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Myalgia-arthralgia and Associated Factors in Patients with COVID-19

COVID-19'lu Hastalarda Kas Eklem Ağrıları ve İlişkili Faktörler

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Abstract

Objective: This study aimed to investigate the psychogenic impact of coronavirus disease-2019 (COVID-19) and its association with myalgia-arthralgia in patients who are hospitalized with COVID-19.

Materials and Methods: This study includes patients who were hospitalized with COVID-19 and whose diagnoses were confirmed by thoracic computed tomography findings and positive polymerase chain reaction test. Characteristics of pain were evaluated using the pain quality assessment scale (PQAS). Post-traumatic stress disorder (PTSD) was evaluated with the impact of event scale-revised (IES-R). Scoring over 33 was considered a cut-off point for "probable PTSD". These patients were named PTSD (+). PTSD (+) and PTSD (-) groups were compared in terms of PQAS and laboratory parameters.

Results: Of the participants, 70 (42.9%) were females and 93 (57.1%) were males. The mean IES-R score was 36.89±11.76. The prevalence of PTSD was 47.9% (n=78). The most common pain was back pain (n=52, 50.5%). Patients with myalgia-arthralgia had higher total IES-R score and subgroup scores (p=0.008, p=0.010, p=0.006, and p=0.012, respectively). The patient group with PTSD had higher PQAS score (p=0.001). Additionally, this group had lower leukocyte (p=0.002) and lymphocyte counts (p=0.010) and higher serum creatine kinase level (p=0.02).

Conclusion: Approximately half of the patients who were hospitalized with COVID-19 had PTSD, with a higher incidence and severity of myalgia-arthralgia. Therefore, myalgia-arthralgia was associated with PTSD in patients who were hospitalized with COVID-19.

Keywords: COVID-19, post-traumatic stress, myalgia, arthralgia, inflammation

Öz

Amaç: Çalışmanın amacı, hastanede yatan koronavirüs hastalığı-2019'lu (COVID-19) hastalarda COVID-19'un emosyonel etkisini ve miyalji-artralji ilişkisini araştırmaktır.

Gereç ve Yöntem: Bu çalışmaya, toraks bilgisayarlı tomografi ve polimeraz zincir reaksiyonu sonucuna göre tanısı konulan hastanede yatan COVID-19'lu hastalar dahil edildi. Ağrının karakteristiği, ağrı kalitesi değerlendirme ölçeği (PQAS) kullanılarak değerlendirildi. Travma sonrası stres bozukluğu (TSSB), revize olayların etkisi ölçeği (OEÖ-R) ölçeği ile değerlendirildi. Otuz üç üzeri puan, "olası bir TSSB olgusu" için kesme noktası olarak kabul edildi. Bu olgulara TSSB (+) adı verildi. TSSB (+) ve TSSB (-) grupları PQAS ve laboratuvar parametreleri açısından karşılaştırıldı.

Bulgular: Katılımcıların 70'i (%42,9) kadın, 93'ü (%57,1) erkekti. OEÖ-R puanı ortalaması 36,89±11,76 idi. TSSB prevalansı %47,9 (n=78) idi. En sık görülen ağrı sırt ağrısıydı (n=52, %50,5). Miyalji-artraljisi olan hastalarda OEÖ-R ve alt grup skoru daha yüksekti (sırasıyla; p=0,008, p=0,010, p=0,006 ve p=0,012). PTSB'si olan hasta grubunun PQAS skoru daha yüksekti (p=0,001). Ayrıca bu grupta lökosit (p=0,002), lenfosit (p=0,010) ve serum kreatinin kinaz seviyesi (p=0,02) daha düşüktü.

Sonuç: Hastanede yatan COVID-19'lu hastaların yaklaşık yarısında TSSB vardır. Bu hastalarda miyalji-artralji insidansı ve şiddeti daha yüksektir. Miyalji-artralji, hastanede yatan COVID-19'lu hastalarda TSSB ile ilişkilidir.

Anahtar Kelimeler: COVID-19, travma sonrası stres, miyalji, artralji, enflamasyon

Introduction

The severe acute respiratory syndrome coronavirus 2 infection, called coronavirus disease-2019 (COVID-19), was declared as a pandemic by the World Health Organization in March 2020. The disease manifests itself with different symptoms, including fever, cough, dyspnea, headache, diarrhea, arthralgia, myalgia, fatigue, and rarely with joint pain (1). Some patients may be asymptomatic,

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whereas others present with mild prodromal symptoms. However, some patients present with severe respiratory failure and multiple organ dysfunction (2).

Musculoskeletal symptoms (especially fatigue, myalgia, and arthralgia) are common during the onset and course of COVID-19. However, the prevalence of these symptoms has not been systematically determined. Studies are generally single-centered and retrospective (3,4). The presence and severity of these symptoms negatively affect the activities of daily life and prevent a good quality of life (5,6). Musculoskeletal symptoms are associated with inflammation and the emotional effect of the disease (3,7).

The frequency of depression and anxiety was reported to increase during the past pandemics. Additionally, high mortality and fear of contact with infected people also affect the emotional state of people (8,9). Moderate to severe post-traumatic stress disorder (PTSD) symptoms (especially in females) have been reported in the normal population and patients during the quarantine period (9). The COVID-19 pandemic has resulted in the largest quarantine period worldwide from December 2019 to present that resulted in serious psychosocial effects (10). In our clinical follow-up of patients with COVID-19 follow-ups, many psychosomatic symptoms (especially myalgia and arthralgia) were observed to be associated with the pandemic.

This study aimed to investigate the psychogenic effect of COVID-19 and its relationship with myalgia-arthralgia in patients who are hospitalized with COVID-19. The results will help us evaluate neuropsychological problems and their relationship with myalgia-arthralgia in patients who are hospitalized with COVID-19. Additionally, this neuropsychological problem will gain a scientific character.

Materials and Methods

Study Design and Patient Selection

In this cross-sectional and prospective study, we obtained data from patients who were treated with COVID-19. After getting the approval from the Ministry of Health (approval number: 2020-07-06T21_32_41), the study protocol was approved by the KTA Karatay University Local Ethics Committee (approval number: 2020/053). Additionally, informed consent was obtained from patients for the use of clinical data in our study.

Patients who were diagnosed with COVID-19 pneumonia by thoracic computed tomography and polymerase chain reaction test were included in the study. Patients with dementia, malignancy, chronic liver, rheumatologic, orthopedic, psychiatric, and hematological diseases were excluded from the study, as well as patients with a history of antidepressant or antipsychotic treatment were excluded from the study. Age, gender, smoking and alcohol habits, and initial symptoms (fever, cough, dyspnea, fatigue, anorexia, and weakness) were evaluated in the patients.

The Impact of Event Scale-Revised (IES-R)

The IES-R was used to detect the emotional impact of the COVID-19 pandemic. The presence of PTSD was revealed with this scale.

The IES-R consists of 22 questions. Each question was scored between 0 and 4 on a 5-point Likert scale (0: None, 4: Extremely). High scores indicated severe PTSD. The total score ranged from 0 to 88 (11). Some studies have revealed various threshold values for the presence of PTSD in the IES-R scale (between 22 and 44) (12,13). Çorapçıoğlu et al. (14) conducted validation studies of this scale for the Turkish population. Additionally, Vanaken et al. (15) showed that the IES-R was a valid and safe test for PTSD associated with COVID-19.

Our study used 33 as the cut-off value. Patients with a cut-off point above 33 were considered as having PTSD (+). Following which, patients were grouped as PTSD (+) and PTSB (-).

Pain Quality Assessment Scale (PQAS)

PQAS evaluates the presence of myalgia-arthralgia and pain severity. This scale evaluates the symptoms of patients for the last 1 week. Moreover, it determines the pain localization of patients. Patients are asked to choose one of the following three main headings to describe their pain: 1: Intermittent pain, 2: Unstable and continuous pain, 3: Stable and continuous pain. The scale consists of 20 questions. Each question was scored on an 11-point Likert scale (0: No pain, 10: Most severe pain). Total scores ranged from 0 to 200. Higher scores indicated greater pain intensity (16).

Blood Tests

Blood samples that were collected on the first day of hospitalization were analyzed. Gel tubes were used for serum tests and potassium-ethylenediaminetetraacetic acid tubes were used for blood count. Blood samples were centrifuged at 5000 rpm for 10 min and separated into sera. Samples were analyzed using spectrophotometric measurements with the Automated Blood Cell Analyzer using an immunoturbidimetric method (WakoChemicals, Osaka, Japan) (on the c702 modular analyzer, Cobas 8000 series). D-dimer, creatine kinase (CK), amylase, lipase, lactate dehydrogenase, ferritin, fibrinogen, and C-reactive protein (CRP) levels, as well as leukocyte, neutrophil, lymphocyte, and platelet counts were obtained as parameters.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 17.0 software (SPSS Inc., Chicago, IL, United States). Numerical data were presented as mean ± standard deviation and median (minimum-maximum). Categorical data were expressed as numbers (n) and percentages (%). Categorical data were analyzed using the chi-square test. Data distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical data between the two groups were analyzed with the Student's t-test or Mann-Whitney U test (according to normality analysis results). Cut-off point and sensitivity-specificity values were determined by receiver operating characteristic (ROC)-curve analysis. The area under the curve (AUC) was calculated and confidence interval (CI) was determined. Correlation between numerical data was evaluated with Spearman's test. Correlation coefficients of 0.05-0.30 represented low correlation, 0.30-0.60 medium correlation, 0.60-0.75 good correlation, and 0.75-1.00 very good correlation. Linear regression analysis was used to estimate the factors that affect PTSD. A p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

This study included 163 patients. The study group consisted of 70 (42.9%) females and 93 (57.1%) males with a mean age of

56.81±16.32 years. Additionally, 31 patients (19.0%) had a history of smoking, whereas and 5 (3.1%) had history of alcohol use. The most common initial symptom was fatigue (n=114, 69.9%), followed by anorexia, shortness of breath, weakness, cough, and fever. Demographic characteristics, initial symptoms, localization of pain, and presence of PTSD in patients are presented in Table 1.

Characteristics of Post-traumatic Stress Disorder

The mean IES-R score in all patients was 36.89±17.76 (3-86). The frequency of PTSD (PES-R ≥33) in patients was calculated as 47.9% (n=78). No statistically significant difference was found between the male and female patients in terms of the IES-R score (p=0.065). No statistically significant difference was found between patients with or without cigarette and alcohol habits in terms of IES-R scores (p=0.150 and p=0.052, respectively). Patients with symptoms of fatigue upon admission had a higher IES-R score (p=0.044). No difference was found in the IES-R score between patients with other initial symptoms (p>0.05).

Characteristics of Myalgia-arthralgia

The prevalence of myalgia-arthralgia was 63.2% (n=103). The most common sites of pain were as follows: back (n=52, 50.5%), feet-ankle (n=51, 49.5%), and knees (n=49, 47.6%). The most common type of pain was intermittent (n=69, 67.0%), followed by unstable-continuous (n=30, 29.1%) and stable-continuous pain (n=4, 3.9%). The mean total PQAS score was 57.82±40.38 (2.0-156.0). No difference was found in the PQAS scores between the male and female patients (p=0.742). No difference was found in the PQAS score, according to smoking and alcohol habits. Myalgia-arthralgia was more common in patients with fever, malaise, anorexia, and malaise at admission (p<0.001).

Table 1. Demographic characteristics, initial symptoms, emotional status, and myalgia-arthralgia in patients who were included in the study

Parameters		Number (n)	Percentage (%)
Gender	Women	68	42.9
	Men	93	57.1
Cigarette and alcohol consumption	Cigarette	31	19
	Alcohol	5	3.1
Presenting symptom	Fire	52	31.9
	Cough	75	46.0
	Dyspnea	98	60.1
	Tiredness	114	69.9
	Nausea-diarrhea	105	64.4
Post-traumatic stress disorder	Yes	78	47.9
	No	85	52.1
Myalgia-arthralgia	Yes	103	63.2
	No	60	36.8
Myalgia-arthralgia localization	Neck	35	34
	Shoulder	31	30.1
	Back	52	50.5
	Eyebrow	23	22.3
	Waist	39	37.9
	Hip-thigh	38	36.9
	Knee	49	47.6
	Foot-ankle	51	49.5

Factors Associated with Post-traumatic Stress Disorder and Myalgia-arthralgia

Myalgia-arthralgia frequency and PQAS score were higher in patients with PTSD (p=0.001), whereas the leukocyte and lymphocyte counts were lower and the CK level was higher (p=0.002; p=0.010; p=0.020, respectively). No statistical difference was found in other blood parameters according to the presence of PTSD. Blood parameters and PQAS results according to IES-R score are presented in Table 2. According to ROC curve analysis for PTSD, the leukocyte cut-off value was calculated as 5.96 K/Ul with 70% sensitivity and 55% specificity (p=0.007; AUC: 0.625; CI: 0.534-0.716). The lymphocyte cut-off value was 1.015 K/Ul with 70% sensitivity and 52% specificity (p=0.001; AUC: 0.654; CI: 0.569-0.739). Additionally, the CK cut-off value was 68.0 IU/l with 68% sensitivity and 50% specificity (p=0.025; AUC: 0.604; CI: 0.515-0.692). The leukocyte and lymphocyte counts and CK values of patients according to the presence of PTSD are shown as the ROC curve analysis graph in Figure 1.

The mean IES-R score was higher in patients with COVID-19 with myalgia-arthralgia (p=0.008). Additionally, CK levels were higher in these patients (p=0.016). No statistical difference was found in other blood parameters, according to the presence of myalgia-arthralgia (p>0.05). IES-R scores and blood parameters according to the presence of myalgia-arthralgia are presented in Table 3.

A positive correlation was found between IES-R and PQAS scores (p=0.001; r=0.369). A multiple linear regression model was created with age, gender, smoking and alcohol consumption habits, IES-R score, and white blood cell and lymphocyte counts

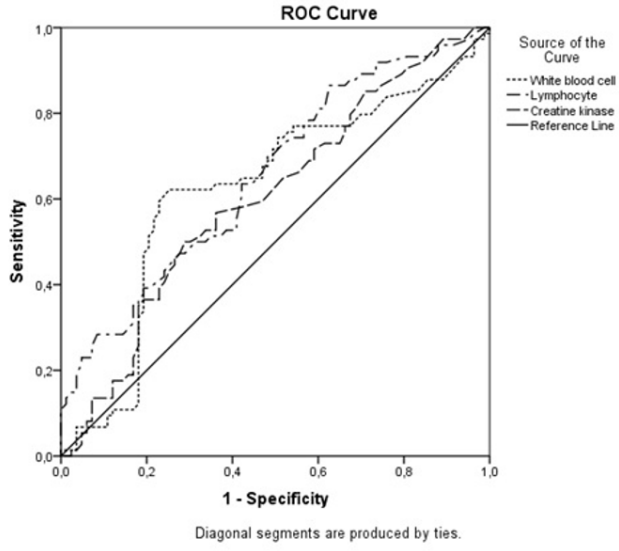

Figure 1. Leukocyte and lymphocyte counts and creatine kinase levels, according to post-traumatic stress disorder in patients with COVID-19
COVID-19: Coronavirus disease-2019, ROC: Receiver operating characteristic

Table 2. Blood parameters and pain quality assessment scores, according to COVID-19-related post-traumatic stress disorder. Data are expressed as mean ± standard deviation and median (minimum-maximum)

	Post-traumatic stress disorder (-) n=85 (52.1%)		Post-traumatic stress disorder (+) n=78 (47.9%)		p value
White blood cells (K/Ul)	7.74±2.80	7.84 (2.14-17.29)	7.01±2.99	5.78 (2.84-16.85)	0.002*
Neutrophil (K/Ul)	5.47±3.16	4.49 (1.20-14.47)	6.13±3.56	5.03 (1.47-15.50)	0.309
Lymphocyte (K/Ul)	1.35±0.70	1.18 (0.39-4.55)	1.02±0.38	0.99 (0.30-2.14)	0.010*
Platelet (K/Ul)	237.97±100.52	222.00 (41-506)	236.87±78.83	218.00 (41-493)	0.729
D-dimer (ng/ml)	1.11±1.26	0.60 (0.20-9.0)	1.13±1.34	0.70 (0.20-9.5)	0.804
LDH (U/l)	399.45±214.95	356.50 (118-1316)	372.35±112.26	382.50 (145-617)	0.814
Ferritin (ml/ng)	481.66±522.68	255.90 (9.9-1285)	443.30±377.31	269.60 (8.6-1987)	0.731
CK (IU/l)	110.86±180.97	69.0 (9.0-1110)	116.13±112.50	88.0 (12.0-694.0)	0.020*
Amylase (U/l)	67.69±38.47	58.0 (13-207)	65.05±30.67	60.5 (11.0-208)	0.951
Lipase (U/l)	33.07±29.67	29.0 (1.0-227.0)	33.02±20.39	29.5 (2.0-125.0)	0.605
Fibrinogen (mg/dl)	654.68±550.53	496.0 (250-3738)	588.55±224.38	530.0 (150-1110)	0.762
CRP (mg/dl)	49.98±52.76	31.35 (3.0-205.0)	24.98±26.71	15.50 (3.0-114.0)	0.094
PQAS	45.38±36.64	33.0 (2.0-156.0)	68.26±40.71	59.5 (42.0-144.0)	0.001*

*Statistically significant values, WBC: White blood cell, LDH: Lactate dehydrogenase, CK: Creatine kinase, CRP: C-reactive protein, PQAS: Pain quality assessment scale, COVID-19: Coronavirus disease-2019

Table 3. The evaluation of blood parameters and COVID-19-related emotional state, according to the presence of myalgia and arthralgia. Data are expressed as mean ± standard deviation and median (minimum-maximum)

	Patients with myalgia-arthralgia n=103 (63.2%)		Patients without myalgia-arthralgia n=60 (36.8%)		p value
White blood cells (K/Ul)	6.73±1.79	7.08 (2.84-10.45)	7.73±3.35	6.89 (2.14-17.29)	00.186
Neutrophil (K/Ul)	5.74±3.49	4.57 (1.20-15.50)	5.86±3.33	4.82 (1.20-15.50)	0.673
Lymphocyte (K/Ul)	1.03±0.36	1.04 (0.39-1.94)	1.26±0.66	1.16 (0.30-4.52)	0.052
Platelet (K/Ul)	240.92±93.47	222.00 (41-506)	231.42±85.22	211.00 (41-485)	0.588
D-dimer (ng/ml)	1.17±1.44	0.65 (0.20-9.5)	1.03±0.98	0.60 (0.20-5.30)	0.807
LDH (U/l)	388.6±182.01	368.0 (118-1316)	382.21±156.74	386.0 (136-1029)	0.911
Ferritin (ml/ng)	453.15±482.76	267.30 (8.6-1987)	480.86±533.24	250.4 (9.9-1285)	0.859
CK (IU/l)	140.66±185.63	76.0 (9.0-1110)	68.78±71.50	71.5 (9.0-168.0)	0.016*
Amylase (U/l)	65.76±33.45	58.5 (11-207)	67.46±37.11	60.5 (11.0-207.0)	0.656
Lipase (U/l)	34.41±28.12	29.0 (1.0-227.0)	30.60±19.69	30.0 (1.0-125.0)	0.810
Fibrinogen (mg/dl)	611.0±398.23	524.0 (150-3738)	651.24±501.87	521.0 (251-1110)	0.098
CRP (mg/dl)	41.59±44.89	21.85 (3.0-205.0)	24.61±33.75	12.65 (3.52-160)	0.094
IES-R	40.53±20.19	37.0 (3.0-86.0)	30.65±9.92	29.0 (10.0-51.0)	0.008*

*Statistically significant values, WBC: White blood cell, LDH: Lactate dehydrogenase, CK: Creatine kinase, CRP: C-reactive protein, IES-R: The impact of event scale-revised, COVID-19: Coronavirus disease-2019

to predict the quality of pain (PQAS). Variables in the model explained 25.2% of PQAS (multiple R: 0.502). An increase in IES-R score by one unit was equivalent to an increase of 1.615 units in the PQAS score.

Discussion

COVID-19 is a highly contagious disease; therefore, social isolation is important (17). The curfew has especially affected many people in our country. Severe social isolation is associated with loneliness, anxiety, and loss of control. Additionally, economic problems, social effects, and social media increased the psychological effects (18). Most studies on the psychological impact of the COVID-19 pandemic were conducted in China. Wang et al. (19) conducted a study in the general population and found the rates of depression, PTSD, and anxiety as 16.5%, 8.5%, and 28.8%, respectively. Moreover, female patients were more emotionally affected using the pandemic process than male patients (19). Patients who were hospitalized for various diseases reported feeling anxiety, stress, irritability, and anger during the COVID-19 pandemic (20,21,22). These symptoms are more common in patients who are hospitalized for COVID-19. Bo et al. (23) found the rate of PTSD as 96.2% in patients who were hospitalized due to COVID-19. This rate is high and is associated with the first period of the pandemic (23). Our study revealed the rate of PTSD as 47.9%. This rate confirmed that approximately half of the patients who are hospitalized with COVID-19 have PTSD.

The clinical presentation of COVID-19 ranges from asymptomatic to severe pneumonia. Fever, cough, fatigue, and myalgia-arthralgia are the most common symptoms (2,3,4). Most studies that evaluate myalgia and arthralgia in COVID-19 were retrospective, of which most were from China. Therefore, the effect

of socio-geographical factors on the association of musculoskeletal symptoms with COVID-19 is unclear. Fatigue and myalgia-arthralgia have been reported with different frequencies in studies. Xu et al. (24) reported that the frequency of fatigue and musculoskeletal symptoms were 4% and 16%, respectively. Mo et al. (25) revealed the rate of fatigue as 73.2% and the rate of myalgia/arthralgia as 61%. Studies conducted in Europe reported more common musculoskeletal symptoms e.g., Lechien et al. (26) analyzed the data of 417 patients with COVID-19 from 12 European hospitals and reported myalgia in 246 (59%) and arthralgia in 129 (31%) patients. Our study revealed that the frequency of myalgia-arthralgia was 63.2% (n=103). This rate is, especially similar to the studies that are conducted in Europe.

The mechanism of muscle pain and arthralgia in viral diseases is still unclear. However, it is believed to be due to increased pro-inflammatory cytokines (27). The relationship between musculoskeletal symptoms and inflammation (leukocyte, lymphocyte, CRP, etc.) in patients with COVID-19 has not been studied in detail yet. Our study revealed no relationship between the inflammatory markers and the presence of myalgia-arthralgia in patients with COVID-19. However, serum CK level was higher in patients with myalgia-arthralgia.

Previous studies have revealed that pandemic processes might trigger some neuropsychological problems and bring along somatic problems (28,29). Few studies were identified in the literature that examined pain comorbidities in patients with PTSD. Some diseases (chronic tension-type or migraine headache, irritable bowel syndrome, myofascial pain syndrome, temporomandibular disorders, etc.) are reported to be associated with PTSD (30). Our study revealed that the severity and frequency of myalgia-arthralgia were higher in patients with COVID-19 and PTSD. Additionally, PTSD severity was higher in patients with fatigue symptoms. Patients with COVID-19 and PTSD have lower leukocyte and lymphocyte counts and higher CK levels. This indicated that inflammation was associated with PTSD in patients with COVID-19.

This study had certain limitations, including the small sample size. Myalgia-arthralgia was a subjective clinical symptom; therefore, the assessment was difficult. Other limitations include local biopsy sample was being taken for myalgia-arthralgia and patients not being divided into groups according to thoracic tomography findings and COVID-19 severity.

Conclusion

Approximately half of the patients who were hospitalized with COVID-19 had PTSD. The frequency and severity of myalgia-arthralgia were high in these patients. A relationship was found between PTSD and inflammation. Myalgia-arthralgia was associated with PTSD in patients who were hospitalized with COVID-19.

Ethics

Ethics Committee Approval: After getting the approval from the Ministry of Health (approval number: 2020-07-06T21_32_41), the study protocol was approved by the KTA Karatay University Local Ethics Committee (approval number: 2020/053).

Informed Consent: Informed consent was obtained from patients for the use of clinical data in our study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.E., B.Ö., A.D., Concept: F.E., A.D., Design: F.E., B.Ö., Data Collection or Processing: F.E., B.Ö., A.D., Analysis or Interpretation: F.E., B.Ö., Literature Search: F.E., B.Ö., A.D., Writing: F.E.

Conflict of Interest: The authors have not declared any conflict of interest related to this article.

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