Section: General Medicine

Systematic Review

EXPLORING THE DYNAMICS OF INFLAMMATORY MARKERS: NEUTROPHIL/LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN RHEUMATOID ARTHRITIS - A SYSTEMATIC REVIEW

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Abstract

Background: Rheumatoid Arthritis (RA) is an autoimmune disorder that is characterised by persistent inflammation, joint degradation, and synovial membrane growth. Neutrophil/Lymphocyte Ratio and Platelet to Lymphocyte Ratio are potential indicators. The autoimmune nature of Rheumatoid Arthritis (RA) makes its management challenging. **Objectives:** The primary objective of this study was to elucidate the intricate relationship between neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and RA, providing a comprehensive understanding of their roles in assessing disease activity. Through a meticulous synthesis of the existing literature, this review aims to contribute to refining the diagnostic and therapeutic strategies for RA. **Material and Methods:** A systematic search was conducted using major scientific databases, including PubMed, Scopus, and Web of Science, up to February 2024. The inclusion criteria encompassed studies investigating NLR and PLR in association with RA published in English. A qualitative synthesis of methodologies, participant demographics, and key findings was employed to capture the diverse landscape of these inflammatory markers in RA patients. **Results:** This review of 14 studies showed that patients have higher NLR and PLR than controls. The NLR and PLR can be used as diagnostic and therapeutic markers, respectively. Some studies have highlighted these limitations compared to traditional markers. New markers, such as PIV and LMR, are being explored to improve diagnostic accuracy. LMR is an important inflammatory marker of RA disease activity. **Conclusion:** The synthesis of 14 studies on inflammatory markers in Rheumatoid Arthritis highlights the complex landscape of disease activity indicators, with potential utility in comprehensive management, but also highlights discrepancies and variations.

INTRODUCTION

Rheumatoid Arthritis (RA) is a complex autoimmune disorder characterized by persistent inflammation, excessive growth of the synovial membrane, and gradual degradation of the joints. Despite significant progress in understanding the underlying causes and development of targeted therapies, understanding the intricate interplay of inflammatory markers in the context of RA remains an ongoing challenge.[1]

In recent years, attention has turned to the Neutrophil/Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) as potential indicators, providing valuable insights into the overall systemic inflammatory status across various medical

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conditions.[2] However, a comprehensive systematic review is required to fully understand the specific dynamics and clinical implications of these ratios in the context of Rheumatoid Arthritis. The objective of this review was to elucidate the complex relationship between inflammatory markers, particularly NLR and PLR, and Rheumatoid Arthritis. By meticulously analysing the existing literature, we aimed to provide a comprehensive overview of the current evidence, uncovering patterns, associations, and potential clinical implications. This exploration seeks to significantly contribute to the expanding knowledge base surrounding RA, shedding light on the inflammatory processes of the disease, and potentially guiding future diagnostic and therapeutic strategies. Based on this systematic review, the significance of NLR and PLR as dynamic indicators of systemic inflammation was evident. These ratios, obtained from routine blood tests, offer a cost-effective and easily accessible method to assess the overall inflammatory environment. Unravelling their relevance within the complex immunological landscape of RA holds the promise of refining our understanding of disease activity and progression.[3] Through the lens of this review, we aim not only to consolidate existing knowledge but also to stimulate further investigation into the potential clinical usefulness of NLR and PLR in managing Rheumatoid Arthritis. By systematically examining the available evidence, our goal was to bridge current gaps in understanding, provide clinicians with valuable insights, and inspire future research endeavours that could pave the way for improved patient outcomes. As we delve into the intricacies of inflammatory markers in Rheumatoid Arthritis, this systematic review strives to be a fundamental cornerstone in advancing our understanding of the disease, fostering innovation, and ultimately enhancing the quality of care for individuals affected by RA.

MATERIALS AND METHODS

1. Literature Search Strategy

A systematic and exhaustive search of major scientific databases, including PubMed, Scopus, and Web of Science, was conducted to identify pertinent studies related to the dynamics of inflammatory markers, specifically the Neutrophil/Lymphocyte Ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in Rheumatoid Arthritis (RA). The search included studies published up to February, 2024. Keywords employed in the search strategy included variations of "Neutrophil/Lymphocyte Ratio," "Platelet to Lymphocyte Ratio," and "Rheumatoid Arthritis." Boolean operators (AND, OR) were used to refine the search and capture the intersection of these terms.

2. Inclusion and Exclusion Criteria

Studies were included if they met the following criteria.

- Studies investigating the association between the Neutrophil/Lymphocyte Ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with Rheumatoid Arthritis (RA).
- Peer-reviewed articles published in English until February 2024.
- Included Human Subjects.

Studies were excluded if they were as follows

- Published in languages other than English.
- Case reports, reviews, or conference abstracts.
- Studies not directly relevant to the exploration of NLR and PLR in the context of Rheumatoid Arthritis.
- Articles lacking sufficient information for comprehensive data synthesis.

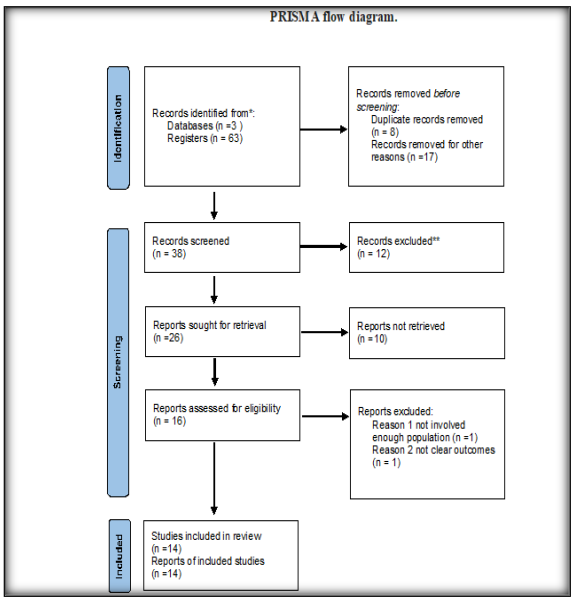
3. Synthesis of Findings

Data synthesis involved a narrative summary of pertinent study characteristics, methodologies employed, and key findings related to the NLR and PLR in the context of RA. Due to the anticipated heterogeneity in study designs, a qualitative approach was adopted, emphasising the unique contributions of each study to the overarching understanding of inflammatory markers in RA.

4. Ethical Considerations

As this review was based on an analysis of previously published studies, ethical approval was not applicable. All the included studies adhered to ethical standards, as outlined in their respective publications.

RESULTS



Neutrophil/Lymphocyte Ratio (NLR) in Rheumatoid Arthritis

The Neutrophil/Lymphocyte Ratio (NLR) is a calculated parameter derived from the absolute

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neutrophil count (ANC) and absolute lymphocyte count (ALC) in complete blood count. Typically, NLR is computed as ANC divided by ALC. Normal values range from 1 to 3, but variations exist owing to factors such as age, sex, and overall health. Numerous studies have explored the link between NLR and rheumatoid arthritis (RA), demonstrating an elevated NLR in patients with RA compared to that in healthy individuals. This ratio serves as a potential biomarker for predicting the presence of RA and for assessing disease activity, with higher values correlating with increased disease severity. This association is likely attributable to the imbalance between pro-inflammatory neutrophils and anti-inflammatory lymphocytes, reflecting the systemic inflammatory environment in RA. Although promising, further research is needed to elucidate the underlying mechanisms and establish the clinical significance of NLR in the context of RA management.[4]

Platelet to Lymphocyte Ratio (PLR) in Rheumatoid Arthritis

The platelet-to-lymphocyte ratio (PLR), a haematologic marker derived by dividing the absolute platelet count by the absolute lymphocyte count, is a significant parameter in RA. Similar to NLR, PLR has garnered attention as a potential indicator of inflammatory conditions, particularly RA. Its relevance lies in its depiction of a thrombo-inflammatory state, where an elevated PLR may signify an amalgamation of increased inflammation and a pro-thrombotic tendency. In RA, which is characterised by pronounced inflammation, PLR holds promise as a composite marker, reflecting both inflammatory and thrombotic processes. The implications of PLR in RA extend to provide insights into the overall inflammatory burden, offering supplementary information beyond what is captured by other markers. Moreover, considering the established association between RA and cardiovascular comorbidities, PLR assumes importance in cardiovascular risk assessment for individuals with RA, thereby contributing to a more comprehensive understanding of the disease and its systemic implications.[5]

A comprehensive analysis of 14 studies investigating inflammatory markers in rheumatoid arthritis (RA) revealed consistent trends, indicating an elevated neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with RA compared to controls. These ratios, correlated with established disease activity indices, such as DAS28, ESR, and CRP, demonstrate their potential as markers for assessing RA disease activity. Studies have proposed NLR and PLR not only as diagnostic indicators, especially when used in combination, but also as potential therapeutic markers, with associations noted in anti-TNF therapy response. However, caution is advised, as some studies have highlighted these limitations compared with traditional markers. The exploration of novel markers such as nuclear magnetic resonance (NMR) and particle image velocimetry (PIV) suggests ongoing efforts to enhance diagnostic accuracy. While the lymphocyte-monocyte ratio (LMR) has been inconsistently reported, its significance as an inflammatory marker for RA disease activity has been noted. Overall, this synthesis underscores the promising role of NLR and PLR in RA assessment but emphasises the need for further validation and consideration of additional markers to enhance precision in evaluating disease activity.

Table 1: Demographic variable of the patients of both groups

Study Authors	Study Design	Participants (n)	NLR Findings	PLR Findings	Discussion
Lijuan W, et al. [6]	Cross-Sectional	547	NLR: ↑ in active RA (4.2 vs 3.4, P = .034)	PLR: ↑ in active RA (222.3 vs 176.9, P = .006)	NLR and PLR may not be useful independent diagnostic or complementary markers for disease activity in RA.
Uslu AU, et al. [7]	Case-Control	104	NLR: ↑ in RA (2.12 vs 1.58, P < 0.0001)	PLR: ↑ in RA (136.50 vs 114.84, P = 0.001)	NLR and PLR are new inflammatory markers associated with DAS-28, suggesting their utility in assessing disease activity in RA.
Sargin G, et al. [8]	Longitudinal	38	NLR: Higher in RA; Correlated with DAS28-ESR	PLR: Higher in RA; Correlated with DAS28-ESR	NLR and PLR decrease with rituximab; useful indices for RA disease activity after 6 months.
Obaid JMAS, et al. [9]	Case-Control	62	NMR: Useful marker with AUC of 0.861; cutoff = 4.7	LMR, NLR: AUC of 0.807 (cutoff = 4.35) and 0.699 (cutoff = 1.35), respectively; NMR outperforms LMR and NLR.	NMR is a convenient and low-cost inflammatory marker, outperforming LMR and NLR in association with RA activity.
Jin Z, et al. [10]	Multicenter	1009	NLR:	PLR:	NLR is less effective than CRP

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	Retrospective		Significantly higher in RA	Significantly higher in RA	and RF but superior to ESR; can be used as a complementary diagnostic indicator in RA.
Peng YF, et al. [5]	Case-Control	104	NLR, PLR: Higher in RA than controls	NLR positively correlated with PLR, RF, and CRP	PLR is associated with RA, indicating chronic subclinical inflammation.
Chandrashekara S, et al. [11]	Pilot Study	124 RA patients	NLR is consistent in predicting remission; CRP, ESR, and/or DAS are not very effective	NLR and pain perception help predict sustained remission	NLR effective in predicting remission; CRP, ESR, and DAS limitations in assessing remission
Mercan R, et al. [4]	Observational	136 RA patients, 140 AS patients, 117 healthy controls	Higher NLR in RA and AS patients; NLR correlated with ESR and CRP; NLR increased with worsening disease activity	Not specified	NLR is a cheap and readily available marker for disease activity in RA
Tekeoglu I, et al. [12]	Observational	102 RA patients	NLR values varied by disease activity; Higher NLR in high-level disease activity; No significant difference with PDW	Not specified	NLR may be a marker of acute-phase disease; PDW is not significant in disease activity
Zhang Y, et al. [13]	Observational	125 RA patients, 126 healthy individuals	High NLR and PLR in active and non-active RA patients; Combination of NLR and PLR as a panel had high diagnostic accuracy	NLR and PLR positively correlated with ESR	NLR and PLR are valuable for diagnosing RA; Correlation with ESR indicates severity
Chandrashekara S, et al. [14]	Cross-sectional observational	489	NLR values corresponded with DAS28-CRP(3); NLR had the least bias at lower ranges with DAS28-CRP(3); NLR cutoff of 1.4 classified deep remission with 90% specificity	Not specified	NLR is less expensive and effective than traditional markers in assessing inflammation in RA
Du J, et al. [15]	Retrospective	205 RA patients, 112 ERA patients, 104 healthy controls	Significant difference in NLR and PLR between patient and control groups	NLR and PLR significant in active disease vs. remission	NLR may be useful in assessing disease activity in RA; PLR for anti-TNF therapy but not for diagnosing ERA
Zengin O, et al. [16]	Prospective Observational	72 RA patients	IL-6, IL-10, and duration of illness were significantly different between remission and treatment-naïve groups	Not specified	NLR ≤ 2 associated with increased likelihood for sustained remission
Hussein S, et al. [17]	Case-Control	87 RA patients & 87 Controls	Higher NLR and PLR in RA patients; Positively correlated with RA activity	Not specified	NLR and PLR are useful, simple, and cheap markers for evaluating RA disease activity

DAS-28, Disease Activity Score of 28 joints; PIV: Platelet Inverse Value, CBC: Complete Blood Count, CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, IL: Interleukin, ERA: Early Rheumatoid Arthritis, AUC: Area Under the Curve; ↑, increased.

DISCUSSION

This comprehensive synthesis brings together findings from 14 diverse studies that investigated the usefulness of various inflammatory markers in evaluating disease activity in rheumatoid arthritis. The primary outcome measures in these studies included the neutrophil-to-lymphocyte ratio (NLR),

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platelet-to-lymphocyte ratio (PLR), Disease Activity Score-28 (DAS-28), platelet volume (PIV), lymphocyte-monocyte ratio (LMR), and neutrophil-to-monocyte ratio (NMR). The combined results of these studies demonstrated a range of associations between these markers and RA activity.[4-9]

The strength of this synthesis lies in the comprehensive review of a diverse set of studies, including cross-sectional, case-control, longitudinal, and retrospective designs, involving different patient populations and marker assessments.

By synthesising these findings, we can gain a broader perspective on the role of inflammatory markers in the context of RA disease activity. It is important to acknowledge the limitations of this study. These limitations include the inherent heterogeneity across studies, variations in sample sizes, and inconsistent reporting of outcomes. Furthermore, the lack of uniformity in defining disease activity and the diversity in marker cut-off values also contributed to the limitations of this study. In light of the totality of the evidence, this synthesis provides valuable insights into the potential use of NLR, PLR, PIV, LMR, and NMR as markers for assessing RA activity.[4-19] The findings support the idea that NLR and PLR hold promise in reflecting RA disease activity, while PIV, LMR, and NMR exhibit varying degrees of association. Despite the controversies arising from the diverse outcomes of the included studies, this study suggests that a systematic review could be beneficial in consolidating evidence and providing clearer guidance.

Some studies have highlighted the significance of increased NLR and PLR in active RA, while others have emphasised the potential of PIV, LMR, and NMR as markers.[19]

The controversies raised by this study primarily revolve around discrepancies in the findings among the analysed studies. Variability in patient characteristics, disease definitions, and marker assessments contribute to these controversies. Therefore, future research should focus on standardising the methodologies and exploring the underlying mechanisms to enhance the reliability and consistency of these markers.

Further clinical research is needed to validate the specific markers and establish their roles in routine RA assessments. In conclusion, this synthesis offers a nuanced understanding of the potential utility of inflammatory markers in the assessment of RA disease activity. This study highlights the importance of standardisation, further research collaboration, and systematic reviews in advancing our understanding of the roles of these markers in RA and in improving patient care. This synthesis serves as a valuable resource for clinicians and researchers seeking a comprehensive overview of existing evidence on inflammatory markers in RA.

CONCLUSION

This synthesis of 14 diverse studies on inflammatory markers in Rheumatoid Arthritis elucidates the complex landscape of potential indicators of disease activity. The amalgamation of findings underscores the promising roles of the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in reflecting RA activity. However, this study also revealed discrepancies and variations in the results across different markers and studies. Heterogeneity in patient populations, disease definitions, and cutoff values contributes to the complexity of interpreting these findings. Consequently, the varied associations between platelet inverse value, lymphocyte–monocyte ratio, neutrophil–monocyte ratio, and RA activity necessitate further research to establish their roles definitively. Standardisation of methodologies, larger sample sizes, and systematic reviews are recommended to enhance the reliability and clinical applicability of these inflammatory markers for routine RA assessment. This synthesis provides valuable insights, highlighting the need for a nuanced approach to understand the potential utility of inflammatory markers in the comprehensive management of Rheumatoid Arthritis.

REFERENCES

1. Silman AJ, Pearson JE. Arthritis Res. 2002;4(Suppl 3): S265. Available from: http://dx.doi.org/10.1186/ar578
2. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann Lab Med. 2019;39(4):345–57. Available from: http://dx.doi.org/10.3343/alm.2019.39.4.345
3. Macfarlane FR, Chaplain MAJ, Eftimie R. Quantitative predictive modelling approaches to understanding rheumatoid arthritis: A brief review. Cells. 2019;9(1):74. Available from: http://dx.doi.org/10.3390/cells9010074
4. Mercan R, Bitik B, Tufan A, Bozbulut UB, Atas N, Ozturk MA, et al. The association between neutrophil/lymphocyte ratio and disease activity in rheumatoid arthritis and ankylosing spondylitis. J Clin Lab Anal. 2016;30(5):597–601. Available from: http://dx.doi.org/10.1002/jcla.21908
5. Peng Y-F, Cao L, Zeng Y-H, Zhang Z-X, Chen D, Zhang Q, et al. Platelet to lymphocyte ratio and neutrophil to lymphocyte ratio in patients with rheumatoid arthritis. Open Med (Warsz). 2015;10(1). Available from: http://dx.doi.org/10.1515/med-2015-0037
6. Lijuan W, Yuting Z, Chaoyang L, Ju Y. Neutrophil-lymphocyte, platelet-lymphocyte and lymphocyte-monocyte ratios may not be useful markers to assess disease activity in rheumatoid arthritis: A STROBE-compliant article. Medicine (Baltimore). 2021;100(45): e27631. Available from: http://dx.doi.org/10.1097/md.0000000000027631
7. Uslu AU, Küçük A, Şahin A, Ugan Y, Yılmaz R, Güngör T, et al. Two new inflammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. Int J Rheum Dis. 2015;18(7):731–5. Available from: http://dx.doi.org/10.1111/1756-185x.12582
8. Sargin G, Senturk T, Yavasoglu I, Kose R. Relationship between neutrophil-lymphocyte, platelet-lymphocyte ratio and disease activity in rheumatoid arthritis treated with rituximab. Int J Rheum Dis. 2018;21(12):2122–7. Available from: http://dx.doi.org/10.1111/1756-185x.13400
9. Obaid JMAS, Almjydy MMA, Garban MAQ, Al-hebari FSQ, Al-washah NAH. Neutrophil-to-monocyte ratio is the better new inflammatory marker associated with rheumatoid arthritis activity. Health Sci Rep. 2023;6(8). Available from: http://dx.doi.org/10.1002/hsr2.1478
10. Jin Z, Cai G, Zhang P, Li X, Yao S, Zhuang L, et al. The value of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte

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ratio as complementary diagnostic tools in the diagnosis of rheumatoid arthritis: A multicenter retrospective study. J Clin Lab Anal. 2021;35(1). Available from: http://dx.doi.org/10.1002/jcla.23569
11. Chandrashekara S, Rajendran A, Bai Jaganath A, Krishnamurthy R. Neutrophil-lymphocyte ratio, pain perception, and disease activity score may serve as important predictive markers for sustained remission in rheumatoid arthritis. Reumatismo. 2015;67(3):109–15. Available from: http://dx.doi.org/10.4081/reumatismo.2015.838
12. Tekeoğlu İ, Gürol G, Harman H, Karakeçe E, Çiftçi İH. Overlooked hematological markers of disease activity in rheumatoid arthritis. Int J Rheum Dis. 2016;19(11):1078–82. Available from: http://dx.doi.org/10.1111/1756-185X.12805
13. Zhang Y, Yin Y, Kuai S, Shan Z, Pei H, Wang J. Combination of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as diagnostic biomarker for rheumatoid arthritis. Int J Clin Exp Med. 2016;9(11):22076–81. https://e-century.us/files/ijcem/9/11/ijcem0036774.pdf
14. Chandrashekara S, Mukhtar Ahmad M, Renuka P, Anupama KR, Renuka K. Characterization of neutrophil-to-lymphocyte ratio as a measure of inflammation in rheumatoid arthritis. Int J Rheum Dis. 2017;20(10):1457–67. Available from: http://dx.doi.org/10.1111/1756-185X.13157
15. Du J, Chen S, Shi J, Zhu X, Ying H, Zhang Y, et al. The association between the lymphocyte-monocyte ratio and disease activity in rheumatoid arthritis. Clin Rheumatol. 2017;36(12):2689–95. Available from: http://dx.doi.org/10.1007/s10067-017-3815-2
16. Zengin O, Onder ME, Kalem A, Bilici M, Türkbeyler IH, Ozturk ZA, et al. New inflammatory markers in early rheumatoid arthritis. Z Rheumatol. 2018;77(2):144–50. Available from: http://dx.doi.org/10.1007/s00393-016-0187-y
17. Hussein S, M Tawfik N, Abdelrahman NF, Abobakr A, Hafez R, Thabet MM. Correlation between Rheumatoid arthritis activity with neutrophil-lymphocyte ratio and platelet lymphocyte ratio: A case-control study. Clin Med & Helt Res J. 2023;3(6):637–42. Available from: http://dx.doi.org/10.18535/cmhrj.v3i6.229
18. Chandrashekara S, Lingaraju DC, Renuka P, Anupama KR. Potential of neutrophil to lymphocyte ratio in predicting sustained remission in rheumatoid arthritis compared to other immune activation markers. Indian J Med Res. 2020;152(3):234–43. Available from: http://dx.doi.org/10.4103/ijmr.IJMR_1676_18
19. Tutan D, Doğan AG. Pan-immune-inflammation index as a biomarker for rheumatoid arthritis progression and diagnosis. Cureus. 2023; Available from: http://dx.doi.org/10.7759/cureus.46609.

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