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Neutrophil/Lymphocyte, Platelet/Lymphocyte and Neutrophil/Monocyte Rates in Carpal Tunnel Syndrome

Karpal Tünel Sendromunda Nötrofil/Lenfosit, Trombosit/Lenfosit ve Nötrofil/Monosit Oranları

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ABSTRACT Objective: The aim of this study was to investigate the relationship between these inflammation markers, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), neutrophil/monocyte ratio (NMR) and lymphocyte/monocyte ratio (LMR) in patients with diagnosed carpal tunnel syndrome (CTS). **Material and Methods:** A total of 260 participants including 130 healthy volunteers and 130 patients diagnosed with bilateral or unilateral CTS were included in this retrospective study. Patients with CTS diagnosis were classified as mild, moderate and severe according to electroneuromyography (ENMG) results. Hemogram parameters, NLR, PLR, NMR, LMR and C-reactive protein (CRP) values were calculated in the study and control groups. The data obtained were compared between patients with CTS and healthy volunteers. **Results:** NMR, CRP and platelet values of patients with CTS were found to be significantly higher than healthy group. No significant difference between NLR, PLR, LMR values in both groups. When we classified patients with CTS as mild, moderate, and severe and compared with the control group, each group was found to have a significantly higher CRP value than the control group. However, there were no changes in NLR, PLR, NMR, LMR and hemogram parameters. **Conclusion:** In our study, we demonstrated systemic inflammation in these patients by finding high levels of NMR, platelet (PLT) and CRP in patients with CTS. However, we did not detect any relationship between the severity of the disease and these parameters.

Keywords: Carpal tunnel syndrome; inflammation; lymphocyte; monocyte

ÖZET Amaç: Bu çalışmanın amacı karpal tünel sendromu (KTS) tanılı hastalarda nötrofil/lenfosit oranı (NLO), trombosit/lenfosit oranı (PLO), nötrofil/monosit oranı (NMO) ve lenfosit/monosit oranını (LMO) değerlendirerek bu inflamasyon belirteçlerinin hastalık ile ilişkisini araştırmaktır. **Gereç ve Yöntemler:** Bu retrospektif çalışmaya 130 KTS tanısı olan, 130 sağlıklı gönüllü olmak üzere toplam 260 katılımcı dahil edildi. Bilateral veya unilateral KTS tanısı olan hastalar elektronöromiyografi (ENMG) sonuçlarına göre hafif, orta, ağır olarak gruplandırıldı. Çalışma ve kontrol gruplarında hemogram paremetreleri, NLO, PLO, NMO, LMO ve C-reaktif protein (CRP) değerleri hesaplandı. Elde edilen veriler KTS tanılı hastalar ve kontrol grubu arasında karşılaştırıldı. **Bulgular:** KTS tanılı hastaların NMO, CRP ve platelet değerleri sağlıklı gruptan anlamlı derecede daha yüksek bulundu. NLO, PLO, LMO değerlerinde iki grup arasında anlamlı fark bulunamadı. KTS'li hastaları hafif, orta, ağır olarak sınıflandırıp kontrol grubu ile karşılaştırdığımızda her grubun CRP değeri kontrol grubundan anlamlı olarak yüksek bulundu. Fakat NLO, PLO, NMO, LMO ve hemogram parametrelerinde değişiklik saptanmadı. **Sonuç:** Çalışmamızda KTS'li hastalarda NMO, platelet (PLT) ve CRP değerlerini yüksek bularak bu hastalardaki sistemik inflamasyonu göstermiş olduk. Fakat hastalığın ağırlık derecesi ile bu parametreler arasında bir ilişki saptamadık.

Anahtar Kelimeler: Karpal tünel sendromu; inflamasyon; lenfosit; monosit

Carpal tunnel syndrome (CTS) is the most common neuropathy of the upper limb, affecting about 6%-12% of the general population. It is more common in females than males, and prevalence and severity increase with age.[1] CTS is the clinic table characterized by pain and pares-

thesia in the median nerve innervation area, resulting in compression of the median nerve at the wrist level. In the beginning, the only symptom may be nocturnal pain and paresthesia, but atrophy and weakness in tenar muscles may be added to the table future.[2] CTS diagnosis is made by clinical findings and electrophysiological examinations. Conservative treatments may be useful in some CTS patients, but ultimately surgical intervention is necessary in most patients.[3]

The pathophysiology of CTS involves mechanical trauma in the carpal tunnel, increased pressure and ischemic damage to the median nerve.[4] Significant tendon and sheath degeneration and fibrosis in biopsies made in patients with CTS coexist with inflammatory and proliferative changes.[5] Tissue injury cytokines elicit an acute inflammatory response leading to the release of neutrophils and subsequent collagen and fibronectin fragments that attract macrophages.[6]

Previously localized tendon and sheath biopsy studies as well as proinflammatory cytokines such as IL-1alpha, IL-6, and TNF-alpha in serum were also performed to evaluate inflammation in CTS .[7-9] Neutrophil/lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR), neutrophil / monocyte (NMR) and lymphocyte/monocyte (LMR) ratios are used as an inexpensive and easily calculated index to evaluate systemic inflammation in recent years.[10,11] These parameters have been determined to play an important role in immunological and inflammatory events.[12] In this study, we aimed to investigate the relationship between NLR, PLR, NMR, LMR and CRP rates in carpal tunnel syndrome.

MATERIAL AND METHODS

This study was approved by Ankara Numune Training and Research Hospital Ethics Committee (approval No: E-18-1767). All procedures have been applied in accordance with the principles of the Declaration of Helsinki .

PATIENT POPULATION

A total of 130 patients diagnosed with carpal tunnel were included in this retrospective study between January 2017 and December 2017 as a result of ENMG evaluation in one or both upper extremities. The study included 130 healthy subjects as a control group. Patients with chronic illnesses such as diabetes mellitus, hypertension, rheumatic disease, atherosclerotic heart disease, cancer, who had a history of infections and drug use in the last month were not included in the study. Pregnant women, smoking and alcohol use history, those with electrodagnostic radiculopathy / plexopathy, polyneuropathy were excluded from the study. The control group included those without systemic disease, no drug use, and no neuropathy complaints. Demographic characteristics, complete blood count and CRP values of the control group were recorded.

The blood parameters of the patients who were diagnosed as carpal tunnel syndrome by electrophysiological examination were evaluated. Patients without blood values were excluded from the study.The complete blood count was measured with the automatic blood count (ADVIA 2120I) in our hospital and the CRP with the turbidimeter (BECKMAN COULTER AU680). NLR was obtained by dividing the number of neutrophils by the number of lymphocytes, PLR by dividing the number of platelets by the number of lymphocytes, LMR by dividing the number of lymphocytes by the number of monocytes, and NMR by dividing the number of neutrophils by the number of monocytes.

ELECTROPHYSIOLOGICAL EVALUATION

Nicolet EDX device was used for electrophysiological evaluation. The extremity temperature was maintained above 31°C. The study was performed with surface electrodes, using standard nerve conduction techniques, according to the protocol recommended by the American Electrodiagnostic Medical Association.[13] Patients of whom the both upper extremities were examined included in the study, median and ulnar nerve conduction in one extremity was performed, while only median nerve conduction study in the other extremity was performed.

The median motor nerve conduction was recorded using standard techniques through stim-

ulation of the surface of the abductor pollicis brevis muscle located in the center of the muscle and wrist and antecubital fossa. For median nerve (8 cm) stimulation the upper limit of the motor distal latency was 4 ms and the lower of the transmission rate was 50 m/sec. The sensory neurotransmission study was performed on the second finger and the mixed nerve conduction study was performed from the palm of the hand, recorded orthodromatically from the wrist. The distance between the recording and the stimulator was 12-14 cm, the upper limit of sensory neural action potential (DSAP) peak latency difference was 0.5 ms, and the median sensory nerve conduction velocity at the wrist level was 50 m/sec. Patients were divided into the following three groups by electrophysiological evaluation.[14]

Mild severe CTS: Slowed median sensory transmission (speed of <50 m/sec in the second finger-wrist and palm-wrist section).

Moderate severe CTS: Slowed median nerve sensory transmission rate and the prolongation of the distal latency of the median motor nerve (> 4.0 ms).

Severe CTS: Loss/absence of median nerve sensory potential amplitude, prolonged motor and sensory distal latency, and high rate of deceleration in motor conduction velocity.

STATISTICAL ANALYSIS

Study data was completed by transferring to the IBM SPSS Statistics 23 program. Frequency distributions for categorical variables and descriptive statistics for numerical variables (mean±sd) were given.

The Kolmogorov Smirnov normality test was applied to the numerical variables (Age, CRP, Leukocyte (WBC), PLT, Neutrophil (NEU), Llymphocyte (LYM), Monocyte (MON), NLR, PLR, NMR, LMR) to be statistically tested to determine the analyzes to be applied. Some of the test results showed that some of the variables did not provide normality assumptions. For this reason, parametric and nonparametric tests were used in their comparison. The difference between the two independent groups was examined by the Mann-Whitney U Test for those who did not have the Independent Sample T test for those who provided the assumption of normal distribution. Differences between independent groups more than one were checked by the Kruskal Wallis test.

RESULTS

While 77.7% of the subjects in the healthy group were women, 86.9% of the patients in the CTS group was women. The mean age of the control group was 45.65±13.00, while the average age of the group with CTS diagnosis was 47.51±8.14 years.

As a result of the statistical analyses performed, there was no statistically significant difference between the control and CTS groups in terms of gender and age.

CRP level of CTS diagnosed group was 0,29± 0,32 while the WBC level was 7,03±1,54, the PLT level was 262,15±54,66, the NEU level was 4,06± 1,14, the LYM level was 2,32 ± 0,58 and the MON level was 0,43±0,14. NLR level of the control group was 1,93±1,03, while the PLR level was 122,45±55,13, the NMR level was 9,16±3,25, the PMR level was 599,65±225,12 and the LMR level was 5,25±1,91. NLR level of the patient group was 1,85±0,67 while the PLR level was 118,70±34,37, the NMR level was 10,42±7,05, and the LMR level was 6,10±4,95 (Table 1).

As a result of the statistical analyses performed, there was a statistically significant difference between the control and CTS groups in terms of CRP and PLT. According to this, the CRP and PLT levels of the group diagnosed with CTS were significantly higher than the control group (p=0,000, p=0.024). As a result of the statistical analyses performed, there was a statistically significant difference between the control and CTS groups in terms of NMR. According to this, the NMR level of the patient group with CTS was significantly higher than the control group (p=0.037) (Table 1).

As a result of the statistical analyzes performed, there is a statistically significant difference in CRP between the 4 groups. Accordingly, the CRP levels of the control subjects were signifi-

TABLE 1: Comparison of hemogram parameters and rates between groups.

	Control (n=130) Avg±S.D.	CTS (n=130) Avg±S.D.	p
CRP *(mg/l)*	0.13±0.11	0.29±0.32	**0.000***
WBC *(x10³ul)*	6.80±1.56	7.03±1.54	0.237
PLT *(x10³ul)*	249.51±56.68	262.15±54.66	**0.024***
NEU (x10³ul)	3.93±1.19	4.06±1.14	0.413
LYM *(x10³ul)*	2.23±0.68	2.32±0.58	0.132
MON (x10³ul)	0.46±0.17	0.43±0.14	0.488
NLR	1.93±1.03	1.85±0.67	0.899
PLR	122.45±55.13	118.70±34.37	0.974
NMR	9.16±3.25	10.42±7.05	**0.037***
LMR	5.25±1.91	6.10±4.95	0.070

***:** p<0,05 (statistically significant); **Avg:** Average; **SD:** Standard Deviation; **CRP:** C-reactive protein (mg/l); **WBC:** Leukocyte (x10³ul); **PLT:** Platelet (x10³ul); **NEU:** Neutrophils (x10³ul); **LYM:** Llymphocytes (x10³ul); **MON:** Monocytes (x10³ul); B Neutrophil / lymphocyte ratio; **PLR:** Platelet /lymphocyte ratio; **NMR:** Neutrophil/monocyte ratio; **LMR:** Lymphocyte/monocyte ratio.

cantly lower than the patients with mild, moderate and severe CTS (p=0.000). As a result of the statistical analyses performed, there was no statistically significant difference between the 4 groups in terms of NLR, PLR, NMR and LMR (Table 2).

DISCUSSION

CTS has a multifactorial etiology and there is no specific factor in the majority of patients. With the repetitive movements of the hand and the wrist, the increased pressure on the carpal tunnel triggers a series of inflammatory and proliferative changes.[15] In acute or chronic phases of inflammation, the release of proinflammatory cytokines into the extracellular matrix may stimulate the systemic immune reaction.[16,17] Although carpal tunnel syndrome has previously shown many localized median nerve and tenosynovium biopsies and inflammation, a limited number of studies have been performed to evaluate inflammation in serum.[5,18]

It has been reported that NLR, PLR, NMR and LMR values may lead to diagnosis and prognosis in many systemic diseases such as malignancies, chronic inflammatory diseases, acute myocardial infarction, renal artery stenosis, diabetes mellitus.[19,20] In our study NMR, CRP and platelet values were found to be significantly higher in patients with CTS, but there was no difference in NLR, PLR, and LMR values. CRP is one of the most prominent acute phase reactants but is not specific, but plasma level increases in response to cell damage or tissue injury.[21] Previously, complete blood count parameters have also been shown to change significantly in number and quality during inflammatory events. There is a decrease in lymphocyte counts, especially when

TABLE 2: Comparison of hemogram parameters and rates according to CTS severity.

	Severe (n=33) Avg±SD	Moderate (n=47) Avg±SD	Mild (n=50) Avg±SD	Control (n=130) Avg±SD	p
CRP	0.44±0.50	0.24±0.18	0.25±0.22	0.13±0.11	0.000*
WBC	7.03±1.88	7.16±1.53	6.91±1.30	6.80±1.56	0.397
PLT	266.09±45.13	262.96±61.67	258.80±54.25	249.51±56.68	0.095
NEU	4.08±1.16	4.12±1.22	4.00±1.07	3.93±1.19	0.848
LYM	2.44±0.59	2.35±0.61	2.21±0.54	2.23±0.68	0.187
MON	0.44±0.13	0.43±0.15	0.43±0.13	0.46±0.17	0.836
NLR	1.74±0.61	1.85±0.69	1.91±1.93	1.93±1.03	0.741
PLR	113.46±28.30	117.62±34.32	123.17±37.97	122.45±55.13	0.845
NMR	9.84±3.54	9.99±2.69	11.21±10.71	9.16±3.25	0.173
LMR	5.95±2.02	5.90±2.10	6.40±7.59	9.16±3.25	0.132

***:** p<0,05 (statistically significant); **Avg:** Average; **SD:** Standard Deviation; **CRP:** C-reactive protein (mg/l); **WBC:** Leukocyte (x10³ul); **PLT:** Platelet (x10³ul); **NEU:** Neutrophils (x10³ul); **LYM:** Llymphocytes (x10³ul); **MON:** Monocytes (x10³ul); **NLR:** Neutrophil/lymphocyte ratio; **PLR:** Platelet/lymphocyte ratio; **NMR:** Neutrophil/monocyte ratio; **LMR:** Lymphocyte/monocyte ratio.

an increase in the number of neutrophils and platelets is observed.[22,23] We think that platelet and CRP levels in patients with CTS in our study are indicative of inflammation in these patients. NMR elevation supported this conclusion and showed that NMR could be a more valuable marker than the single count of neutrophil and monocyte counts. In recent years, the results of NMR ratio in chronic inflammatory diseases such as malignancy and osteoarthritis have been a guide as in our study.[24,25]

We classified patients diagnosed with CTS as mild, moderate and severe according to EMG findings. When we compared these groups with the control group, each group was found to be significantly higher than the CRP value control group. However, there was no change in NLR, PLR, LMR, NMR and blood parameters. Previously PGE2, IL-6 and malondialdehyde were examined in the serum in the carpal tunnel syndrome and only malondialdehyde was detected and no difference was found in the levels of PGE2 and IL-6.[7] In another study, CTS was developed with repetitive motor performance in rats and IL-1 alpha was elevated in serum as well as local inflammation.[26] In our study, when we compared the CTS patients with the control group, although we found that the NMR, platelet, and CRP levels were significantly higher, we found only elevated levels of CRP when we grouped the disease by the severity of the disease.

The fact that our study is performed in one center and retrospectively is one of the limiting factors. In addition, following up the patients and looking at the hemogram parameters may help to better evaluate the prognosis.

CONCLUSION

As a result, CTS is a very common musculoskeletal disease that constitutes 90% of all traumatic neuropathies in the community. NMR, LMR, NLR, PLR, whole blood counts are easily accessible parameters and show systemic inflammation for many diseases and lead to disease prognosis. It is known that different pathophysiological mechanisms play a role in the development of CTS and inflammation is one of the important factors. In our study, we demonstrated systemic inflammation in these patients by finding high levels of NMR, platelet and CRP in patients with CTS. However, we did not detect any relationship between the severity of the disease and these parameters. We believe that multi-centered studies with a larger number of patient groups for the enlightenment of pathophysiological mechanisms in the formation of CTS will contribute to early diagnosis, prevention and treatment of the disease.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

REFERENCES

1. Thiese MS, Gerr F, Hegmann KT, Harris-Adamson C, Dale AM, Evanoff B, et al. Effects of varying case definition on carpal tunnel syndrome prevalence estimates in a pooled cohort. Arch Phys Med Rehabil 2014;95(12): 2320-6.
2. Bland JD. Carpal tunnel syndrome. Curr Opin Neurol 2005;18(5):581-5.
3. Iida J, Hirabayashi H, Nakase H, Sakaki T. Carpal tunnel syndrome: electrophysiological grading and surgical results by minimum incision open carpal tunnel release. Neurol Med Chir (Tokyo) 2008;48(12):554-9.
4. Werner RA, Andary M. Carpal tunnel syndrome: pathophysiology and clinical neurophysiology. Clin Neurophysiol 2002;113(9): 1373-81.
5. Campligio GL, Di Giuseppe P, Migliorini L, Cazzaniga M, Lamperti E, Romorini A. Histopathology of the flexor tendon sheaths and its relevance in idiopathic carpal tunnel syndrome. Eur J Plast Surg 1999;22(5-6):230-3.
6. Kent TH, Hart MN. Injury, inflammation and repair. Introduction to Human Disease. 3rd ed. Norwalk, CT: Appleton & Lange; 1993. p.493.
7. Freeland AE, Tucci MA, Barbieri RA, Angel MF, Nick TG. Biochemical evaluation of serum and flexor tenosynovium in carpal tunnel syndrome. Microsurgery 2002;22(8):378-85.
8. Takasu S, Takatsu S, Kunitomo K, Kokumai Y. Serum hyaluronic acid and interleukin-6 as possible markers of carpal tunnel syndrome in chronic hemodialysis patients. Artif Organs 1994;18(6):420-4.
9. Barr AE, Barbe MF, Clark BD. Work-related musculoskeletal disorders of the hand and wrist: epidemiology, pathophysiology, and sensorimotor changes. J Orthop Sports Phys Ther 2004;34(10):610-27.
10. Sen BB, Rifaioglu EN, Ekiz O, Inan MU, Sen T, Sen N. Neutrophil to lymphocyte ratio as a measure of systemic inflammation in psoriasis. Cutan Ocul Toxicol 2014;33(3):223-7.
11. Feng JR, Qiu X, Wang F, Chen PF, Gao Q, Peng YN, et al. Diagnostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in Crohn's disease. Gastroenterol Res Pract 2017;2017:3526460.
12. Briggs C. Quality counts: new parameters in blood cell counting. Int J Lab Hematol 2009;31(3):277-97.
13. American Academy of Neurology, American Association of Electrodiagnostic Medicine, and the American Academy of Physial Medicine and Rehabilitation. Practice parameter for electrodiagnostic studies in carpal tunnel syndrome (summary statement). Neurology 1993;43(11):2404-5
14. Stevens JC. AAEM minimonograph #26: the electrodiagnosis of carpal tunnel syndrome. American Association of Electrodiagnostic Medicine. Muscle Nerve 1997;20(12):1477-86.
15. Jinrok O, Zhao C, Amadio PC, An KN, Zobitz ME, Wold LE. Vascular pathologic changes in the flexor tenosynovium (subsynovial connective tissue) in idiopathic carpal tunnel syndrome. J Orthop Res 2004;22(6):1310-5.
16. Barr AE, Barbe MF, Clark BD. Work-related musculoskeletal disorders of the hand and wrist: epidemiology, pathophysiology, and sensorimotor changes. J Orthop & Sports Phys Ther 2004;34(10):610-27.
17. MacIntyre DL, Reid WD, McKenzie DC. Delayed muscle soreness. The inflammatory response to muscle injury and its clinical implications. Sports Med 1995;20(1):24-40.
18. Al-Shatti T, Barr AE, Safadi FF, Amin M, Barbe MF. Increase in inflammatory cytokines in median nerves in a rat model of repetitive motion injury. J Neuroimmunol 2005;167(1-2):13-22.
19. Marín Hernández C, Piñero Madrona A, Gil Vázquez PJ, Galindo Fernández PJ, Ruiz Merino G, Alonso Romero JL, et al. Usefulness of lymphocyte-to-monocyte, neutrophil-to-monocyte and neutrophil-to-lymphocyte ratios as prognostic markers in breast cancer patients treated with neoadjuvant chemotherapy. Clin Transl Oncol 2018;20(4):476-83.
20. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med 2012;5(1):2.
21. Agassandian M, Shurin GV, Ma Y, Shurin MR. C-reactive protein and lung diseases. Int J Biochem Cell Biol 2014;53:77-88.
22. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340(6):448-54.
23. Kapci M, Turkdogan KA, Duman A, Avcil M, Gülen B, Küçükdağlı ÖT, et al. [Biomarkers in the diagnosis of acute appendicitis]. J Clin Exp Invest 2014;5(2):250-5.
24. Ceylan Y, Günlüsoy B, Degirmenci T, Bolat D, Kozancioglu Z, Vardar E, et al. Neutrophil-to-lymphocyte and neutrophil-to-monocyte rates in the decision for a prostate re-biopsy in patients with a previous benign pathology and consistently 2,5-10 ng/ml PSA value. Arch Esp Urol 2016;69(9):627-35.
25. Shi J, Zhao W, Ying H, Du J, Chen J, Chen S, et al. The relationship of platelet to lymphocyte ratio and neutrophil to monocyte ratio to radiographic grades of knee osteoarthritis. Z Rheumatol 2018;77(6):533-7.
26. Barbe MF, Barr AE, Gorzelany I, Amin M, Gaughan JP, Safadi FF. Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. J Orthop Res 2003;21(1):167-76.