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# Plasma Calprotectin Level as a Potential Biomarker in Different Phases of Pediatric Hemato-Oncological Malignancies: A Pilot Study

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**Abstract**

**Background:** Calprotectin has been known as a biomarker for systemic inflammation, especially in autoimmune disorders. Inflammation is a process associated with malignant progression, and calprotectin is a potential prognostic biomarker in some hematologic malignancies. Our pilot study aimed to evaluate the plasma calprotectin level as a promising biomarker in the relapsed/refractory phase of pediatric hemato-oncological malignancies.

**Materials and Methods:** This pilot research is a case-control study. A total of 168 individuals were included in the study. The analyses were conducted on 73 pediatric patients diagnosed with acute leukemia and 60 others with solid tumor cancers who had referred to Ahvaz Shafa Hospital in Iran. The patients were subdivided based on the three phases of the disease, including on-treatment, relapsed/refractory, and remission phases. Also, 35 healthy children were considered as the control group. After consent was received from all the participants, their blood samples were collected in ethylene diamine tetra acetate (EDTA) tubes to measure plasma calprotectin levels by the enzyme-linked immunosorbent assay (ELISA) method. The data were analyzed using the SPSS26 software. Kruskall-Wallis, Bonferroni Post hoc, and bivariate correlation tests were used, and a two-sided p-value $< 0.05$ was significant.

**Results:** There was no statistically significant difference among the plasma calprotectin levels in different phases of acute leukemia ($P = 0.099$); however, the mean levels of the studied groups were higher than the healthy controls. This increase in the average calprotectin level was also observed in different phases of solid tumor cancers compared to the control group. Besides, a significant difference was seen between the on-treatment and remission groups compared to the control group ($p = 0.011$ and $p = 0.016$, respectively).

**Conclusion:** The mean plasma calprotectin levels increase in different phases of some pediatric hemato-oncological malignancies, but it cannot be used as a specific biomarker for the relapsed/refractory phase.

**Keywords:** Biomarkers, Leukemia, S100A8 protein, S100A9 protein, S100 proteins

## Introduction

Calprotectin, an alarmin from the S100 protein family, plays a key role in inflammatory responses and is involved in various cellular processes, particularly in immune regulation (1). Calprotectin consists of two subunits, namely S100A8 and S100A9 found in the cytoplasm of myeloid cells, especially neutrophils, monocytes, and macrophages (2). Neutrophils and monocytes are the first innate immune cells recruited to the inflammation site. These cells release heterodimeric protein S100A8/A9, and the plasma level of calprotectin rises during injury and inflammatory conditions (3). In addition to its involvement in immune responses, calprotectin has gained recognition as a reliable biomarker of systemic inflammation, with its plasma levels often reflecting the severity of inflammatory and autoimmune diseases



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like inflammatory bowel disease (IBD), rheumatoid arthritis (RA), multiple sclerosis (MS) and systemic lupus erythematosus (SLE) (1, 4, 5). For instance, calprotectin levels in cerebrospinal fluid (CSF) might reflect disease activity in MS (6). Hematologic malignancies are often accompanied by systemic inflammation, which can promote malignant progression. Studies have shown that elevated plasma levels of S100A9, a component of calprotectin, are associated with the progression of diseases like chronic lymphocytic leukemia (CLL) (7), and this increase is due to the activation of the nuclear factor kappa B (NF-kB) pathway (8). Other studies also suggest a rise in plasma calprotectin levels in acute myeloid leukemia (AML), particularly in FAB classifications M4 and M5, and the overexpression of S100A8 in these patients is associated with a poor prognosis (9). An overexpression of calprotectin was also detected in relapsed B-acute lymphoblastic leukemia (B-ALL) patients who participated in a meta-analysis (10), particularly in the aggressive or prednisolone-resistant B-ALL forms (11). Therefore, the overexpression of S100A8 and/or S100A9 in acute leukemia is associated with poor prognosis and lower survival rates (12). The expression level of calprotectin changes during different phases of hematologic malignancies like progression or treatment (13); hence, evaluating the plasma level of calprotectin in relapsed/refractory acute leukemia patients and comparing it with the other phases of the disease like on-treatment or remission phase can clarify the value of this biomarker as a prognostic biomarker. From another perspective, studies have been conducted to investigate the upregulation of S100A8 and S100A9 in other solid tumors such as gastric, colorectal, breast, and prostate cancers in adult patients (14-16). The overexpression of S100A8 is associated with poor prognosis in breast and bladder cancers (17). Our research focuses on the pediatric age group (2-18 years old); according to the latest statistics, almost 30% of pediatric cancers involve solid tumors. Brain tumors are the most common type of solid tumor in children (18), followed by neuroblastoma (NB) as the most prevalent childhood extracranial solid tumor. The incidence of relapse or progression in high-risk patients with NB is almost 50%, which increases the necessity of finding a predicting biomarker for relapse in these patients (19). S100A9 is probably responsible for inflammation, angiogenesis, and metastasis in NB by activating the NF-kB signaling pathway. Therefore, calprotectin might be a useful biomarker for predicting tumor migration in patients with NB (20). There is a lack of data related to the evaluation of serum/plasma calprotectin in pediatric patients diagnosed with other common solid tumors such as brain tumors, Wilm's tumor, or sarcomas. The level of plasma calprotectin is probably valuable as a potential biomarker because the overexpression of S100A8/A9 has been detected in several hematologic malignancies. The strong correlation between the calprotectin overexpression and poor prognosis in hematologic malignancies and solid tumors motivated us to measure its plasma levels in the relapse/refractory phase of the disease. Further research will help solidify the valuable prognostic role of this biomarker in predicting disease progression and treatment outcomes, especially in pediatric oncology.

## Materials and Methods

### Sample collection

This pilot research is considered a case-control study. The research participants were 133 pediatric patients who were







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consecutively referred to Ahvaz Shafa Hospital in Iran. The patients were categorized into two groups. The first included 73 patients diagnosed with acute leukemia (27 patients in on-treatment phase, 23 in relapsed/refractory phase, and 23 in remission phase), and the second group comprised 60 patients diagnosed with solid tumors (20 patients in on-treatment phase, 20 in relapsed/refractory phase and 20 in remission phase). The participants' diagnosis was confirmed by our medical team including pediatric hematologist-oncologists. Thirty-five healthy children referred to the laboratory for routine checkups were also included as the control group. An informed consent form was obtained from all the patients and the healthy children's parents. Blood samples were taken from the participants and collected in a tube containing ethylene diamine tetra acetate (EDTA). After a complete blood count (CBC) test was performed for each patient, the EDTA tubes were centrifuged at 3500 RPM for 10 minutes. The supernatant plasma was separated and aliquoted in microtubes stored at -80°C until use.

**Eligibility criteria**

A literature search of PubMed, Scopus, and Google Scholar databases was performed for the publications up to January 1, 2024. The search terms in various combinations were 'acute leukemia', 'solid tumor', 'calprotectin', 'S100A8', 'S100A9', 'biomarker', and 'relapse'. The patients of both sexes (< 18 years old) diagnosed with acute leukemia or solid tumor cancers included those who were in their treatment, relapsed/refractory, or remission phase. All the pediatric patients with other acute or chronic inflammatory diseases were excluded. Since calprotectin is known as a specific biomarker for inflammatory diseases, it was necessary to exclude the patients who suffer from certain inflammatory diseases such as acute renal failure, inflammatory bowel diseases, and urinary infections. This was done for the better validity of the study.

**Ethical considerations**

All the procedures performed on human participants in this study followed the ethical standards of the local Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS) (IR.AJUMS.REC.1402.674) as well as the 1964 Helsinki Declaration.

**Testing methods**

A number of studies have indicated that plasma calprotectin is more reliable than serum calprotectin (21); therefore, we chose to measure plasma calprotectin levels using the enzyme-linked immunosorbent assay (ELISA) technique. Plasma calprotectin was measured by BIOHIT Calprotectin ELISA kits according to the instructions of the manufacturer, and the absorbance was measured at 405 nm using an ELISA plate reader. The sandwich ELISA method was also used to provide results with high specificity and sensitivity.

**Statistical analysis**

The data were analyzed using the SPSS26 software. As the Kolmogorov-Smirnov test showed, the distribution of plasma calprotectin levels in different stages of the acute leukemia and solid tumor cancer groups was not normal. Moreover, Kruskall-Wallis, Bonferroni Post hoc, and bivariate correlation tests were used, and a two-sided p-value of less than 0.05 was considered statistically significant.

## Results

In total, 133 pediatric patients participated in our pilot study. They were classified into the two groups of acute leukemia (n = 73) and solid tumors (n = 60). The acute leukemia group consisted of 27 on-treatment (5 AML + 22 ALL), 23 relapsed/refractory (4 AML + 19 ALL), and 23 in-remission patients (1 AML + 22 ALL). Also, the solid tumor group







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consisted of 20 on-treatment (6 Lymphoma + 4 Ewing sarcoma + 3 Neuroblastoma + 2 Osteosarcoma + 2 Rhabdomyosarcoma + 2 Brain tumor + 1 Wilms tumor), 20 relapsed/refractory (7 Neuroblastoma + 6 Brain tumor + 2 Wilms tumor + 2 Lymphoma + 1 Ewing sarcoma + 1 Osteosarcoma + 1 Medullary Thyroid Carcinoma) and 20 in-remission patients (5 Brain tumor + 5 Osteosarcoma + 5 Lymphoma + 1 Ewing sarcoma + 2 Neuroblastoma + 1 Rhabdomyosarcoma + 1 Synovial sarcoma).

**Acute leukemia group**

In this group, 108 subjects (73 patients + 35 healthy individuals) were examined, including 53 females (49.1%) and 55 males (50.9%) with the mean age of 9.23 ± 4.89. The mean and standard deviation values of the CBC parameters in different phases of acute leukemia are reported in Table I. Plasma calprotectin levels were investigated in different phases of acute leukemia. A Kruskall-Wallis Test revealed no significant difference between the plasma calprotectin levels in the acute leukemia groups (P = 0.099). Plasma calprotectin level was 175.60 ± 150.54 ng/ml in the on-treatment, 105.53 ± 120.09 ng/ml in relapsed/refractory, 138.77 ± 145.10 ng/ml in remission, and 100.77 ± 114.68 ng/ml in control groups. The highest and lowest levels were observed in the on-treatment and control groups, respectively (Table II, Figure 1). In the remission group, there was a significant and direct relationship between plasma calprotectin and the percentages of neutrophils, hemoglobin, and hematocrit levels (P = 0.002, P = 0.012, P = 0.022, respectively). So, with the increase of calprotectin, these percentages also increased (and vice versa). On the other hand, there was a significant and inverse relationship between plasma calprotectin and the percentage of lymphocytes (P = 0.003); that is, with the increase of calprotectin, the lymphocyte count decreased (and vice versa). In the control group, there was a significant and direct relationship between calprotectin and the percentage of neutrophils (P = 0.027), as well as a statistically significant and inverse relationship between calprotectin and the percentage of lymphocytes (P = 0.020) (The corresponding information is provided in the supplementary file).

**Solid tumor group**

In this group, 95 subjects including 60 patients and 35 healthy individuals were examined. There were 43 females (45.3%) and 52 males (54.7%) with the mean age of 9.53 ± 4.96. The mean and standard deviation of the CBC parameters in different phases of solid tumor cancers are reported in Table III. Plasma calprotectin levels were investigated in various phases of solid tumors. A Kruskall-Wallis test showed the significant effect of the different stages of solid tumor cancers on plasma calprotectin levels (P-value = 0.003). A post hoc test also showed that the plasma calprotectin levels in the control group were significantly lower than those in the on-treatment (P-value = 0.011) and remission (P-value = 0.016) groups. The plasma calprotectin level was 193.90 ± 136.89 ng/ml in the on-treatment, 183.89 ± 178.71 ng/ml in relapsed/refractory, 209.71 ± 156.13 ng/ml in remission, and 100.77 ± 114.68 ng/ml in control groups. The highest and lowest levels were observed in the remission and control groups, respectively (Table II, Figure 2). There was a significant and direct relationship between plasma calprotectin level and WBC count in the relapsed/refractory and remission groups, respectively (P = 0.026, P = 0.040); that is, with the increase of WBC count, the plasma calprotectin increased too (and vice versa). In the control group, there was a significant and direct relationship between the plasma calprotectin and the percentage







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of neutrophils (P = 0.027). There was also a significant and inverse relationship between the plasma calprotectin and the percentage of lymphocytes (P = 0.020) (The corresponding information is provided in the supplementary file).

*Table I: Demographic characteristics for the CBC parameters in different phases of acute leukemia*

| Variable | On-treatment Mean ± SD | Relapsed/Refractory Mean ± SD | Remission Mean ± SD | Control Mean ± SD | Total Mean ± SD |
|---|---|---|---|---|---|
| **Age(year)** | 8 ± 4.54 | 12.48 ± 4.79 | 9.78 ± 4.67 | 7.69 ± 4.42 | 9.23 ± 4.89 |
| **WBC count (10^3 /µL)** | 3.77 ± 2.39 | 17.9 ± 40.17 | 6.95 ± 3.14 | 8.2 ± 2.39 | 8.89 ± 19.03 |
| **Neutrophils%** | 61.07 ± 11.83 | 47.22 ± 25.27 | 56.09 ± 21.15 | 51.2 ± 13 | 53.86 ± 18.36 |
| **Lymphocytes%** | 35.48 ± 11.90 | 50.3 ± 26.6 | 40.65 ± 21.26 | 41.89 ± 11.83 | 41.84 ± 18.53 |
| **Monocytes%** | 2.56 ± 0.97 | 1.83 ± 1.64 | 2.3 ± 1.39 | 5.17 ± 2.96 | 3.19 ± 2.43 |
| **Eosinophils%** | 0.96 ± 0.75 | 0.35 ± 0.64 | 0.91 ± 0.51 | 1.63 ± 1.66 | 1.04 ± 1.17 |
| **RBC count (10^6 /µL)** | 3.84 ± 0.76 | 3.41 ± 0.53 | 4.62 ± 0.54 | 4.58 ± 0.55 | 4.15 ± 0.78 |
| **Hemoglobin (g/dL)** | 10.03 ± 1.79 | 9.81 ± 1.38 | 11.83 ± 1.89 | 11.57 ± 1.51 | 10.87 ± 1.85 |
| **Hematocrit%** | 33.32 ± 6.32 | 29.76 ± 4.89 | 37.49 ± 5.66 | 35.62 ± 3.84 | 34.2 ± 5.77 |
| **Platelets (10^3 /µL)** | 258.41 ± 196.18 | 182.78 ± 192.69 | 241.48 ± 100.34 | 299.57±95.69 | 252.04 ± 154.17 |

WBC: white blood cell, RBC: red blood cell

*Table II: The plasma calprotectin levels in different phases of hemato-oncological malignancies*

| Variable | On-treatment Mean ± SD | Relapsed/Refractory Mean ± SD | Remission Mean ± SD | Control Mean ± SD | P-value* |
|---|---|---|---|---|---|
| **Plasma Calprotectin in Acute Leukemia (ng/ml)** | 175.60 ± 150.54 | 105.53 ± 120.09 | 138.77 ± 145.10 | 100.77 ± 114.68 | 0.099 |
| ***Plasma Calprotectin in Solid Tumor Cancers (ng/ml)*** | 193.90 ± 136.85 | 183.89 ± 178.71 | 209.715±156.13 | 100.77 ± 114.68 | 0.003 |

*****Using Kruskall-Wallis Test

*Table III: Demographic characteristics for the CBC parameters in different phases of solid tumors*

| Variable | On-treatment Mean ± SD | Relapsed/Refractory Mean ± SD | Remission Mean ± SD | Control Mean ± SD | Total Mean ± SD |
|---|---|---|---|---|---|
| **Age (year)** | 10.95 ± 5.42 | 9.25 ± 4.49 | 11.65 ± 4.90 | 7.68 ± 4.42 | 9.53 ± 4.96 |
| **WBC count (10^3 /µL)** | 5.91 ± 6.30 | 7.76 ± 8.07 | 6.72 ± 2.27 | 8.20 ± 2.39 | 7.31 ± 5.01 |
| **Neutrophils%** | 68.50 ± 10.20 | 71.10 ± 17.50 | 59.85 ± 12.33 | 51.2 ± 13 | 60.85 ± 15.63 |
| **Lymphocytes%** | 28.35 ± 10.35 | 26.80 ± 17.38 | 38 ± 11.33 | 41.89 ± 11.83 | 35.04 ± 14.23 |
| **Monocytes%** | 2.30 ± 1.34 | 1.5 ± 1.23 | 2.40 ± 0.88 | 5.17 ± 2.96 | 3.21 ± 2.52 |
| **Eosinophils%** | 0.90 ± 0.71 | 0.70 ± 0.80 | 1.20 ± 1.67 | 1.63 ± 1.66 | 1.18 ± 1.39 |
| **RBC count (10^6 /µL)** | 3.67 ± 0.45 | 3.66 ± 0.78 | 4.56 ± 0.64 | 4.58 ± 0.55 | 4.19 ± 0.75 |
| **Hemoglobin (g/dL)** | 9.83 ± 1.21 | 9.81 ± 1.75 | 11.62 ± 1.16 | 11.57 ± 1.51 | 10.84 ± 1.67 |
| **Hematocrit%** | 30.52 ± 4.32 | 30.43 ± 5.24 | 37.62 ± 3.65 | 35.62 ± 3.84 | 33.87 ± 5.13 |
| **Platelets (10^3 /µL)** | 219.40 ± 162.68 | 199.80 ± 127.35 | 230.03 ± 86.63 | 299.57 ±95.69 | 247.04 ± 123.22 |

WBC: white blood cell, RBC: red blood cell



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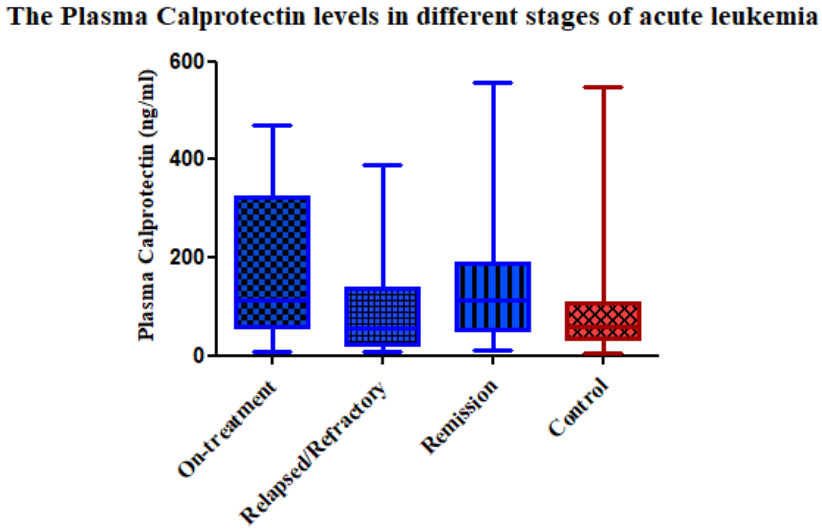


Figure 1. The plasma calprotectin levels are higher in different phases of acute leukemia compared to the healthy control group. The highest calprotectin level was observed in the on-treatment phase (175.60 ± 150.54 ng/ml).

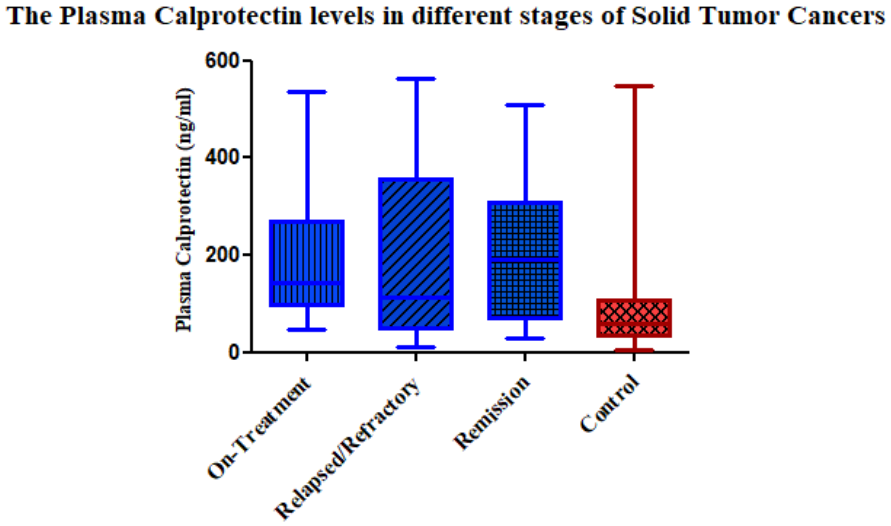


Figure 2. The plasma calprotectin levels are higher in different stages of solid tumors compared to the healthy control group. The highest calprotectin level was observed in the remission phase (209.715±156.13 ng/ml).

## Discussion

### Overview

Calprotectin is a ligand for several PRRs, including TLR4, and CD33, as well as a receptor for advanced glycation end products (RAGE). Its binding to these receptors activates the inflammation process through the NF-kB pathway. When the inflammation cascade is triggered, inflammatory cells are recruited to the tumor microenvironment. Besides, the production of pro-inflammatory cytokines and chemokines increases, and this loop continues until inflammation becomes chronic (22). Chronic







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inflammation in cancer is a factor for the increased survival and proliferation of cancerous cells. It is also associated with angiogenesis and metastasis (23). Patients with hematologic malignancies or solid tumors experience fever, anemia, recurrent infections, and systemic inflammation in the relapsed/refractory phase, which is similar to the onset of the initial diagnosis. In addition, systemic inflammatory biomarkers such as calprotectin are more likely to increase in these two phases of the disease. For instance, several studies showed an overexpression of calprotectin in newly diagnosed and relapsed B-ALL pediatric patients (10, 24). Therefore, our hypothesis regarded a rise in plasma calprotectin levels in the relapsed/refractory phase of hemato-oncological malignancies due to the probable presence of systemic inflammation.

**The measurement technique**

Plasma calprotectin levels are more sensitive to inflammation than other common inflammation markers such as C-reactive protein (CRP) (13). Finding a diagnostic/prognostic biomarker becomes important if it is easy to measure in a clinical laboratory compared to gene expression tests that are technically more complicated. The enzyme-linked immunosorbent assay (ELISA) is a routine and widely available laboratory test that can be used to measure serum/plasma calprotectin levels. Due to the fact that the upregulation of a gene is not always associated with the secretion of its encoded proteins in peripheral plasma (12), we chose this technique for our pilot research to measure its efficiency for comparing plasma calprotectin values in various phases of hematologic malignancies.

**Interpretation of the main findings**

Calprotectin has been known as a factor contributing to inflammation-associated diseases. Many studies have mentioned the overexpression of S100A8/S100A9 in tumor inflammatory microenvironment. Shabani et al. (25) stated that there is a positive feedback mechanism between S100A8/A9 proteins and pro-inflammatory factors like TNF-α, IL-1, IL-6, chemokines, angiogenic factors, matrix metalloproteases (MMPs), and anti-apoptotic proteins. Marelli et al. (26) believed that cancer-promoting inflammation should be targeted for therapy in oncology. So, we assume that S100A8/A9 proteins as inflammatory factors might be promising anti-cancer targets for therapy. On the other hand, introducing calprotectin as a potential biomarker in cancer is still controversial because some studies highlight the opposite effects of calprotectin on tumor development despite its role in tumorigenesis and cancer progression (27). Allgöwer et al. (28) showed that the function of the S100 family is strongly dependent on the tissue context. For instance, S100A2 operates as a tumor suppressor in oral cancer, while it promotes tumor growth in lung cancer.

Since the mean plasma calprotectin levels in our pilot study were higher in both acute leukemia and solid tumor groups compared to the healthy controls, it can be concluded that this biomarker may be related to systemic inflammation in the body. However, there was no significant correlation between the plasma level of this potential biomarker in different stages of pediatric acute leukemia (Table II, Figure 1). Therefore, our hypothesis about the rise of the plasma calprotectin level in the relapsed/refractory phase of acute leukemia is rejected. For the solid tumor group, the highest calprotectin level was observed in the remission phase. In general, it can be understood that plasma calprotectin is not increased in any phases of acute leukemia but it has a rise in the remission phase of solid tumors. Considering the novelty of our study and







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the lack of similar studies, we cannot give a definite opinion on the reason; obviously, future studies are needed.

However, there was a positive correlation between plasma calprotectin and neutrophil count, hemoglobin, and hematocrit levels in the acute leukemia remission group. Since S100A8/A9 is also known as myeloid-related protein 8/14 (MRP8 and MRP14) due to its release origin (3), a positive correlation was also detected between plasma calprotectin level and its original series (WBC count) in solid tumors. The direct relationship between plasma calprotectin and the neutrophils percentage, as well as a negative correlation between plasma calprotectin and lymphocyte percentage in our healthy control group, indicates a correlation between calprotectin level and its original myeloid series like neutrophils. This was an expected conclusion that justifies the accuracy of this study. In fact, the higher the percentage of neutrophils in the WBC population, the lower the percentage of lymphocytes and the higher the calprotectin level.

**Strengths and limitations**

A notable strength of this study is the inclusion of both hematologic and oncologic malignancies, which allows for a broader understanding of the relationship between plasma calprotectin levels and the different stages of the disease. However, several limitations are to be acknowledged. For instance, the duration of the disease in the on-treatment and relapsed/refractory groups was not evaluated in this study, despite its being an important factor that might influence plasma calprotectin level. We assume that the longitudinal studies which track calprotectin levels over time might provide more insight into its utility as a biomarker. In addition, rejecting the hypothesis of a rise in calprotectin during the relapsed/refractory phase might have many unclear reasons including the heterogeneity of tumor subtypes or variations in treatment protocols. So, it is suggested to select a more homogeneous group of patients for future studies.

These limitations highlight the importance of the careful interpretation of the research findings and suggest avenues for future research such as including another measurement technique, like gene expression alongside plasma measurement, and considering the duration of the disease. Addressing these aspects can lead to the better understand of the role of plasma calprotectin levels as a biomarker in different phases of hemato-oncological diseases.

**Clinical aspects**

S100A8/A9 has emerged as a promising target for therapy in hemato-oncological malignancies, especially in AML. AML is a disease that requires newer treatments such as targeted therapies, given the limited range of the current treatments. Fan et al. (29) stated that silencing S100A9 leads to increased apoptosis and reduced cell viability in AML, highlighting its potential as a therapeutic target. S100A8/9 targeted therapies can be an alternative to traditional chemotherapies for the treatment of solid tumors; unlike conventional chemotherapies, targeted therapies have improved efficacy and reduced adverse effects because of focusing on regulating specific inflammatory pathways (30). In general, despite all the advances that have occurred in the field of S100A8/A9-targeted therapies, more clinical studies are needed.

## Conclusion

In conclusion, calprotectin might be an individual potential biomarker for systemic inflammation in hemato-oncological malignancies; however, it cannot be introduced as a specific







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biomarker for the relapsed/refractory phase. Further investigations with a larger sample size are needed to decisively speak on this issue.

## Data Availability

All the data generated or analyzed in the study are included in this article. The corresponding author can be contacted for more information in this regard.

## Ethical Considerations

All the procedures performed on human participants in this study followed the ethical standards of the local Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS) (IR.AJUMS.REC.1402.674) as well as the 1964 Helsinki Declaration.

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## Authors' Contributions

Kaveh Jaseb: conceptualization and supervision. Bita Bandar: investigation, methodology, writing the original draft, review and editing. Fatemeh Bakhshipour: investigation, methodology, and writing the original draft. Najmaldin Saki: conceptualization and supervision. Azar Babaahmadi: data curation, software implementation and formal analysis. All the authors have read and agreed to the final version of the manuscript.

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## Conflict of Interest

The authors declare no conflict of interests regarding this paper.

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