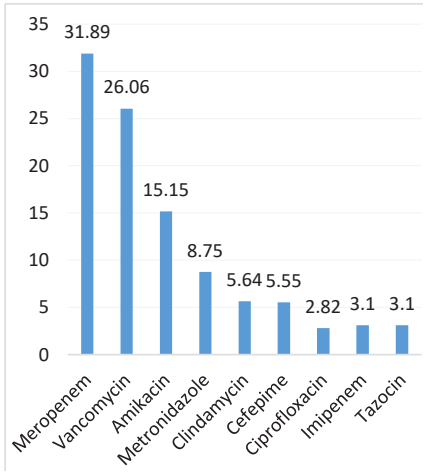


**Figure 2.** Secondary antibiotic treatment

hospitalization duration ($P=0.034$) and fever duration ($P=0.008$).

CRP levels, the mean fever duration for patients with CRP levels below 30 mg/dL stood at 5.4 ± 3.74 days, whereas for those with CRP levels above 30 mg/dL, it was 5.05 ± 3.17 days ($P=0.79$). In terms of hospital stay, patients with CRP levels below 30 mg/dL were hospitalized for an average of 9.4 ± 4.32 days, whereas those with CRP levels above 30 mg/dL had an average hospitalization period of 12.8 ± 11.38 days ($P=0.37$). No significant correlation was observed between CRP levels and either hospitalization duration or fever duration (Table 2).

According to the data presented in Table 3, the mean absolute neutrophil count for patients with IL-6 levels greater than 30 pg/mL was 274.36 ± 142.11 cells, while for those with IL-6 levels below 30 pg/mL, it was 197.05 ± 106.34 cells. The *t* test analysis did not reveal a significant correlation between these counts ($P=0.15$). Similarly, the mean absolute neutrophil count for patients with CRP levels below 30 pg/mL was 169.4 ± 139.37 cells, compared to 238.9 ± 119.1 cells for those with CRP levels above 30 pg/mL. The T-test results indicated no significant

**Table 2.** Correlation between hospitalization and fever duration with IL-6 and CRP in patients

| | | Hospitalization (Mean ± SD) | *P* value | Fever duration (Mean ± SD) | *P* value |
|---|---|---|---|---|---|
| IL-6 | <30 | 10.6 ± 3.8 | 0.034 | 6.0 ± 2.8 | 0.008 |
| | >30 | 7.85 ± 2.8 | | 3.14 ± 1.95 | |
| CRP | <30 | 12.8 ± 11.38 | 0.37 | 5.4 ± 3.74 | 0.79 |
| | >30 | 9.4 ± 4.32 | | 5.05 ± 3.17 | |

Independent samples *t* test.

**Table 3.** Correlation between absolute neutrophil count with IL-6 and CRP in patients

| | | Absolute neutrophil count (Mean ± SD) | *P* value |
|---|---|---|---|
| IL-6 | <30 | 197.05 ± 106.34 | 0.015 |
| | >30 | 274.36 ± 142.11 | |
| CRP | <30 | 169.4 ± 139.37 | 0.37 |
| | >30 | 238.9 ± 119.1 | |

Independent samples *t* test.

relationship between these counts either ($P=0.37$).

The Pearson correlation coefficient tests showed a positive correlation between IL-6 levels and fever duration, as well as with the length of hospitalization, but these correlations were not statistically significant ($r=0.013$, $P=0.48$ and $r=0.293$, $P=0.20$, respectively). Similarly, there was a positive correlation observed between CRP levels and both fever duration and hospital stay, but these correlations were not statistically significant either ($r=0.564$, $P=0.119$ and $r=0.112$, $P=0.313$, respectively). Additionally, an inverse correlation was noted between absolute neutrophil count and the duration of hospitalization ($r=0.326$, $P=0.193$) as well as fever duration ($r=0.020$, $P=0.454$), although these correlations were not found to be significant in the analysis (Figure 3).

## Discussion

The incidence of pediatric malignancies is on the rise, posing a growing concern. Fever and neutropenia present pivotal challenges in the management of treatment, resulting in disruptions to the tumor treatment regimen, prolonged hospital stays, administration of broad-spectrum antibiotics, and detriment to the patient's quality of life (25). The present research aimed to evaluate the diagnostic utility of IL6 and CRP biomarkers in forecasting bacterial infections among pediatric patients with fever and FN.

This research revealed that the average age of the patients was 7.2 ± 3.46 years, a figure similar to previous studies by Urbonas et al (24) reporting mean ages of 8 years in the fever group and 6 years in the sepsis group, Chaudhary et al (4) indicating a mean age of 6 years, and Shokripour and colleagues' study (26) showing a mean age of 7.3 years, which are consistent with the findings of the present study. Conversely, Angel's study (27) documented a higher mean patient age of 12 years.

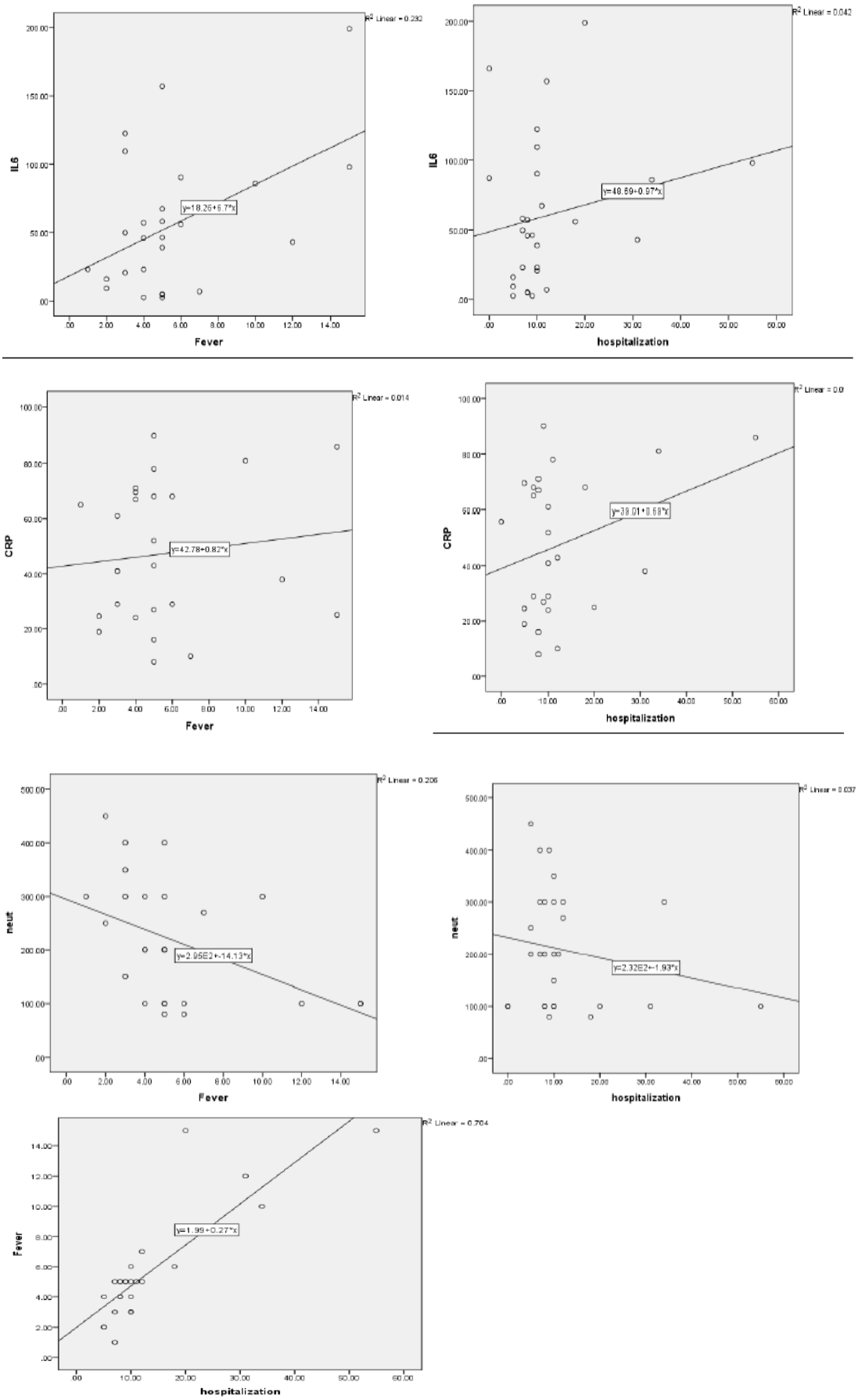


**Figure 3.** Relationship between IL-6, CRP, and absolute neutrophil count with hospitalization and fever

Furthermore, the gender distribution in this study for fever and neutropenia indicated a ratio of 70% male to 30% female. This ratio was comparable to Shokripour and colleagues' (26) with 52.9% male and 47.1% female, as well as Urbonas et al study (25) with a ratio of 58% male to 42% female, reflecting consistency with the results obtained in our investigation.

The IL-6 levels measured upon admission in this study exhibited a significant association of 0.008 with the duration of the patients' fever, which is consistent with the findings from other studies (4,16,23). Notably, IL-6 at admission has been identified as a valuable indicator of disease severity and a potentially superior early discriminator compared to CRP in identifying children at risk of developing serious infectious complications (27-29).

Furthermore, a significant correlation was observed between serum IL-6 levels and the length of hospital stay, with a significance level of 0.034. Consistent with previous findings, IL-6 levels on the first day of a febrile neutropenia episode could serve as a predictive marker for episode severity (16). Hashemi Shahri et al conducted daily monitoring of serum IL-6 levels in neutropenic patients, noting peak IL-6 levels within the initial 24 hours of fever onset (30).

While our study did not involve daily IL-6 level monitoring, the results suggest that assessing plasma IL-6 levels at the time of blood withdrawal for hemoculture on the first day of fever could aid in predicting infection severity. This discovery holds implications for identifying patients necessitating hospitalization and close monitoring. Contrary to some reports, two prior studies found that IL-6 levels upon admission did not predict bacteremia (31,32). Jaing et al (33) observed elevated serum levels of CRP, IL-6, and consistently IL-8 during FN; however, these markers were unable to differentiate between various study groups consistently. These discrepancies across studies may be attributed to the short plasma half-life of cytokines and the presence of blocking factors, which are inherent limitations of cytokine assessment (34).

Several studies corroborate our conclusion that CRP does not effectively distinguish between study groups upon presentation (35,36). In our investigation, no notable association was observed between CRP serum levels and the duration of fever or hospital stay among the groups. Comparative evaluations of the biomarkers indicated that CRP exhibited the weakest performance among them. CRP levels are typically utilized to evaluate and track acute-phase responses (37).

In the present research, IL-6 levels emerged as more indicative than CRP in assessing the severity of febrile neutropenic episodes. Parallel studies proposed that the assessment of IL-6 may offer superior diagnostic utility compared to CRP in monitoring the acute response to infection in patients with neutropenia (38,39).

In the majority of investigations, only about half of the patients diagnosed with fever demonstrate a clinically or microbiologically confirmed infection (7,18,23). The necessity of antibiotic treatment for these fevers, which may or may not indicate an infection, remains uncertain. A recent outpatient study has suggested that serum IL-6 levels, with a cutoff point set at 30 ng/L, could serve as a crucial factor in stratifying patients into low or high probability categories for bacterial infection (22,23). Within our study cohort, 16.6% (equivalent to five patients) received antifungal therapy due to the severe nature of their condition and persistent fever, coupled with IL-6 levels surpassing the specified IL-6 cutoff value. In a study conducted by Chaudhary et al, it was observed that the group necessitating antifungal therapy exhibited elevated levels of IL-6 and CRP compared to the group treated with initial antibiotics (24).

In this study, all five cases with positive cultures, comprising two positive blood cultures and three positive urine cultures, revealed the growth of gram-negative microorganisms, specifically E. coli in three cases, Enterobacter in one case, and Acinetobacter baumannii in one case. In a similar investigation involving 32 febrile neutropenic patients, seven individuals exhibited positive blood cultures, among whom five had gram-negative cultures and two had gram-positive cultures. Notably, the average IL-6 level of 196 pg/mL in the gram-negative sepsis group significantly surpassed the average IL-6 level of 17.5 pg/mL in patients with gram-positive sepsis (39). Additionally, Urbonas et al (24) reported that 58% of positive blood cultures contained gram-negative bacteria, with *E. coli, Enterobacter, Klebsiella*, and *Pseudomonas aeruginosa* being the most prevalent, aligning with the microorganisms identified in our study. In the investigation by Chaudhary et al (4), among 57 patients with fever and neutropenia, positive blood cultures yielded *E. coli, Klebsiella, Pseudomonas putida*, group B *Streptococcus*, and *Staphylococcus aureus*. Notably, the number of gram-negative cases exceeded that of gram-positive cases. Considering the findings of our study and the synthesis of previous research, initiating treatment targeting gram-negative microbes upon hospital admission appears justified.

One of the constraints of our study is the limited sample size, prompting us to advocate for its assessment in broader studies. The restricted number of participants was attributable to financial constraints in purchasing the IL-6 kit, so we were forced to consider small the sample size. Since the research was conducted at a single center (which is the study limitation), variations in antibiotic protocols were inevitable. Treatment with antibiotics was determined by the attending physician according to the institution's sensitivity profile. Another limitation pertained to the absence of standardized care

for patients, and clinical data along with biomarkers were not monitored at multiple intervals (specifically, after 24 hours and 48 hours).

## Conclusion

Our findings indicate that the initial serum IL-6 levels can serve as an indicator for predicting fever and neutropenia in pediatric cancer patients, thereby proving to be a valuable parameter in a risk assessment framework for identifying a low-risk cohort. Conversely, there was no statistically significant variance in the levels of CRP across different groups upon presentation.

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**Authors' Contribution**

**Conceptualization:** Farid Ghazizadeh, Mehran Noroozi.
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**Investigation:** Bahare Derakhshi.
**Methodology:** Farid Ghazizadeh.
**Project administration:** Farid Ghazizadeh, Mehran Noroozi.
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**Software:** Mehran Noroozi.
**Supervision:** Farid Ghazizadeh.
**Validation:** Farid Ghazizadeh.
**Visualization:** Farid Ghazizadeh, Mehran Noroozi.
**Writing–original draft:** Farid Ghazizadeh, Mehran Noroozi, Bahare Derakhshi.

**Competing Interests**

The authors declare that they do not have any conflict of interest.

**Ethical Approval**

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Urmia University of Medical sciences (Ethical code: IR.UMSU.REC.1400.337).

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