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

Serum ürik asit, C-reaktif protein ve nötrofil/lenfosit oranının psoriazis ile ilişkisi: Bir olgu kontrol çalışması

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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: Psoriazisli hastaların periferik kan örneklerinde yararlı biyobelirteçler bulmak amacıyla çok sayıda araştırma yapılmış olmasına rağmen, psoriazise özgü 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 indeksi (PAŞİ) ile hesaplanan hastalık şiddeti arasındaki ilişkiyi değerlendirmektir.

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

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Bulgular: Psoriazis olguları arasında ortalama SÜA düzeyi kontrollere göre anlamlı derecede yüksekti (p<0,01). Ancak CRP düzeyleri ve NLO arasında fark gözlenmedi (p>0,05). Psoriazisli hastalarda SÜA ve NLO ile, PAŞİ skoru ile belirlenen hastalık şiddeti arasında anlamlı bir korelasyon gözlendi. Çok değişkenli analizde, sadece SÜA'nın, psoriazis şiddeti ile bağımsız olarak bir ilişki gösterdiği belirlendi (p<0,05).
Sonuç: Bu çalışmanın sonuçları, yalnızca SÜA'nın bağımsız olarak psoriazis şiddeti ile ilişkili olduğunu gösterdi. CRP seviyeleri ile NLO ve hastalık şiddeti arasında hiçbir ilişki gözlenmedi, hastalık ve kontrol grupları arasında da herhangi bir fark kaydedilmedi.
Anahtar Kelimeler: C-reaktif protein, nötrofil-lenfosit oranı, psoriazis, serum ürik asit

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[1]. It is considered an immune-mediated inflammatory disorder, in association with other immune-mediated disorders like Crohn's disease, rheumatoid arthritis, and multiple sclerosis[2].

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[3].

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[4,5]. The rate of CRP synthesis and secretion increases multiple folds within hours of inflammation and peaks wat 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 correlates with the disease extent. In addition, although CRP levels decrease with treatment by 12 weeks, it never returns to the normal limit[6].

Recently, the neutrophils-to-lymphocytes ratio (NLR) has been recognized as an inflammatory marker[7,8]. 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 over-hydration or dehydration, dilution, and handling of blood specimen[9]. NLR is also a potential predictor of subclinical atherosclerosis in patients with psoriasis[10].

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.[11], the sample size was calculated using the following equation:

$$n = [2S_p^2 [Z (1-\alpha/2) + Z (1-\beta)]^2]/\mu d^2$$

$$S_p^2 = [S_1^2+S_2^2]/2$$

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)][2].

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[12]. With elevated markers of inflammation, psoriasis is a systemic inflammatory disorder leading to impaired endothelial dysfunction and a higher risk of atherosclerotic heart disease[13].

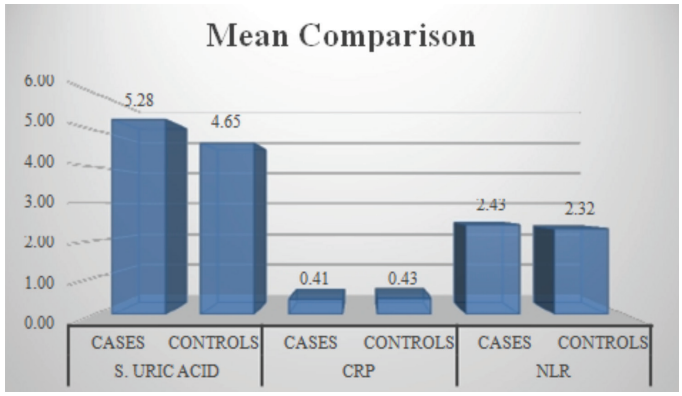

Figure 1. Bar graph showing the comparison of mean serum uric acid and CRP levels and NLR between cases and controls
CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio

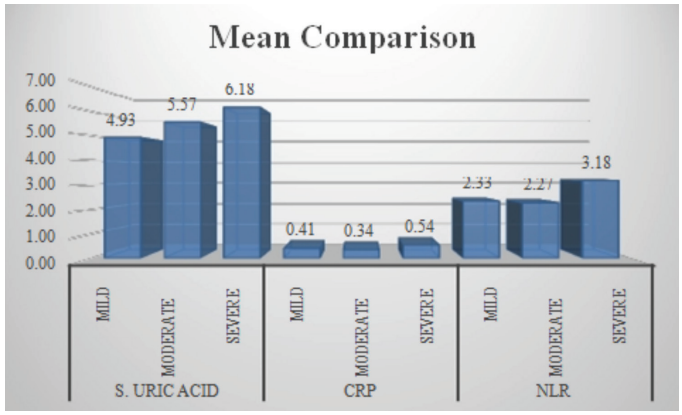

Figure 2. Bar graph showing the association of serum uric acid, C-reactive protein, and neutrophils-to-lymphocytes ratio with severity of psoriasis

Table 1. Distribution of study cases as per severity of disease (PASI)

Severity (PASI)	Number of cases	Percentage
Mild	26	57.8%
Moderate	13	28.9%
Severe	6	13.3%
Total	45	100.0%

PASI: Psoriasis area severity index

Table 2. Comparison of mean serum uric acid, CRP, and NLR between cases and controls

Variables	Group	N	Mean	SD	p-value
Serum uric acid (mg/dL)	Cases	45	5.28	1.20	<0.01
	Controls	45	4.65	0.98	
CRP (mg/dL)	Cases	45	0.41	0.28	0.68
	Controls	45	0.43	0.18	
NLR	Cases	45	2.43	0.16	0.576
	Controls	45	2.32	0.47	

CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation

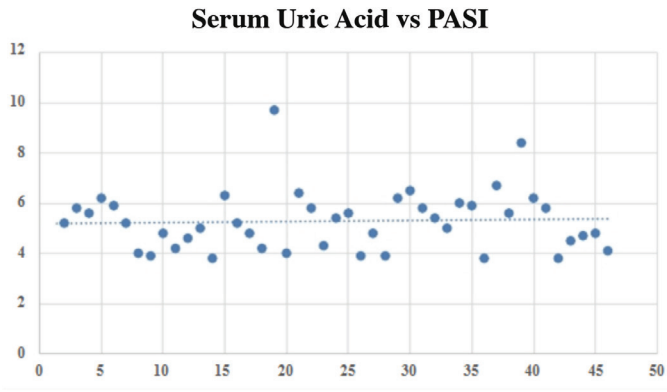

Figure 3. Scatter plot showing the correlation of serum uric acid with severity of psoriasis (PASI)

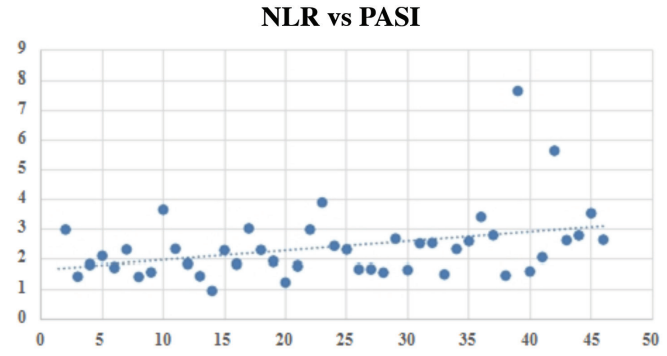

Figure 4. Scatter plot showing the correlation of neutrophils-to-lymphocytes ratio with severity of psoriasis (PASI)

Table 3. Association of serum uric acid, CRP, and NLR with severity of psoriasis

Variables	PASI	Number of cases	Mean	SD	p-value
Serum uric acid (mg/dL)	Mild	26	4.93	0.87	0.037 (mild vs severe)
	Moderate	13	5.57	1.54	
	Severe	6	6.18	1.14	
CRP (mg/dL)	Mild	26	0.41	0.29	0.359
	Moderate	13	0.34	0.26	
	Severe	6	0.54	0.32	
NLR	Mild	26	2.33	1.03	0.237
	Moderate	13	2.27	0.57	
	Severe	6	3.18	2.24	

PASI: Psoriasis area severity index, SD: Standard deviation, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio

Table 4. Correlation of serum uric acid, CRP and NLR with severity of psoriasis (PASI)

PASI	r-value	p-value
Serum uric acid	0.44	<0.01
CRP	0.13	0.389
NLR	0.37	0.013

CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PASI: Psoriasis area severity index

Recent studies report that hyperuricemia is independently associated with hypertension, atherosclerosis, renal disease, and metabolic syndrome[13,14].

Hyperuricemia has been proposed to enhance oxidative stress and inflammation which, in turn, lead to endothelial dysfunction, promoting atherosclerosis[14-17]. Several studies report hyperuricemia in patients with psoriasis[18-20]. 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 ($p<0.05$). Solak et al.[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[22,23]. Some studies on NLR showed increased NLR values in psoriasis compared with controls[24,25]. Studies provide conflicting results regarding the association between NLR and psoriasis severity, with some showing a significant association[21], and others not[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.[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.[28] with 40 patients showed no significant correlation between NLR and psoriasis severity. However, a metanalysis conducted by Paliogiannis et al.[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[30,31]. Few previous studies showed significantly increased CRP levels in patients with psoriasis compared with patients in the control group[32-34]. 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.[21] also observed that CRP is not independently associated with PASI in patients with psoriasis. A case-control study conducted by Gupta et al.[35] on 38 patients showed that CRP levels increased significantly in psoriasis. Vadakayil et al.[36] 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.

Table 5. Linear Regression analysis for assessing severity of psoriasis

Linear Regression analysis for PASI							
Variables	**Unstandardized coefficient (B)**	**S.E.**	**Stand. beta**	**t-value**	**p-value**	**95% CI**	
						Variable	**Upper**
Constant	0.22	0.483	-	0.457	0.65	-0.754	1.195
Serum uric acid	0.217	0.087	0.359	2.497	0.017	0.042	0.393
NLR	0.077	0.09	0.124	0.862	0.394	-0.104	0.259

PASI: Psoriasis area severity index, NLR: Neutrophil-to-lymphocyte ratio, CI: Confidence interval

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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