Correlation between serum uric acid, C-reactive protein, and neutrophil-to-lymphocyte ratio in patients with psoriasis: A case-control study

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Abstract

Background and Design: Although multiple investigations have been conducted to identify important serum biomarkers in patients with psoriasis, no simple, useful biomarker that could be specific for psoriasis has been identified. Objectives: 1) To determine the levels of serum uric acid (SUA), C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR) among individuals with psoriasis and controls, 2) to assess the correlation of SUA and CRP levels and NLR with disease severity calculated through the psoriasis area severity index (PASI) in patients with psoriasis.

Materials and Methods: A hospital-based, case-control study included 45 patients clinically diagnosed with psoriasis and 45 age- and sex-matched controls attending the outpatient dermatology clinic of our hospital. After a complete history was taken, and general, systemic, and cutaneous examinations were performed, all the cases were subjected to the following investigations: Complete blood count (NLR), CRP, and SUA.

Results: Mean SUA level was significantly higher in the patients with psoriasis compared to the controls (p<0.01). However, no difference in CRP levels and NLR was observed (p>0.05). A significant correlation of SUA level and NLR was found with disease severity in the patients with psoriasis as determined by the PASI. In multivariate analysis, only SUA was found to be independently associated with psoriasis severity (p<0.05).

Conclusion: The results showed that only SUA to be independently associated with psoriasis severity. No association was found between CRP levels and NLR and disease severity, as well as no difference between the disease and controls groups.

Keywords: C-reactive protein, neutrophil-to-lymphocyte ratio, psoriasis, serum uric acid

Öz

Amaç: Psoriazis hastaların periferik kan örneklerinde yararlı biyobelirteçler bulmak amacıyla çok sayıda araştırma yapılmış olmasına rağmen, psoriazis özgür olabilecek basit ve klinik olarak yararlı bir biyobelirteç tanımlanmamıştır. Hedefler: 1) Psoriazisli hastalar ve kontroller arasında serum ürik asit (SÜA), C-reaktif protein (CRP) ve nötrofil/lenfosit oranını (NLO) belirlemek, 2) psoriazisi olan hastalarda SÜA seviyeleri, CRP nötrofil/lenfosit oranı ve psoriazis alan şiddet indeksleri (PAŞI) ile hesaplanan hastalık şiddetini arasındaki iliği değerlendirmektir.

Gereç ve Yöntem: Hastane bazlı bir olgu kontrol çalışması, hastanemizin dermatoloji poliklinine başvuran, klinik olarak teşhis edilmiş 45 psoriazis olgusu, 45 yaş ve cinsiyet uyumlu kontrol dahil edilmiş. Tam öykü, genel, sistemik ve kutanöz muayeneleri yapıldıktan sonra tüm olgularda tam kan sayımı (NLO), CRP ve SÜA İncelemeleri yapılmıştır.

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Introduction
Psoriasis is a chronic papulosquamous, inflammatory dermatoses that manifests clinically as erythematous papules and plaques with silvery scales, commonly located over the elbows, knees, scalp, extensor aspects of the forearm and legs, and the lumbosacral area. It affects approximately 1-3% of the world population. It is considered an immune-mediated inflammatory disorder, in association with other immune-mediated disorders like Crohn’s disease, rheumatoid arthritis, and multiple sclerosis.

Multiple investigations have been conducted to identify a specific biomarker for psoriasis in peripheral blood; however, no single, simple, clinically useful biomarker that could be specific for the disease has yet been found.

C-reactive protein (CRP), an acute phase reactant, increases significantly during acute inflammation and has been suggested as a biomarker in several diseases like rheumatoid arthritis, tuberculosis, cancer, and psoriasis. The rate of CRP synthesis and secretion increases multiple folds within hours of inflammation and peaks at 24-48 h. It mainly identifies autogenous, toxic substances that are released from damaged cells, and also helps in binding and detoxifying these potentially toxic substances. CRP levels also correlate with the disease extent. In addition, although CRP levels decrease with treatment by 12 weeks, it never returns to the normal limit.

Recently, the neutrophils-to-lymphocytes ratio (NLR) has been recognized as an inflammatory marker. NLR is an easily determined inflammatory index. It is relatively stable in comparison to individual white blood cell parameters, which are known to be altered by overhydration or dehydration, dilution, and handling of blood specimen. NLR is also a potential predictor of subclinical atherosclerosis in patients with psoriasis.

Given the paucity of studies on these parameters collectively, this study aimed to evaluate the levels of serum uric acid (SUA) and CRP, and the NLR among patients with psoriasis compared to controls. Further, this study aimed to understand the relationship of these parameters with disease severity, which may help to monitor the therapeutic response.

Objectives of the study
1. To determine the levels of SUA and CRP, and NLR among individuals with psoriasis and controls.
2. To assess the correlation of SUA and CRP levels and NLR with disease severity calculated through the psoriasis area severity index (PASI) in patients with psoriasis.

Materials and Methods
This study was approved by the Ethics Committee of Vydehi Institutional Ethics Committee University Faculty of Medicine (approval number: ECR/747/Inst/KA/2015, date: 20.11.2017). A written informed consent was obtained from each participant willing to be included in the study.

Source of data
Department of Dermatology, VIMSRC, Bangalore.

Study population
Patients clinically diagnosed with psoriasis and matched controls (age and sex matched) attending the outpatient department of Dermatology, VIMSRC, Bangalore.

Study design
Case-control study

Study duration/period
January 2018 to June 2019: One year and six months duration.

Sample size
Based on the study by Sen et al., the sample size was calculated using the following equation:

\[ n = \left[ \frac{Z_{\alpha/2} \times \sqrt{S_x^2 + S_y^2}}{\mu_d} \right]^2 \]

Therefore, 45 patients with psoriasis and 45 controls (age and sex matched) attending the outpatient department of dermatology were included.

Inclusion criteria

Cases
Patients clinically diagnosed with psoriasis, age 18 years and above, and of both sexes were included. Patients with psoriasis who gave voluntary written informed consent to participate in the study.

Controls
Individuals (age and sex matched) attending the outpatient department of Dermatology as a part of a health check-up, who gave voluntary written informed consent to participate in the study, after ruling out psoriasis.

Exclusion Criteria

Cases
Patients with psoriasis currently on systemic therapy or who have been taking systemic therapy for the past 1 month.

Patients receiving allopurinol, thiazide-type diuretics at the start of the study.

Patients with a history of diabetes mellitus, hypertension, or other cardiovascular diseases.

Patients smoking tobacco or using non-smoking tobacco products.

Active infection or overt malignancy

Known liver and renal diseases

Pregnant women

Controls
Individuals with any known underlying disease.
Methods of data collection
Demographic data was collected, a detailed history taken, dermatological examination performed, and the PASI score calculated. Skin biopsy was performed in doubtful cases to confirm the diagnosis of psoriasis. Diagnosed cases of psoriasis fulfilling the inclusion and exclusion criteria were investigated for complete blood count, CRP, and SUA.

Statistical Analysis
Data collected was entered into MS-Excel. All statistical analysis was carried out using SPSS software version 21. Quantitative data was presented as mean ± standard deviation. Categorical and nominal data were expressed in percentage. Data analysis was conducted using the unpaired t-test for normally distributed quantitative data, the Mann-Whitney U test for non-parametric data, and the chi-square test for categorical data. Pearson’s correlation coefficient was used to determine the correlation among quantitative variables. Multivariate regression analysis was done to identify the predictors of disease severity i.e., PASI. The significance threshold of p-value was set at <0.05.

Outcome measures
1. The levels of SUA and CRP, and the NLR noted for patients with psoriasis and the controls.
2. The relationship between SUA and CRP levels, the NLR, and disease severity (PASI) was evaluated among patients with psoriasis [Severity of the disease graded as: Mild (PASI <10), moderate (PASI -11-20), and severe (PASI >20)].

Results
Both cases and controls were comparable with respect to age and sex (p>1.0). Most of the cases were aged between 21 and 40 years (64.4%), with a mean age of 36.1 years and a male predominance (62.2%). The most common type of psoriasis was plaque psoriasis (77.8%), followed by guttate and scalp psoriasis (6.7% each). Joint and nail involvement was noted in 4.4% of cases each. As per PASI (Table 1), mild-to-moderate psoriasis was observed in 57.8% and 28.9% of cases, whereas severe psoriasis was observed in 13.3% of cases. Mean SUA was significantly higher among cases compared to the controls (p<0.01). However, no difference in CRP levels and NLR was found between both groups (p>0.05) (Table 2 and Figure 1). The mean SUA level was significantly higher among psoriatic patients with severe disease compared to those with mild disease (p<0.05). However, no difference in CRP levels and NLR (p>0.05) was observed with respect to the severity of psoriasis (Table 3 and Figure 2). A significant correlation of SUA and NLR was observed with disease severity in psoriasis as determined by PASI (Table 4 and Figure 3, 4). In multivariate analysis (Table 5), only SUA was found to be an independently associated with psoriasis severity (p<0.05).

Discussion
Psoriasis is a chronic inflammatory skin disorder with an immunological basis. Hypertension, atherosclerotic heart disease, and metabolic syndromes are more frequent in patients with psoriasis, probably because they share a common genetic background of systemic inflammation\(^1\). With elevated markers of inflammation, psoriasis is a systemic inflammatory disorder leading to impaired endothelial dysfunction and a higher risk of atherosclerotic heart disease\(^1\).
Recent studies report that hyperuricemia is independently associated with hypertension, atherosclerosis, renal disease, and metabolic syndrome \textsuperscript{13,14}. Hyperuricemia has been proposed to enhance oxidative stress and inflammation which, in turn, lead to endothelial dysfunction, promoting atherosclerosis \textsuperscript{15-17}. Several studies report hyperuricemia in patients with psoriasis \textsuperscript{16,20}. In our study, hyperuricemia was found to be significantly correlated with the severity of psoriasis (PASI index). In multivariate analysis, only SUA was found to be independently associated with psoriasis severity \textsuperscript{(p<0.05)}. Solak et al.\textsuperscript{21} reported hyperuricemia more frequently in patients with psoriasis compared with the controls. The NLR is a novel inflammatory marker that increases in many disease states and correlates with conventional inflammatory markers, which have also been shown to be associated with CV morbidity and mortality and all-cause mortality in some patient cohorts \textsuperscript{22-23}. Some studies on NLR showed increased NLR values in psoriasis compared with controls \textsuperscript{24-25}. Studies provide conflicting results regarding the association between NLR and psoriasis severity, with some showing a significant association \textsuperscript{21}, and others not \textsuperscript{26,27}. In our study, there is a significant correlation between NLR and PASI scores. Moreover, regression analysis showed that NLR is not one of the independent risk factors of severity (PASI score) in patients with psoriasis. Contrary to our findings, Solak et al.\textsuperscript{21} in their study found that PASI score is independently associated with NLR in patients with psoriasis. A case-control study by Yadav et al.\textsuperscript{28} with 40 patients showed no significant correlation between NLR and psoriasis severity. However, a metaanalysis conducted by Paliojannis et al.\textsuperscript{29} showed that NLR is significantly associated with psoriasis and disease severity. Further studies are needed to evaluate this relationship in more detail.

CRP is a non-glycolyzed pentameric protein made by hepatocytes with a molecular weight of 118 kilodaltons (kD). The molecule is known as a major acute phase reactant that increases rapidly after infections or tissue damage, is widely used as a laboratory parameter for the follow-up of inflammatory and infectious disease activity, and is accepted as a very sensitive inflammatory marker \textsuperscript{6,21}. Few previous studies showed significantly increased CRP levels in patients with psoriasis compared with patients in the control group \textsuperscript{22-24}. Our results were in contradiction with these studies showing no significant difference between CRP values in psoriasis cases to the control group. However, similar to the present study, Solak et al.\textsuperscript{21} also observed that CRP is not independently associated with PASI in patients with psoriasis. A case-control study conducted by Gupta et al.\textsuperscript{15} on 38 patients showed that CRP levels increased significantly in psoriasis. Vadakayil et al.\textsuperscript{30} conducted a case-control study with 100 patients and showed significantly high levels of CRP in psoriasis, suggesting that it could be a useful marker for psoriatic severity.

**Study Limitations**

The limitation of our study is the small sample size. In summary, the results of this study show that uric acid was increased in patients with psoriasis compared with healthy volunteers. Multivariable linear regression analysis also revealed that hyperuricemia was independently associated with inflammation in patients with psoriasis. Therefore, SUA levels seem to be a driver of increased inflammation or psoriasis disease severity in our cohort. However, further studies are needed to better elucidate the precise role of increased SUA in patients with psoriasis.
Considering the ever-increasing role of elevated SUA levels in the pathogenesis of atherosclerotic disease and other metabolic diseases, more robust data are needed to confidently accept the possible role of uric acid in patients with psoriasis.

Conclusion

SUA was found to be independently associated with psoriasis severity. SUA levels were also higher in patients with psoriasis compared to healthy controls. No association was observed between CRP levels and disease severity, as well as no difference between patients with psoriasis and the controls.

NLR correlated with disease severity on univariate analysis, but the difference was non-significant on multivariate analysis. Thus, SUA seems to modulate inflammation in patients with psoriasis and is a potential predictor of subclinical atherosclerosis in these patients.

To summarize, results of this study show that uric acid was increased in patients with psoriasis compared with healthy volunteers. Multivariable linear regression analysis also revealed that hyperuricemia was independently associated with inflammation in patients with psoriasis. Thus, SUA levels seem to be a driver for increased inflammation or psoriasis disease severity in our cohort. However, further studies are needed to better elucidate the precise role of increased SUA in patients with psoriasis. Considering the ever-increasing role of elevated SUA levels in the pathogenesis of atherosclerotic disease and other metabolic diseases, more robust data are needed to confidently accept the possible role of uric acid in patients with psoriasis.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Vydehi Institutional Ethics Committee University Faculty of Medicine (approval number: ECR/747/Inst/KA/2015, date: 20.11.2017).

Informed Consent: A written informed consent was obtained from each participant willing to be included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.M., M.K., S.R.J., H.K., R.A., S.B., Concept: S.M., S.R.J., Design: S.M., M.K., H.K., Data Collection or Processing: S.M., R.A., S.B., Analysis or Interpretation: S.M., S.R.J., S.B., Literature Search: S.M., M.K., H.K., Writing: S.M., M.K., S.R.J., H.K., R.A., S.B.

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References

1. Weinberg JM, Lebwohl M: Advances in psoriasis. A Multisystemic Guide, Springer; 2014.
2. Naldi L, Gambini D: The clinical spectrum of psoriasis. Clin Dermatol 2007;25:5108.
3. Villanova F, Di Meglio P, Nestle FO: Biomarkers in psoriasis and psoriatic arthritis. Ann Rheum Dis 2013;72:104-10.
4. Pepys MB, Hirschfield GM: C-reactive protein: A critical update. J Clin Invest 2003;111:1805-12.
5. Paller D, Petrou I: Pediatric psoriasis: C-reactive protein levels associated with disease severity. J Invest Dermatol 2009;102:219-27.
6. Strober B, Teller C, Yamauchi P et al.: C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol 2008;159:322-30.
7. Balta S, El Cek T, Mikhailidis DP et al.: The relation between atherosclerosis and the neutrophil-lymphocyte ratio. Clin Appl Thromb Hemost 2016;22:405-11.
8. Özer S, Yilmaz R, Sönmezgöz E, et al.: Simple markers for subclinical inflammation in patients with familial mediterranean fever. Med Sci Monit 2015;21:298-303.
9. Qin B, Ma N, Tang Q, et al.: Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol 2016;26:376-7.
10. Janik S, Raunegger T, Hacker P, et al.: Prognostic and diagnostic impact of fibrinogen, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio on thymic epithelial tumors outcome. Oncotarget 2018;9:21861-75.
11. Sen BB, Rifaioğlu EN, Ekiz O, Inan ML, Sen T, Sen N: Neutrophil to lymphocyte ratio as a measure of systemic inflammation in psoriasis. Cutan Ocul Toxicol 2014;33:223-7.
12. Lubrano E, Cantini F, Costanzo A, et al.: Measuring psoriatic disease in clinical practice. An expert opinion position paper. Autoimmun Rev 2015;14:864-74.
13. Grozdev I, Korman N, Tsankov N: Psoriasis as a systemic disease. Clin Dermatol 2014;32:343-50.
14. Kanbay M, Solak Y, Dogan E, Lasapua MA, Covic A: Serum uric acid in hypertension and renal disease: the chicken or the egg? Blood Purif 2010;30:288-95.
15. Billiet L, Doaty S, Katz JD, Velasquez MT: Hyperuricemia as new marker for metabolic syndrome. ISRN Rheumatol 2014;2014:852954.
16. Ishizaka Y, Yamakado M, Toda A, Tani M, Ishizaka N: Relationship between serum uric acid and serum oxidative stress markers in the Japanese general population. Nephron Clin Pract 2014;128:49-56.
17. Kanbay M, Yilmaz MI, Apetrii M, et al.: Relationship between serum magnesium levels and cardiovasculinar events in chronic kidney disease patients. Am J Nephrol 2012;36:228-37.
18. Kanbay M, Huddam B, Azak A, et al.: A randomized study of allopurinol in endothelial function and estimated glomerular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol 2011;6:1887-94.
19. Gisondi P, Targher G, Cagalli A, Girolomoni G: Hyperuricemia in patients with chronic plaque psoriasis. J Am Acad Dermatol 2014;70:127-30.
20. Li X, Miao X, Wang H, et al.: Association of serum uric acid levels in psoriasis: A systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e5676.
21. Solak B, Dikicier BS, Erdem T: Impact of elevated serum uric acid levels on systemic inflammation in patients with psoriasis. Angiology 2017;68:266-70.
22. Ciray H, Aksoy AH, Ulu N, Cizmeciglu A, Gaipov A, Solak Y: Nephropathy, but not angiographically proven retinopathy, is associated with neutrophil to lymphocyte ratio in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2015;123:267-71.
23. Biyik M, Ucar R, Solak Y, et al.: Blood neutrophil-to-lymphocyte ratio independently predicts survival in patients with liver cirrhosis. Eur J Gastroenterol Hepatol 2013;25:435-41.
24. Ataseven A, Bilgin AL, Kurtipek GS: The importance of neutrophil lymphocyte ratio in patients with psoriasis. Mater Sociomed 2014;26:231-3.
25. Kim DS, Shin D, Lee MS, et al.: Assessments of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in Korean patients with psoriasis vulgaris and psoriatic arthritis. J Dermatol 2016;43:305-10.
26. Ataseven A, Bilgin AL, Kurtipek GS: The importance of neutrophil lymphocyte ratio in patients with psoriasis. Mater Sociomed 2014;26:231-3.
27. Sunbul M, Seckin D, Durmus E, et al.: Assessment of arterial stiffness and cardiovascular hemodynamics by oscillometric method in psoriasis patients with normal cardiac functions. Heart Vessels 2015;30:347-54.
28. Yadav SK, Sharma S, Singh S, Khurana VK, Sarin N: Neutrophil to lymphocyte ratio and platelet lymphocyte ratio: Novel markers of inflammation in psoriasis. Annals of Pathology and Laboratory Medicine 2019;6:387-91.
29. Paliogiannis P, Satta R, Deligi G: Association between neutrophil lymphocyte ratio and platelet lymphocyte ratio and presence of psoriasis: A systematic review and meta-analysis. Clin Exp Med 2019;19:37-45.
30. Blake GI, Ridker PM: Novel clinical markers of vascular wall inflammation. Circ Res 2001;89:763-71.
31. Choudhury RP, Leyva F: C-Reactive protein, serum amyloid A protein and coronary events. Circulation 1999;100:65-6.
32. Steel DM, Whitehead AS: The major acute phase reactants: C reactive protein, serum amyloid P component and serum amyloid A protein. Immunol Today 1994;15:81-8.
33. Balta S, Balta I, Mikhailidis DP, et al.: Bilirubin levels and their association with carotid intima media thickness and high-sensitivity C-reactive protein in patients with psoriasis vulgaris. Am J Clin Dermatol 2014;15:137-42.
34. Balta I, Balta S, Demirkol S, et al.: Elevated serum levels of endocan in patients with psoriasis vulgaris: correlations with cardiovascular risk and activity of disease. Br J Dermatol 2013;169:1066-70.
35. Gupta S, Garg P, Gupta N, Gupta N: High sensitivity C-reactive protein, a predictor of cardiovascular mortality and morbidity and psoriasis: A case control study. Int J Res Dermatol 2019;5:338-41.
36. Vadakayil AR, Dandekeri S, Kambli SM, Ali NM: Role of C-reactive protein as a marker of disease severity and cardiovascular risk in patients with psoriasis. Indian Dermatol Online J 2015;6:322-5.