REVIEW

The Independent Value of Neutrophil to Lymphocyte Ratio in Gouty Arthritis: A Narrative Review

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Abstract: Since the incidence of gouty arthritis (GA) exhibits yearly increases, accurate assessment and early treatment have significant values for improving disease conditions and monitoring prognosis. Neutrophil to lymphocyte ratio (NLR) is a common indicator in blood routine, which has the characteristics of easy access and low cost. In recent years, NLR has been proven to be an effective indicator for guiding the diagnosis, treatment, and prognosis of various diseases. Moreover, NLR has varying degrees of relationship with various inflammatory biomarkers, which can affect and reflect the inflammatory response in the body. This paper reviews the independent value of NLR for GA and its underlying molecular pathological mechanisms, intending to contribute to the further application of NLR.

Keywords: neutrophil to lymphocyte ratio, gouty arthritis, inflammatory response, neutrophils, disease activity

Introduction

Gouty arthritis (GA) is one of the most common forms of inflammatory arthritis, bringing huge economic and social burdens.[1,2] According to the study data of the Global Burden of Disease, there are 41.2 million GA patients worldwide as of 2017.[3] The estimated global age-standardized incidence rate and annual incidence rate of GA are 510.6 and 91.8 per 100,000 people, respectively, which increases by 7.2% and 5.5% compared with 1990.[4,5] These changes are more pronounced in economically developed countries or regions.[6]

The gold standard for GA diagnosis is the presence of birefringent urate crystal in synovial fluid under a polarization microscope.[1] However, patients show low acceptance due to the invasive nature of this procedure. Currently, the examination methods for GA include X-ray, ultrasound, computed tomography, magnetic resonance imaging, etc. However, these imaging techniques are complex, restrictive, and expensive.[7,8] The indicators reflecting the inflammatory activity of GA include C-reactive protein, erythrocyte sedimentation rate and IL-1β, etc.[9] However, the sensitivity and specificity of these indicators are not excellent.[10] There are many comorbidities in patients with GA, which are the main causes of death in patients with GA.[11] At present, the method to accurately predict the risk and prognosis of GA comorbidities has not been found. Therefore, it is urgent to find a simpler, cheaper, and less restrictive assessment method for GA while ensuring its effectiveness.

During the GA process, there exists a persistent immune inflammatory response mediated by inflammatory biomarkers such as immune cells, inflammatory mediators, and chemokines.[12] Emerging evidence has indicated that biomarkers can be used as characteristic indicators to evaluate the activity and prognosis of GA, facilitating the optimization of treatment plans.[9,13–15] Neutrophil to lymphocyte ratio (NLR) is a composite biomarker obtained by dividing the neutrophil count by the lymphocyte count in blood routine, which is the most common test in clinical practice.[16,17] In

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recent years, NLR has been found to predict the activity and prognosis of rheumatic diseases (including GA).[17–21] This review summarizes existing evidence on the relationship between NLR and GA, evaluates whether NLR can guide clinical measures, explores the potential pathophysiological mechanisms of NLR, and thereby provides a foundation for future research.

Overview of NLR

NLR is a parameter in blood routine testing, which is easy to obtain, cost-effective, rapid to test, and integrates two different but complementary immune pathways. As a composite biomarker, NLR is more capable of reflecting systemic inflammation than individual biomarkers, and its potential role in clinical practice is supported by its ability to predict the occurrence and development of various diseases.[22,23]

The NLR value of healthy adults ranges from 0.78 to 3.53, with an average of 1.65.[24] Elevated NLR often indicates that the disease is in a high-risk stage of progression, leading to ineffective treatment and poor prognosis.[25] NLR is also positively correlated with a variety of hematology parameters, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), mean platelet volume (MPV), and platelet distribution width (PDW).[26,27]

Keisuke Toya et al believed that NLR could independently predict the healing time of pancreatic fistula after distal pancreatectomy, indicating that elevating NLR may shorten the healing time after surgery.[28] Cheng et al suggested that a higher NLR was significantly associated with an increased risk of depression, and the increase in NLR was more pronounced among depression patients with suicidal behavior.[16] Dowlati et al pointed out that in cerebral vasospasm after aneurysmal subarachnoid hemorrhage, Hunt-Hess score > 2, NLR > 8.0, and early fevers were predictive of the need for multiple endovascular interventions, and these patients had poorer functional outcomes and higher rates of complications.[29] Li et al demonstrated that NLR could predict the mortality rate of patients with cerebral hemorrhage, showing positive significance in observing disease conditions and guiding clinical treatment.[30] All the above findings indicate that NLR can be used for early diagnosis and prognosis monitoring of various benign and malignant tumors, cardiovascular diseases, infectious diseases, and immune system diseases.

However, some researchers hold that the clinical value of NLR does not have a significant advantage. A study on prosthetic joint infections showed that the diagnostic specificity and sensitivity of NLR were not superior to those of ESR and CRP.[31] Mukadder Korkmaz et al believed that NLR seemed to be unrelated to the degree of upper respiratory obstruction and therefore could not be used to evaluate the systemic inflammatory status of obstructive sleep apnea syndrome.[32]

To sum up, NLR is of positive significance in diagnosing diseases and judging activity, but large-sample randomized controlled trials are warranted to clarify the clinical value of NLR for some diseases (such as GA).

NLR is Related to GA Activity

The role of NLR in GA diagnosis, activity evaluation, and prognosis has been extensively studied. The early increase in NLR after acute inflammation may be the reason why NLR is more sensitive than other laboratory indicators. A study[33] assigned 106 gout patients who met the diagnostic criteria of the American College of Rheumatology (ACR) to Group I (active phase) and Group II (intermittent phase), with 148 age and gender-matched healthy individuals as the control group. Statistical analysis showed that there was a significant difference in NLR levels between Group I and Group II (2.88 vs 2.19, P < 0.001), proving that NLR can serve as an inflammatory marker to indicate the activity of certain systemic diseases. The NLR levels in Group II were also higher than those in the healthy control group (P < 0.001). Therefore, NLR may function as an effective marker of disease activity in GA patients.

Similarly, Kadiyeran et al[21] included 110 GA patients and 90 healthy volunteers as controls and collected blood samples within 24 to 48 hours of GA onset according to ACR 2012 standards. Their results showed that the NLR (P < 0.001), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), MPV (P < 0.05), ESR (P < 0.001), and CRP (P < 0.001) of GA patients in the onset period were higher than those in the intermittent period and the control group. In the correlation analysis during the onset period, the authors found a positive correlation between serum uric acid (SUA) (P < 0.001), CRP (P < 0.001) and NLR. Linear stepwise regression analysis showed that there was an independent strongly correlated material between GA attacks and NLR (P = 0.014), SUA (P < 0.001), ESR (P < 0.001),

CRP (P < 0.001), MLR (P < 0.001). Therefore, NLR can serve as an independent predictor of GA onset, which is more effective than NE count in reflecting systemic inflammatory status. NLR is also associated with test indicators including SUA, ESR, CRP, PLR, and MLR in GA, which contributes to judging the disease condition of GA. The results of AŞahin were also consistent with this study.[34]

Another monocentric and retrospective study[35] also supports this viewpoint, but there are differences. Compared with healthy controls, gout patients showed a significant increase in NLR and PLR (P < 0.001), but a significant decrease in MPV (P < 0.001). The authors found that NLR was positively correlated with inflammatory factors such as ESR (R = 0.253, P = 0.006) and CRP (R = 0.367, P < 0.001), but the intensity of all correlations was weak (all R < 0.5). Therefore, the authors believed that NLR was not an independent predictor of GA activity and needed to be used together with other hematology parameters. At last, the authors drew the receiver operating characteristic (ROC) curve of NLR in predicting gout attacks. The area under the curve (AUC) was 0.765. When the cut-off value of NLR was 3.810, the sensitivity was 57.9% and the specificity was 78.3%. Thus, it could be seen that NLR had low sensitivity and specificity in predicting GA attacks and was not a reliable predictive indicator.

The above studies are presented in Table 1. The reliability of NLR as an inflammatory marker to judge the activity of GA has been recognized, but there is still a lack of multi-center large-sample observational studies to further verify it. The sensitivity and specificity of NLR with different cut-off values in predicting GA attack, as well as the correlation strength between NLR and inflammatory markers such as ESR and CRP, still need to be observed.

NLR and GA Comorbidities

The common complications of GA include cardiovascular diseases,[38,39] diabetes,[40] renal function impairment,[41] sexual dysfunction,[42] and ophthalmic diseases.[43] Recent studies have found that NLR may be able to predict the risk and outcome of GA comorbidities.

A retrospective study on the relationship between NLR and renal function impairment in GA patients by Zhu et al[36] included 499 GA patients and divided them into the chronic kidney disease (CKD) group and the non-CKD group. Statistical results showed that the NLR of the CKD group was significantly higher than that of the non-CKD group (P < 0.001). Multivariable logistic regression analysis indicated that NLR was associated with an increased risk of renal dysfunction in GA patients (OR = 1.122, 95% CI: 1.036–1.215). ROC curve analysis showed that the AUC of NLR for predicting CKD in GA patients was 0.646 (95% CI: 0.597–0.694), with a sensitivity of 60.19% and a specificity of 60.41%. Consistently, we also assume that elevated NLR may be associated with enhanced inflammation and reduced estimated glomerular filtration rate, both of which increase the risk of renal function impairment in GA patients. NLR can serve as an effective biomarker for predicting renal function impairment in GA patients and also evaluate the degree of inflammatory response in CKD patients at different stages, representing an independent predictor of advanced CKD progression.

In 2017, a cohort study[37] included 122 GA patients and 61 healthy controls. The survival period, history of atherosclerosis, NLR and MPV were recorded during an average follow-up period of 105 months. The researchers only observed that the NLR of GA patients was higher than the healthy controls, but there was no sufficient evidence that NLR can independently predict the outcomes of GA patients complicated with atherosclerosis. In contrast, multivariate analysis suggested the only independent adverse prognostic factor was the initial MPV value.

The above studies are also presented in Table 1. In summary, monitoring the NLR of GA patients is necessary, which may help identify the risk of comorbidities in GA.[36,37] However, further research is needed to confirm these findings and determine the optimal cutoff value for NLR to predict the risk and outcome of comorbidities in GA patients.

NLR Elevation is Characterized by an Increase in NEs

NE and Lym are key cellular components of the human defense system.[44,45] NE is involved in innate immunity and mediates inflammatory reactions through chemotaxis, phagocytosis, and cytokine release.[46] Lym mainly represents specific immune system regulatory pathways.[47] The composite marker NLR that combines the two can reflect the dynamics and balance of innate and specific immunity in immune function.[48]

Table 1 Summary of the Studies of GA Mentioned in This Review

Study	Year	Group	Group 1				Group 2				Comparison of NLR
			n	Age	Gender (M/F)	NLR	n	Age	Gender (M/F)	NLR	
Ayse Balkarli et al[33]	2017	Group 1:Control Group 2:GA	148	59 ± 11.33	128/20	1.72 (0.78–11.25)	106	59.46 ± 12.93	91/15	2.88 (1.21–21.16)	P<0.001
Cengiz Kadiyeran et al[21]	2019	Group 1:Control Group 2:GA	90	58.5 ± 14.9	64/26	1.8 (0.8–6.4)	110	58.1 ± 11.8	86/24	3.1 (0.4–8.8)	P<0.001
A Şahin et al[34]	2015	Group 1:Control Group 2:GA	45	56.2 ± 10.3	26/19	2.07 ± 1.01	45	60.8 ± 12.0	30/15	4.19 ± 3.37	P<0.001
Haihua Wu et al[35]	2022	Group 1:Control Group 2:GA	93	62.00(53.00, 72.50)	84/9	2.38 (1.62, 3.12)	118	63.00 (48.75, 71.00)	110/8	3.89 (2.57, 6.81)	P<0.001
Zhu et al[36]	2022	Group 1:GA Group 2:GA complicated with CKD	293	44.00(33.00–53.00)	278/15	2.38 (1.61–3.80)	206	58.50 (49.75–64.00)	195/11	3.38 (2.21–5.44)	P<0.001
Muhammet MADEN et al[37]	2017	Group 1:Control Group 2:GA	61	65.3 ± 4.8	34/27	1.9 ± 0.7	122	64.6 ± 13.4	96/26	3.7 ± 2.3	P<0.001

Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; GA, Gouty arthritis; CKD, Chronic kidney disease.

Inflammation of GA is mainly mediated by NE and macrophage.[6] Lym primarily participates in chronic inflammatory responses, and no conclusive evidence has been found that Lym such as innate lymphoid cells and natural killer T cells are involved in acute inflammation of GA, which may be related to the rapid onset of GA and the intense inflammatory response. Another view is that when inflammation occurs in an acute manner, a large amount of Lyms in the peripheral blood will quickly migrate to the damaged tissues, resulting in a decrease in the number of Lyms in the blood.[49]

The increase in NE count alone leading to an increase in NLR is mainly seen in the following situations:[48] bacterial infection, stroke, myocardial infarction, trauma, cancer, and any disease characterized by inflammatory responses, as the early stages of inflammation are characterized by a pro-inflammatory state, while NE mainly mediates this process.[50] As an important participant in innate immunity, massive NEs recruits, activates, and encodes other immune cells, as well as secrets a series of pro-inflammatory factors, immune regulatory factors, and chemokines, enhancing the recruitment and function of immune cells.[46] Therefore, an increase in NLR is typically characterized by an increase in NEs.

NLR and GA Inflammatory Mechanisms
Classical Mechanisms
The NLRP3 inflammasome-caspase-1-IL-1β signaling produced by NE is currently recognized as the classical mechanism of GA inflammatory responses.[51–54] During the acute onset of GA, monosodium urate (MSU) crystals induce massive infiltration of immune cells such as NEs to the local response site and activate NLRP3. Then, the activated NLRP3 produces caspase-1 and promotes the secretion of IL-1β. IL-1β activates the release of pro-inflammatory cytokines and chemokines, which further exacerbates the chemotaxis and infiltration of NE, forming a rapid and intense inflammatory cascade reaction.[55]

NE and Protein-MSU Complexes
MSU can bind to various serum proteins to form protein-MSU complexes, such as the C1q, C5, and C6 part of complements, Fc fragments of IgG and IgM, and apolipoprotein.[56–58] The physical and chemical properties of the complex will not change, but the spatial structure will change into a form more conducive to the recognition of NE and phagocytosis of macrophage.[59]

IgG and apolipoprotein can occupy the surface of MSU crystals and mediate the process of NE stimulation during the inflammatory activity and regression phases.[60] Xu et al[59] discovered an intriguing relationship between type II collagen-MSU complex (CII-MSU) and NE. CII-MSU enhanced the secretion of CC chemokine ligand 2 and C-X-C chemokine ligand 2, thereby promoting the ability of NE to recruit to inflammatory sites in migration experiments. The number of NEs in the synovium of mice injected with CII-MSU was significantly higher than that of mice injected with MSU. CII-MSU mainly mediated the TLRs/MyD88/NF-κB pathway in an ITGB1-dependent manner, thereby promoting the recruitment and activation of NE.

In brief, different protein-MSU complexes may affect the inflammatory effect of NE through different pathways to mediate the inflammatory response of GA.[61] Understanding the formation process and inflammatory regulation ability of different protein-MSU complexes may help elucidate the novel relationship between GA and NE.

NE and Intestinal Microbiota in GA Patients
At least 100 trillion bacteria live in the human intestinal micro-ecosystem and participate in the metabolism, immune regulation, and internal environment homeostasis.[62–64] The intestine is an important organ for the excretion of uric acid outside the kidneys, with two-thirds of uric acid being excreted from the kidneys and one-third being excreted through the intestine.[65] The intestinal excretion of uric acid is mainly achieved through the catabolism of uric acid transporters and intestinal microbiota. Accumulating studies have revealed the relationship between intestinal microbiota and GA.[66–68]

Dipti Karmarkar1 and Kenneth L. Rock[69] found that intestinal microbiota regulated the recruitment of NE stimulated by MSU through the myeloid differentiation factor MyD88-dependent pathway. Jonas Schluter et al[70] revealed that there was a correlation between intestinal bacteria and immune cell dynamics, that is, metabolites of intestinal microbiota changed the permeability of the intestinal barrier and promote NE to enter the blood. A similar study[71] indicated that

short-chain fatty acid (SCFA) produced by intestinal microbiota metabolism, such as acetate, propionate, and butyrate, could promote related immune responses. Acetate could induce caspase-dependent apoptosis of NE, leading to inflammation regression.[72] Sodium butyrate reduced the UA levels in mice, reversed the reduction of MUC2, ZO-1, Occludin, and ABCG2 proteins in intestinal tissues, and decreased the levels of inflammatory factors[73].

These studies indicate that the intestinal microbiota plays a vital role in GA inflammation caused by NE activation. Recovery and improvement of intestinal microbiota and its metabolites may be a new method for the treatment of GA, but the current limitation is that the flora is significantly different among individuals. With the development of intestinal microbiota-related detection technologies, we can determine the number and types of intestinal microbiota in patients with GA, which may provide novel insights into the treatment of GA.

Neutrophil Extracellular Traps (NETs) and GA Inflammation

As one of the most prominent research highlights in the inflammation mechanism of GA in recent years, NETs are extracellular net-like structures decorated with histones and antimicrobial proteins released by activated NE. Estrella Garcia-Gonzalez et al[74] found that microcrystalline particles such as MSU can promote the generation of NETs, and the amount generated is not related to NE, but positively correlated with the number of microcrystals. One of the functions of NETs is to capture MSU in the blood, thereby blocking the onset of GA. However, the large accumulation of NETs and their encapsulation of MSU may also be the cause of gouty tophi.

Maximilien Euler and Markus H. Hoffmann[75] reported two opposite effects of NETs in GA. The net-like structure of NETs can capture and degrade pro-inflammatory factors due to the presence of NE serine protease (NSPs) on the DNA backbone of NETs, and the combination of NETs and NSPs hydrolyzes and destroys the protein structure of pro-inflammatory factors, thus promoting the regression of inflammation. However, the DNA and proteins on NETs are the sources of autoantigens in a disordered immune system. The binding of antigens and antibodies forms immune complexes and in turn induces the production of NETs, forming inflammatory self-amplification.

Olga Tatsiy et al[76] delved deeper into the signaling pathways of NETs and found that MAPK and Akt in NE were activated by MSU under the control of TAK1 and Syk, which then participated in the production of cytokines and the formation of NETs in GA inflammatory responses. Similarly, Tang et al[77] found that the NFIL3/REDD1/mTOR signaling pathway was a key pathway leading to NE autophagy, NET formation, and gouty inflammation.

In short, NETs activate and eliminate GA inflammation at different levels, constituting an important component of inflammation regulation. The focus of future research on NETs should be on how NEs transforms into NETs at the physiological level and maintains a quantitative balance of NETs. Moreover, the quantitative detection of NETs by Western blotting and ELISA is not yet complete, and a quantitative detection method for NETs needs to be explored.

Summary and Prospect

In summary, NLR is a simple and low-cost biomarker for systemic inflammation. NLR is reliable in determining GA activity and predicting GA comorbidities and prognosis. However, some scholars believe that NLR can only serve as a clinical reference factor and does not have exact significance.

In clinical practice, GA is usually diagnosed based on clinical symptoms and serum uric acid levels, and the onset of GA can be effectively suppressed by a short course of non-steroidal anti-inflammatory drugs.[1] Therefore, it is of no great significance to use NLR to diagnose or predict the onset of GA. However, inflammation remains the most crucial pathological mechanism underlying GA.[6] Following physical examination and history collection, an objective test index is still required to evaluate the inflammatory activity of GA. The aforementioned multiple observational studies have consistently demonstrated the reliable ability of NLR to evaluate inflammatory activity in GA.[21,33–35] Similarly, comorbidities are major contributors to mortality in patients with GA, and NLR has a better significance in predicting GA comorbidities, especially cardiovascular and cerebrovascular diseases and endocrine diseases.[37,40]

We need to conduct more large-sample randomized control trials or cohort studies to clarify the clinical value of NLR. It is also necessary to elucidate the molecular mechanism of the relationship between NLR and related biomarkers and signaling pathways. We still have doubts about NLR as the following questions have not been answered:

1. Is the normal range of NLR the same in different races? What do different NLR outliers represent?
2. What biomarkers should NLR be used with to improve predictive ability?
3. Can prediction ability be improved by measuring the ratio of neutrophils of a specific subtype to lymphocytes of a specific subtype?

Addressing the above issues remains a huge challenge, but exploring these issues may advance our understanding of the inflammatory mechanisms and thereby help us evaluate the immune inflammatory response status of the body, predict the activity and various complications of GA, identify different targets and signaling pathways for treating GA, and determine potential specific treatment strategies.

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