Comparison of Platelets-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratios in Rheumatoid Arthritis and Ankylosing Spondylitis

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ABSTRACT

Objective: To calculate and compare the platelets-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), to be used as a complementary diagnostic tool in patients of rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

Study Design: Cross-sectional, comparative study.

Place and Duration of the Study: Pak Emirates Military Hospital (PEMH), Rawalpindi, from February to November 2022.

Methodology: A total of two hundred and ten patients, aged between 25 to 70 years, were included in the study. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) along with platelets, leukocyte, and neutrophil count were estimated. PLR and NLR were calculated and compared between the groups.

Results: The PLR was significantly high in the RA group (p-value $<0.001$) followed by AS and control groups. NLR also followed the same trend and was significantly raised in both the disease groups as compared to controls. Pearson correlation depicted significant positive correlation between PLR and ESR ($r = 0.43, p <0.001$), NLR and ESR ($r = 0.34, p <0.001$), PLR and CRP ($r = 0.15, p = 0.034$) and NLR and CRP ($r = 0.18, p = 0.018$). Logistic regression analysis displayed the diagnostic value of PLR and NLR.

Conclusion: Both PLR and NLR are effective as complementary diagnostic indices in RA and AS patients. These may be used in addition to the inflammatory markers ESR and CRP as cost-effective and promptly available indices.

Key Words: Ankylosing spondylitis, Platelets-lymphocyte ratio, Neutrophils-lymphocyte ratio, Rheumatoid arthritis.


INTRODUCTION

Among the category of inflammatory arthritis, rheumatoid arthritis and spondyloarthropathies hold a pivotal position. Ankylosing spondylitis being the most prevalent is considered as the prototype in the class of spondyloarthropathies.\(^2\) Both of the diseases have a chronic autoimmune nature which involves widespread inflammation encompassing multi-systems. Rheumatoid arthritis mostly involves the diarthrodial joints and is characterised by the inflammation of synovium. Ankylosing spondylitis, on the other hand, involves the axial skeleton and may present with articular manifestations from the peripheral skeleton.\(^2\) Both, genetic predisposition and epigenetic factors, contribute towards the manifestation of rheumatic diseases. Human leukocyte antigen is suggested to have a great impact in this avenue.

Individuals with HLA-DR4 are more susceptible to develop rheumatoid arthritis,\(^3\) whereas the presence of HLA-B27 is characterised as a confirmatory sign for individuals of ankylosing spondylitis.\(^4\) Epigenetic factors such as female sex hormones, bacterial and viral-based infections, and smoking also have a role in the disease expression. In addition to the clinical presentation of the diseases which helps the physicians reach the final diagnosis, several biochemical markers confirm the inflammatory pathogenesis of these rheumatic diseases. Among the serological parameters which are available, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values are significant in determining the diagnosis and the disease activity of both rheumatoid arthritis and ankylosing spondylitis.\(^5\) The recent studies have proposed the utilitarian role of several haematologic indices in the diagnosis. Among these, platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are of paramount importance which not only have a diagnostic role but also have predictive and prognostic roles in rheumatic diseases.\(^6\)\(^7\)

This study aimed at the calculation and comparison of these ratios, PLR and NLR, in patients of rheumatoid arthritis and ankylosing spondylitis.

METHODOLOGY

A total of 210 individuals were enrolled in the cross-sectional study that was carried out in collaboration with the Department...
of Rheumatology, Pak-Emirates Military Hospital (PEMH), Rawalpindi. The study commenced after the formal approval by the ethical review committee of Army Medical College, and was conducted over a period of ten months, i.e. from February till November 2022. World Health Organization (WHO) sample calculator was used to estimate the sample size with prevalence taken as 1.5%, confidence interval 95% and margin of error 5%. Sampling was done using non-probability purposive sampling technique. During the course, samples of 210 individuals aged between 25 till 70 years, were collected which were categorised under 3 groups, namely controls constituting of 60 healthy individuals, 90 rheumatoid arthritis patients, and 60 patients of ankylosing spondylitis. Diagnosis of rheumatoid arthritis was made in accordance with the 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) criteria. Patients with synovitis (pain or swelling) in at least one joint, usually involving symmetrical fashion, presence of joint stiffness especially in the morning and raised levels of ESR or CRP were diagnosed as RA cases. Those fulfilling the criteria of the Assessment of Spondyloarthritis International Society (ASAS) were classified as ankylosing spondylitis (AS) patients. Patients with <45 years of age, with pain in lower back lasting since ≥3 months, with radiographic findings of sacroiliitis and presence of at least another SpA feature such as dactylitis or enthesitis, were diagnosed as AS cases. Alternatively, the presence of HLA-B27 antigen with at least two other SpA features confirmed the diagnosis of AS. Platelet and neutrophil count was the highest among the inflammatory disease groups compared to controls. One-way ANOVA followed by Post Hoc Tukey test of both inflammatory markers, i.e. ESR and CRP, were carried along with platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios in all the groups. All parameters displayed high significance (p-value <0.05) except CRP which was not significant in any of the groups.

Pearson correlation analysis, represented in the form of a scatter plot in Figure 1, revealed a significantly positive correlation between ESR, PLR, and NLR (p <0.05) and between CRP, PLR, and NLR (p <0.05).

Multinomial logistic regression analysis was carried out, keeping ESR, CRP, PLR and NLR as the independent variables and groups as the dependent variables. The results are displayed in Table II.

### Results

A total of 210 participants, comprising of 60 (28.6%) controls with 28 males and 32 females, 90 RA patients (42.9%) with female predominance (58/90), 60 AS (28.6%) with all the patients of male gender were included in the study. The mean ages of all the groups varied and are represented in Table I along with other parameters. The mean ESR in RA patients was markedly raised followed by the group of AS, CRP was raised in RA patients, followed by controls, while its values were lowest in the case of AS. Platelet and neutrophil count was the highest among the group of RA, followed by AS, as compared to controls. Lymphocyte count declined in these inflammatory disease groups as compared to the healthy controls, with the lowest levels in RA. PLR and NLR were the highest in RA, followed by AS when compared to controls. One-way ANOVA followed by Post Hoc Tukey test of both inflammatory markers, i.e. ESR and CRP, were carried along with platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios in all the groups. All parameters displayed high significance (p-value <0.05) except CRP which was not significant in any of the groups.

DISCUSSION

Rheumatological diseases like rheumatoid arthritis and ankylosing spondylitis are frequently assessed by inflammatory markers like ESR and CRP. The values of these markers are usually pronounced as compared to healthy controls suggesting the underlying inflammatory process, however, this may not always be the case. ESR and CRP levels may be within the normal ranges despite the evident clinical manifestations of the disease.
Platelets-to-lymphocyte and neutrophil-to-lymphocyte ratios in rheumatoid arthritis and ankylosing spondylitis

Table I: Demographic and clinical characteristics of the study groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls n = 60</th>
<th>RA Group n = 90</th>
<th>AS Group n = 60</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.9 ± 6.4</td>
<td>46.6 ± 11.9</td>
<td>35.9 ± 7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>12.9 ± 2.3</td>
<td>11.8 ± 1.9</td>
<td>13.0 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR (mm)</td>
<td>8.0 ± 2.7</td>
<td>31.9 ± 22.5</td>
<td>20.7 ± 15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>9.1 ± 3.2</td>
<td>16.8 ± 39.0</td>
<td>7.1 ± 8.8</td>
<td>0.055</td>
</tr>
<tr>
<td>Platelet count (x 10^9/L)</td>
<td>265.9 ± 91.6</td>
<td>331.1 ± 98.7</td>
<td>289.8 ± 97.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutrophil count (x 10^9/L)</td>
<td>3.7 ± 1.0</td>
<td>5.9 ± 1.6</td>
<td>5.2 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte count (x 10^9/L)</td>
<td>2.8 ± 0.9</td>
<td>2.4 ± 7.4</td>
<td>2.6 ± 0.8</td>
<td>0.004</td>
</tr>
<tr>
<td>PLR</td>
<td>102.5 ± 42.8</td>
<td>152.8 ± 69.7</td>
<td>117.5 ± 32.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NLR</td>
<td>1.4 ± 0.6</td>
<td>2.7 ± 0.9</td>
<td>2.2 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mean values of parameters along with p-value (by One-way ANOVA test).

Table II: Multinomial logistic regression analysis results.

<table>
<thead>
<tr>
<th>Group</th>
<th>Independent variable</th>
<th>B</th>
<th>Wald</th>
<th>Sig</th>
<th>Exp (B)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>ESR</td>
<td>0.316</td>
<td>17.58</td>
<td>&lt;0.001</td>
<td>1.372</td>
<td>1.183 - 1.590</td>
</tr>
<tr>
<td></td>
<td>CRP</td>
<td>-0.022</td>
<td>4.19</td>
<td>0.041</td>
<td>0.979</td>
<td>0.958 - 0.999</td>
</tr>
<tr>
<td></td>
<td>PLR</td>
<td>0.606</td>
<td>21.35</td>
<td>&lt;0.001</td>
<td>1.009</td>
<td>0.992 - 1.019</td>
</tr>
<tr>
<td></td>
<td>NLR</td>
<td>2.299</td>
<td>15.058</td>
<td>&lt;0.001</td>
<td>1.438</td>
<td>1.195 - 1.570</td>
</tr>
<tr>
<td>AS</td>
<td>ESR</td>
<td>0.291</td>
<td>0.004</td>
<td>0.949</td>
<td>1.297</td>
<td>0.869 - 1.013</td>
</tr>
<tr>
<td></td>
<td>CRP</td>
<td>-0.077</td>
<td>0.072</td>
<td>0.929</td>
<td>1.077</td>
<td>0.857 - 1.099</td>
</tr>
<tr>
<td></td>
<td>PLR</td>
<td>0.000</td>
<td>0.044</td>
<td>0.997</td>
<td>1.126</td>
<td>0.986 - 1.208</td>
</tr>
<tr>
<td></td>
<td>NLR</td>
<td>1.863</td>
<td>15.318</td>
<td>&lt;0.001</td>
<td>6.445</td>
<td>2.535 - 16.368</td>
</tr>
</tbody>
</table>

This fact necessitates the need of other inflammatory markers which are reliable, economical, and practically feasible for the accurate depiction of inflammation within the body. PLR and NLR are such ratios, which have been employed conveniently for determination of inflammation in many autoimmune diseases, diseases of cardiovascular system, and varied malignancies.\(^{10}\)

In this study, the two haematologic ratios namely PLR and NLR were found to be raised in case of both rheumatic diseases, being the highest in RA, followed by AS, as compared to controls. The outcome of this study also suggested a significant positive correlation of ESR with PLR and NLR. CRP was also significantly and positively correlated to PLR and NLR.\(^{11,12}\) These results are suggestive of the potential role of PLR and NLR for the assessment of rheumatoid arthritis and ankylosing spondylitis as complementary diagnostic indices, in addition to the conventionally used inflammatory markers. These findings have been backed by a few studies which were conducted on Pakistani patients where patients of AS exhibited an increase in the levels of PLR and NLR as compared to healthy controls.\(^{13}\) Similarly another study conducted on RA patients in Lahore, showed a surge in PLR in active disease subjects.\(^{14}\)

The levels of the platelets and neutrophils were significantly raised in the disease groups as compared to the healthy controls, signifying the underlying inflammatory picture in RA and AS. This finding was consistent with the results of many observational studies which indicated a higher level of platelets in rheumatoid arthritis and other rheumatic diseases with the radiological and clinical progression of the disease.\(^{15}\) Activated platelets have the ability to release several microparticles which interact with neutrophils primarily by the expression of platelet-type lipoxygenase and stimulation of the eicosanoid pathway.\(^{16}\) Patients of RA show synovial neutrophils studded with these microparticles of platelets and are capable of intensifying the synovitis. The role of inflammatory mediating interleukins such as IL-6 and TNF-α is also established in bringing about deleterious effects in these diseases and are held responsible for increased maturation and recruitment of neutrophils and platelets.\(^{17}\) Platelets also regulate the chemotaxic and cytotoxic functions of neutrophils by special surface receptors and the subsequent formation of platelet and neutrophil conjugates. These conjugates in the presence of anti-citrullinated protein antibodies (ACPA) in RA, stimulate pathways that lead to inflammatory polyarthritis.\(^{18}\) Levels of lymphocytes are reported to decline in the active disease phase. This study had also shown this trend in patients of RA. This reduction in the lymphocyte levels together with the increase in platelets and neutrophils, served as the basis of the surge in PLR and NLR.

The importance of PLR and NLR had already been established in other diseases of inflammatory basis and various malignancies.\(^{19,20}\) The role of these ratios in various rheumatic diseases was also a topic of interest for the researchers. The findings of this study, i.e. the significant rise in the PLR and NLR in rheumatoid arthritis were consistent with the results of many previously conducted researches which reinforced the use of these ratios as novel markers of inflammation in rheumatoid arthritis and other rheumatic diseases.\(^{21,22}\) Al Osami revealed a positive association of PLR and NLR values in 132 ankylosing spondylitis suffering patients. The difference between diseased individuals and healthy controls was not very remarkable, the values, however, were significantly different in the active disease...
state of patients as compared to inactive ankylosing spondylitis patients. The study’s results suggested a positive correlation of PLR and NLR with the disease activity markers namely ESR and CRP and these are congruous with the findings of Seng et al. who conducted the study on Asian patients of axial spondyloarthopathies, and found PLR and NLR to be associated with the diseased individuals presenting with raised ESR and CRP values.

The utility of PLR and NLR in tracking the efficacy of treatment and amelioration of disease process has also been researched upon. These ratios are reported to wane once the treatment of the rheumatic diseases commence. Enginar et al. demonstrated this change by conducting a research on patients of rheumatoid arthritis and ankylosing spondylitis and proved a significant decline in the values of PLR and NLR, after 6 months usage of anti-TNF medication.

The availability of limited time and funding led to limited sampling, which were the main limitations of this study. Extensive sampling involving multi-centres, ensuring the participation of both genders equally will yield more reliable findings.

CONCLUSION

Both PLR and NLR were found to be elevated in RA and AS patients. The study was in favour of the use of these ratios to be used as complementary diagnostic means in addition to the conventionally assessed inflammatory markers i.e. ESR and CRP.

ETHICAL APPROVAL:
This study was approved by the Ethical Review Committee of the Army Medical College, Rawalpindi (ERC/ID/179, dated 17/01/2022), affiliated with National University of Medical Sciences (NUMS).

PATIENTS’ CONSENT:
Informed consents were obtained from all participants of the study through written consent form.

COMPETING INTEREST:
All the authors declared no competing interest in regard to the content of this research.

AUTHORS’ CONTRIBUTION:
SK, JY: Study design and conception, patient selection, and manuscript writing. AR, AM: Review of the content of intellectual importance, and provided clinical expertise in the rheumatology department. All authors approved the final version of the manuscript to be published.

REFERENCES


