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CLINICAL RESEARCH ARTICLE

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Correlation of neutrophil/lymphocyte and platelet/lymphocyte ratios with the severity of idiopathic carpal tunnel syndrome

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Abstract

Background: The aim of the present study was to investigate the correlation of the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio with the severity of idiopathic carpal tunnel syndrome (CTS).

Methods: A total of 407 patients with idiopathic CTS (neurophysiologically 150 mild, 144 moderate, and 113 severe) and 206 subjects without CTS were included (control group).

Results: There was a positive correlation between the severity of CTS and NLR ($r = 0.224$; $P < 0.001$), age ($r = 0.333$; $P < 0.001$), and body mass index ($r = 0.251$; $P < 0.001$). A 1-unit increase in NLR level was associated with an approximately 1.7-fold higher incidence of CTS ($P = 0.002$; odds ratio = 1.668; 95% confidence interval = 1.199-2.319).

Conclusions: Our results suggest that neurophysiologically more severe CTS is associated with higher NLR levels. The role of systemic inflammation in CTS should be investigated in further studies.

KEYWORDS

idiopathic carpal tunnel syndrome, nerve conduction study, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, systemic inflammation

1 | INTRODUCTION

Although several risk factors have been identified for carpal tunnel syndrome (CTS),[1,2] these factors do not account for all cases. CTS cases with an unknown cause are presumed to be associated with numerous factors and are classified as idiopathic CTS.[3] The pathophysiological mechanism of most idiopathic CTS has only been partially elucidated.[4-8] Histopathological examination of the flexor tenosynovium in idiopathic CTS has demonstrated noninflammatory fibrosis.[4,9] Other studies have suggested a relationship between carotid atherosclerosis and CTS.[10,11]

The neutrophil/lymphocyte ratio (NLR) has been defined as a novel potential indicator of subclinical systemic inflammation.[12] This evidence suggests that these forms of inflammation may play a role in CTS. NLR has been shown to be a valid biomarker of these forms of inflammation, but has not been studied in CTS. We, therefore, studied NLR in a population of CTS patients and control subjects.

2 | METHODS

2.1 | Study population

This study was conducted in the Department of Neurology of Aksaray University Training and Research Hospital between July 2016 and September 2018. Patients with CTS were included, and all who provided informed consent. Our study was conducted in accordance with the Helsinki Declaration and was approved by the Clinical Research

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CTGF, connective tissue growth factor; CTS, carpal tunnel syndrome; ms, milliseconds; mV, millivolts; NCS, nerve conduction study; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; ROC, receiver operating characteristic; SNAP, sensory nerve action potential; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; WBC, white blood cell.

Ethics Committee of KTO Karatay University Medicana Faculty of Medicine.

A diagnosis of CTS was based on clinical symptoms and nerve conduction studies (NCSs). Bilateral upper extremity NCS, which used a supramaximal percutaneous stimulation technique with a constant current stimulator and surface electrode recording, was performed on all patients. Antidromic median and ulnar nerve sensory studies were performed by placing surface recording electrodes on the 2nd and 5th fingers and a stimulating electrode at the wrist. Median and ulnar motor NCS were recorded with surface electrodes from the abductor pollicis brevis and abductor digiti minimi muscles, respectively. "Inching" across the wrist was performed on patients with normal median NCS but with CTS symptoms. The skin temperature of the hand was maintained above 32°C. A two-channel electromyography device (Micromed SpA-Via Giotto, 2–31021 Mogliano Veneto-Italy; 2014) was used.

Patients whose NCS demonstrated a median neuropathy at the wrist were grouped into mild, moderate, and severe categories.[13-16] Mild CTS was defined as a prolonged sensory nerve action potential (SNAP) or mixed nerve action potential distal latency (>3.2 ms) and/or SNAP amplitude below the lower limit of normal (<16 μV). Moderate CTS included patients with a prolonged median nerve distal latency (>4.6 ms) who also satisfied criteria for mild CTS. Severe CTS was considered to be present in those patients with a low amplitude or absent SNAP and a median nerve compound muscle action potential amplitude below the lower limit of normal (<5.0 mV). The control group consisted of healthy volunteers, including hospital staff, relatives of patients, and individuals being seen in the neurology outpatient clinic; these individuals were informed about the study procedures and their written informed consents were obtained. The study subjects were over 18 years of age.

Patients with different severities of bilateral CTS were included in the CTS group of the more severe hand. Routine physical and neurological examinations were performed on patients and healthy volunteers, and the body mass index (BMI) of all study subjects was calculated and recorded. A power analysis was performed for the study. According to the pilot study performed with 10 individuals in each group, the between-group differences were approximately 0.3 units and standard deviations of the groups were approximately 0.8. With a power of 80% and the Type 1 error considered as $\alpha = 0.05$, the minimum sample size was calculated as 113 individuals per group.

We excluded those with missing data; with radiculopathy, plexopathy, and motor neuron disease; with polyneuropathy, pregnancy, upper extremity trauma, arthritis, cancer, vasculitis, and blood diseases such as leukemia; with hypothyroidism, liver and kidney disease, diabetes mellitus, bleeding, and infection, those who had undergone surgery for carpal tunnel syndrome.

Complete blood count; thyroid function tests; liver and kidney function tests; B-12 and D vitamin levels; C-reactive protein (CRP), rheumatoid factor, glucose, electrolytes, and lipid levels of all participants were examined. Peripheral venous blood samples were collected from all study subjects and centrifuged to determine the complete blood count. Blood cell count analyses were performed

TABLE 1 Demographic characteristics of subjects according to severity of carpal tunnel syndrome

		Case				Control
		Mild CTS (mean ± SD)	Moderate CTS (mean ± SD)	Severe CTS (mean ± SD)	Total (mean ± SD)	Non-CTS (mean ± SD)
Age		52 ± 12.7	54.2 ± 13.3	58.5 ± 10.9	54.6 ± 12.7	46.6 ± 12.8
		N (%)	N (%)	N (%)	N (%)	N (%)
Gender	M	42 (28)	42 (29.2)	13 (11.5)	97 (23.8)	60 (29.1)
	F	108 (72)	102 (70.8)	100 (88.5)	310 (76.2)	146 (70.9)

Abbreviations: M, male; F, female; SD, standard deviation.

TABLE 2 Comparison of laboratory parameters with severity of carpal tunnel syndrome

	Control	Case			
	Non-CTS (mean ± SD)	Mild CTS (mean ± SD)	Moderate CTS (mean ± SD)	Severe CTS (mean ± SD)	*P-Value**
WBC	7.6 ± 1.7	7.5 ± 1.7	7.9 ± 1.8	7.8 ± 1.9	.264
CRP	2.8 ± 3.4	2.9 ± 2.5	2.9 ± 2.4	3.7 ± 2.9	<.001
Neutrophil	4.2 ± 1.1	4.2 ± 1.3	4.6 ± 1.6	4.6 ± 1.5	.039
Lymphocyte	2.6 ± 0.7	2.5 ± 0.7	2.5 ± 0.8	2.4 ± 0.8	.032
NLR	1.7 ± 0.6	1.8 ± 0.8	2.0 ± 1.0	2.3 ± 1.6	<.001
Platelet	273.8 ± 68.1	268.4 ± 61.1	276.4 ± 73.2	266.0 ± 66.1	.680
PLR	109.2 ± 33.4	115.5 ± 36.2	118.8 ± 43.7	126.8 ± 57.6	.029

*Kruskal-Wallis test.
Abbreviation: SD, standard deviation.

TABLE 3 Determination of factors affecting carpal tunnel syndrome by logistic regression analysis

	P-Value	OR	95% CILower	95% CIUpper
CRP	.393	0.971	0.907	1.039
NLR	.002	1.668	1.199	2.319
PLR	.733	1.001	0.995	1.007
Age	.000	1.040	1.024	1.056
BMI	.000	1.321	1.231	1.417
Constant	.000	0.000		

Note: Cox and Snell pseudo-R^2 = 0 .236, Nagelkerke pseudo-R^2 = 0.327.
Level of significance is defined as $P < .05$.
Abbreviation: OR, odds ratio.

TABLE 4 Correlation between severity of carpal tunnel syndrome and age, CRP, NLR, PLR, and BMI

		Age	CRP	NLR	PLR	BMI
Severity of CTS	r	0.334	0.200	0.224	0.165	0.251
	P-value	<.001	<.001	<.001	<.001	<.001

using an autoanalyzer (Sysmex XN-1000 hematology analyzer, Kobe, Japan) at our hematology center. NLR was calculated by dividing neutrophil count by lymphocyte count, whereas PLR was calculated by dividing platelet count by lymphocyte count.

2.2 | Statistical analysis

Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, and maximum). The Kolmogorov–Smirnov test was performed to determine whether the variables were normally distributed, and the Kruskal-Wallis and Mann–Whitney *U*-tests were used to compare more than two independent, continuous variables that were not normally distributed. Binary post hoc comparisons were performed using the Mann–Whitney *U*-test to obtain significant results (interpretations were performed based on Bonferroni correction and *P*-values <0.0083 were considered statistically significant). The effect of independent parameters on dichotomous dependent variable (patient/control) was investigated using logistic

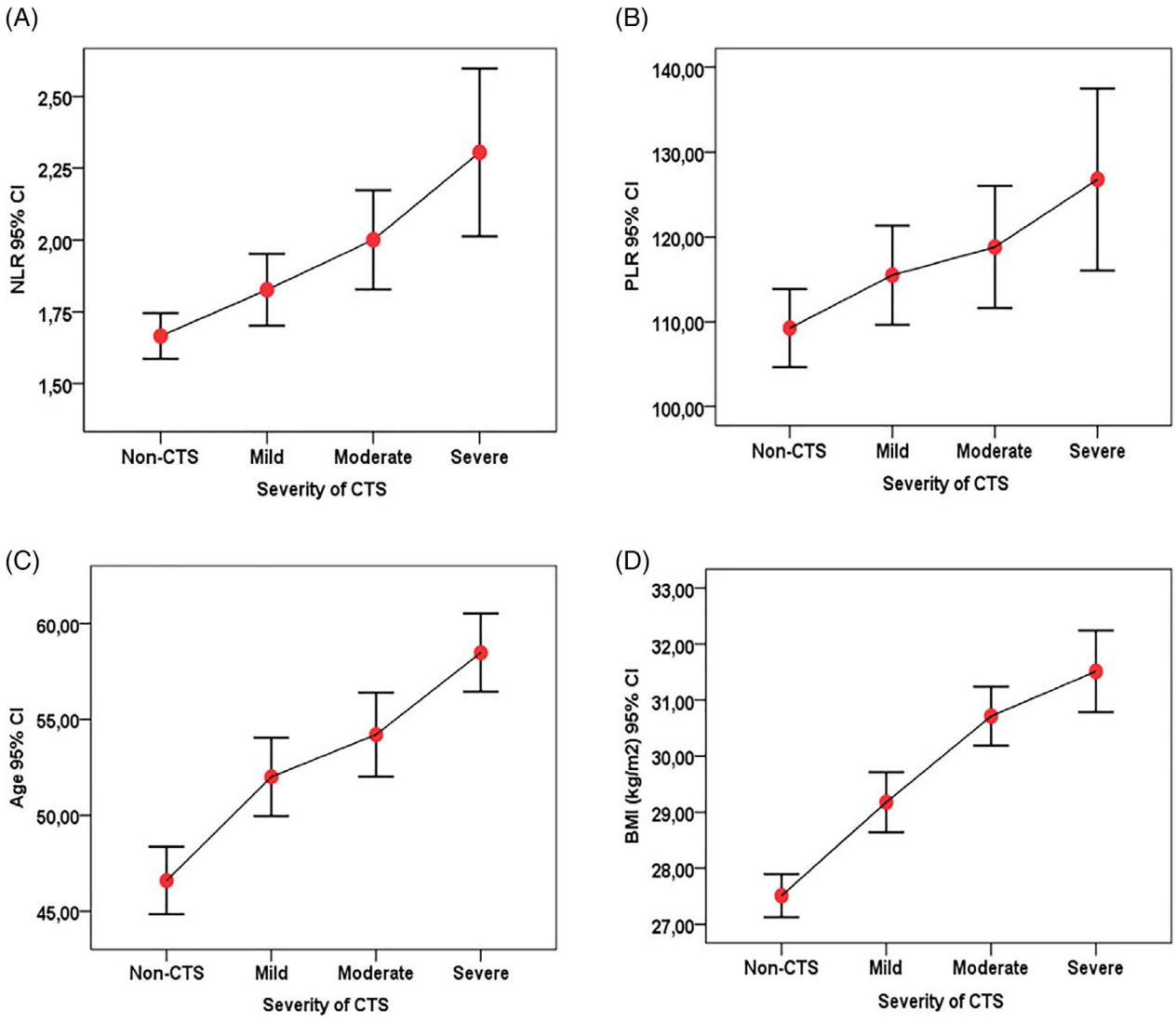

FIGURE 1 Relationships between severity of CTS and (A) NLR, (B) PLR, (C) age, and (D) BMI [Color figure can be viewed at wileyonlinelibrary.com]

regression analysis. The Hosmer-Lemeshow test was performed to assess the suitability of the final model. Cox and Snell pseudo-R^2 and Nagelkerke pseudo-R^2 tests were used to assess the consistency between the variables. The correlation between two continuous variables that were not normally distributed was examined using Spearman's rho. Results were interpreted according to the published principles of Cohen (weak positive correlation, r = 0.10-0.29; moderate positive correlation, r = 0.30-0.49; strong positive correlation, r = 0.50-1.00).[17] A *P*-value <0.05 was considered statistically significant. To evaluate the predictive power of NLR for CTS, the receiver operating characteristic (ROC) curve was plotted. The discrimination of the model was defined as follows with regard to the area under the ROC curve: less than 0.5, none; 0.5-0.7, poor to fair; 0.7-0.8, acceptable; 0.8-0.9, excellent; 0.9-1.0 is a very rare outcome.[18] All analyses were performed using the MedCalc Statistical Software (version 12.7.7, MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

3 | RESULTS

The study were included 407 patients with CTS (150 mild, 144 moderate, and 113 severe) and 206 subjects without CTS. The mean patient age was 54.6 ± 12.7 years (range, 17-90 years). Of the 613 individuals included in the study, 157 (25.6%) were male and 456 (74.4%) were female. No significant difference was observed between the patient and control groups in terms of sex distribution (*P* = 0.155). Mean age of all patients with CTS was significantly higher than that of the control participants (non-CTS) (*P* < 0.001; Table 1).

A significant difference was observed between the CTS subgroups and CRP, neutrophil, lymphocyte, NLR, and PLR levels (*P* < .05). This difference was highly significant in terms of CRP and NLR levels (*P* < .001) (Table 2).

In the univariate analysis, CRP, lymphocyte, neutrophil, NLR, PLR, age, and BMI were significantly different between the CTS and control groups. The variables demonstrating significant differences between the CTS and control groups in the univariate analysis were included in the multiple logistic regression analysis. The logistic regression model was significant (*P* < .001) and suitable for model interpretation (Hosmer-Lemeshow test, *P* = .568). In the model, the relationship between dependent variable and independent variable was found to be 23.6% according to Cox and Snell pseudo-R^2 statistics and 32.7% according to Nagelkerke pseudo-R^2 statistics. Multiple logistic regression analysis showed that a 1-unit increase in NLR level was associated with an approximately 1.7-fold higher incidence of CTS (Table 3).

Correlation analysis was performed between the severity of CTS and age, BMI, NLR, CRP, and PLR (Table 4). A significant, positive, and moderate correlation between age and the severity of CTS was observed. Moreover, a significant, positive, and weak correlation was observed between the severity of CTS and BMI, NLR, CRP, and PLR. The comparison of NLR, PLR, age, and BMI with CTS subgroups is shown in Figure 1.

We observed a significant, negative, and very weak correlation between white blood cells (WBCs) and neutrophil levels in the control group. In the patient group, a significant, negative, and very weak correlation between platelet levels and age was observed. However, there was no correlation between NLR and PLR levels and age in the patient and control groups (Supporting Information Table S1, which is available online). In other words, because NLR does not change with age, the age difference between patients in the CTS group and participants in the control group did not affect the results of the present study. Therefore, this age difference between participants of both study groups, who were randomly selected, was neglected.

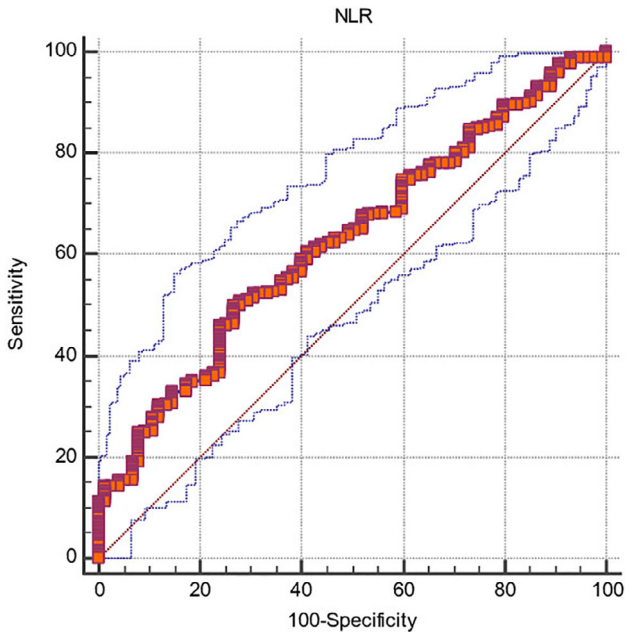

FIGURE 2 ROC curve analysis of the predictive power of the NLR for CTS. The area under ROC curve: 0.626; 95% CI: 0.581–0.669; *P* < 0.001. Cutoff value: 1.729. Sensitivity: 50.2% and specificity: 73.3% [Color figure can be viewed at wileyonlinelibrary.com]

The NLR parameter was evaluated for CTS diagnosis using ROC analysis. The model had a weak distinguishing power (area under ROC curve: 0.626; 95% confidence interval [CI]: 0.581-0.669; *P* < .001). The cutoff value was calculated as 1.729, and the sensitivity and specificity at the cutoff point were 50.2% and 73.3%, respectively (Figure 2).

4 | DISCUSSION

The findings of our study revealed a positive correlation between the severity of CTS and NLR, PLR, age, and BMI. A 1-unit increase in NLR level was associated with an approximately 1.7-fold higher incidence of CTS.

NLR is an inexpensive and effective biomarker that reflects systemic inflammation.[12] Histological studies on the flexor tenosynovium have reported ischemic changes in the carpal tunnel rather than inflammation.[7,19] Chronic infections can increase the production of extravascular inflammatory cytokines; these cytokines can accelerate the development of distant atherosclerotic plaques. Intravascular

infections can result in a local inflammatory stimulus that accelerates atherogenesis. Several human atherosclerotic plaques contain microbial agents such as *Chlamydia pneumoniae*.[20] The detection of systemic inflammation causing atherosclerosis[20-23] and association of carotid atherosclerosis with CTS[10,11] suggest that the atherosclerotic process occurs in the vasa nervorum that feeds the median nerve. A possible atherosclerotic process in this vasa nervorum due to systemic inflammation can cause microvascular insufficiency in the carpal tunnel. As a result, nerve blood flow may be impaired, which can further cause neural damage to the median nerve, eventually leading to CTS.

The transforming growth factor-β (TGF-β) plays a major role in triggering fibrosis during idiopathic CTS.[4,24] It is a multifunctional protein involved in the pathogenesis of chronic inflammation and fibrosis.[25,26] Interleukins are molecules that act as growth factors for inflammatory and immune cells.[27] An increase in mechanical pressure in the wrist increases the release of interleukins (IL-1, IL-2, and IL-6). These elevated levels of interleukins increase the expression of growth factors, including TGF-β and vascular endothelial growth factor (VEGF).[27] Chikenji et al.[4] reported that in patients with idiopathic CTS, connective tissue growth factor (CTGF) expression increased with TGF-β, which plays a role in the pathogenesis of fibrosis. CTGF expression is rapidly induced by the action of TGF-β in mesenchymal-derived cells and is effective in the formation of fibrosis.[28] NLR indicates subclinical chronic systemic inflammation.[12] In the present study, we found that NLR levels were higher in patients with CTS than in healthy controls. Subclinical systemic inflammation may increase the expression of numerous cytokines and growth factors. Therefore, we consider that the increase in cytokines and growth factors caused by subclinical systemic inflammation possibly play a role in the development of fibrosis during CTS. Further studies investigating the role of systemic inflammation in fibrosis during CTS are warranted.

Age and obesity are important risk factors for CTS.[1,2] CTS particularly affects middle-aged women (range, 41-60 years).[1] A positive correlation between age and BMI and the severity of CTS was observed in our study.

Although the control group was randomly selected from a population without clinical symptoms of CTS, the present study was limited to a patient population referred for neurophysiological assessment. Another possible limitation was that the participants included in the study were examined using a single laboratory sample obtained at the time of initial admission, without long-term follow-up.

In conclusion, the present study revealed a positive correlation between the severity of idiopathic CTS and NLR, PLR, age, and BMI. In light of these findings, we believe that systemic inflammation plays a role in CTS by contributing to atherosclerosis in the vasa nervorum of the median nerve and to fibrosis in sub-synovial connective tissue. Systemic inflammation may be a risk factor for the severity of CTS. NLR has poor prognostic performance. Nevertheless, we believe that NLR can be a useful prognostic tool in some patients. Systemic anti-inflammatory drugs may be more useful in the treatment of CTS in patients with systemic inflammation than in those without. Further studies are needed to explain the role of systemic inflammation in CTS, including histopathological studies on the median nerve.

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CONFLICT OF INTEREST

There is no conflict of interests among the authors.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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