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Neutrophil to lymphocyte ratio may be used as a predictor in tendinopathy

İsmail Kaya[1], Aydan Örsçelik[2], İlker Solmaz[3], Burak Karaaslan[2], Esra Şafak Yılmaz[4]

[1]Department of Sports Medicine, Gülhane Training and Research Hospital, Ankara, Turkey; [2]Department of Sports Medicine, University of Health Sciences, Gülhane Faculty of Medicine, Ankara, Turkey; [3]Department of Anesthesia and Reanimation, University of Health Sciences, Gülhane Training and Research Hospital, Traditional and Complementary Medicine Practice Center, Ankara, Turkey; [4]Department of Medical Informatics, University of Health Sciences, Gülhane Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objectives: Tendinopathy is a very common clinical disorder and a complex inflammation and degeneration process. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been studied and accepted as biomarkers of inflammation, predictors of progression and prognosis in several studies. We aimed to show that NLR and PLR levels can help predict prognosis for tendinopathy by comparing NLR and PLR levels of patients with tendinopathy with healthy control groups.

Methods: Tendinopathy and healthy cases whose complete blood test was requested, were included in the study. Age, gender, white blood cell (WBC), neutrophil, lymphocyte, platelet counts, NLR and PLR of these cases were examined.

Results: There is a statistically significant difference between the tendinopathy (n = 140) and control (n = 51) groups in WBC and NLR values ($p < 0.001$). One unit increase in WBC and NLR levels increases the risk of tendinopathy 1.74 and 10.616 times respectively. According to the results of the ROC analysis, the threshold value of the WBC and NLR values to increase the risk of tendinopathy is 6.47, and 1.64 respectively.

Conclusions: Our study suggested NLR and WBC values are significant indicators of tendinopathy. We consider these results to be a guide for all physicians, especially sports medicine physicians.

Keywords: Tendinopathy, neutrophil to lymphocyte ratio, inflammation, neutrophil

Tendinopathy is a very common clinical problem in the population and athletes [1]. Thirty percent of all running injuries are chronic tendon disorders and a prevalence of 40% in tennis players [2]. Tendinopathy may cause severe morbidity and disability that can last for several months despite appropriate treatment [3]. The words "tendinitis", "tendinosis" and "tendinopathy" are used interchangeably in the literature. According to the consensus prepared to eliminate this terminology confusion, persistent tendon pain and loss of function are called "tendinopathy" [4]. The source of this confusion in terminology is the unclear etiological disagreement about inflammation. The source of this disagreement is the interchangeability of "neutrophil count" and "inflammation" [1]. In the first histopathological studies, unlike other inflammatory processes, it is claimed that "no inflammatory cells" or "few inflammatory cells" were found in sam-

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Address for correspondence: *Aydan Örsçelik, MD., Associate Professor, University of Health Sciences, Gülhane Faculty of Medicine, Department of Sports Medicine, General Doktor Tevfik Sağlam Cad., 06010Etlik, Keçiören, Ankara, Turkey. E-mail: aydan.orscelik@sbu.edu.tr, aydanozcan@yahoo.com, Phone: +90 312 304 25 57*

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ples of patients with tendinopathy only because they could not find neutrophils. With this result, it is evaluated that a false perception has been created for years [1]. Neutrophils are seen only in the first two days. The inflammatory process continues with platelets, macrophages, growth factors, matrix metalloproteins (MMPs) and cytokines [2]. Until recent decade, tendinopathy has been defined as tendon degeneration without inflammation due to overuse in the literature [5, 6]. Tendon overload has been shown to be associated with changes in shape of the cell as well as inflammation markers and matrix degradation. It is assumed that tendinopathy develop as a result of the remodeling of the matrix due to inflammation and damage, and is also the source of this condition in cytokines and inflammatory cells. In addition, the number of macrophages in the diseased tendon tendinopathy increasingly used in recent years increased pathogenesis studies showing that support the role of inflammation [1, 7]. The macrophage activation pathways assigned in rotator cuff tendinopathy samples show rised genes and proteins expression stimulated by interferons and NF-kB37 at an early stage and by STAT6 and glucocorticoid receptor activation pathways at an advanced stage [1]. These may be evidence of a complex inflammatory process and persistent inflammation in tendinopathy [1, 7]. Tendinopathy that does not improve in 3-6 weeks in athletes means pain and loss of function, loss of performance, or loss of training/match. The loss of the training/match brings serious losses for both the athlete and the team. Treatment choices should be determined correctly to ending the complaints and returning to sport. Nonsteroidal anti-inflammatory medicines do not help in tendinopathy. Tendinopathy can be diagnosed by examination, the use of imaging method for diagnosis is not the gold standard [4].

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been studied and accepted as biomarkers of inflammation obtained from complete blood, predictors of progression and prognosis in various cancers, rheumatoid arthritis, cardiovascular and inflammatory and infectious pathologies [8, 9]. However, no similar study on tendinopathy has been found in the literature.

In the light of all this information, we aimed to show that NLR and PLR levels can help predict prognosis for tendinopathy by comparing NLR and PLR levels of patients with tendinopathy with healthy control group.

METHODS

Tendinopathy and healthy cases who applied to the sports medicine outpatient clinic of our hospital between January 2016 and November 2020, and whose complete blood test was requested, and included in the study. Achilles, patellar, biceps, lateral and medial elbow, rotator cuff, and hamstring tendinopathies without inflammatory diseases, infection or any other reason that causes inflammation were included in the study as tendinopathy from records and these cases were defined as tendinopathy group. Individuals who were investigated for a complete blood test to evaluate for iron deficiency and vitamin deficiencies and had a normal result were accepted as healthy cases and were defined as healthy group. Age, gender, white blood cell (WBC), neutrophil, lymphocyte, platelet counts, NLR and PLR of these groups were compared.

Diagnosis of tendinopathy can be done by only physical examination and imaging is not a gold standard [4]. So, we did not compare their diagnosis accuracy retrospectively with imaging results, but the tendinopathies were diagnosed by 3 different experienced sports physician experts in 4 years.

The local ethics committee was approved this retrospective study (Ethics Committee of Health Sciences University Turkey, Date: 25.03.2021 and number: 2021/78).

Statistical Analysis

Statistical analysis was performed using R 3.5.0 (R Core Team, 2018) software. Data were shown as mean ± standard deviation or median (minimum-maximum) values. In univariate comparisons, the Shapiro Wilk test was used to evaluate whether the continuous variables were normally distributed, and the Levene test for the homogeneity of variances. When parametric assumptions were not provided, the Mann-Whitney U test was used to compare two independent groups in terms of a numerical variable, and when parametric assumptions were provided, the significance test of the difference between the two means (student t-test) was used. In categorical variables, the data will be summarized in percentages. In the comparison of two inde-

pendent groups in terms of a categorical variable, the chi-square test or Fisher Exact test was applied by evaluating their assumptions. In multivariate comparisons, a logistic regression model was used for multivariate analysis of prognostic factors. ROC analysis was performed to determine the threshold value for continuous variables that were found to be significant as a result of the logistic regression and threshold val-

Table 1. Paired comparison results in groups with and without tendinopathy

Variable		Control	Tendinopathy	Overall	*p* value
Gender, n (%)	Total	51 (26.70)	140 (73.30)	191	0.623
	Female	31 (60.78)	79 (56.43)	110 (57.59)	
	Male	20 (39.22)	61 (43.57)	81 (42.41)	
Age (years)	Mean ± SD	28.65 ± 9.76	30.41 ± 11.89	29.94 ± 11.36	0.622
	Median (IQR)	27.00 (15.00)	25.50 (22.00)	26.00(21.00)	
	Q1-Q3	21.00-36.00	20.00-42.00	20.00-41.00	
	Min-Max	15.00-50.00	15.00-50.00	15.00-50.00	
WBC	Mean ± SD	5.66 ± 1.12	7.14 ± 1.66	6.75 ± 1.67	**< 0.001**
	Median (IQR)	5.40 (1.65)	7.00 (1.73)	6.60 (2.10)	
	Q1-Q3	4.90-6.55	6.27-8.00	5.45-7.55	
	Min-Max	3.90-8.30	3.40-14.30	3.40-14.30	
Neutrophil	Mean ± SD	3.06 ± 0.73	4.49 ± 1.61	4.11 ± 1.56	**< 0.001**
	Median (IQR)	2.90 (1.15)	4.30 (1.73)	3.90 (1.60)	
	Q1-Q3	2.50-3.65	3.40-5.12	3.10-4.70	
	Min-Max	1.70-4.70	2.10-14.90	1.70-14.90	
Lymphocyte	Mean ± SD	2.02 ± 0.40	2.04 ± 0.54	2.04 ± 0.50	0.774
	Median (IQR)	2.00 (0.45)	2.00 (0.60)	2.00 (0.60)	
	Q1-Q3	1.80-2.25	1.70-2.30	1.70-2.30	
	Min-Max	1.20-3.20	0.70-3.50	0.70-3.50	
Platelet	Mean ± SD	247.57 ± 67.83	266.39 ± 60.61	261.37 ± 62.99	**0.016**
	Median (IQR)	242.00 (67.50)	260.00 (75.75)	255.00 (75.00)	
	Q1-Q3	204.00-271.50	225.75-301.50	221.00-296.00	
	Min-Max	131.00-559.00	133.00-452.00	131.00-559.00	
NLR	Mean ± SD	1.52 ± 0.28	2.37 ± 1.26	2.14 ± 1.15	**< 0.001**
	Median (IQR)	1.50 (0.34)	2.07 (1.02)	1.84 (0.95)	
	Q1-Q3	1.35-1.68	1.65-2.66	1.50-2.45	
	Min-Max	1.04-2.15	1.02-10.43	1.02-10.43	
PLR	Mean ± SD	125.43 ± 34.54	138.83 ± 47.78	135.25 ± 44.94	0.093
	Median (IQR)	115.26 (40.04)	129.98 (55.42)	125.79 (49.53)	
	Q1-Q3	103.50-143.55	106.63-162.05	106.06-155.59	
	Min-Max	63.90-217.51	61.75-320.00	61.75-320.00	

WBC = white blood cell, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, Min = minimum, Max = maximum, SD = standard deviation

ues were determined according to the minimum-maximum rule. In the calculations, the type 1 error rate was accepted as alpha 0.05. Tables were created with Microsoft Excel.

RESULTS

A total of 191 cases were included in the study as 140 tendinopathy group and 51 control group. Comparison of demographics and laboratory features of cases are shown in Table 1. According to paired comparisons of tendinopathy and control groups, there is a statistically significant difference between the groups in terms of WBC and NLR values ($p < 0.001$ for both) (Table 1). There is no significant difference between groups in terms of PLR values ($p = 0.093$). Comparison of NLR and PLR values with box-plot in tendinopathy and control groups are shown in Figs. 1 and 2, respectively.

The results of the logistic regression model made for multivariate analysis are given in Table 2. WBC and NLR were found to be important model variables with the backward selection method. Accordingly, one unit increase in WBC level increases the risk of tendinopathy OR = 1.74 times. Similarly, one unit increase in NLR increases the risk of tendinopathy OR = 10.616 times.

According to the results of the ROC analysis, the threshold value of the WBC value to increase the risk of tendinopathy is 6.47, and the threshold value of the NLR value to increase the risk of tendinopathy is 1.64 (Fig. 3).

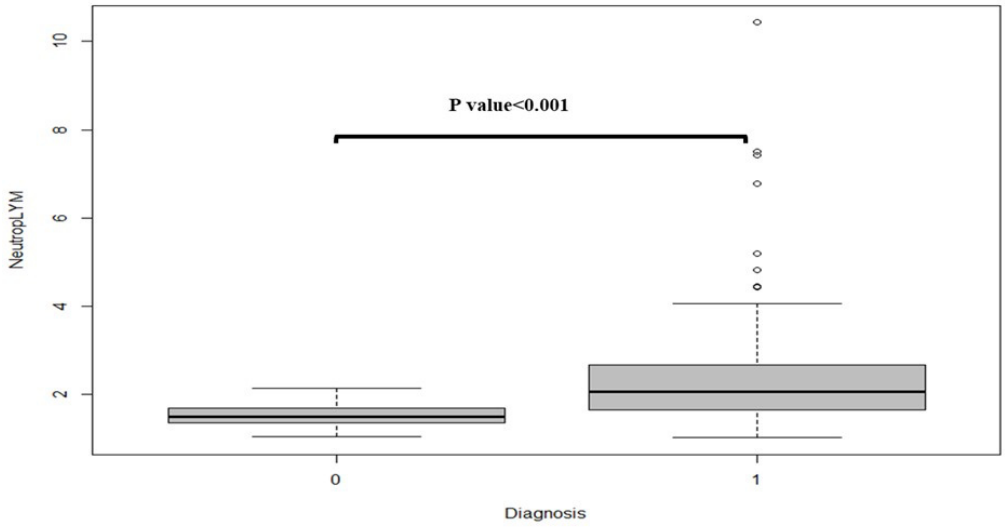


Fig. 1. Comparison of NLR value with box-plot in tendinopathy and control groups.

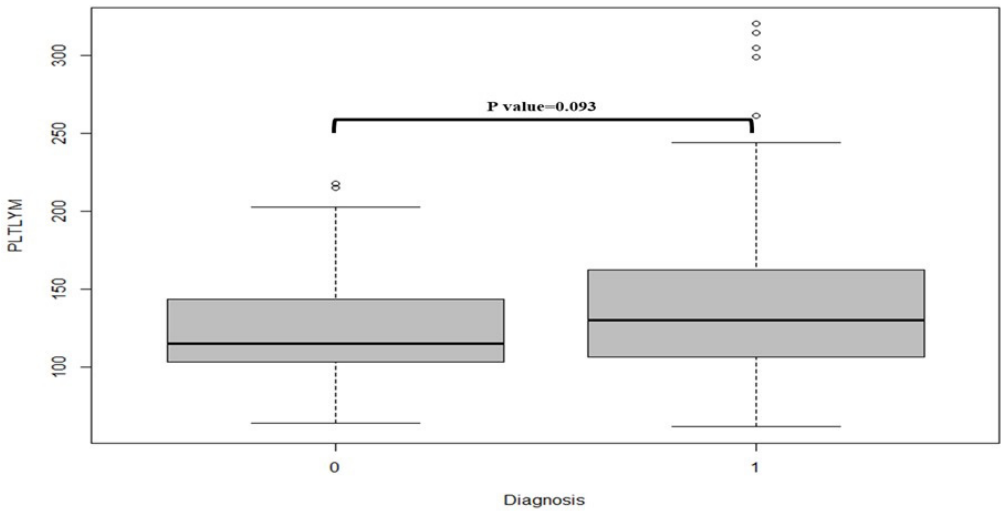


Fig. 2. Comparison of PLR value with box-plot in tendinopathy and control groups.

Table 2. Logistic regression results

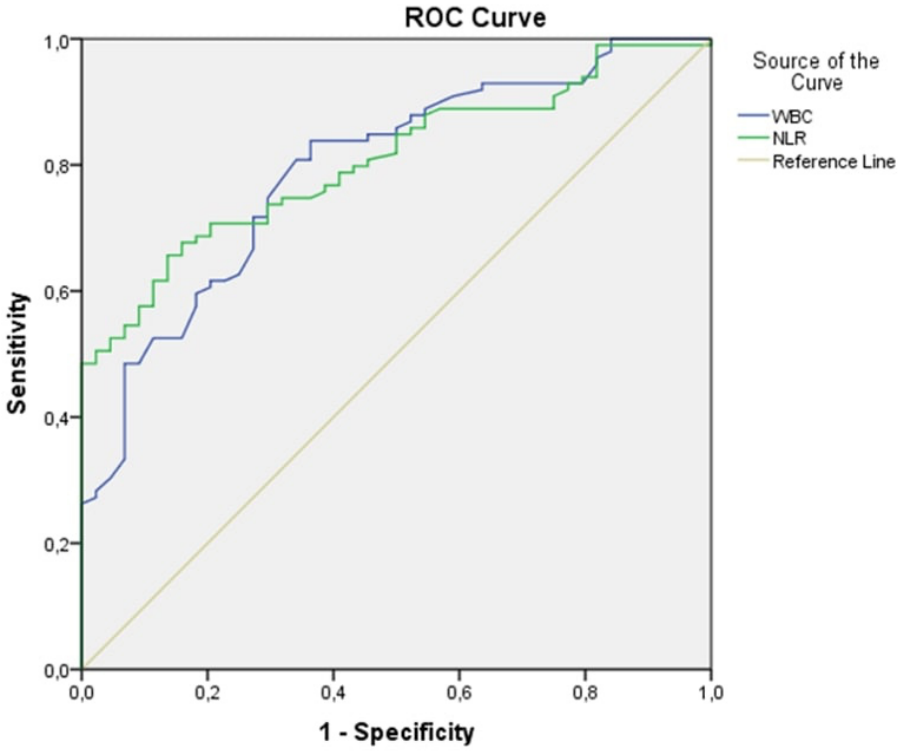
	Dependent variable:
	Diagnosis
WBC	1.746*** (1.261, 2.493)
NLR	10.616*** (3.773, 35.966)
Constant	0.001*** (0.0001, 0.013)
Observations	191
Log Likelihood	-77.892
Akaike Inf. Crit.	161.785

WBC = white blood cell, NLR = neutrophil to lymphocyte ratio

DISCUSSION

This study evaluated NLR and PLR in patients with tendinopathy and in control cases. Our results support the association between NLR and tendinopathy. Moreover, WBC also associated with tendinopathy. NLR and WBC may be a simple and cost-effective method for tendinopathy and also increased NLR and WBC may be predictors of tendinopathy. According to the results of the ROC analysis, the threshold value of 1.64 for NLR and 6.47 for WBC was defined to separate between tendinopathy patients and controls. This is the first study to evaluate the value of NLR and WBC to predict the prognosis of tendinopathy in athletes.

The definition of tendinopathy and the presence of inflammation in tendinopathy has been a discussion issue and opinions change within the framework of histopathological findings over the years. Although it is claimed that it develops with non-inflammatory degeneration due to loading over time [10], some studies showed that inflammatory responses and degeneration are simultaneous with the Iceberg Theory [5, 11]. While the presence of inflammation is being discussed in tendinopathy, our findings supply new evidence for inflammation. A statistically meaningful difference was found in WBC, neutrophil, platelet and NLR values between tendinopathy and healthy group in our



Test Result Variable(s)	AUC	Cut-Off	Asymptotic Sig.[b]	95% CI Lower Bound	95% CI Upper Bound
WBC	,793	6,470	,000	,716	,869
NLR	,806	1,640	,000	,737	,875

Fig. 3. ROC curve analyses of WBC and NLR.

study. Lymphocyte ratios are similar. This shows that the NLR value of tendinopathy group increases due to the rising in the number of neutrophils not from decrease of the lymphocyte counts. In addition, PLR value was found to be high, although it was not statistically significant ($p = 0.093$). Maybe it would have been meaningful if it had been studied with a larger group. High values of WBC, neutrophils and NLR are also indicators of inflammation.

In addition, we can say that the most important result of this study is to show that each unit increase after exceeding the cut-off value in the WBC and NLR values increase the tendinopathy risk 1.7 and 10.6 times respectively. Neutrophils may not be demonstrated or maybe a little demonstrated in tendinopathy in histopathological studies, the fact that the NLR value is such an effective indicator may be evidence of how complex the inflammation cascade is.

WBC and NLR values are obtained from the complete blood test, which is a simple and inexpensive test to apply. NLR value had shown as a valuable inflammatory marker in Ankylosing Spondylitis with a cut off value off 1.91 [12]. Another study had demonstrated the correlation of higher NLR and interleukin-6 in chronic kidney diseases [13]. A study had been found the association between NLR and TNF-α in end stage renal diseases [14] . Fawzy *et al*. [15]'s study proved NLR as a significant inflammation marker in rheumatoid arthritis and showed the correlation between NLR and erythrocyte sedimentation rate, C-reactive protein. In a study comparing inflammation biomarkers of patients with upper extremity overuse musculoskeletal problems for less than 12 weeks and a control group, TNF-α, IL-1β, and IL-6 were moderately correlated, but CRP was strongly associated [16]. Long-term continuous loading increases IL-10 which is a serum biomarker. Serum biomarkers are seen as a useful method considering the relationship between stress, exercise, and injury [17]. TNF-α, IL-1β, IL-6 and IL-10 are beneficial serum biomarkers but more expensive than WBC and NLR.

In a retrospective study by Karakoyun *et al*. [18], there was no correlation between NLR and PLR values and epicondylitis. Different from our study they included patients with medial and lateral epicondylitis and the mean age of patient group was 55.31 ± 2.30 years and the 56.45 ± 4.81 years in healthy group. The mean age of the patient with tendinopathy was 30.41 and control group's was 28.65 in our study. Inflammation in tendon healing and regeneration may be change by age. Excessive inflammation is seen with aging [19], inflammation with tendinopathy may be underestimated due to this excessive inflammation.

Limitations

Our study has some limitations. The main limitation is retrospective design. We did not compare their diagnosis accuracy with imaging results. We did not compare or discuss the duration, grade of tendinopathy, recreational or elite sportsperson or branches of the individuals due to retrospective design. Another limitation is deficiency of comparing with other proinflammatory and inflammatory markers. These findings should be evaluated carefully and repeated with a prospective design for the verification. The strength sides of the study are that it consists of recreational individuals and athletes (absence of sedentary individuals) and an average age of approximately 30.

CONCLUSION

Our study suggested NLR and WBC values are significant indicators of tendinopathy. Also using these values are simple, cheap and cost effective. We consider these results to be a guide for all physicians, especially sports medicine physicians.

Authors' Contribution

Study Conception: AÖ; Study Design: AÖ, İK; Supervision: AÖ, İK; Funding: AÖ, BK, İK, İS; Materials: BK, İK, AÖ; Data Collection and/or Processing: BK, AÖ; Statistical Analysis and/or Data Interpretation: ESY; Literature Review: AÖ, BK, İS, İK; Manuscript Preparation: AÖ, İK and Critical Review: AÖ, İK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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