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Original Article

Relationships between serum mercaptoalbumin/non-mercaptoalbumin ratio, 25(OH)D level, symptom severity, functional status and median nerve cross-sectional area in carpal tunnel syndrome

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ABSTRACT

Objectives: This study aims to investigate mercaptoalbumin and non-mercaptoalbumin (HNA%) levels in the serum of patients with idiopathic carpal tunnel syndrome (CTS) and to explore the correlation between serum HNA% and symptom severity, functional status, electrophysiological findings (EPFs), median nerve cross-sectional area (MNCSA) measured by ultrasound, and vitamin D levels.

Patients and methods: Between April 2022 and November 2023, this prospective, case-controlled study included a total of 47 patients diagnosed with bilateral CTS (6 males, 41 females; mean age: 45.4±9.0 years; range, 25 to 60 years) and 34 healthy controls (4 males, 30 females; mean age: 42.5±10.8 years; range, 27 to 60 years) were included. Evaluation parameters included pain as measured by Visual Analog Scale (VAS), pinch grip strength (kg), Boston Carpal Tunnel Questionnaire (BCTQ), EPF, MNCSA by ultrasonography (mm^2), mercaptoalbumin and non-mercaptoalbumin ratio in serum (HNA%=HNA /Total albumin ×100) and 25(OH)D.

Results: The MNCSA was significantly higher in patients with CTS than healthy controls ($p<0.001$). The HNA% was significantly higher and 25(OH)D levels were significantly lower in patients with CTS than in healthy controls ($p<0.001$ and $p=0.003$, respectively). The HNA% was positively correlated symptom severity score (SSS) and functional status score (FSS) ($r=0.396$, $p=0.006$; $r=0.29$, $p=0.042$, respectively), and negatively correlated with 25(OH)D ($r=-0.320$, $p=0.028$). There was no relationship between HNA% and EPF and MNCSA.

Conclusion: Our study results suggest that HNA% may be a new biomarker of oxidative stress in CTS. There is a relationship between HNA% and symptom severity, functional status, and low vitamin D levels.

Keywords: Carpal tunnel syndrome, median nerve cross-sectional area, non-mercaptoalbumin ratio, oxidative stress, vitamin D.

Carpal tunnel syndrome (CTS) is considered the most common compressive focal mononeuropathy worldwide. It occurs when the median nerve is compressed while passing through the osteofibrous carpal tunnel.[1] The prevalence of CTS varies between 3.8 and 16% in different societies and in the general population.[2] The syndrome is characterized by pain in the hand, numbness, paresthesia, weakness. It may lead to a decrease in physical functions. Clinical evaluation, electrophysiological evaluation, and ultrasonography are accepted as diagnostic tools.[3]

The etiology and pathogenesis of CTS are unclear.[4] The etiology is mostly idiopathic. Risk factors such as occupational conditions involving repetitive movements of the hand, systemic and metabolic diseases, trauma, inflammatory and infective diseases have been identified.[3] Ischemia-reperfusion damage caused by increased carpal tunnel pressure plays a role in the pathogenesis of idiopathic CTS.[5] This contributes to the pathophysiology by increasing the levels of various proinflammatory cytokines in the tenosynovium.[6] It has been reported that ischemic vascular damage and disruption of the blood-nerve

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barrier may lead to axonal degeneration by causing intrafascicular edema and hypoxia.[7] Edema in the median nerve is seen ultrasonographically as an increase in the cross-sectional area (CSA) of the median nerve.[8] Non-inflammatory fibrosis of the subsynovial connective tissue is the most common histopathological finding.[9] Evidence suggests that oxidative cellular damage and biochemical changes mediate the emergence of idiopathic CTS. It is thought that intermittent local ischemia and reperfusion cause oxidative cellular and tissue injuries.[5,10-12] Freeland et al.[11] found malondialdehyde, an oxidative stress marker, to be significantly higher in both serum and synovial tissue in patients with idiopathic CTS compared to controls. Kim et al.[5] reported that the immunoreactivities of endothelial nitric oxide synthase (eNOS), nuclear factor kappa B (NF-κβ) and transforming growth factor (TGF)-β RI, which are oxidative stress products, were significantly upregulated in the subsynovial connective tissue of CTS patients. Human serum albumin is the most abundant oxidative stress marker in the blood.[13] Albumin can be found in blood as a mixture of its reduced cys-34 form (Human Mercaptoalbumin, HMA) and its oxidized forms (Human non-mercaptoalbumin, HNA).[14,15] Under oxidative stress, HMA buffers reactive oxidized species and converts to HNA. The ratio of HNA to total serum albumin (HNA%) is considered a biomarker reflecting the redox state of the human body. The HNA% was associated with the development of oxidative stress-related diseases.[16]

Evidence has also shown an association between CTS and low levels of vitamin D.[17,18] The relationship between low serum 25(OH)D level and disease symptoms is controversial.[18,19] Previous studies have reported that low vitamin D levels in the body are associated with increased oxidative stress markers in systemic diseases. It is also known that vitamin D supplements have antioxidant properties against oxidative stress and provide a significant decrease in oxidative stress markers.[20-22]

To the best of our knowledge, there is no study in the literature evaluating the relationship between CTS and serum mercaptoalbumin and non-mercaptoalbumin ratio. The primary objective of this study was to determine the ratio of mercaptoalbumin and non-mercaptoalbumin (HNA%), which are oxidative stress markers, in the serum of patients with idiopathic CTS. The secondary objective was to determine the relationship between serum HNA% and symptoms severity, functional status, electrophysiological findings, median nerve CSA measured by ultrasound, and vitamin D.

PATIENTS AND METHODS

This single-center, prospective, case-controlled study was conducted at University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital, Department of Physical Medicine and Rehabilitation between April 2022 and November 2023. A total of 50 patients aged between 18 and 65 years, clinically and electrophysiologically diagnosed with bilateral CTS, who presented to our outpatient clinic were included in the study. The control group consisted of 40 healthy volunteers, matched with the patient group in terms of age, sex, and body mass index (BMI) who underwent clinical evaluation for CTS. Only volunteers showing no clinical signs of CTS were invited to participate in the study. Both the patient and control groups were excluded from the study, if they had any of the following: endocrinological diseases such as diabetes mellitus, hypothyroidism; systemic diseases such as liver or kidney failure, heart failure, inflammatory rheumatic diseases, acute or chronic infection, malignancy; polyneuropathy, plexopathy, or radiculopathy; chronic drug use; pregnancy; alcoholism; smoking; morbid obesity; history of surgical intervention to the hand or wrist; history of trauma to the hand or wrist; arthritis of the hand or wrist; or intense exercise activity in the last 15 days. Three CTS patients and six healthy controls were excluded for not meeting the criteria. Finally, a total of 47 CTS patients (6 males, 41 females; mean age: 45.4±9.0 years; range, 25 to 60 years) and 34 healthy controls (4 males, 30 females; mean age: 42.5±10.8 years; range, 27 to 60 years) were included. The study flowchart is shown in Figure 1. Written informed consent was obtained from each participant. The study protocol was approved by the University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Date: 23.03.2022, No: 2011-KAEK-25 2022/03-13). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection and data analysis

Sociodemographic data of CTS patients and controls were recorded. Clinical evaluation: Patients were evaluated for numbness, pain, and night symptoms in the median nerve area.

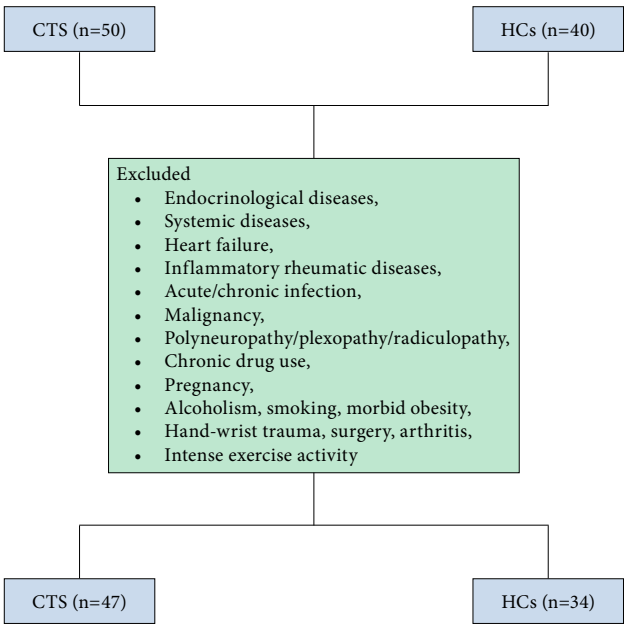

Figure 1. Study flowchart.
CTS: Carpal tunnel syndrome; HCs: Healthy controls.

Physical examinations included assessments for thenar atrophy, weakness in palmar abduction, Phalen's test, Tinel's test, and impaired two-point discrimination.[23] A positive result in at least one of these assessments was considered a clinical sign of CTS. The study included the dominant hands of patients diagnosed with bilateral CTS, with symptom duration of three months or more, and clinical findings supported by electrophysiological findings.

Pain was evaluated with a Visual Analog Scale on a 10 cm scale (0= no pain, 10= unbearable pain).

Pinch grip strength was measured with a pinch meter and recorded in kg by taking the average of three consecutive measurements.

Boston Carpal Tunnel Questionnaire (BCTQ): The Turkish version of the BCTQ, validated by Sezgin et al.[24] was used. The scale consists of two parts: symptom severity score (SSS) and functional status score (FSS). Each question is scored from 1 point (mildest) to 5 points (most severe). A higher score in the total score indicates a worse result.

Electrophysiological evaluation: Electrom-yographic (EMG) reports performed by the same neurophysiologist were considered. The electrophysiological examinations followed the recommendations of the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM).[25] The following information about the median nerve was recorded from the EMG reports obtained from hospital records: Distal motor latency (DML), motor conduction velocity (MCV), motor amplitude (MAP) and sensory nerve latency (SNL), and the sensory conduction velocities (SCV), sensory amplitude (SAP). For the study, dominant hand findings of patients electrophysiologically diagnosed with bilateral CTS were recorded. The electrophysiological severity of CTS, classified according to the following criteria,[26] was recorded from the patients' EMG reports:

- *Mild CTS:* Prolongation of median distal sensory conduction + DAP amplitude falling below normal, with orthodromic, antidromic or palmar pathway.
- *Middle CTS:* In addition to the above, prolonged distal latency of the median motor nerve
- *Severe CTS:* Often low/absent sensory potential amplitude and reduced motor response amplitude or delayed latency. Partial denervation findings in thenar EMG.

Ultrasonographic evaluation

Ultrasonography was performed in both groups with real-time equipment (Chison, China) and a 5 to 12 MHz broad linear probe (D7L40L). Median nerve CSA was measured at the scaphoid-pisiform level (carpal tunnel inlet). The measurement was made by excluding the hyperechogenic edge of the median epineurium.[8] Measurements were performed by a physiatrist with neuromuscular ultrasound experience who was blinded to clinical and electrophysiological data. In both groups, the average of three consecutive measurements made on the dominant hand was recorded.

Laboratory analysis

The 12-h fasting blood taken from the patients was centrifuged at 3,500 rpm for 10 min and the serum was separated. Vitamin D level was measured with Architect i2000 analyzer (Abbott Diagnostics, CA, USA). C-reactive protein (CRP) levels were measured using a BN II system nephelometer (Siemens Healthcare Diagnostics Inc., NY, USA).

After collecting the sample for measurements of mercaptoalbumin (HMA, reduced form) and non-mercaptoalbumin (HNA, oxidized form), which are human serum albumin subgroups, it was kept at –80°C until analysis. The HNA measurements

were made by a colorimetric method which involves determining the ratio of non-mercaptoalbumin-to-total albumin using bromocresol violet, as previously published by Yoshihiro et al.[27] Measured values were calculated with the formula HNA%= HNA/Total albumin ×100.[14]

Statistical analysis

Study power analysis and sample size calculation were performed using the G*Power version 3.0.10 software (Heinrich Heine University Düsseldorf, Düsseldorf, Germany). The study power (1-β) was found to be 0.92 with a post-hoc analysis of n1=47, n^2=34, α=0.05 and effect size d=0.78

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp, Armonk, NY, USA). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. Variables were tested for normality using the Kolmogorov-Smirnov test. In binary analyses, the chi-square test was used for categorical variables, while the t-test and Mann-Whitney U test for measured variables. Correlation coefficients and statistical significance were calculated by the Spearman correlation test. A p value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference between the two groups in terms of age, sex, BMI (kg/m^2)

TABLE 1
. Demographic features of participants

	CTS (n=47)					HCs (n=34)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			45.44±9.01					42.50±10.75			0.184
Sex											0.892
Female	41	87.2				30	88.2				
Male	6	12.8				4	11.8				
BMI (kg/m^2)				30.40	20.00-33.91				28.41	22.76-34.29	0.688

CTS: Carpal tunnel syndrome; HCs: Healthy controls; SD: Standard deviation; BMI: Body mass index.

TABLE 2
Clinical and electromyographic findings in patients with CTS (n=47)

	n	%	Mean±SD	Median	Min-Max
Symptom duration (mon)				5	3-15
Pain VAS (mm)				6	0-10
Pincer grip strength (kg)				10	1-22
BCTQ (SSS)				29	15-43
BCTQ (FSS)					
Sensory nerve latency			20.16±8.14	16	8-27
Sensory amplitude				3.96	2.40-5.49
Median nerve					
Sensory conduction velocities			41.58±5.48		
Motor latency				5.00	3.12-10.8
Electrophysiology					
Motor amplitude			10.49±3.28		
Motor conduction velocity				53.7	45.8-69
Electrophysiological CTS severity					
Mild	11	23.4			
Moderate	33	70.2			
Severity	3	6.4			

CTS: Carpal tunnel syndrome; SD: Standard deviation; VAS: Visual Analog Scale; BCTQ: Boston Carpal Tunnel Questionnaire; SSS: Symptom severity score; FSS: Functional status score.

(p>0.05). Demographic features of participants are shown Table 1.

The dominant hand was the right hand in all patients and healthy controls. The median duration of symptoms in patients with CTS was 5 (range, 3 to 15) months. The Tinel test was positive in 38 (80.9%) of the patients, the Phalen test was positive in 36 (76.6%) of the patients. Clinical and electrophysiological findings of patients with CTS are given in Table 2.

The median nerve CSA was significantly higher in patients with CTS than healthy controls (p<0.001). Among the laboratory parameters, HNA% was significantly higher and 25(OH)D levels were significantly lower in patients with CTS than in healthy controls (p<0.001 and p=0.003, respectively). Comparison of ultrasonographic and laboratory findings of both groups is given in Table 3.

Correlations between HNA% and clinical, electrophysiological, ultrasonographic and

TABLE 3
Comparison of ultrasonographic and laboratory findings of CTS patients and healthy controls (HCs)

	CTS (n=47)		HCs (n=34)		
	Median	Min-Max	Median	Min-Max	*p*
Median nerve CSA (mm²)	11.36	7.06-18.44	8.62	5.47-11.49	**<0.001**
C-reactive protein	3.34	3-4.15	3.34	3.11-3.63	0.149
Albumin	47.1	34.2-51.8	46.4	38.8-51.50	0.150
HNA%	57.4	55.5-59.6	56.10	50.0-57.7	**<0.001**
Vitamin D	9.9	4.9-35.6	16.2	3.4-38.8	**0.003**

CTS: Carpal tunnel syndrome; HCs: Healthy controls; CSA: Cross- sectional area; HNA: Human non-mercaptoalbumin; p<0.05 significant.

TABLE 4
Correlations among HNA%, 25(OH)D, clinical, electrophysiological, ultrasonographic and laboratory findings in patients with CTS (n=47)

	%HNA		25(OH)D	
	r	*p*	r	*p*
Symptom duration (mo)	0.039	0.796	0.025	0.869
Visual Analog Scale	0.074	0.622	0.032	0.833
Pincer grip strength (kg)	-0.167	0.261	0.210	0.157
BCTQ (SSS)	0.396	**0.006**	0.141	0.346
BCTQ (FSS)	0.298	**0.042**	-0.155	0.298
Median nerve CSA (mm²)	0.186	0.210	-0.101	0.500
Sensory nerve latency	0.136	0.364	0.112	0.459
Sensory amplitude	-0.108	0.471	0.249	0.096
Sensory conduction velocities	-0.007	0.965	0.090	0.551
Motor latency	0.156	0.295	-0.212	0.153
Motor amplitude	0.004	0.977	0.214	0.149
Motor conduction velocity	0.016	0.916	0.172	0.247
CTS severity	0.060	0.690	-0.187	0.209
C-reactive protein	0.019	0.900	0.157	0.293
Vitamin D	-0.320	**0.028**	-	-
Albumin	0.228	0.123	-0.125	0.403
HNA%	-	-	-0.320	**0.028**

HNA: Human Nonmercapto-albumin; 25(OH)D: 25-hydroxyvitamin D; CTS: Carpal tunnel syndrome; BCTQ: Boston Carpal Tunnel Questionnaire; SSS: Symptom severity score; FSS: Functional status score; CSA: Cross-sectional area.

laboratory findings were evaluated (Table 4). There was a moderate correlation between HNA% and SSS and FSS (r=0.396, p=0.006; r=0.29, p=0.042, respectively). A moderate negative correlation was also observed between HNA% and 25(OH)D levels (r=-0.320, p=0.028).

DISCUSSION

To the best of our knowledge, the present study is the first to investigate non-mercaptoalbumin% (HNA%) as a marker of oxidative stress in the serum of patients with CTS. It is also the first to investigate the relationship between oxidative stress marker and median nerve CSA measured by ultrasound. While comparing patients and healthy controls, the study found that HNA% was significantly higher in the patient group than in the control group. Additionally, this study showed that the HNA% ratio in the serum of CTS patients was significantly associated with symptom severity, functional status score, and vitamin D levels.

Pathophysiological changes in idiopathic CTS are increased carpal tunnel pressure, ischemic changes caused by this, increased capillary permeability and median nerve edema, respectively. Swelling and fibroplasia in tenosynovial tissue and median nerve impair blood flow and oxygenation in the nerve.[5-7] This causes a delay in sensory and motor nerve conduction. The clinical manifestation of this condition is pain, paresthesia, decreased sensation and weakness. Intermittent ischemia and reperfusion contribute to tissue damage through the release of oxygen free radicals.[11] It has been proven by previous studies that oxidative stress and impairment of antioxidant defense play an active role in the pathophysiology of CTS.[5,10-12] Freeland et al.[11] studied malondialdehyde as an oxidative stress marker in both serum and tenosynovium of patients with CTS and found it to be significantly higher than healthy controls. Kim et al.[5] found that the expressions of eNOS, NF-κβ and TGF-β RI in fibroblasts and vascular endothelial cells of subsynovial connective tissues of patients with CTS were significantly higher than controls. In the current study, we evaluated the ratio of the oxidized form of albumin as a marker of oxidative stress in the serum of patients with CTS. While there was no significant difference in serum albumin levels between the two groups, we observed that the HNA% ratio of patients with CTS was significantly higher than healthy controls. Moreover, this result also supported the results of Kim et al.[5] and Freeland et al.[11]

Serum albumin is the most abundant protein in circulation in humans. Albumin plays an active role in colloidal osmotic pressure and redox homeostasis in the circulation. It exists in three isoforms depending on the redox state of the free cysteine residue at position 34: Mercaptoalbumin (HMA: reduced form (in healthy young individuals, HMA is found in 70 to 80%]) and non-mercaptoalbumin 1 and 2 (HNA: oxidized form (in healthy young individuals, HNA1 and 2 are present in 20 to 30% and 2 to 5%, respectively).[14,28] The ratio of human non-mercaptalbumin-to-mercaptoalbumin is considered a marker of systemic oxidative stress.[16] Studies have reported that the rate of HNA increases in systemic diseases such as liver and kidney diseases, and this is related to the severity of the pathological condition. Additionally, high HNA rates may worsen pathological conditions, contribute to the progression of symptoms, and negatively affect the quality of life.[14,29] Our results showed that the redox state of serum albumin shifted toward the oxidized form in patients with CTS. The HNA% was significantly higher in patients with CTS than healthy controls. Decreasing total antioxidant status and increasing total oxidative stress have been documented to correlate with the degree of subjective symptoms in CTS, leading to signal dysregulation in the tenosynovium and median nerve.[5,12] Kim et al.[5] found a significant positive correlation between the subjective symptom severity of CTS and the immunoreactivities of eNOS and NF-κβ. Our results showed a significant linear relationship between HNA% and subjective symptom severity and functional status scale. Our results supported the results of Kim et al.[5]

In the current study, we evaluated the median nerve CSA with ultrasound. Ultrasonography can demonstrate median nerve swelling in the carpal tunnel, distinguish between normal and abnormal electrodiagnostic findings, and has become accepted as a diagnostic tool for CTS.[30,31] Although there are studies claiming the contrary,[32] the general opinion is that the increase in median nerve CSA in patients with CTS reflects the severity of the disease.[31,33,34] In the current study, we found that median nerve CSA of patients with CTS was significantly higher than healthy controls. There was also a significant correlation between the electrophysiological severity

of CTS and nerve CSA (r=0.461; p=0.001). Our results confirmed those of previous studies.[30,31,33,34] We believe that this result increases the reliability of the distinction between patient and control groups in terms of CTS. Our study did not find a significant correlation between HNA% and objective disease severity determined by both median nerve CSA and the severity of electrophysiological findings in patients with CTS. We could not find any other study in the literature that evaluated the relationship between oxidative stress markers and objective disease severity determined ultrasonographically and electrophysiologically in CTS.

Previous studies have shown the association between CTS and low vitamin D.[17,18] In our study, although vitamin D levels were significantly lower in patients with CTS than in healthy controls, consistent with literature,[17,18] they were low in both groups. The relationship between vitamin D level and symptoms in CTS is controversial.[18,19] Demiryürek et al.[18] found a relationship between vitamin D deficiency and pain severity. Gürsoy et al.[19] found no relationship between vitamin D and symptom severity, functional status, and pain severity. Consistent with the studies of Gürsoy et al.,[19] we found no significant relationship between vitamin D and symptom severity, functional status and pain severity. Additionally, there was no significant correlation between vitamin D and neurophysiological and ultrasonographic findings of CTS. However, we found a moderate relationship between HNA% and 25(OH)D. Previous studies have documented that a decrease in vitamin D levels increases other markers of oxidative stress and a decrease in the level of oxidative stress markers with vitamin d supplementation.[20-22] Our results are consistent with these results. Furthermore, although HNA% was significantly higher in patients with CTS than healthy controls in the current study, HNA% was higher than expected in healthy controls. The relationship between HNA% and vitamin D may explain this result. In addition, we emphasize that the current study is the first to examine the relationship between HNA% and vitamin D in CTS.

One of the main limitations to our study was the inability to perform electrophysiological evaluations in the control group. However, we thoroughly assessed the carpal tunnel and median nerve using ultrasound in both groups. This approach was crucial in minimizing the likelihood of undetected asymptomatic CTS cases in the control group. The majority of participants in our study were females. This sex distribution may impose limitations on how our findings can be applied to the general population. The higher proportion of females could potentially influence the prevalence of CTS and increase the potential for our results to show variability across sexes.

In conclusion, our study results indicate that HNA%, a marker reflecting the redox status of human serum albumin, could serve as a novel biomarker for CTS, potentially correlating with subjective symptom severity and functional status. Additionally, low vitamin D levels may contribute to oxidative stress by increasing HNA% levels. Further studies are warranted to assess the role of HNA% in CTS. We also recommend that future research should focus on investigating the impact of vitamin D supplementation on HNA% levels in patients with CTS.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, literature review: İ.A.K., Y.Ü.; Control/supervision, critical review, references and fundings, materials: İ.A.K., Y.Ü., B.Y., E.Y.A., H.Ö.; Data collection and/or processing: İ.A.K., Y.Ü., B.Y., E.Y.A.; Analysis and/or interpretation: İ.A.K., H.Ö., Y.Ü.; Writing the article: İ.A.K.

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