Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Are C-reactive protein, neutrophil to lymphocyte, and platelet to lymphocyte ratios related to the severity of idiopathic carpal tunnel syndrome?

Yasar Altun

Adiyaman University, Faculty of Medicine, Adiyaman University, Department of Neurology, Adiyaman, Türkiye

ARTICLE INFO

Keywords:
Carpal tunnel syndrome
Inflammation
C-reactive protein
Haematological parameters
Red cell distribution width

Received: Jan 14, 2022
Accepted: Aug 25, 2022
Available Online: 27.09.2022

DOI:
10.5455/annalsmedres.2022.01.012

Abstract

Aim: The aim of this study was to investigate the correlation of C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and red cell distribution width (RDW) in patients with idiopathic carpal tunnel syndrome (CTS).

Materials and Methods: One hundred patients with CTS and 60 control subjects were included in this study. Medical records and laboratory findings of the participants were analyzed retrospectively between March 2019 and February 2020. Laboratory result values obtained from the members included in the study were examined.

Results: There was a correlation between CRP and the severity of CTS ($p<0.01$). There was also a positive correlation between CRP and symptom severity scale ($p<0.01$) and functional status scale ($p<0.01$). No statistically significant changes were observed in the measurements of blood values other than CRP in the patients.

Conclusion: In this study, a relationship was found between CRP, one of the hematological parameters, and the presence or severity of CTS.

Introduction

Carpal tunnel syndrome (CTS) is the most common compression neuropathy of the upper extremity, manifested by pain and numbness in the hand and arm. CTS, affects approximately 6% to 12% of general population and with a higher prevalence and severity in female patients as they age [1]. Although CTS is associated with a multifactorial pathophysiology, the increase of pressure in carpal tunnel plays a key role in the development of the disease [2]. CTS is caused by compression and retraction of the median nerve at carpal tunnel level, restricted by carpal bones, and flexor retinaculum transversely [3]. Physiological evidences indicate that pressure increases inside carpal tunnel (CTS is not caused by combined pressure and retraction of median nerve); and addresses the decrease of function in the median nerve at this level [4]. Furthermore, such pressure increase in the carpal tunnel may directly injure the median nerve and cause axon damage as well as median nerve ischemia through compression on the vessels at perineurium [5]. The majority of CTS cases are considered without a nonspecific origin, and defined as idiopathic cases [6]. Although it has been reported that CTS may be a chronic inflammatory disease, there are limited studies on this subject [7,8]. Platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) are easily calculated from absolute platelet count, absolute lymphocyte count, and absolute neutrophil count. These tests are simple, practical, cheap and feasible parameters to evaluate systemic inflammation [9]. It is emphasized that NLR is a new potential biomarker for subclinical inflammation [9]. These parameters were reported as key components in immunological and inflammatory cases [10]. This evidence reminds that such inflammation forms may play a role in CTS. There are studies indicating that PLR is a biomarker for systemic inflammation like NLR, and more significant results are obtained when PLR is evaluated with NLR [11]. There are insufficient studies on this subject [12,13]. The red cell distribution width (RDW), which is included in all standard hemogram tests. RDW is particularly closely associated with many chronic inflammatory conditions [14]. There is a single study addressing mean platelet volume

*Corresponding author:
Email address: yasaraltun02@gmail.com (Yasar Altun)

(MPV) as a predictive marker in chronic inflammatory diseases such as CTS for the individuals over 65v years of age [15]. A recent meta-analysis on the role of chronic inflammation showed a significant associated with C-reactive protein (CRP) [16].

We aimed to determine whether hemogram parameters are predictive factors for disease severity, and guiding for diagnosis and monitoring in patients that present clinical signs of CTS and cannot undergo electroneuromyographically (ENMG). Our results would contribute to medical literature defining laboratory parameters and inflammation biomarkers required during neurophysiological CTS monitoring.

Materials and Methods

Subjects and study design

Our study was executed in Neurology Clinic of Adıyaman Training and Research Hospital according to Helsinki Declaration between April, 2020 and May, 2020, and approved by Ethical Committee of Adıyaman University (approval code: 2020/3-1). For this study, patients who applied to the ENMG laboratory of our hospital and were diagnosed with CTS within the last one years were included. First of all, patient and control groups were included in this study. Patients with bilateral and idiopathic CTS who meet the inclusion criteria were enrolled into the study. Consequently, 100 patients (18 males, 82 females; mean age of 46.78±10.74 years; age range, 22 to 66 years, 100 forearm) identify with CTS as claimed by clinical and nerve conduction velocity findings were inclusive in the study. The control group be formed of 60 healthy volunteers (17 males, 43 females; mean age 43.95±9.57 years; age range 27 to 65 years; 60 wrists) without chronic or systemic disease that were referred to the neurology clinic with varying complaints. The individuals in the control group were informed about how the study was conducted. In addition, informed consent forms were obtained from each individual individually.

The inclusion criteria of the patient group were as follows: an evident CTS case presenting typical medical history, symptoms and findings (i.e. intermittent, especially at nights, numbness, tingling or burning sense in the first four fingers; positive tinnel and phalen tests), and individuals presenting similar findings with CTS through ENMG tests.

The exclusion criteria of the patient group were as follows: individuals below 18 years of age and above 65 years of age; the individuals with occupying lesions on the wrist area; motor neuron disease; radiculopathy; plexopathy; polyneuropathy; pregnancy; wrist injury or history of wrist surgery; arthritis; cancer; vasculitis, and blood disease that will affect nerve conduction work.

Clinical evaluation

All of the participants included in the study had a neurological examination. Control subjects also underwent equally extensive neurophysiological evaluations. Tinel's sign and Phalen's test were noted as positive or negative. Functional and clinical statuses of patients were evaluated by Boston Questionnaire (BQ) [17,18]. In addition, those with hemogram parameters, NLR, and PLR values were included in the study and these values were calculated. The data obtained were compared according to the severity of the disease in patients with CTS. A control group consisted of voluntary individuals that had normal ENMG results. There were 60 healthy individuals (120 hands, 60 right/60 left) under 65 years of age in the control group who had no known risk factors for neuropathy and no neurological abnormality. Age, CRP, hemogram parameters, NLR and PLR values and BQ assessments of healthy controls were recorded.

Electrophysiological studies

Each subject was treated as a single observation for statistical analysis. In bilateral cases the severity of their CTS was taken as being that of the more severely affected hand, or the right hand if both were equally affected. CTS was diagnosed according to American Academy of Neurology criteria [19]. A Medelec Synergy (Oxford Instruments Medical, Inc, UK) ENMG device was used for all works. All studies were performed in the ENMG unit at normal room temperature. Nerve conduction studies and CTS grading were done with reference to the study values of Stevens et al. [20]. The severity of CTS was graded as follows: Grade 1, mild CTS (SNCV slowing [<50 m/s]); Grade 2, moderate CTS (SNCV slowing [<50 m/s] and delayed MNDL [>4.5 ms]); and Grade 3, severe CTS (no SNAP) [20]. The study included patients with mild, moderate and severe CTS based on the above grading system.

Biochemical assessments

Venous blood samples of all participants were studied on the CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, USA). CRP levels were measured by rate nephelometry (IMAGE, Backman, USA) method.

Statistical analyses

The data obtained from the study were uploaded to SPSS program (version 22.0). Mean, standard deviation, median, lowest, and highest frequency values and ratios were estimated as descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov Smirnov test. Comparisons between groups were made using the Tukey test, Kruskal-Wallis tests, or the Mann-Whitney U test. A p value less than 0.05 was considered statistically significant.

Results

The current study included 100 patients with CTS (29 patients with mild CTS; 47 patients with moderate CTS, and 24 patients with severe CTS), and 60 individuals without CTS. The age average of the patient group including 82 females (82%) and 18 males (18%) was 46.78±10.74 (min-max: 20-66) years. The age average of the control group including 43 females (78.3%) and 17 males (21.7%) was 43.95±9.57 (min-max: 27-65) years. There was not any significant difference for age and gender distribution in the patient and control groups (p=0.095 and p=0.356, respectively) as a result of statistical analyses. SSS and FSS values of all patients with CTS were significantly higher (P<0.01). Furthermore, there was a significant association

Table 1. Demographic characteristics of subjects.

		Case				
		Control Non-CTS (mean±SD)	Mild CTS (mean±SD)	Moderate CTS (mean±SD)	Severe CTS (mean±SD)	Total (mean±SD)
Age		43.95±9.57	45.13±10.20	47.97±10.67	46.41±11.64	46.78±10.74
		N (%)	N (%)	N (%)	N (%)	N (%)
Gender	F	43 (78.3)	21 (72.4)	41 (87.2)	20 (83.3)	129 (80.6)
	M	17 (21.7)	8 (27.6)	6 (12.8)	4 (16.7)	31 (19.4)
WC		93.00±10.63	91.24±8.89	94.64±8.05	96.63±12.89	94.13±9.76
HC		110.68±11.55	105.14±14.15	106.96±8.06	111.50±16.22	107.52±12.40
WHR		0.84±0.7	0.88±0.06	0.88±0.47	0.87±0.49	0.86±0.06
BMI		28.55±5.21	27.48±4.45	27.93±4.95	30.39±5.61	28.39±5.06
SSS		11.00±0.00	29.10±7.06	30.94±4.95	36.16±7.04	31.66±6.64
FSS		8.00±0.00	23.58±5.32	25.97±4.98	28.21±6.93	25.82±5.79

Abbreviations: F, female; M, male; WC, waist circumference; HC, hip circumference WHR, waist-hip ratio; BMI, body mass index; SSS, symptom severity scale; FSS, functional status scale; SD, standard deviation.

Table 2. Comparison of laboratory parameters with patients and controls.

	Case				
	Control Non-CTS (mean±SD)	Mild CTS (mean±SD)	Moderate CTS (mean±SD)	Severe CTS (mean±SD)	p value*
WBC (10^3/Ul)	8.12±1.63	7.99±2.32	8.64±2.43	9.01±2.38	0.360
CRP (mg/dL)	0.13±0.65	0.21±0.09	0.36±0.08	0.47±0.04	0.000
RDW (%)	12.19±1.18	12.62±1.43	12.71±1.57	12.31±0.99	0.625
MPV (fL)	7.80±1.32	8.79±1.22	8.58±1.17	9.49±1.16	0.058
Neutrophile (x10^6/uL)	4.68±1.30	4.54±1.69	5.25±2.15	5.65±2.69	0.236
Lymphocyte (x10^3/uL)	2.68±0.71	2.54±0.70	2.67±0.80	2.81±0.83	0.373
Platelet (x10^9/uL)	263.51±56.41	253.01±48.89	284.80±56.54	260.75±78.94	0.217
NLR	1.37±1.03	2.33±1.37	1.92±1.02	2.09±1.05	0.120
PLR	92.02±19.50	106.13±23.86	99.01±24.28	95.55±26.33	0.105

*Kruskal Wallis Test.

Table 3. Correlation between severity of carpal tunnel syndrome with age and hematological parameters.

		Age	MPV	RDW	CRP	NLR	PLR
Severity of	R	0.067	0.222	-0.050	0.799	-0.085	-0.179
CTS	p-value	0.510	0.027	0.624	0.000	0.402	0.074

with disease severity and SSS and FSS values (P<0.01) (Table 1).

In the CTS group; the CRP level was 0.34±0.12, white blood cell (WBC) level was 8.54±2.39, PLT level was 269.81±61.80; neutrophile level was 5.14±2.19, and lymphocyte level was 2.67±0.78. Moreover, NLR and PLR levels of the patient group were 2.09±1.15 and 100.25±24.75, respectively. NLR and PLR levels of the control group were 1.37±1.03 and 92.02±19.50, respectively. The association between CTS subgroups and WBC, RDW, neutrophil, and CRP revealed a significant association between subgroups and CRP (p<0.01). There was no significant association between CTS, NLR, and PLR (p>0.05). However, a significant association exists between moderate and severe CTS and MPV (p>0.05) (Table 2).

A correlation analysis was performed between CTS severity and age, CRP, MPV, RDW, NLR, and PLR (Table 3). A significant (positive) correlation was observed between CTS severity and CRP, MPV.

Discussion

In this study, a data analysis was performed for the association between complete blood count parameters commonly ordered for the patients with idiopathic CTS and electrophysiological disease severity. CTS is a multifactorial disease with an etiopathogenesis of pressure increase in the carpal tunnel [2]. Histological studies conducted on flexor then synovium on the wrist indicate ischemic changes rather than inflammation in the carpal tunnel [21]. Intravascular infections may result with a local inflammatory stimulus, which accelerated atherogenesis [22]. Pathophysiological mechanism of CTS was not yet clarified [23]. There are limited number of studies suggesting

that NLR indicates subclinic chronic systemic inflammation [11,12]. As far as we have searched, NLR, PLR, RDW, and MPV, which are inflammatory markers for CTS, were not evaluated together in any previous study. From this point of view, we investigated the role of ischemia and systemic inflammation using these parameters in this disease of limited etiopathogenesis understanding. Our findings revealed a significant difference on high WBC, neutrophil, MPV, and CRP between idiopathic CTS patients and healthy controls. These results are simple and cheap systemic biomarkers that indicate the damage associated with prognosis in different diseases. WBC, neutrophil, and platelet counts were not different between two groups. This finding did not show NLR and PLR as more sensitive and significant than neutrophil and platelet counts. To the best of our knowledge, ENMG, WBC and CRP are most common tests used for routine clinical setting for CTS patients. However, there are rare studies suggesting this finding [12,13]. Two studies investigated NLR and PLR values in idiopathic CTS only up to date [12,13]. We consider that the common deficiency in each study was the lack of review of the association between disease severity and RDW and MPV. CRP and platelet values were detected significantly higher in the patients diagnosed with CTS in the first study. There was not any significant difference in NLR and PLR values between two groups. The patients with CTS were classified as mild, moderate, and severe. CRP levels of each group were found significantly higher than the control group [12]. Another study reported that higher NLR and PLR values were caused by the decrease in lymphocyte count and the increase in neutrophil and platelet counts. The aforementioned study also suggested that CRP may be a useful predictor for systemic inflammation in idiopathic CTS patients [13]. High leukocytes including neutrophils affect systemic inflammation and contribute to native and adaptive immune responses [15]. Our results showed that neutrophil count increased in idiopathic CTS with similar findings. Similar results from recent studies are consistent with our finding in this study. CRP levels were detected higher in the patient group when compared with the control group. Such outcomes reveal the role of inflammation in etiopathogenesis of CTS.

Chronic compression may depend on long term pressure on the median nerve bearing and first inflammatory reaction of idiopathic CTS [5,7,8]. There are studies addressing that MPV and RDW are associated with many diseases and chronic inflammation as inflammation markers [14]. Furthermore, the role of RDW and MPV on chronic inflammation conditions such as ankylosing spondylitis were stressed out [16]. However, no study on the role of RDW and MPV in the patients with CTS has been documented. High MPV levels were detected in moderate and severe CTS patients in the present study.

Moreover, SSS and FSS values of the patient group were significantly higher in the patient group than the control group. Among patient subgroups which were determined by electro-diagnostic means, SSS level of the patients with severe CTS were found higher than mild and moderate CTS. However, no significant difference for FSS levels in patient subgroups were found. Different results were obtained in the studies investigating the association between electro-diagnostic findings and SSS and FSS. Some studies have not detected any significant association between symptoms and functional scale scores, and disease severity, which was determined electrophysiologically [25]. However, a strong association was detected in some studies [7]. Another study detected a higher functional restriction in severe CTS patients whereas no association was detected between SSS and disease severity [26]. However; an opposite outcome was obtained in a recent study [27]. The cause for different outcomes obtained in the studies may due to first scales used depending on subjective findings.

Conclusion

We assumed in the present study that RDW, MPV, NLR, PLR, and CRP may be used as a predictive marker to decide on mild, moderate or severe CTS. But our study results did not confirm this. However, our study results only confirmed an association between CTS and CRP. Such a biomarker has some advantages such as being routinely available, non-invasive, and low cost. In this study, a relationship was found between CRP, one of the hematological parameters, and the presence or severity of CTS.

Limitations

A retrospective case control design was used with the patients diagnosed with idiopathic CTS and healthy controls. Our findings should not be generalized due to limited number of patients enrolled into the study. Rather, further studies including sufficient number of patients are needed. Other limitations of the present study are retrospective and single-centered design.

Ethics approval

Adiyaman University, Ethics Commite. Date: 21/04/2020. Number of decisions: 2020/3-1.

References

1. Thiese MS, Gerr F, Hegmann KT, et al. Effects of varying case definition on carpal tunnel syndrome prevalence estimates in a pooled cohort. Arch Phys Med Rehabil. 2014 Dec;95(12):2320-6.
2. Boland JB. Carpal tunnel syndrome. Curr Opin Neurol. 2005 Oct;18(5): 581-5.
3. Alfonso C, Jann S, Massa R, Torreggiani A. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. Neurol Sci. 2010 Jun;31(3):243-52.
4. Graham B, Peljovich AE, Afra R, et al. The American Academy of Orthopaedic Surgeons Evidence-Based Clinical Practice Guideline on: Management of Carpal Tunnel Syndrome. J Bone Surg Am. 2016 Oct 19;98(20):1750-4.
5. Amirfeyz R, Gozzard C, Leslie IJ. Hand elevation test for assessment of carpal tunnel syndrome. J Hand Surg Br. 2005 Aug;30(4):361-4.
6. Aboonq MS. Pathophysiology of carpal tunnel syndrome. Neurosciences (Riyadh). 2015 Jan;20(1):4-9.
7. Altun Y, Tak AZA. Can serum C - reactive protein and Procalcitonin levels associate with Carpal Tunnel Syndrome? Medical Science and Discovery. 2019;6(2):18-23.
8. Joshi P, Lele V. Lighting the tunnel: FDG PET/CT findings leading to incidental diagnosis of carpal tunnel syndrome. Clin Nucl Med. 2014 Jan;39(1):e78-9.
9. Yang DH, Qian MZ, Wei MM, et al. The correlation of neutrophil-to-lymphocyte ratio with the presence and activity of myasthenia gravis. Oncotarget. 2017 Jun 16;8(44):76099-107.
10. Briggs C. Quality counts: new parameters in blood cell counting. Int J Lab Hematol. 2009 Jun;31(3):277-97.

11. Zhao QT, Zhang XP, Zhang H, et al. Prognostic role of platelet to lymphocyte ratio in esophageal cancer: A meta-analysis. Oncotarget. 2017 Nov 20;8(67):112085-93.
12. Sarıcam G. Neutrophil/Lymphocyte, Platelet/Lymphocyte and Neutrophil/Monocyte Rates in Carpal Tunnel Syndrome. J Cardiovasc Sci. 2018;30(3):107-12.
13. Güneş M, Büyükgöl H. Correlation of neutrophil/lymphocyte and platelet/lymphocyte ratios with the severity of idiopathic carpal tunnel syndrome. Muscle Nerve. 2020 Mar;61(3):369-74.
14. Hassan S, Antonelli M, Ballou S. Red cell distribution width: a measure of cardiovascular risk in rheumatoid arthritis patients? Clin Rheumatol. 2015 Jun;34(6):1053-7.
15. Tutoglu A, Boyacı A, Kocatürk O, et al. The relationship of carpal tunnel syndrome and mean platelet volume in geriatric patients. Eur J. Ther. 2014;20:182-5.
16. Song GG, Lee YH. Red cell distribution width, platelet-to-lymphocyte ratio, and mean platelet volume in ankylosing spondylitis and their correlations with inflammation: A meta-analysis. Mod Rheumatol. 2020 Sep;30(5):894-9.
17. Kurt S, Cevik B, Kaplan Y, et al. The relationship between Boston Questionnaire and electrophysiological findings in Carpal Tunnel Syndrome. Archives of Neuropsychiatry. 2010;47(3):237-40.
18. Levine DW, Simmons BP, Koris MJ, et al. A self- administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone Surg Am. 1993 Nov;75(11):1585-92.
19. American Academy of Neurology Practice parameter for carpal tunnel syndrome (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 1993 Nov;43(11):2406-9.
20. Stevens JC. AAEM minimonograph #26: the electrodiagnosis of carpal tunnel syndrome. American Association of Electrodiagnostic Medicine. Muscle Nerve. 1997 Dec;20(12):1477-86.
21. Freeland AE, Tucci MA, Barbieri RA, et al. Biochemical evaluation of serum and flexor tenosynovium in carpal tunnel syndrome. Microsurgery. 2002;22(8):378-85.
22. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002 Mar 5;105(9):1135-43.
23. Chikenji T, Gingery A, Zhao C, et al. Transforming growth factor-β (TGF-β) expression is increased in the subsynovial connective tissues of patients with idiopathic carpal tunnel syndrome. J Orthop Res. 2014 Jan;32(1):116-22.
24. Anthony W. Segal. How neutrophils kill microbes. Annu Rev Immunol. 2005;23:197-223.
25. Schrijver HM, Gerritsen AA M, Strijers RLM, et al. Correlating nerve conduction studies and clinical outcome measures on carpal tunnel syndrome: lessons from a randomized controlled trial. J Clin Neurophysiol. 2005 Jun;22(3): 216-21.
26. Padua L, Padua R, Lo Monaco ML, et al. Multi perspective assessment of carpal tunnel syndrome: a multicenter study. Italian CTS Study Group. Neurology. 1999 Nov 10;53(8):1654-9.
27. Alimohammadi E, Bagheri SR, Hadidi H, et al. Carpal tunnel surgery: predictors of clinical outcomes and patients' satisfaction. BMC Musculoskelet Disord. 2020 Jan 28;21(1):51.