Chron Precis Med Res 2023; 4(1): 29-33
DOI: 10.5281/zenodo.7718532

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Investigating the Presence of Inflammation in Lateral Epicondylitis with Platelet/Lymphocyte Ratio, Neutrophil/Lymphocyte Ratio, and Systemic Immune-Inflammation Index

Lateral Epikondilitte Enflamasyon Varlığının Trombosit/Lenfosit Oranı, Nötrofil/Lenfosit Oranı ve Sistemik İmmün-İnflamasyon İndeksi ile Araştırılması

Alper Uysal

Hatay Training and Research Hospital, Physical Medicine and Rehabilitation Clinic, Hatay, Turkey

ABSTRACT

Aim: This study aims to assess the existence of inflammation in the physiopathology of lateral epicondylitis (LE) and to evaluate the levels of blood inflammation parameters.

Material and Method: 72 patients with LE and 50 healthy individuals were included in this retrospective study. Age, gender, erythrocyte sedimentation rate (ESR), neutrophil, white blood cell (WBC), C-reactive protein (CRP), lymphocyte, platelet counts, platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) levels were scanned retrospectively from the hospital information system.

Results: While the patient and control groups were similar in terms of gender, age, CRP, ESR, lymphocyte, NLR and PLR values (p=0.902, p=0.108, p=0.193, p=0.902, p=0.523, p=0.140 and p=0.253, respectively), the median value of neutrophils, mean platelet, mean WBC and median SII score parameters were higher in the patient group (P=0.022, p=0.037, p=0.037, p=0.038, respectively). A strong correlation was detected between SII and NLR and PLR (both p<0.001, r:0.833 and r:0.778, respectively). The area under the curve (AUC) was calculated as 0.61 for SII via the receiver operating characteristics (ROC) curve analysis, (p=0,038).

Conclusion: The SII value, which is an indicator of inflammation, was more elevated in the LE group than in the healthy group. More study is needed on this subject.

Keywords: Lateral epicondylitis, systemic immune-inflammation index, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, inflammation

ÖZ

Amaç: Bu çalışma lateral epikondilitin (LE) fizyopatolojisinde inflamasyonun varlığını ve kan inflamasyon parametrelerinin düzeylerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: LE tanılı 72 hasta ve 50 tane sağlıklı birey bu retrospektif çalışmaya dahil edildi. Hasta ve kontrol gruplarında yaş, cinsiyet, eritrosit sedimentasyon hızı (ESH), nötrofil, beyaz kan hücresi (WBC), C-reaktif protein (CRP), lenfosit, trombosit sayıları, trombosit-lenfosit oranı (PLO), nötrofil-lenfosit oranı (NLO) ve sistemik immün-inflamasyon indeksi (Sİİ) düzeyleri hastane bilgi sisteminden retrospektif olarak tarandı.

Bulgular: Hasta ve kontrol grubu cinsiyet, yaş, CRP, ESH, lenfosit, NLO ve PLO değerleri açısından benzer iken (sırasıyla p=0,902, p=0,108, p=0,193, p=0,902, p=0,523, p=0,140 ve p=0,253), nötrofillerin medyan değeri, ortalama trombosit, ortalama WBC ve medyan SII skor parametreleri hasta grubunda daha yüksekti (sırasıyla P=0,022, p=0,037, p=0,037 ve p=0,038). Sİİ ile NLO ve PLO arasında güçlü bir korelasyon saptandı (her iki p<0.001, sırasıyla r:0.833 ve r:0.778). İşlem karakteristik (ROC) eğrisi analizi ile Sİİ için eğri altındaki alan (AUC) 0,61 olarak hesaplandı (p=0,038).

Sonuç: Enflamasyonun göstergesi olan Sİİ değeri LE grubunda sağlıklı gruba göre daha yüksekti. Bu konuda daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Lateral epikondilit, sistemik immün-enflamasyon indeksi, nötrofil-lenfosit oranı, trombosit-lenfosit oranı, inflamasyon

Corresponding Author: Alper UYSAL
Address: Hatay Training and Research Hospital, Physical Medicine and Rehabilitation Clinic, Hatay, Turkey
E-mail: alperuysal82@gmail.com

Başvuru Tarihi/Received: 28.01.2023
Kabul Tarihi/Accepted: 26.02.2023

INTRODUCTION

Lateral epicondylitis (LE) is an overuse tendinopathy of the wrist extensor muscles and tendons and pain is often seen in the lateral epicondyle of the humerus, which is the attachment site. This pain can radiate to the forearm (1). In addition, patients often have difficulty grasping and lifting objects. On physical examination, punctate tenderness is typically detected around the lateral epicondyle. In addition, there is an increase in pain with excessive wrist flexion and resistant elbow extension (2).

Histopathological studies have shown the absence of inflammatory cells in chronic LE biopsies. It was named angiofibroblastic hyperplasia because of the abundant fibroblasts, vascular hyperplasia and collagen in the biopsy (3). However, Al-Dhafer et al. compared patients' extensor carpi radialis brevis tendons with those of the healthy controls in their study published in 2021. They showed that expression levels of glutamate receptors, neuropeptides and inflammatory mediators were significantly increased, as well as macrophage in the LE group. These findings imply that inflammation has a function in the physiopathology of chronic LE (4).

Since two conflicting studies have been conducted to research the existence of inflammation in the pathogenesis of epicondylitis or tendinopathy (5, 6), conducting studies on this situation can contribute to the literature. Therefore, this study aims to reveal whether low-level systemic inflammation is effective in the etiopathogenesis of LE and the relationship between hematological parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII), which are markers in inflammatory conditions.

MATERIAL AND METHOD

Patients between the ages of 18-65 who were diagnosed with LE and admitted to the outpatient clinic between 2018 and 2022 were accepted to the current study. The data of LE patients were scanned retrospectively from the hospital automation system. Exclusion criteria of the study were the presence of malignancy, infection, pregnancy, metabolic disease, inflammatory rheumatic disease, fracture in the upper extremity, neuropathy, radiculopathy, arthropathy and injection or physical therapy for lateral epicondylitis. The control group consisted of people who applied to the outpatient clinic between 2018 and 2022, whose hemogram, ESR and CRP tests were requested due to iron deficiency and vitamin deficiencies or acute muscle pain and whose results were within normal limits. The control group was formed to be similar in age and gender to the patient group. Blood parameters were collected retrospectively from the hospital automation system (FONET) by scanning patient files. The NLR value was calculated by the ratio of the neutrophil count to the lymphocyte count, while the PLR value was calculated by the ratio of the platelet count to the lymphocyte count. SII was calculated by multiplying the platelet count by the neutrophil count and dividing by the lymphocyte count (7).

Age, gender, white blood cell (WBC), neutrophil, lymphocyte, platelet counts, NLR, PLR, SII, ESR and CRP values were compared between these two groups.

Statistical analysis

Conformity of continuous data to normality assumption was assessed according to the Kolmogrov Smirnov Test and coefficient of variation. Normally distributed continuous data and non-normally distributed continuous data were defined as mean±standard deviation and median (minimum-maximum), respectively. Categorical data were given as frequency and percentage. If the assumption of normality was satisfied, the Independent Sample t-test was used to assess the statistical difference between groups for continuous variables; If not, the Mann Whitney-U Test was preferred. Statistical difference between groups for categorical variables was determined by Pearson Chi-Square Test. The relationship between numerical variables was evaluated with Spearman correlation analysis. ROC analysis was performed to assess the sensitivity and specificity of SII. All statistical analyzes were performed with SPSS 22 program. A p-value below 0.05 was approved as significant.

RESULTS

The patient and control groups were statistically similar in terms of gender, age, ESR, CRP, lymphocyte, NLR and PLR values (p=0.902, p=0.108, p=0.902, p=0.193, p=0.523, p= 0.140 and p=0.253, respectively) (**Table 1**).

The median value of neutrophils, mean platelet, mean WBC and median SII score in the LE group were more elevated than the control group (p=0.022, p=0.037, p=0.037 and p=0.038, respectively) (**Table 1**).

A very weak positive correlation was determined between ESR and CRP (r:0.208, p=0.022). A moderate positive correlation was determined between NLR and PLR (r:0.546, p<0.001). A high level of positive correlation was found between SII score and NLR and PLR (both p<0.001, r:0.833, r:0.778, respectively) (**Table 2**).

The ideal SII cut-off value was determined as 458.50 by ROC analysis. The area under the ROC curve was 0.611. Confidence intervals for this area were determined as 0.508 and 0.713. Taking this point as the optimal cut-off point, the sensitivity was 0.556 and the specificity was 0.440. The obtained area was considered statistically significant (p=0.038) (**Figure 1**) (**Table 3**).

Table 1. Comparison of demographic and laboratory parameters of the patient and control groups

Variables	Patient Group (n=72)	Control Group (n=50)	P
Gender			0,902*
Male (n/%)	44 (61,1)	30 (60,0)	
Female (n/%)	28 (38,9)	20 (40,0)	
Age (Mean±SD)	47,88±9,12	50,66±9,54	0,108**
ESR (Median (min-max))	9,0 (3,0-30,0)	10,0 (2,0-30,0)	0,902***
CRP (Median (min-max))	2,42 (0,29-10,0)	1,86 (0,15-6,11)	0,193***
Nötrofil (Median (min-max))	4,40 (2,30-7,00)	3,63 (1,92-7,22)	0,022***
Lenfosit (Mean±SD)	2,32±0,66	2,25±0,58	0,523**
Platelet (Mean±SD)	275,79±67,50	251,44±54,87	0,037**
WBC (Mean±SD)	7,41±1,53	6,81±1,57	0,037**
NLR (Median (min-max))	1,91 (0,74-5,16)	1,67 (0,86-3,48)	0,140***
PLR (Median (min-max))	126,08 (41,25-266,43)	117,16 (62,75-364,71)	0,253***
SII (Median (min-max))	473,53 (144,38-1628,33)	422,90 (212,61-1086,28)	0,038***

n: Number, CRP: C-reactive protein, WBC: White blood cell, NLR: Neutrophil-lymphocyte ratio, SII:Systemic immune inflammation index, PLR: Platelet-lymphocyte ratio, ESR: Erythrocyte sedimentation rate, *Pearson Chi-Square Test, **Independent Sample T-Test, ***Mann Whitney -U Test

Table 2. Correlation analysis of laboratory parameters

		ESR	CRP	NLR	PLR	SII
ESR	r	1,000	0,208	0,023	0,075	0,097
	p*	.	0,022**	0,797	0,412	0,288
CRP	r	0,208	1,000	-0,017	-0,014	0,146
	p*	0,022**	.	0,850	0,882	0,109
NLR	r	0,023	-0,017	1,000	0,546	0,833
	p*	0,797	0,850	.	<0,001**	<0,001**
PLR	r	0,075	-0,014	0,546	1,000	0,778
	p*	0,412	0,882	<0,001**	.	<0,001**
SII	r	0,097	0,146	0,833	0,778	1,000
	p*	0,288	0,109	<0,001**	<0,001**	.

r: Spearman correlation coefficient, *Spearman correlation analysis (<0.25 very weak relation; 0.26-0.49 weak relation; 0.50-0.69 medium relation; 0.70-0.89 high relation; 0 .90-1.0 very high correlation) **p<0.05

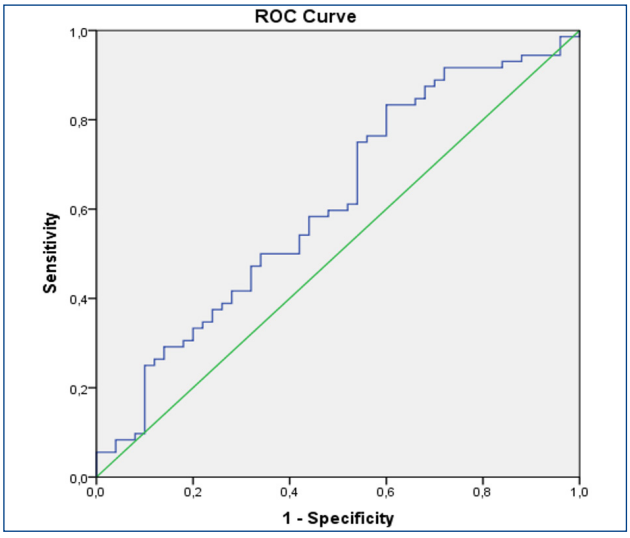

Figure 1. ROC analysis of SII score in patients with lateral epicondylitis

Table 3. ROC analysis of SII score in patients with lateral epicondylitis

	SII
AUC	0,611
95 % CI	0,508-0,713
Sencitivity %	%55,6
Specificity %	%44,0
P	0,038
Cut-off	458,50

AUC: Area Under The Curve

DISCUSSION

In this study, ESR, CRP, lymphocyte, NLR and PLR values were similar between the LE group and the healthy control group. When the groups were compared in terms of median neutrophil value, mean platelet, mean WBC and median SII score, higher values were found in the patient group. A high level of positive correlation was observed between SII score and PLR and NLR. According to the results of our study, it may be thought that inflammation plays a role in the pathogenesis of LE.

ESR and CRP are the most frequently used laboratory parameters in clinical practice as indicators of inflammation. In addition, PLR and NLR have been used as a marker of inflammation in diverse diseases in recent years (5). Another new marker of inflammation is the SII (7). SII has been shown in many studies to be a good indicator of inflammation and disease activity (8-11).

In a meta-analysis published in 2018, PLR and NLR values were shown to be more elevated in individuals with rheumatoid arthritis (RA) compared to healthy people (12). Wu et al. found that the SII level was higher in ankylosing spondylitis (AS) patients than in healthy individuals in their study published in 2021. They found that the active AS group had higher SII levels than the remission AS group (9). Li et al showed that PLR, NLR and lymphocyte to monocyte ratio (LMR) are good indicators of RA disease activity in their study published in 2021 (13).

In addition to rheumatic diseases, PLR and NLR values have been studied as inflammation markers in diseases such as cardiovascular disease, malignancy, cerebrovascular diseases, kidney diseases, diabetes mellitus, hypertension and ulcerative colitis. High PLR and NLR values have been related to poor prognosis in various studies (5).

The relationship between blood inflammation parameters and musculoskeletal system diseases has been evaluated in various studies (6, 14, 15). Cai et al. found that NLR values were more elevated in patients with OA than in healthy individuals. They suggested that NLR level is associated with disease progression and is an independent risk factor (14). Tasoglu et al. evaluated the blood parameters of patients with knee

OA and they showed that the severe OA group had higher mean NLR levels than the mild-to-moderate OA group (16). Büyükavcı et al. found that blood NLR levels were associated with radiographic staging (Kellgren-Lawrence) of knee OA in their study published in 2018. They detected higher NLR levels in patients with advanced knee OA compared to individuals with mild to moderate knee OA (17). Low-grade systemic inflammation is one of the theories proposed in the etiopathogenesis of OA (18) and the above studies support this idea.

In a study published in 2021, it was shown that mean ESR levels were more elevated in patients with fibromyalgia syndrome (FMS) compared to healthy people and PLR and NLR values were alike between both groups (19). Aktürk et al. found that NLR levels were more elevated in FMS patients than in healthy individuals and suggested that NLR could be used as an inflammatory marker in the diagnosis of FMS (15). İlgün et al. found that NLR values were similar between FMS and healthy control groups, while PLR values were more elevated in FMS patients (20). Al-Nimer et al. found PLR and NLR levels to be more elevated in patients with FMS than in healthy people and they found a relationship between these rates and the severity of FMS disease (21). Studies on the use of inflammation-related blood parameters in the diagnosis of FMS contradict each other.

A study published in 2022 found evidence that the NLR value is an important indicator of tendinopathy (elbow, rotator cuff, hamstring, patellar and achilles) (6). However, Karakoyun et al. did not find a significant difference between epicondylitis patients and healthy people in terms of PLR, NLR and other blood parameters in their study published in 2020. They stated that using these parameters to demonstrate the existence of inflammation in the physiopathology of epicondylitis is not significant and there is no relationship between epicondylitis severity and these rates (5). Neither of these studies included the level of SII in the assessment. In the present study, PLR and NLR values were statistically similar between the LE group and the healthy control group whereas SII value was higher in the LE group. This could mean that inflammation contributes to the pathogenesis of the disease.

In previous studies, recurrent microtraumas and related degenerative changes (angiofibroblastic hyperplasia) rather than inflammation were accepted in the pathophysiology of lateral epicondylitis (4).

Since no neutrophils were detected as a result of histopathological evaluation in previous studies, it was thought that inflammation was not effective in the etiopathogenesis of tendinopathy and the term tendinosis was preferred instead of tendinitis (22). However, neutrophils are detected in the first two days of inflammation. Then the process continues with macrophages, platelets, cytokines and growth factors (6, 23).

Al-Dhafer et al. evaluated the extensor carpi radialis brevis muscle tendon of the patients with chronic LE histopathologically and found an increase in inflammatory cytokine levels and macrophage count compared to the healthy group. Macrophages may have modulating effects on pain, tissue remodeling and healing in chronic tendinopathies (4).

The present study is the first in the literature to evaluate the level of SII in patients with LE. Üstündağ et al. suggested that a significant increase in SII and PLR levels may be related to subclinical low-grade inflammation (24). In the current study, the SII value was more elevated in the LE group compared to the control group. In addition, as a result of the ROC analysis, it was found that SII could be a significant indicator in predicting lateral epicondylitis. The low sensitivity and specificity rates of the present study may be due to the small number of patients. The findings of the present study will contribute to the literature, but more comprehensive studies with a large patient cohort are needed to confirm these results.

The retrospective character of the study and the small study groups are the limitations of the present study.

CONCLUSION

SII value which is an indicator of inflammation was more elevated in the LE group than in the control group. Although this could mean that inflammation contributes to the pathogenesis of the disease, studies with more participants and including histopathological evaluation are needed to understand the presence of inflammation in the pathophysiology of LE.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Hatay Mustafa Kemal University Ethics Committee (Date: 05.01.2023, Decision No: 15)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declares that he has all participated in the design, execution, and analysis of the paper, and that he has approved the final version.

REFERENCES

1. Ahmed AF, Rayyan R, Zikria BA, Salameh M. Lateral epicondylitis of the elbow: an up-to-date review of management. European J Orthopaedic Surg Traumatol 2022:1-6.
2. Faro F, Wolf JM. Lateral epicondylitis: review and current concepts. J Hand Surg 2007;32(8):1271-9.
3. Ma K-L, Wang H-Q. Management of Lateral Epicondylitis: A Narrative Literature Review. Pain Res Manag 2020;2020.
4. Al-Dhafer BAA, Joo HS, Park SY, Shin YH, Kim JK. Increased expression of macrophages and inflammatory cytokines at tendon origin in patients with chronic lateral epicondylitis. J Shoulder Elbow Surg 2021;30(7):1487-93.
5. Karakoyun A, Calik Y. May neutrophil lymphocyte ratio and platelet lymphocyte ratio be used as inflammatory markers in patients with epicondylitis? Inflammatory markers in patients with epicondylitis . annalsmedres. 2021;27(10):2604-9.
6. İsmail K, Örsçelik A, Solmaz İ, Karaaslan B, YILMAZ EŞ. Neutrophil to lymphocyte ratio may be used as a predictor in tendinopathy. Eur Res J 2022:1-7.
7. Zhao Y, Xiang Q, Lin J, Jiang S, Li W. High Systemic Immune-Inflammation Index and Body Mass Index Are Independent Risk Factors of the Thoracic Ossification of the Ligamentum Flavum. Mediators of Inflammation. 2022;2022.
8. Xie Y, Zhuang T, Ping Y, Zhang Y, Wang X, Yu P, et al. Elevated systemic immune inflammation index level is associated with disease activity in ulcerative colitis patients. Clinica Chimica Acta. 2021;517:122-6.
9. Wu J, Yan L, Chai K. Systemic immune-inflammation index is associated with disease activity in patients with ankylosing spondylitis. J Clin Lab Anal. 2021;35(9):e23964.
10. Liu X, Guan G, Cui X, Liu Y, Liu Y, Luo F. Systemic Immune-Inflammation Index (SII) Can Be an Early Indicator for Predicting the Severity of Acute Pancreatitis: A Retrospective Study. Int J Gen Med. 2021;14:9483-9489.
11. Satis S. New Inflammatory Marker Associated with Disease Activity in Rheumatoid Arthritis: The Systemic Immune-Inflammation Index. Curr Health Sci J 2021;47(4):553.
12. Erre GL, Paliogiannis P, Castagna F, Mangoni AA, Carru C, Passiu G, et al. Meta-analysis of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in rheumatoid arthritis. Eur j clin invest 2019;49(1):e13037.
13. Li M, Xie L. Correlation between NLR, PLR, and LMR and Disease Activity, Efficacy Assessment in Rheumatoid Arthritis. Evid Based Complement Alternat Med. 2021;2021:4433141.
14. Cai C, Zhang R, Xu X, Li G, Gou H. Diagnostic values of NLR and miR-141 in patients with osteoarthritis and their association with severity of knee osteoarthritis. Exp Ther Med. 2021;21(1):74.
15. Aktürk S, Büyükavcı R. Evaluation of blood neutrophil-lymphocyte ratio and platelet distribution width as inflammatory markers in patients with fibromyalgia. Clin Rheumatol. 2017;36(8):1885-1889.
16. Taşoğlu Ö, Bölük H, Şahin Onat Ş, Taşoğlu İ, Özgirgin N. Is blood neutrophil-lymphocyte ratio an independent predictor of knee osteoarthritis severity?. Clin Rheumatol. 2016;35(6):1579-1583.
17. Büyükavcı R, Aktürk S, Sağ S. Comparison of blood platelet distribution width and neutrophil-lymphocyte ratio in patients with different grades of knee osteoarthritis. J Back Musculoskelet Rehabil. 2018;31(6):1035-1039.
18. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013;21(1):16-21.
19. Guntel M, Uysal A. Detecting the presence of inflammation in fibromyalgia syndrome with neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume. annalsmedres [Internet]. 2021 May 25 [cited 2023 Mar. 6];28(4):0722-5.
20. İlgün E, Akyürek Ö, Kalkan AO, Demir F, Demirayak M, Bilgi M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in fibromyalgia. Eur J Gen Med. 2016;13(2):100-4.
21. Al-Nimer MSM, Mohammad TAM. Correlation of hematological indices and ratios derived from them with FIQR scores in fibromyalgia. Pakistan J Med Sci 2018;34(5):1219.
22. Streit JJ, Shishani Y, Rodgers M, Gobezie R. Tendinopathy of the long head of the biceps tendon: histopathologic analysis of the extra-articular biceps tendon and tenosynovium. Open Access J Sports Med 2015;6:63.
23. Federer AE, Steele JR, Dekker TJ, Liles JL, Adams SB. Tendonitis and Tendinopathy: What Are They and How Do They Evolve?. Foot Ankle Clin. 2017;22(4):665-676.
24. Ustundag Y, Huysal K, Gecgel SK, Unal D. Relationship between C-reactive protein, systemic immune-inflammation index, and routine hemogram-related inflammatory markers in low-grade inflammation. Int J Med Biochem. 2018;1(1):24-8.