**Original Article**

# Etiologies of Leukocytosis in Hospitalized Patients: A Retrospective Study at Shohada-ye Ashayer Hospital, Khorramabad, Iran, 2020–2023

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## Abstract

**Background:** Leukocytosis is defined as a peripheral blood white blood cell (WBC) count >11,000/µL in adults. Because it has diverse causes and may have important diagnostic and management implications, this study investigated the etiologies of leukocytosis among hospitalized patients at Shohada-ye Ashayer Hospital in Khorramabad, Iran, from 2020 to 2023.

**Methods:** This retrospective, cross-sectional, descriptive study included hospitalized adults aged ≥18 years with a WBC count ≥11,000/µL. Patients were evaluated for age, sex, medical and medication history, fever, neutrophil percentage, and predominant clinical symptoms at admission. The primary cause of leukocytosis was determined based on the clinical diagnosis and treatment documented in the medical records.

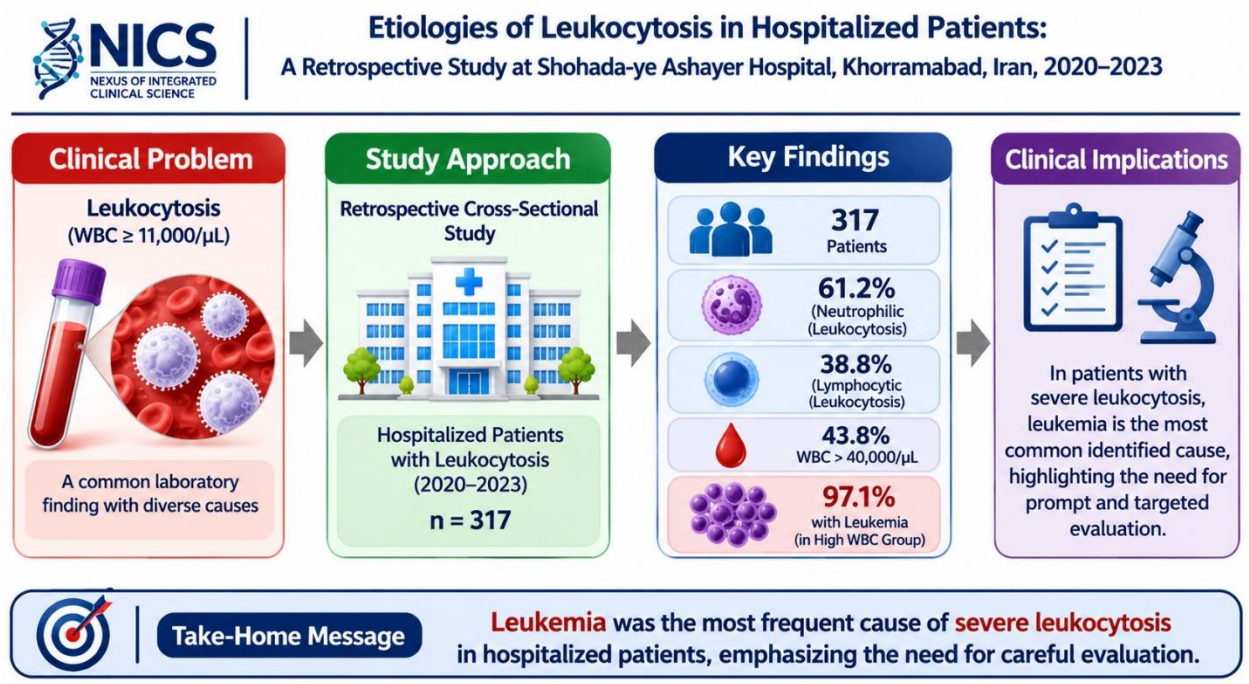
**Results:** Among 317 patients, 194 had neutrophilic and 123 had lymphocytic leukocytosis. The causes of neutrophilic leukocytosis were leukemia in 71 patients (22.4%), acute infection in 63 (19.9%), collagen-vascular diseases in 31 (9.8%), corticosteroid use in 21 (6.6%), and leukemoid reaction in 8 (2.5%). The causes of lymphocytic leukocytosis were leukemia in 76 patients (24.0%), viral infections in 25 (7.9%), drug reactions in 13 (4.1%), and autoimmune diseases in 9 (2.8%). WBC counts exceeded 40,000/µL in 63 patients with leukemia and 3 with leukemoid reaction among those with neutrophilic leukocytosis, and in 72 patients with leukemia and 1 with viral infection among those with lymphocytic leukocytosis.

**Conclusion:** In this hospitalized population, WBC counts >40,000/µL were frequently associated with leukemia and, less commonly, leukemoid reactions or infection. At lower WBC counts, infectious, inflammatory, drug-related, and other underlying conditions should also be considered.

**Implications for Patient Care:** Markedly elevated WBC counts, particularly with neutrophilia or lymphocytosis, should prompt evaluation for hematologic malignancy and leukemoid reaction, while lower levels require broader assessment based on the clinical presentation, medical history, medications, and potential infectious or inflammatory conditions.

**Keywords:** Leukocytosis; Leukemia; Leukemoid Reaction; Infectious Diseases.

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**Graphical Abstract. Etiologies of Leukocytosis in Hospitalized Patients: A Retrospective Study at Shohada-ye Ashayer Hospital, Khorramabad, Iran, 2020–2023.** Leukocytosis is a common laboratory finding in hospitalized patients and may be associated with a variety of underlying conditions, including infections, inflammatory diseases, medication use, and hematologic malignancies. In this retrospective cross-sectional study, the medical records of 317 hospitalized adults with leukocytosis were reviewed to identify its underlying etiologies. Neutrophilic leukocytosis was more common than lymphocytic leukocytosis, accounting for 61.2% and 38.8% of cases, respectively. Notably, among the 139 patients with white blood cell counts exceeding 40,000/µL, leukemia was identified in 135 (97.1%). These findings highlight the predominance of leukemia among hospitalized patients with marked leukocytosis and emphasize the importance of careful clinical and laboratory evaluation to identify the underlying cause and guide appropriate patient management.

## Introduction

Leukocytosis is characterized by an elevated white blood cell (WBC) count exceeding 11,000/µL in adults and is an important laboratory finding that may reflect the immune system's response to various pathological conditions. Leukocytosis can result from a wide range of factors, including infections (bacterial, viral, or fungal), inflammation, physiological stress, hematologic disorders such as leukemia, and other malignancies (1). Approximately 1.6 billion granulocytes are produced per kilogram of body weight each day, with neutrophils accounting for more than half of this production. Leukocytosis is most commonly associated with an increased number of neutrophils (neutrophilia) and, less frequently, with an increased number of lymphocytes (lymphocytosis). Increases in monocytes, eosinophils, and basophils are fewer common causes of leukocytosis (2, 3).

Leukocytosis may result from increased leukocyte production, increased release of leukocytes from bone marrow or other storage pools into the peripheral circulation, decreased adhesion of leukocytes to the vascular endothelium, reduced migration of leukocytes into peripheral tissues, increased leukocyte survival, or a combination of these mechanisms (4). Because of the primary role of leukocytes in host defense, an increased WBC count is frequently associated with infection. Bacterial infections usually cause mild to moderate leukocytosis, with WBC counts generally ranging from 11,000 to 30,000/µL; however, leukemoid

reactions with WBC counts exceeding 50,000/μL have been reported in some patients with conditions such as Clostridioides difficile infection and tuberculosis (5). Conversely, some infections, including typhoid fever, brucellosis, leishmaniasis, and rickettsial diseases, may be associated with leukopenia. Viral infections typically do not cause neutrophilia, although neutrophilia may occur during the early stages of some viral infections. Infectious lymphocytosis is commonly observed in children with coxsackievirus, echovirus, and adenovirus infections and may occasionally be accompanied by splenomegaly and lymphadenopathy. Pertussis is a notable bacterial infection that may cause lymphocytosis rather than the neutrophilia more commonly associated with bacterial infections (6). Leukocytosis may also occur as an adverse effect of medications. Corticosteroids are among the most common drug-related causes and can increase the WBC count by promoting the release of leukocytes from the bone marrow and reducing their migration into tissues (7). Granulocyte colony-stimulating factor (G-CSF) can directly stimulate leukocyte production and release from the bone marrow (8). Other medications, including antiepileptic drugs such as carbamazepine, some antibiotics, and thyroid medications, have also been associated with increased WBC counts. In addition, some medications may cause neutrophilia as part of an allergic or inflammatory drug reaction (9, 10). A leukemoid reaction is characterized by marked leukocytosis, predominantly involving neutrophils, and may occur in response to severe stress, infection, inflammation, or other underlying conditions. Because leukemoid reactions can mimic hematologic malignancies, distinguishing them from leukemia requires careful evaluation of the patient's medical history, physical findings, peripheral blood findings, and other laboratory or ancillary investigations (11).

A substantial number of leukocytes are stored in the spleen; therefore, splenectomy may result in an increased WBC count in the peripheral circulation (3). Tobacco's use has also been associated with mild leukocytosis, which may improve following smoking cessation (12).

Other causes of leukocytosis include tissue injury and physiological stress associated with surgery or myocardial infarction (13, 14), malignancies such as sarcoma, carcinoma, and leukemia (15, 16), poisoning caused by chemicals or animal venoms (17, 18), metabolic disorders such as diabetic coma, gout, and metabolic syndrome (19-21), and autoimmune diseases such as rheumatoid arthritis (22, 23).

Because the etiology of leukocytosis influences the urgency and direction of diagnostic evaluation and treatment, identifying its underlying causes is clinically important. The causes and clinical implications of leukocytosis may vary according to population characteristics, disease burden, and healthcare settings; therefore, locally derived data may provide clinically relevant information (24). Accordingly, this study aimed to investigate the etiologies of leukocytosis among hospitalized patients at Shohada-ye Ashayer Hospital in Khorramabad, Iran, from 2020 to 2023.

## Materials and Methods

### Study Design and Setting

This retrospective, cross-sectional, descriptive study was conducted at Shohada-ye Ashayer Hospital in Khorramabad, Iran. The study included hospitalized adult patients with leukocytosis who were admitted between 2020 and 2023.

### Study Population and Eligibility Criteria

The study population comprised patients aged 18 years or older who were hospitalized at Shohada-ye Ashayer Hospital between 2020 and 2023 and

had a peripheral blood white blood cell (WBC) count of ≥11,000/μL.

**All eligible patients were included using census sampling.**

Patients with incomplete medical records were excluded. Patients for whom the clinical course was incomplete because of death, discharge, personal consent, or transfer to another treatment unit were also excluded when the available medical records did not allow the underlying cause of leukocytosis to be determined.

**Data Collection**

Data were retrospectively extracted from the patients' medical records using a researcher-designed data collection form. The collected information was categorized into three groups. The first category included baseline characteristics, including age and sex. The second included medical and medication history, including the presence of malignancy, underlying diseases, and corticosteroid use during the 14 days preceding hospital admission. The third category included clinical information at the time of hospitalization, including the presence of fever, the neutrophil percentage reported in the complete blood count (CBC), and the predominant clinical symptom at admission.

The underlying cause of leukocytosis was determined based on the physician's documented clinical diagnosis and the treatment prescribed during hospitalization. When multiple potential causes of leukocytosis were present in an individual patient, the main cause was recorded based on the predominant clinical problem documented in the medical record. Patients were categorized according to the predominant leukocyte subtype as having neutrophilic or lymphocytic leukocytosis based on the differential leukocyte count documented in their medical records.

**Definition and Classification of Leukocytosis**

Leukocytosis was defined as a peripheral blood WBC count of ≥11,000/μL in adults. For the analysis of marked leukocytosis, patients were categorized according to whether their WBC count was >40,000/μL.

Patients with neutrophilic leukocytosis were classified according to the documented underlying cause, including leukemia, acute infection, collagen-vascular disease, corticosteroid use, and leukemoid reaction. Patients with lymphocytic leukocytosis were classified according to the documented underlying cause, including leukemia, viral infection, drug reaction, and autoimmune disease.

**Definition and Classification of Leukocytosis**

Leukocytosis was operationally defined in this study as a peripheral blood white blood cell (WBC) count of ≥11,000/μL in adults (7). Patients were classified according to the predominant leukocyte subtype identified on the complete blood count as having neutrophilic or lymphocytic leukocytosis (7). The underlying etiology was determined based on the clinical diagnosis documented in the medical record and the treatment provided during hospitalization. Neutrophilic leukocytosis was classified according to the documented underlying cause as leukemia, acute infection, collagen-vascular disease, corticosteroid use, or leukemoid reaction. Lymphocytic leukocytosis was classified as leukemia, viral infection, drug reaction, or autoimmune disease.

For the analysis of marked leukocytosis, patients were categorized according to a WBC count of >40,000/μL. Leukemoid reaction was identified based on the documented clinical diagnosis and was distinguished from hematologic malignancy using the available clinical, laboratory, and paraclinical findings (25). When more than one potential cause of leukocytosis was present, the primary cause was determined according to the

predominant clinical diagnosis documented by the treating physicians.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS Statistics version 25. Categorical variables were summarized as frequencies and percentages. The distribution of categorical variables was compared using the chi-square test or Fisher's exact test, as appropriate. A two-sided P value <0.05 was considered statistically significant.

**Results**

A total of 317 hospitalized patients with leukocytosis were included in the study at Shohada-ye Ashayer Hospital in Khorramabad, Iran, between 2020 and 2023, including 161 (50.8%) men and 156 (49.2%) women. Among the study population, 24 (7.6%) had no underlying conditions, 39 (12.3%) had diabetes, 99 (31.2%) had hypertension, 48 (15.1%) had heart failure, 23 (7.3%) had chronic obstructive pulmonary disease (COPD), and 84 (26.5%) had two or more underlying conditions (Table 1). Of the total study population, 72 patients (22.7%) had fever, whereas 245 (77.3%) did not. Regarding the WBC count, 178 patients (56.2%) had a WBC count of ≤40,000/μL, whereas 139 (43.8%) had a WBC count of >40,000/μL (Table 1).

Among the 139 patients with WBC counts >40,000/μL, leukemia was identified in 135 (97.1%), including 63 patients with neutrophilic leukocytosis and 72 with lymphocytic leukocytosis (Table 2).

| | Variable | Numbers | Percentage |
|---|---|---|---|
| Sex | Male | 161 | 50.8% |
| | Female | 156 | 49.2% |
| Underlying comorbidities | None | 24 | 7.6% |
| | Diabetes | 39 | 12.3% |
| | Hypertension | 99 | 31.2% |
| | Heart failure | 48 | 15.1% |
| | COPD | 23 | 7.3% |
| | Have two or more underlying diseases | 84 | 26.5% |
| Fever | Do not have | 245 | 77.3% |
| | Have | 72 | 22.7% |
| Leukocytosis > 40,000 | Do not have | 178 | 56.2% |
| | Have | 139 | 43.8% |

**Table 1. Baseline characteristics, underlying comorbidities, and clinical and laboratory findings of the study population**.

**Neutrophilic leukocytosis**

Neutrophilic leukocytosis was identified in 194 patients (61.2%), whereas lymphocytic leukocytosis was identified in 123 patients (38.8%). Among the study population, the underlying causes of neutrophilic leukocytosis were leukemia in 71 patients (22.4%), acute infection in 63 (19.9%), collagen-vascular diseases in 31 (9.8%), corticosteroid use in 21 (6.6%), and leukemoid reaction in 8 (2.5%) (Figure 1). Among the 194 patients with neutrophilic leukocytosis, 66 had a WBC count of >40,000/µL, including 63 patients with leukemia and 3 patients with leukemoid reaction.

| Etiology | Neutrophilic leukocytosis, n (%) | Lymphocytic leukocytosis, n (%) | Total, n (%) |
|---|---|---|---|
| **Leukemia** | 63 (45.3) | 72 (51.8) | 135 (97.1) |
| **Leukemoid reaction** | 3 (2.2) | 0 (0.0) | 3 (2.2) |
| **Viral infection** | 0 (0.0) | 1 (0.7) | 1 (0.7) |
| **Total** | **66 (47.5)** | **73 (52.5)** | **139 (100)** |

**Table 2. Etiologic distribution of patients with WBC counts >40,000/µL. Values are presented as n (%).** Percentages in the total column are calculated using the total number of patients with WBC counts >40,000/µL (n=139) as the denominator.

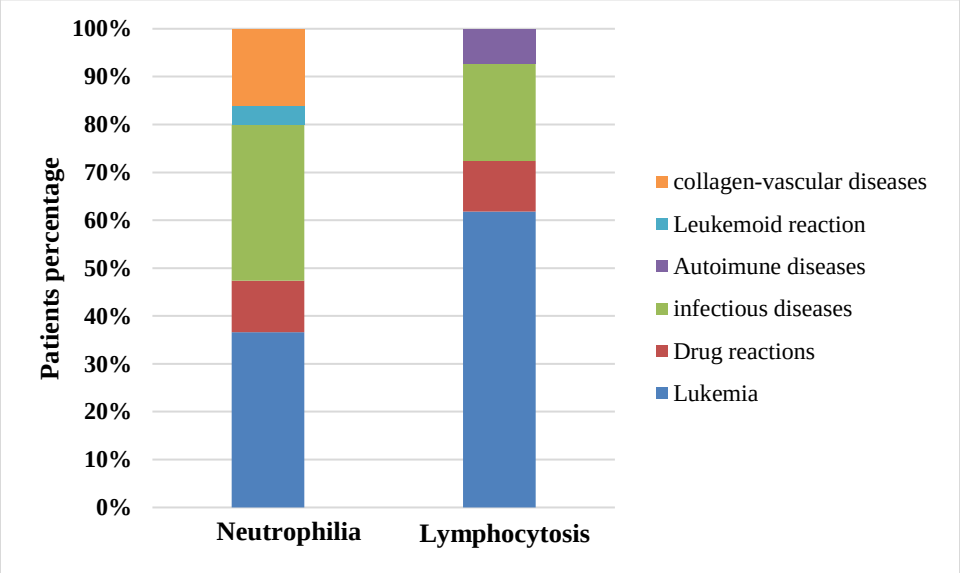



**Figure** 1. **Etiologies of leukocytosis according to the predominant leukocyte subtype.** Patients were grouped according to neutrophilic or lymphocytic leukocytosis, and percentages represent the distribution of identified etiologies within each subgroup.

**Lymphocytic leukocytosis**

Among the study population, the underlying causes of lymphocytic leukocytosis were leukemia in 76 patients (24.0%), viral infections in 25 (7.9%), drug reactions in 13 (4.1%), and autoimmune diseases in 9 (2.8%) (Figure 1). Among the 123 patients with lymphocytic leukocytosis, 73 had a WBC count of >40,000/μL, including 72 patients with leukemia and 1 patient with a viral infection.

**Discussion**

In this retrospective study of 317 hospitalized adults with leukocytosis, neutrophilic leukocytosis was more common than lymphocytic leukocytosis. Notably, 139 patients had a WBC count of >40,000/μL, of whom 135 (97.1%) had leukemia. Among patients with neutrophilic leukocytosis, leukemia was also the most frequently identified underlying cause, followed by acute infection, collagen-vascular diseases, corticosteroid use, and leukemoid reaction. These findings suggest that marked leukocytosis, particularly when the WBC count exceeds 40,000/μL, warrants careful evaluation for an underlying hematologic malignancy while other infectious, inflammatory, and drug-related causes should also be considered.

In the present study, 139 patients (43.8%) had a WBC count of >40,000/μL. Leukemia accounted for 135 of these cases, including 63 patients with neutrophilic leukocytosis and 72 with lymphocytic leukocytosis, whereas leukemoid reaction accounted for 3 cases and viral infection for 1 case. Thus, leukemia was the predominant diagnosis among patients with WBC counts >40,000/μL in this cohort. This finding is broadly consistent with a previous study conducted at a hospital in New York City, which reported that infectious diseases accounted for more than 60% of cases among patients with WBC counts below 50,000/μL, whereas malignancies accounted for more than 70% of cases among those with WBC counts above 50,000/μL (1).

Among hospitalized patients with an infectious etiology of leukocytosis, WBC counts were ≤40,000/μL except for one patient with a viral infection whose WBC count exceeded this threshold. In this cohort, infectious causes were therefore predominantly observed among patients with WBC counts ≤40,000/μL. This finding is clinically relevant because leukocytosis in this range may occur in a variety of infectious and inflammatory conditions, and its interpretation should be guided by the patient's clinical presentation and other available laboratory and diagnostic findings (26).

Tahir et al. reported that primary neutrophilia may occur in association with myeloproliferative neoplasms, whereas infection and inflammation are major causes of secondary neutrophilia. Bacterial infections may be associated with a left shift, toxic granulation, and Döhle bodies on peripheral blood smear, whereas other infectious conditions may produce different patterns of leukocyte abnormalities (27). In our cohort, acute infection was the second most common identified cause of neutrophilic leukocytosis after leukemia. This finding is consistent with the etiologic pattern reported by Viner et al. (1).

Szuber et al. described chronic neutrophilic leukemia (CNL) as a rare myeloproliferative neoplasm characterized by persistent neutrophilic leukocytosis and granulocytic proliferation, whereas atypical chronic myeloid leukemia is characterized by dysplastic neutrophilia and circulating immature myeloid cells (28).

Leukemoid reactions represent a reactive form of marked leukocytosis that may mimic leukemia and are commonly associated with severe

infection, inflammation, malignancy, or certain medications (27). Conventionally, a WBC count >50,000/μL with neutrophilic predominance is often used to describe a leukemoid reaction, although the diagnosis requires consideration of the underlying clinical context and exclusion of hematologic malignancy (24). In our study, leukemoid reaction was identified in 8 patients (4.1% of those with neutrophilic leukocytosis), making it less frequent than leukemia, acute infection, collagen-vascular diseases, and corticosteroid use in this subgroup. Portich et al. investigated hospitalized adults with WBC counts >50,000/μL in a Brazilian hospital between 2016 and 2018 and reported leukemoid reactions in 40% of patients, with infections and non-hematologic malignancies being the most common associated conditions (29). In our study, leukemoid reaction was identified in 8 of 194 patients with neutrophilic leukocytosis (4.1%). The markedly lower proportion observed in our cohort may reflect differences in study population, inclusion criteria, and the WBC threshold used to define the study populations. In the present study, 135 of the 139 patients (97.1%) with WBC counts >40,000/μL had leukemia. Previous studies have reported that marked leukocytosis occurs in approximately 20% of patients with acute myeloid leukemia (AML) and in 10%–30% of those with acute lymphoblastic leukemia (ALL) (12). Mank et al. reported that, in children, a WBC count >50,000/μL was associated with a substantially higher likelihood of leukemia (24). Corticosteroid use was identified as an underlying cause of neutrophilic leukocytosis in 21 patients (10.8% of the neutrophilic subgroup) in our study. This finding is consistent with the recognized association between corticosteroid exposure and neutrophilia (12). In contrast, drug reactions were identified in 13 patients with lymphocytic leukocytosis (10.6% of the lymphocytic subgroup), consistent with previous reports linking drug hypersensitivity reactions to lymphocytic and eosinophilic responses. Collagen-vascular diseases were identified as the underlying cause of neutrophilic leukocytosis in 31 of 194 patients (16.0%) in our cohort. All 31 patients had a WBC count of ≤40,000/μL. This finding is consistent with the recognized association between chronic inflammatory conditions and neutrophilia (30).

## Limitations

This study had several limitations. First, its retrospective design depended on the completeness and accuracy of information documented in patients' medical records. In addition, some clinical and laboratory details were unavailable, which may have limited the completeness of etiologic classification. Second, the study was conducted at a single hospital, which may limit the generalizability of the findings to other healthcare settings and patient populations.

## Conclusion

In this cohort of hospitalized adults with leukocytosis, a WBC count of >40,000/μL was frequently associated with leukemia, with leukemia identified in 135 of 139 patients (97.1%) above this threshold. Nevertheless, marked leukocytosis should not be considered diagnostic of malignancy on its own, and differentiation between hematologic malignancy, leukemoid reaction, and other causes requires integration of the patient's clinical history, physical examination, and laboratory and other diagnostic findings. At lower WBC counts, infectious, inflammatory, and drug-related causes

should also be considered according to the clinical context.

**Implications for Patient Care**

Leukocytosis is a common clinical finding with a broad range of potential etiologies. In this cohort of hospitalized adults, WBC counts of >40,000/μL were predominantly associated with leukemia, although leukemoid reaction and viral infection were also identified. Therefore, marked leukocytosis should prompt careful clinical assessment for potential hematologic malignancy while considering reactive causes. At WBC counts of ≤40,000/μL, infectious, inflammatory, and drug-related causes remained important considerations. Interpretation of the WBC count should be integrated with the patient's clinical history, physical examination, differential leukocyte count, and other relevant laboratory and diagnostic findings rather than being used as an isolated diagnostic criterion.

**Conflict of Interest**

The authors declared no conflicts of interests.

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**Ethics Statement**

This study was approved by the Ethics Committee of Lorestan University of Medical Sciences, Khorramabad, Iran (Ethics Approval Code: IR.LUMS.REC.1404.020). All procedures were conducted in accordance with applicable ethical principles. The authors also confirm that publication ethics were observed, including the avoidance of plagiarism, data fabrication, and duplicate publication.

**Data Availability Statement**

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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**Author Contributions**

All authors contributed to the study including design, literature search, data interpretation, drafting of the manuscript, and critical revision of the article. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

**Artificial Intelligence (AI) Disclosure**

Artificial intelligence (AI) was used solely for language editing and improving the clarity and readability of the manuscript. The authors reviewed and approved the final text and take full responsibility for the accuracy and integrity of the manuscript.

**Publisher's Note**

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