Journal of Inflammation Research

Dovepress
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REVIEW

Advancing Gouty Arthritis Research: The Clinical Value of Complete Blood Cell Count Ratios and Immune-Inflammatory Interactions

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Abstract: Gouty arthritis (GA) is an inflammatory condition resulting from the accumulation of monosodium urate (MSU) crystals in joints and adjacent tissues, with its pathogenesis characterized by a complex immune-inflammatory response. The complete blood cell count ratios (CBCRs), which include the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII), and systemic inflammatory response index (SIRI), serve as composite indicators of inflammation. These ratios integrate hematopoietic cell subsets that reflect interactions between innate and adaptive immunity, thereby providing a more comprehensive assessment of the intricate immune-inflammatory network in GA. Additionally, they offer practical benefits due to their accessibility in routine clinical settings. This narrative review consolidates the current research on CBCRs in the context of GA, offering an overview of their clinical significance and potential molecular pathological mechanisms. The aim is to provide new insights and evidence-based references for both clinical practice and translational research.

Keywords: gouty arthritis, biomarkers, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, immune-inflammatory response

Introduction

Gouty arthritis (GA) is a prevalent autoinflammatory disorder resulting from the accumulation of monosodium urate (MSU) crystals within joints and adjacent tissues.[1] According to the Global Burden of Disease study, gout affected approximately 58.8 million individuals globally in 2020, with an age-standardized prevalence of 659.3 per 100,000 population, marking a 22.5% increase in age-standardized prevalence worldwide since 1990. This condition significantly diminishes the quality of life for those affected and imposes substantial economic and social burdens.[2] The primary clinical manifestations of gout encompass acute arthritis, chronic arthritis, tophi, and joint deformities.[3] The clinical progression of gout can be delineated into four stages: (1) asymptomatic hyperuricemia without MSU crystal deposition or gout symptoms, (2) asymptomatic MSU crystal deposition, (3) acute gout flares, and (4) chronic gouty arthritis.[1] Hyperuricemia (HUA), defined as a serum urate concentration exceeding 420 μmol/L (7 mg/dL), is the principal pathogenic factor in the development of GA. When urate levels surpass the physiological solubility threshold, MSU crystals are likely to form. These crystals can deposit in joints, initiating inflammatory responses, and may also accumulate in organs such as the kidneys, resulting in functional impairment.[4] Furthermore, individuals with GA are susceptible to comorbid renal impairment and cardiovascular events.[5–7] Currently, the primary therapeutic strategies for managing GA include urate-lowering drugs, colchicine, and nonsteroidal anti-inflammatory drugs (NSAIDs).[8] However, due to low adherence to urate-lowering therapy, a significant proportion of patients remain at an elevated risk of experiencing recurrent gout attacks.

Received: 29 July 2025
Accepted: 16 November 2025
Published: 26 November 2025

Inflammatory responses remain active throughout the progression of GA, with monocytes/macrophages, neutrophils, and lymphocytes playing crucial roles. The acute manifestations of gout are precipitated by inflammatory reactions to MSU crystals, predominantly mediated by macrophages and neutrophils, underscoring the significant role of innate immunity in the pathogenesis of gout.[9] MSU crystals, as damage-associated molecular patterns (DAMPs), activate the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome signaling pathway,[10] thereby facilitating the production and release of IL-1β and other cytokines, which trigger an inflammatory cascade. During intercritical periods, patients may be asymptomatic; however, low-grade chronic inflammation persists.[11,12] This ongoing inflammatory state may contribute to progressive joint damage and bone erosion, eventually leading to chronic gout characterized by tophi, chronic gouty synovitis, and structural joint destruction. Moreover, the inflammatory response in GA is closely linked to several comorbidities, including chronic kidney disease, obesity, and cardiovascular diseases.[13–15] These comorbidities exacerbate inflammation and adversely affect overall patient health.

Evaluating inflammatory levels in patients with GA offers essential insights into the severity of the disease and the effectiveness of therapeutic interventions, thereby providing valuable guidance for clinical management. Nevertheless, traditional systemic inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), lack specificity for this disease. Although serum inflammatory cytokines, including IL-1β, IL-6, and TNF-α, have mechanistic significance, their clinical application is constrained by high costs, resulting in infrequent use in routine clinical practice. Therefore, there is a pressing need to identify novel inflammatory biomarkers that are both clinically accessible and pathologically specific.

Complete blood cell count ratios (CBCRs) encompass a series of innovative, nonspecific inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI). These emerging biomarkers are indicative of systemic inflammation and are characterized by their clinical accessibility and cost-effectiveness. Recent research has highlighted their utility in assessing disease activity and prognosis in various rheumatic conditions, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[16–19] Although previous reviews have summarized the significance of the NLR in GA,[20] the immune-inflammatory response in GA involves complex interactions among multiple immune cell types. Consequently, relying solely on a single parameter like the NLR may not adequately capture the roles of monocytes and platelets in GA-related inflammation. This narrative review, therefore, broadens the focus to include CBCRs, aiming to provide a more comprehensive evaluation of the inflammatory status, disease activity, and risk of complications in GA. Moreover, we examine and interpret CBCRs findings within the framework of GA's molecular immunopathological mechanisms, including NETosis, macrophage polarization, and Th17/Treg imbalance. This review also critically evaluates the clinical limitations associated with the non-specificity of CBCRs, explores potential strategies to improve their clinical applicability, and seeks to offer insights for future research endeavors.

GA Pathophysiologic Mechanisms

The pathogenesis and progression of GA are characterized by an immunoinflammatory cascade involving multiple cell types. During the acute phases, innate immune cells play a predominant role, with monocyte-macrophages initiating inflammation primarily via the classical TLR/NF-κB-NLRP3-IL-1β axis. This is followed by extensive neutrophil infiltration and NETosis, which contribute to tissue damage and pain.[21] In the chronic stages, an imbalance between Th17 and Treg lymphocytes drives disease progression, while coordinated interactions among macrophages, neutrophils, and monocytes collectively facilitate tophus formation and bone erosion.[22] Additionally, platelets, functioning as extensions of the immune system,[23] exacerbate vascular endothelial injury through activation-induced remodeling of the proinflammatory microenvironment, thereby mediating cardiovascular complications. These interconnected mechanisms synergistically drive the pathological transition of GA from acute flares to chronic progression.

Monocytes and Macrophages

During episodes of acute gout, monocyte-macrophages play a crucial role in initiating inflammatory responses via NLRP3 inflammasome pathway, which is recognized as the central mechanism in this process.[10] The deposition of MSU crystals in joints or periarticular tissues initially activates tissue-resident macrophages, leading to the release of the chemokines CCL2

and CXCL8.[24] These chemokines facilitate the recruitment of circulating monocytes to the sites of inflammation. Upon infiltration, these monocytes differentiate into macrophages that recognize MSU crystals through TLR2/4-MyD88-dependent NF-κB activation, resulting in the upregulation of pro-IL-1β, NLRP3, and other proinflammatory cytokines such as TNF-α and IL-6. The subsequent phagocytosis of MSU crystals causes lysosomal damage, characterized by the release of cathepsin B, potassium efflux, and the generation of reactive oxygen species (ROS), which collectively activate the NLRP3 inflammasome. This activation leads to the cleavage of pro-IL-1β by caspase-1, producing mature IL-1β, which is secreted in abundance.[10] Alongside other mediators such as TNF-α and IL-6, this process promotes extensive neutrophil infiltration, thereby establishing the hallmark acute inflammatory response. Throughout this process, macrophages undergo classical M1 polarization.[25] Simultaneously, circulating IL-1β enhances bone marrow hematopoiesis,[26] while CCL2 facilitates monocyte mobilization into peripheral blood, significantly increasing monocyte counts. As inflammation advances, the microenvironmental presence of IL-4 and IL-10 induces macrophage polarization towards M2 phenotypes.[27] These M2 macrophages contribute to the resolution of inflammation through the secretion of TGF-β and IL-10, as well as the clearance of neutrophil extracellular traps (NETs),[28] ultimately leading to the spontaneous termination of inflammation.[25] IL-1β, as a key mediator, is therapeutically targeted by anakinra (recombinant IL-1 receptor antagonist), which has demonstrated rapid anti-inflammatory effects within five days in clinical trials for acute gouty arthritis.[29]

In chronic phases, persistent MSU crystals sustain macrophage activation, where continuous secretion of IL-1β and TNF-α not only stimulates fibroblast proliferation and collagen deposition to form tophaceous structures but also promotes RANKL-mediated osteoclastogenesis by suppressing osteoprotegerin (OPG), resulting in progressive bone erosion.[11,22] This chronic inflammation, fundamentally driven by sustained macrophage activation, constitutes the pathological basis of advanced gouty arthritis.[30]

Neutrophils

Neutrophils and NETs play a dynamic role in modulating the intensity of inflammation through both pro-inflammatory and anti-inflammatory pathways during the acute phases of gout. In contrast, during the chronic stages, they contribute to fibrosis and bone destruction.[21] In the context of acute flares, neutrophils act as primary effector cells. MSU crystals activate macrophages to secrete IL-1β and IL-8, leading to significant neutrophil infiltration into the joint cavities.[31] Neutrophils recognize MSU crystals through pattern recognition receptors, initiating a burst of ROS via NADPH oxidase and promoting histone citrullination mediated by peptidylarginine deiminase 4 (PAD4), which triggers NETosis. This process is characterized by chromatin decondensation, rupture of the nuclear membrane, and the subsequent release of NETs.[32,33] NETs, which consist of DNA scaffolds, antimicrobial proteins, and pro-inflammatory molecules such as high-mobility group box 1 (HMGB1), have become a focal point in the study of gouty arthritis pathogenesis due to their role in amplifying inflammation.[32] Proteases derived from NETs directly contribute to tissue damage, thereby increasing vascular permeability and pain. In particular, a bidirectional crosstalk between macrophages and neutrophils is evident: macrophage-derived IL-1β facilitates neutrophil recruitment and NETosis,[21] while NETs release DAMPs such as DNA and HMGB1, which support the polarization of M1 macrophages.[34] This interaction significantly enhances the NLRP3 inflammasome and pyroptosis pathways, establishing a proinflammatory feedback loop. As the inflammatory response progresses, aggregated NETs (aggNETs) physically encapsulate MSU crystals while degrading inflammatory mediators, with the release of TGF-β promoting spontaneous resolution.[35] Concurrently, the efferocytosis of apoptotic neutrophils and NETs by macrophages induces M2 polarization, leading to the secretion of IL-10 and TGF-β, which aid in resolving inflammation.[36,37] Nevertheless, insufficient clearance of NETs allows residual components, such as DNA, histones, and matrix metalloproteinase-9 (MMP-9), to continuously activate fibroblasts and osteoclasts, thereby predisposing tissues to chronic damage.[21,38]

Advanced gout is pathologically characterized by structural joint damage, accompanied by bone erosion and focal cartilage destruction.[1] Neutrophils and NETs play an active role in the formation of tophi and the destruction of articular structures. Histological analysis reveals MSU crystals at the core of tophi, encircled by abundant NET remnants, macrophages, and multinucleated giant cells, collectively contributing to chronic granulomatous inflammation.[39] NETs-derived histones and proteases directly impair chondrocyte function and suppress their reparative capacity. Additionally, NETs enhance osteoclast activity via activation of the receptor activator of nuclear factor kappa-B ligand (RANKL) pathway, resulting in the characteristic "punched-out" bone erosions.[40] Within this chronic inflammatory environment,

persistent low-level neutrophil infiltration sustains a pro-fibrotic and pro-osteoclastic microenvironment through ongoing NET-macrophage interactions, ultimately leading to irreversible structural damage to the joints.[41]

Lymphocytes

Acute gout flares primarily engage innate immune cells, with lymphocytes playing a minimal role as the main effectors of the adaptive immune response.[9] In contrast, during the chronic phases of the disease, lymphocytes become central to disease progression through ongoing immune dysregulation. Activated Th17 cells contribute to the maintenance of proinflammatory microenvironments by secreting IL-17 and stimulating RANKL expression, which in turn promotes osteoclast-mediated bone erosion.[22] Simultaneously, a deficiency in Treg function leads to an imbalance between Th17 and Treg cells, reducing anti-inflammatory regulation and hindering the resolution of inflammation. This combination of factors underpins the immunopathological characteristics of chronic gout.[21,39]

Platelets

The mechanistic role of platelets in gouty arthritis remains insufficiently explored. Current evidence suggests that in hyperuricemic conditions, soluble urate contributes to vascular endothelial dysfunction by suppressing nitric oxide (NO), inducing glycocalyx shedding, and impairing mitochondrial function, thereby facilitating platelet adhesion and activation.[42] Elevated levels of VEGF-A, predominantly secreted by activated platelets and macrophages,[43] have been observed in both the serum and synovial fluid of patients with gout, indicating platelet involvement in inflammatory processes through increased vascular permeability and leukocyte infiltration. Furthermore, studies have confirmed increased platelet activity in individuals with gout.[44] As functional extensions of the immune system,[23] platelets exacerbate systemic inflammation in gout. These insights have led to proposals for redefining gout as a "vascular inflammatory disorder", which may better account for its cardiovascular complications.[45] However, the specific mechanisms underlying vascular injury and platelet pathophysiology in gouty arthritis require further investigation, with current pathological mechanisms summarized in Figure 1.

The Clinical Utility of CBCRs in GA

Introduction of CBCRs

CBCRs constitute a set of innovative serum inflammatory indices derived from complete blood cell counts. The formulas for their calculation are delineated as follows:

NLR = neutrophil count ($\times 10^9$/L) / lymphocyte count ($\times 10^9$/L)

MLR = monocyte count ($\times 10^9$/L) / lymphocyte count ($\times 10^9$/L)

PLR = platelet count ($\times 10^9$/L) / lymphocyte count ($\times 10^9$/L)

SII = platelet count ($\times 10^9$/L) * neutrophil count ($\times 10^9$/L) / lymphocyte count ($\times 10^9$/L)

SIRI = monocyte count ($\times 10^9$/L) * neutrophil count ($\times 10^9$/L) / lymphocyte count ($\times 10^9$/L)

CBCRs as Indicators of Systemic Inflammation

Under conditions of inflammation, there is typically an increase in peripheral blood counts of neutrophils, monocytes, and platelets, while lymphocyte counts tend to decrease, making their derived ratios clinically significant for assessing inflammation. Research suggests that acute inflammatory responses preferentially mobilize neutrophils and monocytes and transiently suppress lymphocyte circulation. Early-stage lymphopenia may be associated with cortisol release and the migration of lymphocytes to peripheral tissues, such as lymph nodes or sites of inflammation.[46,47] Neutrophils and monocytes, as principal effectors of the innate immune system, facilitate inflammatory responses through mechanisms such as chemotaxis, phagocytosis, and cytokine release, whereas lymphocytes are primarily involved in adaptive immunity. Consequently, the composite biomarkers NLR and MLR, provide insight into the dynamic balance between innate and adaptive immune responses. Platelets play a crucial role in enhancing the cellular immune system by orchestrating both innate and adaptive immune responses.[23,48] PLR reflects the integration of these two distinct immunological components. Recently developed indices, such as SII and SIRI, incorporate three hematopoietic lineages.

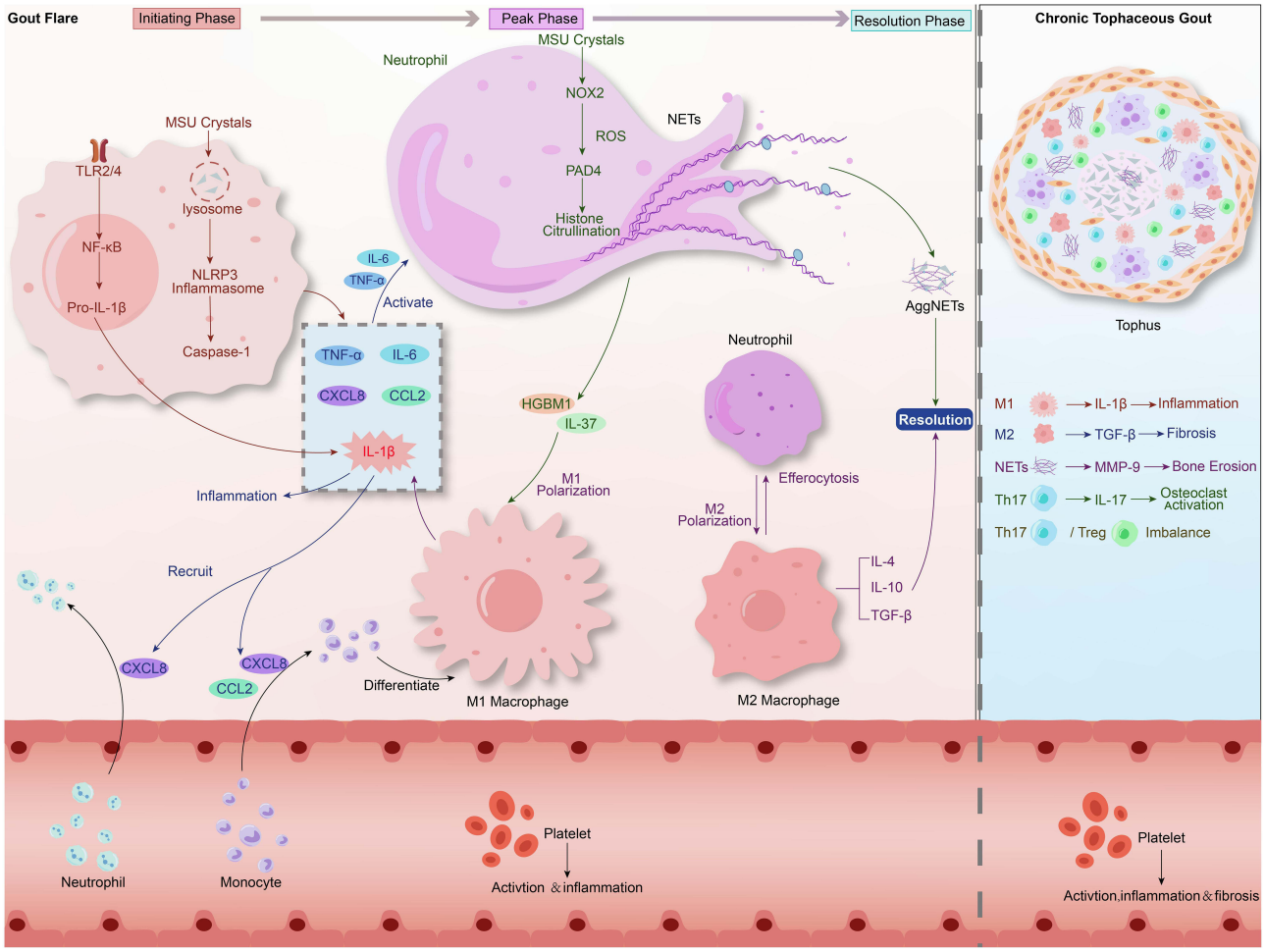

Figure 1 Mechanisms of gouty arthritis and immune cell interactions.

These indices allow for a more comprehensive assessment of inflammation through CBCRs compared to isolated parameters like total leukocyte count.

The Clinical Research Landscape of CBCRs Across Diseases

In recent years, these indices have undergone extensive investigation across a range of diseases and are acknowledged as reliable biomarkers for assessing disease activity and prognosis. Notably, the NLR and PLR have garnered significant research interest. Numerous studies have examined CBCRs in the context of autoimmune diseases. A meta-analysis has shown that the SII effectively differentiates between individuals with and without autoimmune diseases and correlates with disease activity.[49] In patients with RA, the NLR and PLR effectively differentiate between active and inactive disease states,[16] demonstrate excellent diagnostic accuracy for active cases,[20] and correlate with therapeutic responsiveness to disease-modifying antirheumatic drugs (DMARDs).[17] Compared to healthy controls, patients with SLE exhibit significantly elevated NLR and PLR levels, which positively correlate with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores,[18] indicating their potential utility as biomarkers for predicting lupus nephritis.[50] In ankylosing spondylitis (AS) patients, NLR, MLR and PLR are valuable for assessing disease activity and monitoring the efficacy of biologic treatments.[51] Within the context of cardiovascular diseases, the SII and SIRI have shown prognostic value in predicting patient survival and cardiovascular events.[52] In oncology, inflammatory indices such as NLR, PLR, and SII are significantly correlated with the pathological characteristics of non-small cell lung cancer, facilitating tumor staging prediction and informing treatment strategies.[53] In the realm of infectious diseases, research has demonstrated a significant association between the NLR and both the severity and mortality of

COVID-19 patients.[54,55] These findings across various disease domains highlight the potential utility of CBCRs as instruments for assessing inflammation.

In comparison to the aforementioned diseases, investigations into CBCRs in the context of GA commenced at a relatively later stage. Nonetheless, emerging evidence suggests that CBCRs can effectively distinguish between the acute and intercritical phases of GA.[56] Additionally, the NLR and MLR appear promising in predicting comorbidities associated with GA, which is consistent with the inflammatory profile of GA, characterized predominantly by neutrophils and monocyte-macrophages.

Correlation of CBCRs and GA Activity

In individuals with gouty arthritis (GA), inflammation leads to increased counts of neutrophils, monocytes, and platelets, alongside a decrease in lymphocyte counts.[57] Consequently, these hematological ratios can serve as valuable indirect markers for evaluating inflammatory status and cellular immunity. Comparative studies indicate significantly greater infiltration of neutrophils and monocytes in the synovial fluid of gout patients compared to those with osteoarthritis, whereas lymphocyte populations are similar between the two groups.[58] Additionally, serum uric acid levels show significant positive correlations with circulating inflammatory cells, including total leukocytes, neutrophils, and monocytes.[42]

NLR, MLR, and PLR in GA Activity Assessment

Emerging evidence has elucidated the diagnostic and disease-monitoring utility of CBCRs in GA, with particular focus on NLR, MLR, and PLR which integrate two routine hematological parameters. In a large-scale study, Yi Jiang enrolled 474 patients with acute gout (AG), 399 patients with intercritical gout (IG), and 194 healthy controls (HC). Baseline analysis revealed statistically significant differences ($P<0.05$) in NLR and MLR among all three groups, while PLR showed significant variation only between the AG and IG groups ($P>0.05$). Following standardized treatment, AG patients experienced significant reductions in NLR, MLR, and PLR ($P<0.05$), whereas no significant changes were observed in the IG group ($P>0.05$). These findings suggest that NLR and MLR are robust biomarkers for both monitoring disease activity and evaluating therapeutic responses.[56] A study conducted by Cengiz Kadiyoran revealed significantly higher levels of NLR, MLR and PLR in patients with acute gout compared to those with intercritical gout. The study found strong positive correlations between NLR and both serum uric acid ($P<0.001$) and CRP ($P<0.001$) during acute flares. Furthermore, multivariate linear regression analysis identified NLR and MLR as independent predictors of gout flares, whereas PLR did not demonstrate an independent association. These findings suggest that NLR and MLR may provide a more accurate reflection of the systemic inflammatory burden than isolated neutrophil or monocyte counts.[59] In alignment with these findings, A. Sahin illustrated that the NLR and MLR may function as cost-effective and practical inflammatory biomarkers for predicting arthritis flares in patients with gout.[60] Wu et al conducted an evaluation of the correlation between NLR, PLR and gout activity. The study found that NLR and PLR values were significantly elevated during acute flares compared to intercritical periods. Positive correlations were observed with ESR ($R=0.253$, $P=0.006$) and CRP ($R=0.367$, $P<0.001$), while no significant associations were found with serum urate levels or the presence of tophi. Wu concluded that NLR and PLR possess limited predictive value for gout activity when used independently and should be considered alongside other hematological parameters. Receiver operating characteristic (ROC) curve analysis demonstrated an area under the curve (AUC) of 0.765 for NLR, with an optimal cutoff of 3.810, sensitivity of 57.9%, and specificity of 78.3%. For PLR, the AUC was 0.720, with an optimal cutoff of 141.435, sensitivity of 60.0%, and specificity of 60.9%.[57] Further corroborative evidence from A. Balkarli indicated elevated NLR in both acute and intercritical gout patients, suggesting ongoing subclinical inflammation during remission.[61] Similarly, M. Maden reported significantly higher NLR in acute gout patients compared to healthy controls ($P=0.001$), with a notable reduction following a two-week treatment period ($P<0.001$) and normalization to control levels by two months ($P=0.509$).[62]

SII and SIRI in GA Activity Assessment

Studies investigating the association of indices incorporating three routine blood parameters including SII and SIRI with GA activity remain relatively scarce. Yi Jiang's study demonstrated statistically significant differences ($P<0.05$) in SII and SIRI among AG, IG and HC groups. Notably, significant variations were observed in AG patients before and after standardized treatment, whereas no such variations were found in IG patients. Multivariate logistic regression analysis identified ESR, CRP and SIRI as independent factors influencing acute gout flares, with SIRI exhibiting superior performance among CBCRs indices. However, ROC curve analysis indicated only moderate diagnostic efficacy for SIRI (AUC=0.674), which was inferior to that of CRP (AUC=0.755).[56] Utilizing data from the National Health and Nutrition Examination Survey (NHANES) 2017–2018, Jin Yan analyzed 273 gout patients and 4,244 controls. The analyses revealed that an SII value ≥511.8 and a serum urate level ≥7.0 mg/dL were positively associated with gout prevalence, suggesting that SII may serve as a reliable biomarker for assessing inflammatory status in gout.[63] These findings are systematically summarized in Supplementary Table 1.

Synthesis of Evidence on CBCRs and GA Activity

In conclusion, significant variations in NLR, MLR, PLR, SII, and SIRI have been consistently documented across multiple studies when comparing AG and IG groups. This suggests that CBCRs may serve as sensitive markers for acute inflammation in gout. Nonetheless, the existing body of research is characterized by certain methodological limitations. Of the seven studies referenced, six utilized a retrospective design.[56,57,60–63] With one exception, all were conducted at single centers,[56,57,59–62] and several were limited by small sample sizes.[57,59–62] Most studies did not provide clear definitions for the "acute gout phase" or specify the timing of blood sample collection. Only one study detailed that 'Blood samples were taken between 24 and 48 hours after the onset of pain, redness, and swelling complaints in patients with a gout attack according to the ACR 2012 criteria'.[59] In terms of statistical methodology, some studies failed to apply corrections for multiple comparisons,[56,59,60] or utilized inadequate adjustments for confounding variables,[60] which may increase the likelihood of false-positive results. These methodological shortcomings collectively heighten the risk of bias within the existing evidence base. Moreover, two of the studies were available only as conference abstracts,[61,62] which limits the ability to thoroughly assess their methodological rigor.

Despite these limitations, NLR and MLR have consistently demonstrated significant differences across various studies, indicating their potential as sensitive markers for acute inflammation in gout. These markers appear to outperform PLR, which exhibits considerable variability among studies.[56,57,59] This observation is consistent with the pivotal roles that neutrophils and monocytes play in the pathogenesis of gouty inflammation. Composite indices that incorporate three cell types, SII and SIRI, also show promising performance, although the supporting evidence is currently limited. Furthermore, there is inconsistency in the findings regarding whether CBCRs in patients with intercritical gout differ from those in healthy individuals. Some studies have reported significant differences,[56,57] while others have found no significant distinctions.[57,60,62] The observed discrepancy may be attributed to variations in study populations and methodologies, or possibly to significant inter-individual differences in chronic inflammatory burden during the intercritical period. As cost-effective and readily accessible measures, CBCRs could serve as complementary tools to traditional inflammatory markers such as CRP and ESR in evaluating gout activity. However, given that most studies report AUC around 0.7—specifically, AUCs for NLR ranging from 0.650 to 0.765, MLR from 0.652 to 0.655, PLR from 0.559 to 0.720, SII at 0.647, and SIRI at 0.674—CBCRs are not suitable as standalone diagnostic tools. They should be integrated with other indicators such as CRP and ESR for a comprehensive assessment. Although the reported AUCs for CBCRs do not exceed 0.8, their foundation in routinely tested parameters offers the advantages of convenience and low cost, making them appropriate for initial screening of gout activity in primary care settings and for monitoring treatment response during acute attacks.

Correlation Between CBCRs and GA Complications

Common comorbidities of GA include renal impairment,[5] cardiovascular diseases,[6,7] metabolic syndrome,[64] sexual dysfunction,[65] and ocular disorders.[66] Recent evidence indicates that NLR and MLR may serve as predictive markers for the risk and outcomes of comorbidities associated with GA.

CBCRs and Renal Impairment in GA

In a retrospective study conducted by Kai-Jun Zhu, the association between NLR and renal impairment was examined in a cohort of 499 patients with acute GA. These patients were categorized into a chronic kidney disease (CKD) group and a non-CKD group based on their glomerular filtration rate. The study found that the CKD group exhibited significantly elevated NLR values compared to the non-CKD group (3.38 vs 2.38, $p<0.001$). Through multivariate logistic regression analysis, NLR was identified as an independent risk factor for the development of CKD in patients with GA. ROC analysis demonstrated an AUC of 0.646 (95% CI: 0.597–0.694) for NLR in predicting CKD, with a sensitivity of 60.19% and a specificity of 60.41%, suggesting a modest predictive value.[67]

CBCRs and Cardiovascular Disease in GA

RD Stultz investigated the utility of the neutrophil-to-lymphocyte ratio NLR and MLR for assessing disease activity and the 10-year cardiovascular risk score in patients with gout. Their findings demonstrated a significant correlation between MLR and total gout flares ($r=0.39$, $p=0.02$), whereas no such association was observed for NLR. Both NLR and MLR were significantly elevated ($p<0.05$) in gout patients with high cardiovascular disease (CVD) risk. Logistic regression analysis revealed that patients with high NLR or MLR (upper quartile) had substantially increased CVD risk (OR=5.3, 95% CI: 1.1–25.7 for NLR; OR=10.0, 95% CI: 1.7–57.7 for MLR), suggesting their potential as predictive biomarkers for gout-related complications.[68] Conflicting evidence was reported in the study conducted by Muhammet Maden, which monitored gout patients over an average duration of 105 months to investigate the association between NLR and atherosclerotic cardiovascular mortality (ACVM). The study found that patients with GA exhibited significantly higher NLR ($p<0.05$) and lower mean platelet volume (MPV) compared to healthy controls. However, multivariate analysis identified MPV as the sole independent prognostic factor for ACVM, with insufficient evidence supporting the predictive value of NLR.[69] Relevant studies are summarized in Supplementary Table 2.

Synthesis of Evidence on CBCRs and GA Comorbidities

In conclusion, NLR and MLR in patients with GA are indicative of systemic inflammation levels, which act as a common pathological link between GA and its comorbidities, such as CKD and CVD.[70,71] Consequently, CBCRs are theoretically associated with the risk of comorbidities in GA, a hypothesis supported by observations from existing studies,[67] which highlight their potential clinical utility.

However, the three available studies are constrained by small sample sizes, and two utilized a cross-sectional design,[67,68] which hinders the establishment of a temporal sequence necessary for determining causality between CBCRs and comorbidities. The only long-term cohort study did not validate NLR as an independent predictor of atherosclerotic cardiovascular disease ACVD.[69] Methodological limitations, along with heterogeneity in study design, populations, and endpoints, are likely the primary factors contributing to the current inconsistencies in conclusions.

More critically, the interpretation and application of CBCRs as non-specific indicators of systemic inflammation encounter significant challenges. From a pathological standpoint, inflammation serves as a common underlying factor for both GA and its associated comorbidities, such as chronic kidney disease, cardiovascular diseases, and metabolic disorders. In instances where an elevated NLR is detected in a patient suffering from both GA and CKD, existing research can establish a statistical association between NLR and CKD. However, it remains inadequate in effectively distinguishing the clinical origin of this signal, whether it primarily arises from the GA itself, or the micro-inflammatory state of CKD, or a synergistic effect of both conditions. This lack of specificity implies that, although CBCRs can indicate an overall inflammatory risk in patients with comorbidities, they fall short as precise, GA-specific predictive markers for individual comorbidities.

Based on existing evidence, elevated CBCRs are generally associated with an increased overall risk of comorbidities in patients with GA, indicative of a common underlying inflammatory pathology. Nevertheless, the limited specificity of CBCRs constrains their utility for individualized comorbidity risk assessment in GA. Future research should advance beyond the confirmation of associations to quantify the contributions of various etiologies to CBCR values. Additionally, efforts should be directed towards developing dynamic models through longitudinal studies that can differentiate between

gout-specific inflammation and inflammation related to comorbidities, thus enhancing the potential for precise application.

Emerging Applications of CBCRs in GA

In addition to investigations examining the relationship between CBCRs and GA activity/comorbidities, other research has identified significant associations between CBCRs and clinically relevant outcomes in gout. H. Lin conducted a prospective cohort study utilizing data from gout patients in the NHANES database (2007–2018), comprising a total of 1,334 participants with a median follow-up period of 68 months. Participants were categorized into low-, medium-, and high-SII groups. Kaplan-Meier survival analyses indicated the highest mortality rates in the high-SII group. Furthermore, Cox proportional hazards regression analysis, using the low-SII group as a reference, demonstrated a significantly increased risk of mortality in the high-SII group (HR = 1.56, 95% CI: 1.01–2.41). These findings suggest that elevated SII may serve as an independent predictor of all-cause mortality in patients with gout.[72]

Moreover, although hyperuricemia is a prerequisite for the development of gout, only a subset of individuals with hyperuricemia advance to manifest clinical gout. At present, there is an absence of definitive clinical biomarkers capable of identifying individuals within the hyperuricemic population who are at elevated risk for the progression to gout.[73] Considering that the initiation and progression of gout are intricately associated with inflammatory processes and immune responses, these mechanisms may provide critical insights for differentiating gout risk among hyperuricemic individuals. Xiaochan Tian conducted an investigation into the relationship between CBCRs and gout among HUA patients, utilizing data from 6,732 participants in the NHANES database 2007 to 2018. Upon adjusting for covariates, multivariate analysis identified a significant positive correlation between SIRI and gout prevalence specifically within the female subgroup (OR=1.385, 95% CI: 1.187–1.615, $p<0.001$), with SIRI exhibiting superior diagnostic performance (AUC=0.717) relative to other inflammatory markers such as NLR. Although no significant association was detected in male HUA patients, a statistically significant positive correlation was observed in the 20–45 age subgroup ($p<0.05$). These findings indicate that SIRI may serve as a promising predictive biomarker for gout risk in HUA women, necessitating further validation through large-scale studies. Moreover, integrating SIRI with other indicators could potentially enhance predictive accuracy, facilitating the identification of high-risk individuals for targeted early interventions aimed at reducing gout incidence.[74]

Shunshun Cao developed a predictive model utilizing machine learning techniques, specifically employing data from the NHANES database on patients with gout. The study involved constructing an XGBoost model that integrated SII, sex steroid hormones, and dietary antioxidants to identify gout, achieving an AUC of 0.795 for males and 0.822 for females. This model exhibited enhanced accuracy and effectively addressed the limitations associated with traditional linear analysis methods for evaluating inflammatory markers.[75] These studies are summarized in Supplementary Table 2.

Leveraging the extensive sample size advantages of NHANES database, these studies have innovatively applied CBCRs across various domains, including the prediction of gout-related mortality, the screening for gout risk in hyperuricemic populations, and the development of machine learning models for gout diagnosis. Despite limitations such as incomplete data on therapeutic interventions, these findings provide a critical foundation for future clinical validation. Subsequent research should prioritize large-scale prospective studies to ascertain the practical utility of CBCRs in clinical practice.

Summary

CBCRs encompasses a range of systemic inflammatory biomarkers, including NLR, MLR, PLR, SII, and SIRI. Studies have demonstrated the efficacy of CBCRs parameters in evaluating GA activity, as well as in predicting comorbidities and prognosis associated with GA. Nonetheless, some researchers contend that CBCRs serve merely as an auxiliary clinical reference, lacking definitive diagnostic significance. Neutrophils and monocyte-macrophages are integral to the pathogenesis of GA, particularly during acute episodes, which corroborates clinical findings that NLR and MLR provide greater accuracy and sensitivity than PLR in reflecting the inflammatory status of patients with gout. The role of platelets in the pathogenesis of gout and the clinical utility of PLR in assessing disease activity are insufficiently explored, necessitating further research. Composite indices that integrate three blood parameters, such as SII and SIRI, have

attracted increasing attention due to their promising accuracy in evaluating disease activity and predicting outcomes in GA, thereby underscoring their potential clinical significance. Nonetheless, studies yield inconsistent results regarding differences in CBCRs profiles between intercritical GA patients and healthy controls, likely due to considerable interindividual variability in chronic inflammation levels among intercritical gout patients.

Although dual-energy computed tomography (CT) and other imaging modalities can directly visualize urate crystals with high specificity for the diagnosis of GA,[1,8] their clinical utility is constrained by factors such as radiation exposure, high costs, and limited availability of equipment. In contrast, serum inflammatory markers provide a cost-effective and repeatable alternative that addresses the limitations of imaging techniques. These biomarkers facilitate the dynamic quantification of the severity of acute gout flares, aiding in the differentiation between mild, moderate, and severe inflammatory responses, thereby informing clinical decision-making. Prompt initiation of urate-lowering and anti-inflammatory therapies can effectively decelerate disease progression in patients with GA.[8] In the absence of synovial fluid analysis, serial monitoring of inflammatory indicator levels is instrumental in evaluating treatment response and guiding subsequent therapeutic interventions. Multiple observational studies have confirmed the reliability of CBCRs in assessing acute inflammatory activity in GA,[56,57,59–62] with significant reductions in CBCRs observed following standardized treatment,[56,69] thereby demonstrating its utility in reflecting the severity of inflammation and the efficacy of therapy. Additionally, serum inflammatory markers have been shown to correlate with the long-term prognosis of GA, with elevated levels associated with recurrent flares, joint damage, and an increased risk of cardiovascular and renal complications.[76–78] This suggests that CBCRs may also have additional value in predicting comorbidities associated with GA.[64,65]

Nonetheless, the existing body of evidence presents certain limitations. Future research endeavors with larger sample sizes are necessary to conclusively ascertain the clinical utility of CBCRs, evaluate their applicability across diverse populations—including various ethnic groups and patients with different comorbidities—and establish their optimal cut-off values. Additionally, it is crucial to elucidate the molecular mechanisms that connect CBCRs to pertinent biomarkers and signaling pathways. The intrinsic non-specificity of CBCRs poses a substantial obstacle to their clinical application, especially in terms of interpretation in patients with comorbidities. In the context of the burgeoning era of big data, the incorporation of artificial intelligence (AI) to synthesize CBCRs with additional clinical parameters for the development of predictive models demonstrates initial promise for personalized risk assessment and precision medicine.[75,79] However, several critical scientific questions remain to be addressed:

1. Enhancing the specificity of CBCRs for clinical application in GA through the development of novel composite indices or integrated models.
2. Investigating the potential of CBCRs to reflect subclinical disease states, thereby facilitating the identification of individuals at risk for developing gout and enabling early preventive measures.
3. Exploring the applicability of CBCRs during pre-disease stages or in atypical presentations, such as during the phase of crystal dissolution.
4. The investigation into the relationship between CBCRs and the extent of tophaceous burden or the severity of joint damage in individuals with advanced gout.

Addressing these questions presents a significant challenge. A successful exploration of these issues will enhance our comprehension of the inflammatory mechanisms involved in GA, facilitate the clinical application of CBCRs, and ultimately contribute to the refinement of diagnostic and therapeutic strategies for the disease.

Conclusion

Based on a synthesis of current research, we found that CBCRs have been observed to be reliable in assessing acute inflammatory activity in GA, reflecting inflammatory severity and evaluating treatment efficacy, with NLR and MLR showing superior performance. Additionally, CBCRs may correlate with increased risks of cardiovascular and renal complications in gout patients, exhibiting potential value in predicting GA comorbidities. The current evidence base exhibits certain limitations, necessitating further large-scale investigations to establish the clinical utility of CBCRs.

Abbreviations

GA, Gouty Arthritis; MSU, Monosodium Urate; CBCR, Complete Blood Cell Count Ratios; NLR, Neutrophil-to-Lymphocyte Ratio; MLR, Monocyte-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammation Response Index; HUA, Hyperuricemia; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; IL-1β, Interleukin-1 Beta; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor Alpha; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; DAMPs, Damage-Associated Molecular Patterns; TLR, Toll-Like Receptor; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; ROS, Reactive Oxygen Species; NETs, Neutrophil Extracellular Traps; aggNETs, Aggregated Neutrophil Extracellular Traps; Th17, T Helper 17 Cells; Treg, Regulatory T Cells; RANKL, Receptor Activator of Nuclear Factor Kappa-B Ligand; OPG, Osteoprotegerin; VEGF-A, Vascular Endothelial Growth Factor A; CKD, Chronic Kidney Disease; CVD, Cardiovascular Disease; ACVM, Atherosclerotic Cardiovascular Mortality; MPV, Mean Platelet Volume; HR, Hazard Ratio; CI, Confidence Interval; OR, Odds Ratio; AUC, Area Under the Curve; ROC, Receiver Operating Characteristic; ULT, Urate-Lowering Therapy; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; XGBoost, eXtreme Gradient Boosting.

Acknowledgments

This work was supported by funding from National Key Research and Development Program of China (Num: 2022YFC3501200 and 2022YFC3501203), Natural Science Foundation of China (Num: 82374287), Clinical Research Project of Central High-Level TCM Hospitals (DZMG-XZYY-23006 and DZMG-TZZY-24018); Dongcheng District Outstanding Talent Nurturing Program (Num: 2023-dchrcpyzz-3).

Funding

This work was supported by funding from National Key Research and Development Program of China (Num: 2022YFC3501200 and 2022YFC3501203), Natural Science Foundation of China (Num: 82374287), Clinical Research Project of Central High-Level TCM Hospitals (DZMG-XZYY-23006 and DZMG-TZZY-24018), Dongcheng District Outstanding Talent Nurturing Program (Num: 2023-dchrcpyzz-3).

Disclosure

The author(s) report no conflicts of interest in this work.

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