Joint Diseases and Related Surgery

Jt Dis Relat Surg
2025;36(2):366-372

ORIGINAL ARTICLE

The role of high large unstained cell percentages in ongoing inflammation in the intercritical gout

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Gout is the most prevalent form of inflammatory arthritis worldwide, with a global prevalence that has been steadily increasing. Epidemiological studies have demonstrated that the prevalence of gout is 0.31% in an urban area of Türkiye and varies between 1 and 4% worldwide.[1,2] In 2020, approximately 55.8 million individuals worldwide were affected by gout.[3] The prevalence of gout is higher in males than females, and increases with age. Gout is not solely a joint disease; it is a systemic disease with significant clinical implications. It is strongly associated with comorbidities such as hypertension, diabetes, metabolic syndrome

Received: February 01, 2025
Accepted: March 12, 2025
Published online: April 05, 2025

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Doi: 10.52312/jdrs.2025.2188

Citation: Koçak Ulucaköy R, Kayacan Erdoğan E, Orhan K, Gürler EK, Atalar E, Özdemir Ulusoy B, et al. The role of high large unstained cell percentages in ongoing inflammation in the intercritical gout. Jt Dis Relat Surg 2025;36(2):366-372. doi: 10.52312/jdrs.2025.2188.

ABSTRACT

Objectives: This study aims to investigate whether large unstained cells (LUCs) is a marker of inflammation in gout patients and whether it is associated with different clinical conditions such as erosion, tophus, intercritical period, and gout flare.

Patients and methods: Between November 2022 and May 2023, a total of 100 consecutive adult gout patients (81 males, 19 females; mean age 53.8±12.8 years; range, 21 to 79 years) and 30 healthy controls (24 males, 6 females; mean age 57.2±10.6 years; range, 28 to 75) were included in this cross-sectional study. Data including demographics, clinical characteristics, laboratory results and direct radiography images of affected joints at the most recent visit were recorded.

Results: Leukocyte counts were found to be significantly higher in gout patients (p=0.048). The LUC counts and percentages and levels of acute phase reactants were similar between the patient and control groups (p=0.401, p=0.668, p=0.222, and p=0.505, respectively). In subgroup analyses of the gout patients, there were no significant differences in LUC counts and percentages between those with tophaceous disease (p=0.650 and p=0.388, respectively), erosions (p=0.154 and p=0.137, respectively) and elevated serum uric acid levels (p=0.918 and p=0.196, respectively). However, LUC percentages were statistically significantly higher in patients without elevated C-reactive protein (CRP) and in the intercritical gout (p=0.039 and p=0.05, respectively).

Conclusion: Our study results showed similar LUC counts and percentages between the gout patients and healthy controls. However, in the subgroup analysis of the gout patients, the LUC percentages were observed to be significantly higher in those without high CRP levels and in patients with intercritical gout. This finding may suggest that subclinical inflammation persists in intercritical gout.

Keywords: Gout, hematological tests, inflammation.

and cardiovascular disease, which contribute to increased all-cause mortality.[4] Gout has been also shown to impose a substantial burden on healthcare systems across the globe. The disease is associated with significant disability, measured by Years Lived with Disability (YLDs). Elevated body mass index (BMI) and kidney dysfunction have been identified as major contributors to this burden.[3] The economic burden is also notable, driven by hospitalizations, outpatient visits, and the management of comorbidities such as cardiovascular disease and chronic kidney disease.[4]

In the majority of cases, the onset of typical attacks is acute, manifesting in the big toe and lower extremity joints.[5] Even in the absence of treatment, an acute gout attack typically resolves within seven to 14 days. Following the attack, there is an asymptomatic period (intercritical gout) until another gout attack occurs. In some cases, individuals with long-term hyperuricemia may develop tophi, chronic gouty arthritis and structural joint damage.[6] Hyperuricemia is a necessary, but not sufficient condition for the development of a gout attack. The deposition of uric acid crystals in the periarticular and synovial tissues results in the migration and release of proinflammatory cytokines, particularly interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), and IL-6, by macrophages and neutrophils.[7] The pathology of gout is primarily driven by innate immune cell responses, in which inflammasomes play a pivotal role.[8] Neutrophils and monocytes/macrophages are the principal cells responsible for the inflammatory process observed in gout.[9,10] Previous studies have demonstrated that the number of monocytes is significantly elevated during an attack in comparison to the intercritical phase.[11] The role of lymphocytes in the pathogenesis of gout remains poorly understood. It has been demonstrated that uric acid and monosodium urate (MSU) crystals exert stimulatory effects on T cells. Furthermore, the presence of infiltrated T cells was observed in the tissues of gout patients.[12,13]

During an acute attack, both local and systemic inflammation are observed. The presence of elevated C-reactive protein (CRP), leukocytosis and thrombocytosis indicates the presence of systemic inflammation. In addition, lysosomal enzymes released from neutrophils migrating to the site of inflammation cause an increase in reactive oxygen radicals. Reactive oxygen radicals and cytokines cause young and immature blood cells to migrate from the bone marrow to the periphery. A routine hematology analyzer can be used to measure the large unstained cells (LUCs) in addition to the white blood cell (WBC) population. However, the main problem with these cells to date has been their lack of specificity. Large unstained cells may include blast cells, atypical lymphocytes, monocytes, plasma cells, and peroxidase-negative cells. Monocytes and lymphocytes can increase in size during immune activation and can be identified as LUC. Large unstained cells can theoretically be elevated in inflammatory conditions in addition to leukemic blasts.[14,15] It can be hypothesized that LUC may be elevated in gout, in which neutrophils and monocytes play a pivotal role.

In certain hematology analyzers, the percentage and count of LUC is a parameter that is automatically assessed as part of the differential count, making it easy to use. To the best of our knowledge, there is no study examining the clinical use of LUC in gout patients. In the present study, we aimed to investigate whether LUC was a marker of inflammation in gout patients and whether it was associated with different clinical conditions such as erosion, tophus, intercritical period, and gout flare.

PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at Ankara Bilkent City Hospital Rheumatology Clinic between November 2022 and May 2023. A total of 100 consecutive adult gout patients (81 males, 19 females; mean age 53.8±12.8 years; range, 21 to 79 years) and 30 healthy controls (24 males, 6 females; mean age 57.2±10.6 years; range, 28 to 75) were included. Gout patients met the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Gout Classification Criteria.[16] Exclusion criteria were as follows: acute infection, other concomitant inflammatory rheumatic diseases to evaluate the effect of gout alone on LUC, history of malignancy, pregnancy and breastfeeding. The control group consisted of age-, sex-, and BMI-matched individuals. Exclusion criteria of the control group were any inflammatory rheumatic disease, history of malignancy, active infection, pregnancy and breastfeeding. A written informed consent was obtained from each participant. The study protocol was approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee (date: 05.10.2022, no: E1/2931/2022). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data including demographics, clinical characteristics, laboratory results and direct radiography images of affected joints at the most recent visit were recorded. Two rheumatologists evaluated the direct radiography images, as described by Dalbeth et al.[17] In case of disagreement, a third rheumatologist was consulted to reach consensus and the final decision was made.

Venous blood samples were taken at patients the final routine visit. As part of the standard laboratory procedure, the following parameters were analyzed: WBC, platelet (PLT) count, hemoglobin (Hb), serum uric acid (SUA), serum creatinine, glomerular filtration rate (GFR), alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR) and CRP. Additionally, the LUC counts and percentages were recorded. The LUC counts and percentages were derived from the direct complete blood count analysis results. In hematology analyzers, the count of LUC is automatically calculated based on the size and staining of the cells. The LUC percentage is obtained by dividing the LUC number by the total WBC. The reference range for LUC count is 0-0.4 ($\times 10^9$/L), and for LUC percentage is 0 to 4%. The hematological tests were performed by the Siemens Advia 2120i (Siemens Healthineers, Erlangen, Germany) hematology analyzer. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. The CRP was quantified by means of a nephelometric method utilizing a Beckman Coulter instrument (IMMAGE Immunochemistry Systems, Ireland), while the ESR was determined by the Westergren method (Berkhum SDM-100, Türkiye). Serum creatinine levels were quantified by the modified Jaffe method, while SUA levels were determined by the uricase method, both of which were conducted on the Atellica CH Solutions autoanalyzer (Siemens Healthineers, Erlangen, Germany).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The conformity of the numerical data to normal distribution was assessed by both visual and analytical (Shapiro-Wilk test) methods. Continuous data were presented in

TABLE I
Demographic and clinical data of patients and healthy controls

	Gout patients (n=100)					Healthy controls (n=30)					
Characteristics	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)			53.8±12.8					57.2±10.6			0.996
Sex											
Male	81	81				24	80				0.903
BMI (kg/m^2)				28.7	5				27.3	3.9	0.588
Smoking status (ever)	67	67				16	53				0.353
Patients with ≥1 comorbidities	69	69				21	70				0.917
Comorbidities											
Hypertension	47	47				10	33				0.186
Diabetes mellitus	21	21				6	20				0.906
Hyperlipidemia	9	9				5	16.7				0.243
Cardiovascular diseases	20	20				4	13.3				0.592
Chronic kidney disease	26	26				0	0				**0.001**
Urolithiasis	11	11				1	3.3				0.294
Disease duration (month)			56.1±53.8								
Symptom duration (month)			59.3±52.7								
Gout flares (year)			2.1±2								
Patients with a flare at the time of evaluation	38	38									
Presence of erosion on radiography	19	19									
Presence of tophus	20	20									

SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; NSAIDs: Non-steroidal anti-inflammatory drugs.

mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical data were presented in number and frequency. The Mann-Whitney U test was employed for data that were not normally distributed. Categorical data were analyzed using the chi-square test to make comparisons between the groups. A *p* value of <0.05 was considered statistically significant.

RESULTS

The clinical and demographic data of the study population are presented in Table I. There was no significant difference between the patients and the control group in terms of age, sex, BMI, and smoking habits. The rate of participants with at least one comorbid disease was similar (69% *vs.* 70%, p=0.917), while chronic kidney disease was significantly more common in gout patients (26% *vs.* 0%, p=0.001) (Table I).

The WBC, ALT, GFR, SUA and serum creatinine values were found to be significantly different between the patient and control groups (p=0.048, p=0.032, p=0.002, p=0.001, and p=0.001, respectively). The counts and percentages of LUC and the level of acute phase reactants were found to be comparable between the two groups (p=0.401, p=0.668, p=0.222, and p=0.505, respectively) (Table II).

In subgroup analyses of the gout patients, there were no significant differences in LUC counts and percentages between those with tophaceous disease (p=0.650 and p=0.388, respectively), erosions (p=0.154 and p=0.137, respectively) and elevated SUA levels (p=0.918 and p=0.196, respectively). However, LUC percentages were statistically significantly higher in patients without elevated CRP and in the intercritical gout (p=0.039 and p=0.05, respectively) (Table III).

DISCUSSION

Gout is a chronic disease characterized by acute attacks. The intercritical phase begins after the attack of gout patients. During this period, patients are asymptomatic, but subclinical inflammation persists. In the present study, we investigated whether LUC was a marker of inflammation in gout patients and whether it was associated with different clinical conditions. Our study results showed that the counts and percentages of LUC were comparable between gout and control groups,

TABLE II
Hematological and biochemical parameters of patients and healthy controls

	Gout patients (n=100)		Healthy controls (n=30)		
Characteristics	Median	Min-Max	Median	Min-Max	*p*
WBC (×10⁹/L)	7.9	3.7-12.7	6.3	4.6-10.2	**0.048**
Neutrophil (×10⁹/L)	4.4	0.7-10.8	3.6	1.6-6.6	0.189
Neutrophil (%)	57	15-78	58	34-69	0.871
Lymphocyte (×10⁹/L)	2.2	1.1-4.9	2.1	1.3-2.7	0.410
Lymphocyte (%)	31.2	13.3-52.4	30.2	23.1-42	0.810
NLR	1.8	0.3-5.9	1.8	0.7-2.9	0.932
LUC count (×10⁹/L)	0.14	0.05-0.54	0.13	0.06-0.3	0.401
LUC (%)	1.8	0.9-5.6	2	1.1-3.7	0.668
Hemoglobin (g/dL)	14.6	8.9-18.9	13.8	10.9-16.7	0.949
Platelet (×10⁹/L)	242	102-467	235	161-332	0.862
ALT (IU/L)	35	11-141	26	13-50	**0.032**
Serum creatinine (mg/dL)	0.9	0.6-2.1	0.8	0.5-1.1	**0.001**
GFR (mL/min/1.73 m²)	83	33-128	89	65-127	**0.002**
SUA (mg/dL)	6.6	3.2-12.9	5.5	3.2-7.6	**0.001**
CRP (mg/L)	2	0-71	2	0-7	0.222
ESR (mm/h)	8	3-57	12	3-55	0.505

WBC: White blood cell; NLR: Neutrophil-lymphocyte ratio; LUC: Large unstained cells; ALT: Alanine aminotransferase; GFR: Glomerular filtration rate; SUA: Serum uric acid; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

TABLE III
Comparison of LUC count and percentages in gout subgroups

	LUC count (×10⁹/L)			LUC %		
All gout patients (n=100)	Median	IQR	*p*	Median	IQR	*p*
With erosions (n=19)	0.150	0.06	0.154	2.1	0.7	0.137
Without erosions (n=81)	0.140	0.07		1.7	0.7	
With tophi (n=20)	0.140	0.06	0.650	1.85	0.9	0.388
Without tophi (n=80)	0.140	0.07		1.80	0.7	
With a flare (n=38)	0.140	0.07	0.875	1.6	0.6	**0.050**
Intercritical gout (n=62)	0.140	0.08		1.95	0.9	
With elevated CRP (>5 mg/L, n=37)	0.140	0.06	0.318	1.60	0.8	**0.039**
Without elevated CRP (≤5 mg/L, n=63)	0.140	0.07		1.80	0.9	
With elevated SUA (≥6 mg/dL, n=74)	0.140	0.08	0.918	1.70	0.7	0.196
Without elevated SUA (<6 mg/dL, n=26)	0.140	0.07		1.85	1.0	

LUC: Large unstained cells; IQR: Interquartile range; CRP: C-reactive protein; SUA: Serum uric acid.

but in subgroup analysis of gout patients, LUC percentages were significantly higher in those without elevated CRP and intercritical gout. In inflammatory conditions where lymphocytes or monocytes are activated, they may increase in size and result as LUC on automated hematology analyzers.[14,15] In gout disease, in which neutrophils and monocytes are known to play a pivotal role, the observation of a high percentage of LUC in the intercritical period may be indicative of the persistence of subclinical inflammation during this phase.

An increased number of LUCs in a whole blood analysis has been found to be correlated with an immunological activation.[18,19] Vanker et al.[20] suggested that LUC served as a valuable marker of both innate immunity and CD8+ lymphocyte activation. Previously, LUC have only been analyzed in a limited number of studies related to leukemia, myelodysplastic syndromes and viral infection, carotid artery occlusion, and antineutrophil cytoplasmic antibody-associated vasculitis.[14,21,22] Although LUC is an indicator of organism activation in response to various factors, to the best of our knowledge, this is the first study to date to demonstrate a relationship between LUC and gout.

Hyperuricemia is known to have a proinflammatory effect by directly stimulating monocytes and also by facilitating their transformation to macrophages and recruiting them from the circulation into the tissue.[8] Upon activation, monocytes may exhibit an increase in size, which can be quantified as LUC on automated hematology analyzers. A subgroup analysis of patients with gout revealed that LUC percentages were significantly lower in patients with elevated CRP and during an attack. During an attack, there is a marked increase in the leucocyte series, particularly neutrophils. This may explain the proportional decrease in LUC percentages. However, the return of neutrophils and monocytes to the normal range during the intercritical phase may have resulted in a relatively high percentage of LUC in the total blood count. Given that LUC is typically elevated in immunoactivation states, this result may indicate that subclinical inflammation continues in the intercritical period.

Previous studies in patients with gout showed that neutrophil and monocyte counts were higher in patients with gout compared to the control group and during the attack period compared to the intercritical phase. In contrast, lymphocyte counts were significantly lower.[11,23] In our study, no significant differences were observed in lymphocyte counts between gout patients and the control group. However, it should be noted that lymphocyte counts were unable to be compared between the attack and intercritical phases. A subgroup analysis of gout patients revealed that LUC percentages were significantly lower in patients with elevated CRP and during an attack. Considering that activated lymphocytes and monocytes can be defined as LUC in hematological analyzers, the mobilization of activated lymphocytes from peripheral blood to the tissue may have also been effective in the low detection of LUC percentage during the attack.

The NLR is a clinically significant biomarker of systemic inflammation, where elevated levels indicate neutrophilic dominance and lymphocyte depletion, often observed in infections, autoimmune disorders, and chronic inflammatory diseases.[24] It is a more reliable indicator of inflammation than the neutrophil count alone.[25] Previous studies have found NLR to be a strong independent predictive marker for gout attack.[11,23] In the literature, NLR has also been evaluated in various diseases other than gout.[26] In our study, the WBC count was found to be significantly higher in gout patients compared to the control group. However, the NLR was not found to be significantly different. This may be due to the fact that the majority of gout patients were not experiencing an attack at the time of the study.

The cytokine storm observed in severe novel coronavirus disease 2019 (COVID-19) cases is due to hyperactivation of neutrophils and monocytes/macrophages. Low lymphocyte counts, high leukocyte counts, high NLR values and a decrease in the percentage of LUC were observed in the cytokine storm.[27] In our study, similar findings were observed in gout, in which neutrophils and macrophages play an active role, with LUC percentages found to be significantly lower during an attack and at elevated CRP levels.

Nonetheless, there are certain limitations to this study. First, LUC can be influenced by numerous external factors, as well as activated lymphocytes, monocytes, and lymphoblasts. An increase in LUC has been observed in viral, bacterial infections or other inflammatory conditions.[14,21,22] The relationship between LUC and rheumatic drugs used by patients has not been evaluated previously, but steroids may indirectly cause changes in LUC by reducing the number of monocytes and lymphocytes. Second, LUC lacks a clearly defined set of specific features. The reliability of LUC can be enhanced by defining more precise characteristics. This would facilitate more accurate assessments of LUC. Additionally, automated hematology analyzers vary in their sensitivities and thresholds for reporting LUCs, limiting standardization. Finally, a statistical p value of <0.05 was employed. To achieve a more precise conclusion, it would have been preferable to reduce the p value and to employ a larger sample size. All these factors may impact the ability of the LUC percentage to serve as a determining factor of ongoing inflammation in gout patients.

Large unstained cells may reflect immune system activation, given that they can include activated lymphocytes or other inflammatory cells. Increased immune activity often precedes clinical flares. Large unstained cells alone are not definitive predictors of flares, but may serve as a supplementary marker when combined with clinical symptoms, other laboratory results (e.g., acute phase reactants), and imaging. Serial monitoring of LUC trends, rather than single measurements, might better indicate impending flares. In the future, larger and prospective studies are required to determine whether LUC can serve as a predictor of immune system activation and attacks. Once this is established, LUC can be used to identify treatment targets. Subsequently, research should be conducted to investigate the relationship between LUC and other inflammation markers (e.g., cytokines) and the role of LUC in treatment monitoring.

In conclusion, the LUC counts and percentages were found to be similar between the gout and control groups. However, in the subgroup analysis of the gout patients, the LUC percentages were observed to be significantly higher in those without high CRP levels and in patients with intercritical gout. This may suggest that subclinical inflammation persists in intercritical gout. Further multi-center, large-scale studies are warranted to validate LUC as a marker of subclinical inflammation in gout and to establish standard thresholds.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Were responsible for data acquisition: R.K.U., E.K.E., K.O., E.K.G., E.A., B.Ö.U., H.B., B.A., İ.D., S.C.G.; Analysed the data: S.C.G.; Wrote the manuscript: R.K.U., E.K.E., K.O. All authors critically revised the manuscript and approved the final version. Data are available upon reasonable request. All authors were responsible for the study design.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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