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Original Article

Evaluation of musculoskeletal system symptoms and hematological parameters in COVID-19 patients

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Abstract

Objective: Musculoskeletal pain can be seen in COVID-19; however, the data obtained about pain intensity and its relationship with inflammation are not of sufficient. The aim of this study is to investigate the frequency of musculoskeletal pains in patients diagnosed as having COVID-19, and to determine the relationship between these symptoms and inflammatory parameters.

Methods: One hundred twenty-one patients who were diagnosed as having COVID-19 were included. All patients' demographic data, complete blood count parameters, neutrophil/lymphocyte ratios (NLR), platelet/lymphocyte ratios (PLR), lymphocyte-monocyte ratios (LMR), and neutrophil/monocyte ratios (NMR) were recorded. All patients' musculoskeletal pains and fatigue symptoms were investigated, and the severity of pain and fatigue was determined using a visual analog scale (VAS).

Results: The frequencies of myalgia, fatigue, back pain, and low back pain were 43%, 92%, 68%, and 56%, respectively. A positive correlation was determined between the severity of fatigue and platelet levels (p:0.013, r:0.249). A negative correlation was observed between hemoglobin levels and fatigue severity (p:0.014, r:-0.246). A negative clinical correlation was observed between hemoglobin levels and myalgia severities (p:0.013, r:-0.384). There was no significant clinical correlation between myalgia, low back pain, back pain, fatigue severity, and hematologic indices (NLR, NMR, PLR, and LMR) (p>0.05).

Conclusion: No correlation was found between the presence or severity of musculoskeletal symptoms, fatigue, and hematological indices in COVID-19. Further large-series studies are now needed to prove an association between inflammation and symptom severity in COVID-19.

Keywords: COVID-19, hematological parameters, inflammation, musculoskeletal pain.

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INTRODUCTION

Coronavirus disease (COVID-19) was first detected in the city of Wuhan in the Chinese province of Hubei in December 2019 and subsequently led to a pandemic that spread rapidly across the world (1). The disease agent, 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), essentially involves the airways (2). Although an asymptomatic clinical manifestation or mild disease findings are seen in the majority of patients, various fatal complications such as septic shock, organ failure, and acute respiratory distress syndrome may develop in some cases (3). Insufficient data concerning the epidemiologic and clinical characteristics of COVID-19 are currently available. The most frequently reported findings during infections are high fever and cough, although accompanying findings such as fatigue, myalgia, nasal congestions, dyspnea, and pain may be present throughout the disease (4). Pain is a frequently seen symptom at the onset of viral infections and throughout the disease. During COVID-19 infections, myalgia, arthralgia, headache, chest pain, and abdominal pain can be seen. Studies have reported that the incidence of myalgia or arthralgia varies between 5-61% (5). Although these mechanisms have been demonstrated for different viral infections, the viral pathogenesis leading to pain in COVID-19 is still unclear. The reason why myalgia and fatigue symptoms last longer and are more serious in COVID-19 compared with other viral infections may indicate that this virus uses different mechanisms. SARS-CoV-2 has a higher affinity for the angiotensin-converting enzyme receptor 2 (ACE-2), which is used to penetrate the cells (6). Although ACE-2 receptors are expressed in endothelial tissue, they have also been shown in muscle, cartilage tissue, synovial tissue, and other tissues. ACE-2 has many functions, including anti-inflammatory properties and restriction of bone resorption. It is thought that the result of systemic inflammation in COVID-19 elicits musculoskeletal symptoms, which are thought to develop as a result of proinflammatory cytokines, proteolysis in muscle fibers, decreased protein synthesis, fibrosis resulting from increased muscle fibroblast activity, increased osteoclastogenesis, and increased bone fragility as a result of inhibition of osteoblast proliferation and differentiation (7). In COVID-19 infections, lactate levels increase as a result of cell damage. This causes hypoxia by disrupting the oxygen transport mechanism of erythrocytes to the tissues. In muscle tissue that cannot provide oxygen to the tissues, adenosine triphosphate (ATP) levels and tissue pH decrease, suggesting that this situation creates fatigue and pain in the muscles (8). Hypoxia-inducible factor (HIF), which acts as a transcriptional regulator in the cell and activates target genes, reduces the requirement of oxygen and ensures the establishment of a new oxygen balance. The alpha subunit of HIF is an oxygen-dependent factor. Altered gene regulation in prolonged hypoxic conditions may lead to musculoskeletal symptoms (9). The severity of COVID-19, leukocyte (WBC), and platelet count and new markers that have recently come into clinical use are neutrophils to lymphocyte ratio (NLR), platelet-lymphocyte (PLR), lymphocyte-monocyte ratio (LMR), and neutrophil-monocyte (NMR)) (10). Dysregulation in immune responses has been reported in association with hyperinflammation in patients with COVID-19, NLR has been linked to the severity of the patient's clinical status, and an increase in NLR is reported to be an independent risk factor for in-hospital mortality (11,12).

Although the relationship between inflammatory responses and disease severity in COVID-19 has been investigated, there are very few studies investigating the relationship between fatigue and musculoskeletal findings. The purpose of this study was to investigate the prevalence of musculoskeletal pain in patients with COVID-19 and to determine the relationship between these symptoms and inflammatory parameters.

MATERIALS AND METHODS

This cross-sectional, prospective, single-center study was performed in compliance with the Declaration of Helsinki and with permission from the Bolu Abant İzzet Baysal University Faculty of Medicine Clinical Research Ethics Committee (2020/100).

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In line with the study protocol, the participants included in the study were first informed in writing and also verbally, about the aim, duration, and scope of the research using a previously prepared volunteer information form. All individuals agreeing to participate in the study gave verbal and written consent by signing the volunteer consent forms.

One hundred twenty-one individuals (68 women, 53 men) aged 20-69 years who were diagnosed as having COVID-19 and hospitalized at the Abant İzzet Baysal University Medical Faculty Hospital, Turkey, between May 1st and August 23rd, 2020, were included in the study. Diagnosis of COVID-19 was based on the Turkish Ministry of Health's Scientific Committee COVID-19 guideline (13). A confirmed SARS-CoV-2 infection was defined as a positive result in a naso-oropharyngeal swab specimen result using analysis made by real-time reverse-transcription polymerase chain reaction (RT-PCR) tests or high-throughput sequencing. After the naso-oropharyngeal swabs had been collected, the samples were placed into tubes containing virus preservation solutions. A SARS-CoV-2 infection was confirmed using a real-time RT-PCR assay with a SARS-CoV-2 nucleic acid detection kit. Patients with suspected SARS-CoV-2 infection, with two negative RT-PCR tests, who were hospitalized in the intensive care unit (ICU) during inclusion in the study, with musculoskeletal pains in the previous 3 months, with diseases capable of causing myalgia before diagnosis (such as fibromyalgia and inflammatory muscle disease), or with cognitive disorders capable of preventing history-taking and physical examination such as mental disability and dementia, previous history of headache (migraine, tension-type headache), were excluded from the study.

Assessment methods

Pain measurement: Participants were asked about the mean pain levels experienced during the day using a visual analog scale (VAS) to measure the severity of myalgia, arthralgia, and headache. The patients were asked to indicate the severity of pain on a 10-cm line marked from 1 to 10, on which 0 indicated no pain and 10 the worst possible pain (14).

Fatigue perception: A VAS was employed to measure perceived fatigue levels. The patients were asked to indicate the severity of fatigue perceived in the previous week on a 10-cm line (0: no fatigue, 10: very great fatigue) (15).

Laboratory parameters: Peripheral venous blood specimens were collected using standard surgical procedures during presentation and were investigated in the Abant İzzet Baysal University Medical Faculty central laboratory. Complete blood count parameters (hemoglobin, leukocytes, erythrocytes, platelets, and leukocyte subtypes) were analyzed using a Sysmex XN-1000 (Kobe, Japan) automatic analyzer. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, NMR was calculated by dividing the absolute neutrophil count by the absolute monocyte count, LMR was calculated by dividing the absolute lymphocyte count by the absolute monoocyte count, and PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count.

Statistical analysis

The study data were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 21.0 software. Mean, standard deviation, median, minimum and maximum values were calculated for all parameters. Descriptive values are shown in tables as numbers and frequencies (%), mean, and standard deviation. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of numerical variables. Two independent t-tests were used to compare the means between the groups for normally distributed data. The non-parametric Mann-Whitney U test was used to investigate potential between-group differences in non-parametric variables without normal distribution. Pearson correlation analysis was used to determine the relationship between the variables for normally distributed variables, and Spearman correlation analysis was used

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to determine the relationship between the variables for non-normally distributed variables. The results were evaluated at a 95% confidence interval, and p-values <0.05 were considered statistically significant.

RESULTS

The mean age of the 121 participants in this study was 45.8±13.4 years, and the mean body mass index (BMI) was 28.2±5.0 kg/m^2. Fifty-three (44%) participants were men, and 68 (56%) were women. The principal clinical findings were fever in 106 (88%) patients, cough in 50 (41%), fatigue in 111 (92%), and loss of taste and smell in 30 (25%). The most frequent pain manifestations were headache (42%), myalgia (43%), arthralgia (37%), back pain (68%), and low back pain (56%). Participants' demographic and clinical characteristics are shown in Table 1.

Table 1. Demographic data and clinical characteristics of the patients

Clinical characteristics, Symptoms	**Mean+SD or n (%) (n=121)**
Age (year)	
Mean±SD	45.8±13.4
Min-Max	20-69
Gender	
Female	68 (56%)
Male	53 (44%)
Smoking	
Non smokers	102 (84%)
Smokers	19 (16%)
BMI	
Mean±SD	28.2±5.0
Min-Max	19.7-37.9
Symptoms	
Fever	106 (88%)
Cough	50 (41%)
Fatigue	111 (92%)
Anosmia, ageusia	30 (25%)
Headache	51 (42%)
Myalgia	56 (43%)
Arthralgia	30 (37%)
Spine Pain	
Back pain	83 (68%)
Low back pain	68 (56%)

***Abbreviations**; BMI: Body Mass Index, SD: Standart Deviation*

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Participants' VAS values for pain symptoms and median, minimum, and maximum values for laboratory parameters are shown in Table 2.

Table 2. Clinical characteristics laboratory findings of the study patients

	Myalgia			Back pain			Low back pain		
	Positive (n:56)	Negative (n: 65)	p	Positive (n:83)	Negative (n:38)	p	Positive (n:68)	Negative (n:53)	p
VAS	6 (1-10)	-	-	6 (1-10)	-	-	5 (1-10)	-	-
Hb (g/dl)	13.6 (8-18)	13.0 (9-16)	0.33	13.5 (8-18)	13.3 (9-17)	0.74	13.5 (8-18)	13.3 (9-17)	0.92
WBC ($\times 10^9$/L)	5.7 (3.2-14.3)	5.9 (2.9-14)	0.70	5.7 (3.2-14.3)	6.1 (2.9-12.9)	0.55	5.7 (3.2-14.3)	6.0 (2.9-14.0)	0.59
Neut (K/μL)	3.3 (1.6-11.4)	1.7 (1.4-11)	0.37	3.3 (1.6-11.4)	3.5 (1.4-7.9)	0.41	3.3 (1.6-11.4)	3.4 (1.4-11.0)	0.50
Lymp (K/μL)	1.7 (0.8-4.3)	1.6 (0.6-3.8)	0.33	1.7 (0.6-4.3)	1.5 (0.8-3.8)	0.16	1.7 (0.8-4.3)	1.6 (0.6-3.8)	0.55
Mono (K/μL)	0.4 (0.1-1.1)	0.4 (0.1-0.7)	0.91	0.4 (0.1-1.1)	0.4 (0.1-0.7)	0.74	0.4 (0.1-1.1)	0.4 (0.1-0.7)	0.88
Plt (K/μL)	236 (96-417)	251 (119-598)	0.65	252 (96-441)	232 (119-598)	0.47	242 (96-441)	249 (119-598)	0.64
NLR	1.8 (1.0-6.7)	2.6 (1.0-7.6)	0.12	1.8 (1.0-7.6)	2.2 (1.0-5.9)	0.15	1.9 (1.0-7.6)	2.0 (1.0-6.5)	0.33
NMR	8.3 (2.8-31.9)	8.7 (4.1-39)	0.62	8.5 (2.8-39.8)	9.0 (4.1-21.0)	0.74	8.3 (2.8-31.9)	8.9 (4.1-39.8)	0.59
LMR	4.5 (1.4-9.7)	4.0 (1.6-8.8)	0.39	4.4 (1.4-9.7)	3.5 (1.6-8.8)	0.12	4.4 (1.4-9.1)	4.0 (1.6-9.7)	0.65
PLR	129 (74-317)	146 (83-462)	0.07	142 (74-366)	147 (83-462)	0.33	141 (74-317)	146 (83-462)	0.26

***Abbreviations**; VAS: Visual Analog Scale; Hb: Hemoglobin; WBC: White Blood Cell; Neut: Neutrophil; Lymp: Lymphocyte; Mono: Monocyte; Plt: Platelet; NLR: Neutrophil-Lymphocyte Ratio; NMR: Neutrophil-Monocyte Ratio; LMR: Lymphocyte-Monocyte Ratio; PLR: Platelet-Lymphocyte Ratio, $p<0.05$ is accepted as significant. (Median (Min-Max) values are given in the table)*

No statistically significant difference was found between hemogram parameters and hematologic indices in the comparison between groups of patients with and without myalgia ($p>0.05$). No statistically significant difference was found between hemogram parameters and hematologic indices in the comparison between groups of patients with and without back pain and low back pain ($p>0.05$). Pearson and Spearman's correlation analysis results for complete blood count parameters, NLR, LMR, NMR, and PLR in patients with myalgia, fatigue, back pain, and low back pain are shown in Table 3. Statistical analysis based on these data revealed a negative clinical correlation between the severity of fatigue and hemoglobin levels and also a positive

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correlation between the severity of fatigue and platelet counts ($p<0.05$). A negative correlation was found between myalgia severity and hemoglobin levels in patients with myalgia ($p<0.05$). No correlation was found between the severity of myalgia, fatigue, back pain, and low back pain, and complete blood count and hematologic parameters (NLR, NMR, PLR, LMR) ($p>0.05$).

Table 3. Correlation analysis of symptoms and laboratory findings

		Hb	WBC	Lymp	Plt	NLR	LMR	PLR	NMR
Myalgia	r	-0.384	-0.009	-0.135	0.007	0.147	0.165	0.174	0.260
	p	0.013	0.950	0.351	0.961	0.310	0.252	0.232	0.068
Fatigue	r	-0.246	0.195	0.176	0.249*	-0.019	0.066	0.063	0.060
	p	0.014	0.054	0.084	0.013	0.852	0.519	0.540	0.561
Back pain	r	- 0.216	0.072	0.091	0.062	0.095	0.191	0.045	0.214
	p	0.063	0.540	0.440	0.600	0.420	0.102	0.706	0.067
Low back pain	r	-0.009	-0.037	0.123	0.044	-0.040	0.243	0.080	0.129
	p	0.945	0.773	0.336	0.735	0.756	0.055	0.539	0.312

***Abbreviations**; NLR: Neutrophil-Lymphocyte Ratio, LMR: Lymphocyte-Monocyte Ratio, PLR: Platelet-Lymhocyte Ratio, NMR: Neutrophil-Monocyte Ratio. $p<0.05$ is accepted as significant.*

DISCUSSION

Myalgia and fatigue are findings frequently observed in viral airway infections. In the literature review, few publications are investigating the relationship between the severity of pain and fatigue and inflammatory parameters in COVID-19 infections. The main hypothesis of this study was that myalgia, fatigue, back pain, and low back pain severity would be correlated with hemogram parameters and hematologic indices. Accordingly, we compared clinical symptoms and inflammatory parameters and determined a significant positive correlation between the severity of fatigue and platelet levels. Fatigue levels also exhibited a significant negative correlation with hemoglobin levels. We also determined that the severity of myalgia levels had a negative correlation with hemoglobin levels. No correlation was found between the severity of musculoskeletal pain, fatigue, complete blood count, and inflammatory parameters. Pain, musculoskeletal symptoms, and fatigue may occur with the coronavirus as well as other viral infections. In our study, the rate of myalgia was found as 43%. Although myalgia/arthralgia rates have been reported as 5-61% in the literature (5), Lai et al. reported the myalgia rate as 45.5% (16), and Aggarwal et al. reported it as 44% (17); our study is compatible with the literature. In our study, the percentage of fatigue was found as 88%. In a meta-analysis, the fatigue rate was reported to be between 5% and 100% (5). Although it was reported at low rates in a literature review for the symptom of fatigue, there are also studies with a higher percentage in the literature (4,17). Tüzün et al. reported the percentage of fatigue as 85.3%, which is similar to our study (18). In our study, the rate of back pain was 68%, and back pain was 56%, which was found to be higher than in other studies. In a study evaluating the frequency and presentation of pain in COVID-19, it was reported that the frequency of dorsalgia was 44%, and the frequency of low back pain was 33% (19). The reasons for the different frequencies of myalgia, fatigue, back pain, and low back pain symptoms in literature reviews are socio-demographic heterogeneity, differences in individual genetic structure, different pain perception at social and individual levels, and clinical

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conditions such as fibromyalgia, tension-type headache, and chronic fatigue, all of which may have been triggered by COVID-19 (20-22). In addition, ACE-2 gene variation may have established a genetic predisposition to disease or to a severe disease course (23). Moreover, there may be variabilty in the clinical course of the disease and fatality due to the relatively lower incidence of mutations in SARS-CoV-2 genome sequences in certain parts of the world (24).

In our study, the mean VAS values in patients with myalgia were evaluated as 6 for myalgia and back pain, and 5 for low back pain. In one study, the severity of myalgia in COVID-19 was evaluated using a VAS and the mean value was 7.19 (18). In this respect, our study seems to be compatible with the literature. SARS-CoV-2 causes inflammation, and increased inflammation plays an important role in increasing the severity of the disease. COVID-19 causes systemic infection with significant effects on the hematopoietic system and hemostasis. Increased NLR values, in particular, have been described as having a prognostic value in severe cases (25). Studies have shown that the severity of SARS-CoV-2 infection is linked to changes in white blood cell (WBC) levels. Deviation from normal WBC values is associated with disease severity because WBC counts in patients with severe disease are approximately twice as high as those of patients without severe disease. In addition, examination of complete blood count parameters has revealed higher numbers of neutrophils and fewer leukocytes in patients exhibiting severe disease activity compared with those with non-severe disease (4). Although studies are generally related to disease severity, there are very few studies evaluating the relationship between musculoskeletal system symptoms and fatigue levels, and inflammatory parameters. There are different results in the literature on musculoskeletal symptoms and disease activity. In a study, myalgia was reported to be a predictor of the development of severe disease manifestations such as ARDS (26). In another study, Batur et al. investigated the correlation between myalgia and fatigue symptoms using laboratory parameters and reported that lymphocyte counts and creatine kinase levels were significantly higher in patients with myalgia symptoms compared with those without (27). However, they found no significant difference between leukocyte and neutrophil counts. In our study, although lymphocyte counts were higher in the group with myalgia, statistical significance was not found. Parallel to this study, no significant difference was found in neutrophil and leukocyte counts in our study. In another study, Tuzun et al. reported that no relationship was found between disease severity and myalgia in COVID-19 (18). In the line with this study, the presence of myalgia symptoms was found not to be associated with inflammatory parameters and hematologic indices. In a study by Wang et al., it was reported that no significant difference was found between the rates of fatigue and myalgia in patients with COVID-19 with and without severe disease (28). Guan et al. reported musculoskeletal pain in 14.5% of patients without severe disease activity and 17.3% of patients exhibiting severe activity (1). These findings are consistent with the results of the present study. Fatigue is a common symptom in viral infections (18,19). However, it is known that low hemoglobin levels in various diseases may be associated with fatigue (29). In our study, a negative correlation was found between the severity of fatigue and hemoglobin levels. This indicates that the symptom of fatigue that develops in COVID-19 may be due to the disease itself or its complications. In addition, it indicates that the severity of fatigue may increase due to a decrease in hemoglobin levels. There may be different reasons for the positive correlation between platelet levels and fatigue severity in our study. A platelet increase is known to be associated with infections, tissue damage, iron deficiency anemia, and chronic inflammatory diseases (30). In our study, we think that the increase in the level of inflammation may be related to the increase in platelet levels.

Limitations

The principal limitations of this study include the relatively small sample size, and the small number of laboratory parameters studied. Other limitations include the fact that subgroup analysis based on patient disease activity was not performed.

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CONCLUSION

Although several studies have established a direct association between inflammatory parameters and disease prognosis, no clear results capable of establishing a link between pain and inflammatory parameters were elicited in the present study. More extensive studies capable of demonstrating a link between inflammatory parameters and pain and fatigue symptoms are therefore needed.

Conflicts of interest: The authors declare no conflict of interest.

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Ethical approval: The study was approved by the Ethical Committee of Bolu Abant Izzet Baysal University Faculty of Medicine (Date-Number: 2020 -100). The study was carried out in accordance with the statement of Helsinki Declaration.

Author contributions: Design of the study; EY, NA - Supervision; OY, DK - Data collection &/or processing; NA, DK, OY - Performed data analysis; EY, OY - Literature search; OY, DK - Written by; EY, NA - Critical review; OY, DK.

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