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**ORIGINAL ARTICLE**

# Neutrophil/lymphocyte ratio as serum inflammatory biomarker in patients with moderate-to-severe plaque psoriasis

## *Razão neutrófilo linfócito como marcador inflamatório sérico em pacientes com psoríase vulgar moderada-grave*

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## Abstract

**Introduction:** Psoriasis is an immune-mediated, chronic, inflammatory, systemic disease that primarily affects the skin and joints. Despite advances in the comprehension of the disease, there is still a lack of biomarkers available for clinical use. **Objective:** To evaluate neutrophil-lymphocyte ratio (NLR) as a marker of systemic inflammatory status in patients with moderate to severe plaque psoriasis vulgaris, compared with controls. **Methods**: Observational case-control study, conducted in a public hospital unit, focused on skin disease. A total of 165 patients with psoriasis and 187 healthy subjects seen between August and December 2020 were studied. **Results:** The group of cases showed a greater median of NLR compared with controls (medium = 1.96, p = 0.032). When stratified by age, the median NLR was higher in individuals between 31 and 60 years, with statistical significance. No differences were identified in gender, presence of arthritis or comorbidities. **Study limitations**: Observational, retrospective, single-center study based on medical records review. **Conclusion:** NLR was higher in individuals with psoriasis when compared with controls. It is simple, inexpensive and available in all levels of care, based on an elementary laboratory test that is already part of the routine care of patients with psoriasis. Its use in evaluating systemic inflammation could contribute to better management of psoriatic disease.

***Keywords:*** Psoriasis. Neutrophils. Lymphocytes. Autoimmune disease.

## Resumo

**Introdução:** A Psoríase é uma doença crônica, inflamatória, imunomediada, sistêmica, com especial predileção pela pele e pelas articulações. Apesar dos avanços em seu entendimento, faltam biomarcadores laboratoriais para uso clínico. **Objetivo:** Determinar a diferença na razão neutrófilo/linfócito (RNL), como marcador inflamatório sérico, entre pacientes com psoríase vulgar moderada quando comparados a indivíduos sem psoríase. **Métodos:** Estudo observacional, tipo caso-controle, realizado em uma unidade hospitalar e ambulatorial pública de atendimento a pacientes com doenças dermatológicas. Fizeram parte do estudo os pacientes com psoríase (165 casos) e controles sem psoríase (187) atendidos no local, entre agosto de 2018 a dezembro de 2020. **Resultados:** O grupo dos casos apresentou maior mediana de RNL em relação aos controles (md = 1,96,

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p = 0,032). Não houve diferença quanto ao gênero ou presença ou não de comorbidades. Verificou-se, no entanto, quando estratificados por idade, também maior mediana entre casos com 30 e 60 anos, novamente com significância estatística. Não houve diferença entre RNL de pacientes portadores de psoríase, com ou sem artrite. **Limitações do estudo:** Estudo observacional, retrospectivo, unicêntrico, baseado em revisão de prontuários. **Conclusão:** A RNL foi mais elevada em doentes com psoríase em comparação com o grupo controle no presente estudo, de forma similar a outros estudos no assunto. Sugere-se que a RNL possa ser utilizada na avaliação de inflamação sérica destes pacientes, podendo contribuir na condução, manejo e orientação dos pacientes. Constitui marcador simples, acessível em todos os níveis de saúde, cujo exame elementar já faz parte da rotina de cuidado do paciente com psoríase. Hipótese esta a ser testada e corroborada por estudos prospectivos.

***Descritores:*** Psoríase. Doença autoimune. Neutrófilos. Linfócitos.

## Background

Psoriasis is an immune-mediated, chronic, systemic, inflammatory disease which primarily affects the skin and joints. There is no difference in prevalence between gender. A bimodal age of onset has been recognized: the first presentation between 16 and 22 years, and a second peak occurring at 57-60 years of age[1-3].

Psoriatic disease is associated with physical and psychological harm, besides substantial negative effects on a patient's quality of life[1,4].

The cutaneous disease usually presents with erythematous and scaly lesions, but the clinical presentation can vary. Psoriasis vulgaris, also called plaque-type psoriasis, which is the subject of this study, is the most common type of psoriasis, which affects 85% of patients. It typically presents as well-defined erythematous plaques covered with wide silvery scales, most commonly over extensors of extremities, back, and scalp[1-3].

The world's prevalence of psoriasis varies between 0.09 and 11.4%, depending on race and geographic site[5,6]. In Brazil, a national telephonic survey found a prevalence of 1.31%[7].

Psoriasis seems to be determined by an inadequate immune response, influenced by genetic factors associated with a predisposition to the development of the disease and some environmental factors that act as triggers or aggravating factors[8-10]. In chronic inflammatory diseases, it is common to search for biomarkers that can be used to interpret each patient's clinical context, contributing to the diagnosis, evaluation of severity or particular phenotype, or identifying inflammatory activity. The NLR is obtained by dividing the total amount of neutrophils by the number of lymphocytes, and it has been studied as a serum marker of systemic inflammatory activity. In this regard, understanding the behavior of these two groups of cells in patients with psoriasis could be useful in helping interpret the different phenotypes inside the clinical spectrum, making therapeutic decisions, and, eventually, revealing potential new targets for treatment[11].

Therefore, the present study aims to determine the NLR as a serum inflammatory marker in patients with moderate to severe plaque psoriasis, compared with controls.

## Methods

An observational, retrospective case-control study comparing a cohort of adult patients with severe psoriasis followed in an outpatient clinic of reference in Dermatology.

The cases included patients of both genders, aged 18-80, observed between August and December 2020, who were diagnosed with moderate to severe plaque psoriasis. All cases were diagnosed by the same dermatologist, using clinical criteria[1,12,13] and in a few cases with a less atypical presentation, the diagnosis was supported by a histopathological exam. Patients with synthetic or biological disease-modifying antirheumatic drugs (DMARD) or phototherapy stopped treatment for at least 3 months at the time of blood collection for laboratory examination. The use of topical treatment was admitted. Patients with other autoimmune inflammatory comorbidities were excluded from the study.

Cases were classified as moderate to severe disease when body surface area (BSA) ≥ 10% and/or psoriasis area and severity index (PASI) ≥ 10% and/or dermatology life quality index (DLQI) ≥ 10[13]. Psoriatic arthritis was defined according to CASPAR criteria[14].

The control group included adult patients aged between 18 and 80 years old who were seen at the outpatient clinic.

Cases and controls were matched by sex and age. The sample size was calculated using a 5% of significance level and 80% of statistical power, with a 1:1 proportion ratio, based on values of serum NLR in patients with moderate to severe psoriasis and without psoriasis in a study by Karabay et al.[15]. Considerable differences should be achieved with 165 cases and 165 controls.

Data were obtained retrospectively by reviewing medical records of patients aged between 18 and 80 years old,

**Table 1.** Clinical and epidemiological characteristics of the group of psoriatic patients and the control group

| Variables | Psoriasis patients (n = 165) | | Controls (n = 187) | |
|---|---|---|---|---|
| | n | % | n | % |
| Sex | | | | |
| Female | 91 | 55.2 | 146 | 78.1 |
| Male | 74 | 44.8 | 41 | 21.9 |
| Age group | | | | |
| ≤ 30 years | 20 | 12.1 | 12 | 6.4 |
| > 31-60 years | 116 | 70.3 | 88 | 47.1 |
| > 60 years | 29 | 17.6 | 87 | 46.5 |
| Comorbidities | | | | |
| Yes | 125 | 75.8 | 140 | 74.9 |
| No | 40 | 24.2 | 47 | 25.1 |
| Obesity | 54 | 33.8 | 140 | 74.9 |
| Hypertension | 68 | 42.5 | 54 | 28.9 |
| Diabetes mellitus | 36 | 22.5 | 103 | 55.1 |
| Dyslipidemia | 37 | 23.1 | 54 | 28.9 |
| Metabolic syndrome | 47 | 29.4 | - | - |
| Fatty liver | 28 | 17.5 | 69 | 36.9 |
| Heart disease | 13 | 8.1 | 69 | 36.9 |
| Depression/anxiety | 41 | 25.6 | - | - |
| Smoking | 52 | 32.5 | 26 | 13.9 |
| Psoriatic arthritis | | | | |
| Yes | 89 | 53.9 | - | - |
| No | 76 | 46.1 | - | - |
| Use of DMARD* | | | | |
| Yes | 150 | 90.9 | - | - |
| No | 15 | 9.1 | - | - |

*Disease-modifying antirheumatic drugs.

observed between August 2018 and December 2020. The NLR serum level was considered the dependent variable. Independent variables studied were age, gendter, presence of psoriasis and psoriatic arthritis and comorbidities.

Data were organized with Windows Excel and analyzed using the Statistical Package for the Social Sciences (SPSS). Version 20.0. (Computer program). Chicago: SPSS Inc; 2009, with the non-normal distribution of data evaluated by Kolmogorov–Smirnov test. The comparison between the case and the control's RNL was performed using the Mann–Whitney *U* test, adopting a significance level of $p \leq 0.05$.

The study was conducted according to the guidelines of Resolution no 466/2012 of the National Health Council, approved by the Ethics Committee of the University of South of Santa Catarina under CAAE np 40169120.4.0000.5369.

**Table 2.** Anthropometric data and mean psoriasis severity scores of patients

| Anthropometric data | Mean (standard deviation) |
|---|---|
| BMI (kg/m$^2$) | 28.52 (5.18) |
| AC (cm) | 96.10 (12.82) |
| **Psoriasis severity** | |
| BSA | 21.23 (13.47) |
| PASI | 18.33 (20.71) |
| DLQI | 13.94 (5.33) |

BMI: body mass index; AC: abdominal circumference; BSA: body surface area; PASI: psoriasis area and severity index; DLQI: dermatology life quality index.

## Results

A total of 165 patients with psoriasis vulgaris and 187 controls were included in the study. Clinical and epidemiological characteristics are detailed in Table 1.

**Table 3.** Comparison of median NLR serum levels between cases and controls according to demographic and clinical characteristics

| Variables | Patients Median 1.96 | Controls Median 1.78 | p-value 0.032 |
|---|---|---|---|
| Sex | | | |
| Male | 2.04 | 1.79 | 0.227 |
| Female | 1.90 | 1.77 | 0.400 |
| Age group | | | |
| ≤ 30 years | 1.57 | 1.59 | 0.954 |
| > 31-60 years | 2.03 | 1.69 | 0.022 |
| > 60 years | 1.97 | 1.93 | 0.669 |
| Comorbidities | | | |
| Yes | 2.08 | 1.77 | 0.054 |
| No | 1.77 | 1.75 | 0.968 |

**Table 4.** Comparison of median NLR serum levels between cases according to the presence of psoriatic arthritis

| Psoriatic arthritis | NLR | p-value |
|---|---|---|
| Yes | 2.08 | 0.957 |
| No | 1.94 | - |

Anthropometric data and mean psoriasis severity scores are presented in Table 2.

A statistically significant difference was observed (U = 13387.500; p = 0.032) in the NLR between cases and controls, and the case group had a higher median NLR serum level (md = 1.96). Table 3 compares median NLR serum levels between the two groups according to demographic and clinical characteristics.

The present study did not find a statistically significant relationship between NLR and the PASI score (stratifying in patients with PASI ≥ 10 and < 15 vs PASI ≥ 15).

Table 4 demonstrates that there was no difference in NLR between patients with and without psoriatic arthritis.

## Discussion

The present study set out to test the NLR as a tool to assess the persistent systemic inflammatory status by comparing patients with psoriasis vulgaris and individuals without psoriasis.

Several inflammation markers have been used to assess the inflammatory state in psoriasis. Acute-phase inflammatory markers, such as erythrocyte sedimentation rate and ultrasensitive C-reactive protein, showed little clinical correlation with the severity of psoriasis vulgaris and were not always related to the presence or absence of joint disease. NLR has been studied in several settings, including psoriasis. In the present study, a higher median was demonstrated in psoriatic cases compared to controls, and this difference was statistically significant when evaluated separately. This finding becomes particularly remarkable once we observe a high prevalence of metabolic and cardiovascular comorbidities in the control group.

When correlated with gender and the presence or absence of comorbidities, the associations were not significant. When divided by age, psoriatic patients aged between 30 and 60 years old had a statistically significantly higher median of serum NLR levels (md = 2.03) compared to controls (p = 0.022), perhaps due to a more significant inflammatory repercussion among younger patients. However, it cannot be ruled out that such a difference was established merely by a greater representation of this age group (70.3% of cases).

In agreement with our findings, a study conducted by Kim et al.[16] also found that patients with psoriasis had increased mean NLR compared to the control group, despite similar total lymphocyte counts. Similarly, Karaby et al.[14] reinforce the association between higher NLR and psoriasis, again with statistical significance.

In addition, another study by Sen et al.[11] demonstrated not only higher NLR but also significantly higher neutrophil counts, in contrast with lower lymphocyte counts, among patients with psoriasis, compared to controls.

**Table 5.** Summary of NLR studies included in our review.

| Authors and year | Methods | n | Results | Author's comments |
|---|---|---|---|---|
| Sen et al. 2014[11] | Cross-sectional, age and sex-matched controls | 138 Pso × 120 controls | Significantly higher neutrophil and lower lymphocyte count NLR levels significantly higher in psoriasis (2.71 ± 1.25 vs 1.90 ± 1.07 p = 0.01). Positive correlation with PASI (PASI < 10: 2.32 ± 1.21 vs PASI ≥ 10 e < 20: 2.61 ± 1.28 vs PASI ≥ 20: 3.42 ± 1.05 p < 0.01). | NLR is a simple, inexpensive and easily assessable marker of systemic inflammation in patients with psoriasis. |
| Ataseven et al. 2014[18] | Case-control | 104 Pso × 70 controls | NLR significantly elevated in (2.19 ± 1,11 vs 1.80 ± 0.72; p < 0.01). No correlation with PASI. | NLR as an emerging marker of inflammation and psoriasis. |
| Kim et al. 2015[16] | Case-control | 111 Pso (25 PsA) × 94 controls | NLR significantly higher among PsA compared with Pso and controls (2.95 ± 1.16 vs 2.15 ± 1.65 vs 1.76 ± 0.89; p < 0.0001); NLR correlated positively with PASI (higher NLR in PASI ≥ 10). | NLR as a strong predictor of PsA (OR 3.351; 95% confidence interval 1.785–6.292; p = 0.005. |
| Cerman et al. 2016[17] | Case-control | 49 Pso × 47 controls | NLR significantly higher in psoriasis (2.62 ± 1.46 vs 1.60 ± 0.56; p < 0.001); No correlation with disease severity (p > 0.05). | NLR with possible prognostic value for cardiovascular diseases, relevant to check in psoriasis. |
| Asashina et al. 2017[21] | Case-control | 186 Pso × 50 PsA | NLR significantly higher in PsA compared with Pso (3.53 ± 1.84 vs 2.71 ± 1.66; p < 0.001). | Mean NLR decreased significantly after 12 months of biological therapy; possible simple, convenient and cost-effective biomarker to monitor disease course after therapy. |
| Karabay et al. 2019[15] | Case-control | 94 Pso × 118 controls | Higher mean NLR in psoriasis compared to controls [1.96 (1.65–2.34) vs 1.77 (1.31–2.43); p = 0.038] and higher in moderate to severe psoriasis (PASI < 10: 1.94 (1.59–2.18) vs PASI ≥ 10: 2.02 (1.69–2.86); p = 0.024. | Relation between disease and inflammatory parameters. NLR as possible for early detection of cardiovascular comorbidities. |
| Hammad et al. 2020[20] | Case-control | 36 Pso 36 controls | NLR significantly higher than controls (2.48 ± 1.78 vs 1.24 ± 0.30; p < 0.001). NLR positively correlated with disease duration (r = 0.414; p = 0.012). No significant correlation between NLR and PASI (r = 0.265; p = 0.118). | NLR as a biomarker for systemic inflammation in Pso. Increased NLR influenced by disease duration, not severity. |

By analyzing neutrophil-lymphocyte levels and mean platelet volume in psoriasis patients to investigate the relationship between these biomarkers and disease activity, Çerman et al.[18] found that NLR levels were significantly higher in psoriasis patients when compared to the control group.

These authors have come to the conclusion that NLR can be a good alternative in the global assessment of the patient, in evaluating psoriatic disease, in addition to monitoring the remission of skin lesions, since it is easy to access, available and inexpensive. In that regard, with a focus on comorbidities, the assessment of the inflammatory status using NLR could have an impact on cardiovascular comorbidities, which are not rarely associated with psoriatic disease. It is known that psoriasis itself is a major risk factor for cardiovascular and cerebrovascular events. Therefore, besides the intervention in modifiable risk factors, greater attention could be given to patients with higher NLR.

On the other hand, Ataseven et al.[17], despite demonstrating higher mean NLR among sick patients, found no correlation between Psoriasis severity scores (PASI) and NLR. Along these lines, when investigating the association between NLR and clinical severity of psoriasis, through a systematic review of literature, Paliogiannis et al.[19] found that there were no significant differences in NLR values according to disease severity. The authors concluded that NLR could be significantly associated with the presence of psoriasis but not its severity. Hammad et al.[20] suggest that NLR could be more related to the duration of the disease than to its severity.

Neutrophil-lymphocyte ratio (NLR) has been proposed as a possible marker for diagnosing and even predicting the risk of joint disease. Asahina et al.[21], in a case-control study, observed a higher NLR, as well as increased highly sensitive C-reactive protein, among patients with psoriatic arthritis when compared to patients with psoriasis without established joint involvement. Another interesting aspect of the same study was the perception of the normalization of NLR after treatment with immunobiological, suggesting that it can serve as a follow-up tool. Similarly, Kim et al.[16] observed a higher NLR in psoriatic arthritis when compared to patients with only psoriasis vulgaris and with healthy subjects, considering it a strong predictor of joint disease [odds ratio (OR) 3351, p = 0.005]. The present study found no difference in NLR levels between patients with (2.08) and without psoriatic arthritis (1.94/p = 0.957).

A compilation of the studies included in this review is presented in Table 5.

As stated, there is no contradiction that NLR, an emerging biochemical marker of inflammation, is higher in patients with psoriasis compared to the control group. Therefore, it can be used to assess the inflammatory status of psoriasis and serve even in the follow-up of treatment. On the other hand, further studies are needed to determine the additional usefulness of NLR in psoriasis disease.

## Conclusion

Neutrophil-lymphocyte ratio (NLR) was higher in patients with psoriasis compared to the control group. NLR is an emerging inflammatory biomarker that is simple, accessible at all levels of healthcare, and easily calculated as part of the routine care of patients with psoriasis, and it can be used to evaluate inflammation and contribute to the management of psoriatic patients. However, further studies are needed to determine the real value and other applications for NLR in psoriatic disease.

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None.

## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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