Evaluating muscle/joint pains and related factors in patiens with COVID-19

Fettah Eren[1], Aysegul Demir[2], and Bengu Ozkan[2]

[1]Selcuk Universitesi
[2]Affiliation not available

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Abstract

Aim: To investigate the correlation between the clinical characteristics of myalgia-arthralgia, disease anxiety, and blood parameters in COVID-19. Methods: Patients diagnosed with COVID-19 via computed tomography and polymerase chain reaction were included. Disease-related anxiety was evaluated using the Impact of Event Scale-Revised (IES-R). Pain character were evaluated using the Pain Quality Assessment Scale. Laboratory parameters were checked for all patients. The correlation between clinical and laboratory parameters was examined. Results: The sample consisted of 70 (42.9%) females and 93 (57.1%) males. The prevalence of muscle-joint pain was 63.2% (n=103). The most common pains were back pain (n=52, 50.5%). The pain was mostly temporary, intense, and dull. It spread locally to sensitive surrounding areas. Patients with muscle-joint pain were found to have a higher prevalence and severity of disease anxiety (p <0.05). Those with high muscle-joint pain and disease anxiety had high CK and low lymphocyte (p <0.05). Conclusion: Muscle-joint pains are highly frequent in COVID-19 disease. Pain is most commonly in the back. This pain spreads locally to sensitive surrounding tissues. Pain severity and frequency are higher in those with higher disease anxiety. Muscle pain is particularly associated with low lymphocyte and high CK. What's known * It is known that myalgia and fatigue are most common complaints in COVID-19. * However, the characters of these symptoms has not been systematically evaluated. * In addition to this, there is no sufficient data evaluating its relationship with laboratory findings and emotional state What's new * Arthralgia and myalgia are very common and spreads locally to sensitive surrounding tissues, particularly in the back. * Severity and frequency of pain are higher in patients with more disease anxiety. * Muscle pain is associated with low levels of lymphocytes and high levels of creatine kinase.

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Conclusion: Muscle-joint pains are highly frequent in COVID-19 disease. Pain is most commonly in the back. This pain spreads locally to sensitive surrounding tissues. Pain severity and frequency are higher in those with higher disease anxiety. Muscle pain is particularly associated with low lymphocyte and high CK.

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- Severity and frequency of pain are higher in patients with more disease anxiety.
- Muscle pain is associated with low levels of lymphocytes and high levels of creatine kinase.

INTRODUCTION

The novel SARS-CoV-2 (COVID-19) virus infection was recognized as a pandemic by the World Health Organization (WHO) in March 2020. The disease can present with very different symptoms. These symptoms include fever, cough, dyspnea, headache, diarrhea, arthralgia, myalgia, fatigue, and rarely arthritis.[1] The type and severity of these symptoms may vary from patient to patient. Some patients may be asymptomatic or have mild prodromal symptoms, while others may present with severe acute respiratory syndrome (SARS) and multiorgan failure.[2,3]

Musculoskeletal symptoms (particularly fatigue, muscle, and joint pains) are very common at the onset and course of COVID-19. Although, the prevalence of these symptoms has not been systematically established. Studies are often single-center and retrospective in natüre.[4,5] The presence and severity of these symptoms can negatively affect daily life activities, It prevents them from maintaining a good quality of life.[6,7] In the long term, symptoms can progress into muscle atrophy and contractures. Thus, revealing these symptoms and their associated factors is crucial. Musculoskeletal symptoms are closely related to many clinical symptoms, disease severity, and respiratory distress in particular. Also, symptoms appear to be associated with certain blood parameters like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[4,8]

Here, we examined musculoskeletal symptoms, along with their localization and severity in COVID-19 patients. Besides, we investigated the presence-severity of these symptoms and their correlation with disease anxiety and blood parameters.

METHODS

Patient population

Data were prospectively collected (between July 2020 and November 2020). Patients who applied to the COVID-19 outpatient clinic, who had a thorax computed tomography (CT) compatible with COVID-19 pneumonia, and who had a positive Polymerase Chain Reaction (PCR) test were included. Some diseases that were considered to influence the data and results were excluded (Table 1). Age, sex, smoking/alcohol use, and symptoms at admission (fever, cough, dyspnea, fatigue, anorexia, weakness) were inquired.

Questionnaires

The impact of events scale-revised (IES-R)

The scale consists of 22 questions that reveal the psychogenic effect of COVID-19 and the pandemic on patients. Each question is scored from 0 to 4. Increasing scores indicate that higher disease anxiety. Questions included the following examples: Things like viruses, germs, or diseases remind me of the COVID-19 quarantine and related feelings. I can see images related to COVID-19 like photographs. Total scores range from 0 to 88. Higher scores indicate a greater impact by the disease. The cut-off point was set at 33. The scale consists of 3 subscales. These are intrusion at questions 1, 2, 3, 6, 9, 14, 20; avoidance at questions 5, 7, 8, 11, 12, 13, 17, 22, and hyperarousal at questions 4, 10, 15, 18, 19, 21.[9]

The pain quality assessment scale (PQAS)

This scale evaluates muscle joint pain and the quality of pain. Patients' symptoms are examined to cover the last 1 week. Pain localization (neck, shoulder, elbow, hand-wrist, waist, hip-thigh, knee, foot-ankle) is determined. They are asked to choose one of the 3 main headings to define their pain. 1) Temporary pain, sometimes there but other times not. 2) Unstable and constant pain. From time to time, it suddenly becomes severe. 3) Stable and constant pain. The scale consists of 20 questions. Each question is scored between 0-10, Each question is evaluating a different domain and quality of pain. 0 describes no pain, whereas 10 defines the most severe pain felt. Total scores range from 0 to 200. Higher scores indicate worse pain quality.[10,11]

Blood tests

Blood samples were taken from the antebrachial vein. A separator tube with a separator gel was used for serum tests and potassium-EDTA tubes were used for blood counts. The blood samples were centrifuged at 5000 rpm for 10 minutes and separated into the serums. The samples were evaluated on an Automated Blood Cell Analyzer (Pentra 120 Retic Hematology Analysis Device, ABX, Montpellier, France), Hitachi 7600 chemistry analyzer (Hitachi, Tokyo, Japan) using an immunoturbidimetric method (WakoChemicals, Osaka, Japan) by spectrophotometric measurements (on a c702 modular analyzer, Cobas 8000 series) From the samples, D-dimer, white blood cell (WBC), neutrophil, lymphocyte, thrombocyte, creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, amylase, lipase, lactate dehydrogenase, ferritin, fibrinogen, and C-reactive protein parameters were analyzed. For blood CK, the cut-off point was set at 200 U/L. The patients were divided into 2 groups as CK over or below 200 U/L.

Statistical analysis

Data analysis was performed using the SPSS® version 17.0 statistical package software (SPSS Inc., Chicago, IL, United States). Numerical data are given as mean±standard deviation and median (minimum-maximum). Categorical data are presented as number (n) and percentage (%). Categorical data were compared using either the Chi-Squared test or Fisher's exact test. Data distribution was evaluated using Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical differences between the two groups were analyzed using Student's t-test or the Mann-Whitney U test (depending on data distribution). The cut-off point was calculated based on a receiver operator characteristic (ROC) curve analysis. Cut-off points were then determined according to sensitivity and specificity. The area under the curve (AUC) was calculated. The confidence interval (CI) was determined. Spearman's Correlation test was used to assess the correlations between numerical data. Correlation coefficients between 0-0.25 were considered weak, 0.25-0.50 were considered weak-moderate, 0.50-0.75 were considered strong, and 0.75-1.00 were considered very strong. The level of statistical significance was set at 0.05.

RESULTS

A total of 163 patients were included, 70 of whom (42.9%) were female and 93 (57.1%) were male. The patients had an age average of 56.81 ± 16.32. The most common symptom of admission was fatigue (n = 114, 69.9%). It was followed by anorexia, dyspnea, weakness, cough, and fever (Table 2). 31 of the patients (19%) were smokers and 5 (3.1%) were alcohol users.

The prevalence of muscle-joint pain was 63.2% (n = 103). The most common pain locations were the back (n = 52, 50.5%), foot-ankle (n = 51, 49.5%), and the knees (n = 49, 47.6%). Temporary pain was the most common type of pain reported (n = 69, 67.0%). It was followed by unstable-constant pain (n = 30, 29.1%) and stable-constant pain (n = 4, 3.9%). Patients' demographic characteristics, symptoms on admission, and muscle and joint pains are summarized in Table 2. The mean total PQAS score was found to be 57.82 ± 40.38 (2.0-156.0). Pain characteristics according to PQAS are given in Table 3.

Muscle-Joint pain and related factors

Age and sex were similar between patients with and without muscle-joint pain (p = 0.570; 0.278). Muscle-joint pain was higher in patients presenting with fever, fatigue, loss of appetite, and weakness (p <0.001). Those with muscle-joint pain also had a higher prevalence and severity of disease anxiety (p = 0.008; 0.043). These patients had higher intrusion, avoidance, and hyperarousal subscale scores. There was a weak-moderate positive correlation between PQAS and IES-R scores (p <0.001, r = 0.366). Also, there was a weak-moderate negative correlation between PQAS scores and lymphocyte levels (p = 0.012, r = -0.347).

The number of patients with a CK blood level above 200 U/L was 14.9%. This rate was higher at 23.3% in patients with muscle-joint pain. Patients with muscle-joint pain had higher CK and lower lymphocyte levels (p = 0.016; 0.040). Table 4 shows the blood parameters of patients with and without muscle-joint pain.

According to the ROC curve analysis, the CK cut-off value was 71.5, with a sensitivity of 55% and a specificity of 50% (p = 0.016, AUC = 0.614, CI = 0.527-0.701) (Fig. 1). Fig. 2 presents the frequencies of patients with and without muscle-joint pain at a cut-off value of 71.5.

The impact of events scale-revised and related factors

The mean total IES-R score was 36.89 ± 17.76 (3-86). IES-R scores were mild in 85 patients (52.1%) and severe in 78 (47.9%). However, age and sex were similar between patients with mild and severe scores. There was no difference between their complaints at clinical presentation. The group with severe impact had a higher frequency of muscle and joint pain (p = 0.043). For these patients, the pain was more frequent in the shoulder, the back, elbows, and hand-wrist (p = 0.001; 0.039; 0.018; 0.047, respectively).

Regarding blood parameters, the group with severe impact had lower WBC and lymphocyte levels and higher CK levels (p = 0.06; 0.010; 0.009, respectively). Patient groups and blood parameters are summarized in Table 5.

DISCUSSION

The clinical picture for COVID-19 ranges from asymptomatic presentation to severe pneumonia. Fever, cough, fatigue, and muscle-joint pains are among the most common symptoms.[4,12,13] When the literature is reviewed, it is seen that most of the studies on COVID-19-related muscle-joint pain are retrospective. Many of the studies have also been reported from China. Hence, it is unclear whether the musculoskeletal symptoms at the onset are affected by socio-geographic factors.[14] Studies have reported different frequencies of fatigue and muscle-joint pain. In a study on 51 patients by Xu and his co-workers, the frequencies of fatigue and muscle-joint pain were 4% and 16%, respectively.[15]In a study by Mo et al. on 155 patients, fatigue was present in 73.2% of the sample, while myalgia/arthralgia was present in 61%.[16] Research conducted in Europe report higher frequencies of musculoskeletal symptoms. For example, Lechien et al. examined the data of 417 COVID-19 patients from 12 European hospitals and reported myalgia in 246 (59%) and arthralgia in 129 (31%).[17] In our study, 103 (63.2%) of our patients were found to have muscle-joint pain. This rate is similar to those in the literature, particularly to those reported in Europe. However, there is no study that systematically evaluates pain localization and characteristics. In the current study, patients with muscle-joint pain often reported intense and dull pain. The pain spread locally to sensitive surrounding areas. The most common locations were the back, foot-ankle, the knees, and the waist.

The mechanism of muscle-joint pain in viral diseases is yet to be clearly revealed. This mechanism is believed to be based on increased proinflammatory cytokines on muscle tissue during viral infection. Muscle-joint pain is accompanied by high levels of IL-6 and TNF-α. It is thought that muscle pains in COVID-19 may reflect the overall inflammatory state and cytokine response.[18] The correlation between musculoskeletal symptoms and the parameters associated with infection and inflammation (white blood cell, leukocyte, lymphocyte, CRP, etc.) has not yet been studied in detail. To date, there is still no information regarding the presence of COVID-19 in skeletal muscles, joints, or bones. Musculoskeletal symptoms are based on the secondary effects of the inflammatory and/or immune response. The presence of muscle-joint pain has been associated with disease severity. Also, low lymphocyte levels are associated with disease severity, central nervous system involvement, and muscular symptom severity.[19] In our study, lymphocyte levels were lower in patients with muscle-joint pain. Besides, there was a negative correlation between PQAS scores and lymphocyte levels.

Careful monitoring of kidney functions and muscle enzymes is crucial in SARS-CoV-2 infection. One study in China reported high CK levels (>200 U/L) in 19% of hospitalized patients.[19] In our study, 14.9% of our patients had CK levels over 200 U/L. This rate was found to be at 23.3% in patients with muscle-joint pain. Lee et al. determined that the severity of COVID-19 was associated with CK levels, and disease severity increased in parallel to CK levels.[20] Another study found that patients with muscle pain symptoms had higher CK and lactate dehydrogenase blood levels. This is believed to be associated with the angiotensin-converting enzyme 2 (ACE-2) receptors in skeletal muscles and increased proinflammatory process.[21-23] In the present study, there was a statistically significant correlation between the presence of muscle-joint pain and high CK levels. Although, pain intensity and CK levels were not significantly correlated.

It has long been known that epidemics have psychological effects on patients. One study on the presence of anxiety and depression in COVID-19 patients reported frequencies of 18.6% for anxiety 13.4% for depression.[22] Patients with anxiety and depression are at high risk for chronic pain and muscle joint pain. Both the psychogenic effect of COVID-19 and the social isolation caused by the pandemic are thought to facilitate the development of symptoms of anxiety and depression.[24,25] In our study, disease anxiety was found to be very high in patients with muscle and joint pain. This patient group also had higher intrusion, avoidance, and arousal subscale scores. Besides, patients with high disease anxiety had high PQAS scores and blood CK levels.

LIMITATIONS OF THE STUDY

One limitation of this research was not revealing the patients' lung findings and the severity of their clinical conditions, and not analyzing the correlation between muscle joint pain and laboratory parameters. Although patients with a history of psychiatric disease were excluded, muscle-joint pain is still a subjective clinical symptom, Therefore not easy to assess. Also, since joint fluid and muscle biopsy were not taken from patients, correlation with local inflammation could not be examined.

CONCLUSION

The frequency of muscle-joint pain is quite high in COVID-19. Pain spreads locally to sensitive surrounding tissues, particularly in the back. The severity and frequency of pain are higher in patients with more disease anxiety. The presence of muscle pain is associated with low levels of lymphocytes and high levels of CK.

STATEMENT OF ETHICS

Permission to conduct the research was obtained from the Ministry of Health of the Republic of Turkey on 07.07.2020. Approval was obtained from the Clinical Research Ethics Committee at Karatay University (No: 2020/053, Date: 17.07.2020, Number of Meetings: 5,). The Declaration of Helsinki and good clinical practice guidelines were adhered to throughout the research. Consent was obtained from the included patients to use their data.

FUNDING SOURCES

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DISCLOSURE STATEMENT

All authors declare that they have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Conception and design of the work, acquisition, analysis, and interpretation of data: Eren F, Demir A. Drafting the manuscript and critical revision for intellectual content: Eren F, Bakdik B. Final perusal and approval of the manuscript: Eren F, Demir A, Bakdik B.

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TABLE 1 Inclusion and exclusion criteria

TABLE 2 Demographic characteristics and admission complaints of the patients included in the study

TABLE 3 Pain characteristics of patients with muscle-joint pain based on the Pain Quality Assessment Scale (PQAS). Data are expressed as mean ± standard deviation and median (minimum-maximum)

TABLE 4 The Impact of Event Scale–Revised (IES-R) and blood parameters according to muscle-joint pain. Data are expressed as mean ± standard deviation and median (minimum-maximum)

TABLE 5 Comparison of blood parameters and Pain Quality Assessment Scale according to the Impact of Event Scale–Revised. Data are expressed as mean ± standard deviation and median (minimum-maximum)

FIGURE 1 Receiver operator characteristic (ROC) curve analysis for creatine kinase levels according to the presence of muscle-joint pain

FIGURE 2 Number of patients with and without muscle-joint pain according to the creatine kinase cut-off value (71.5 U/L)

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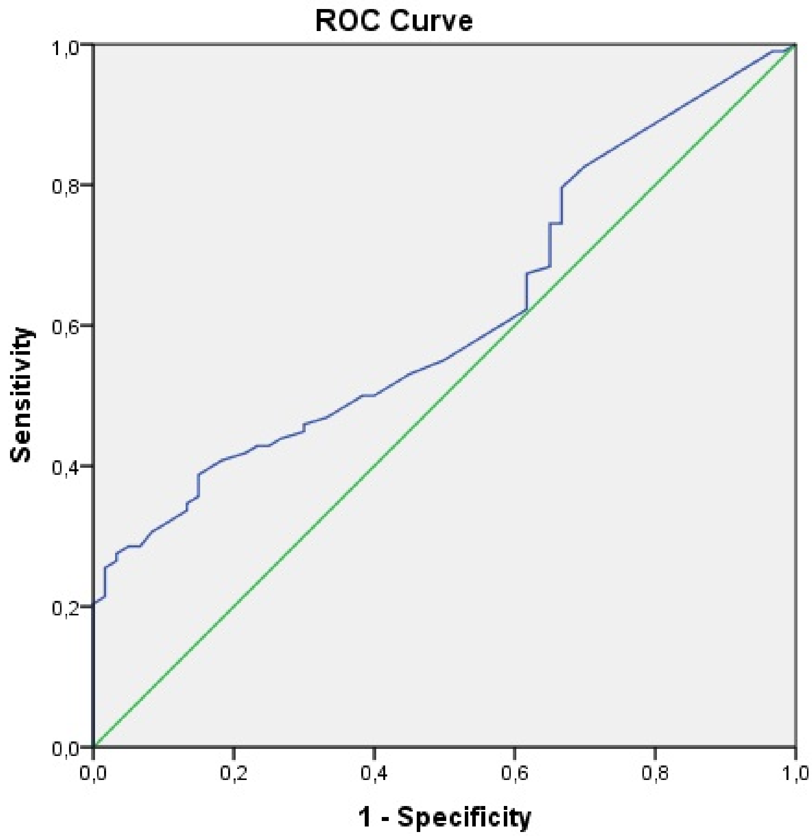
`Tables.pdf` available at https://authorea.com/users/405226/articles/516243-evaluating-muscle-joint-pains-and-related-factors-in-patiens-with-covid-19



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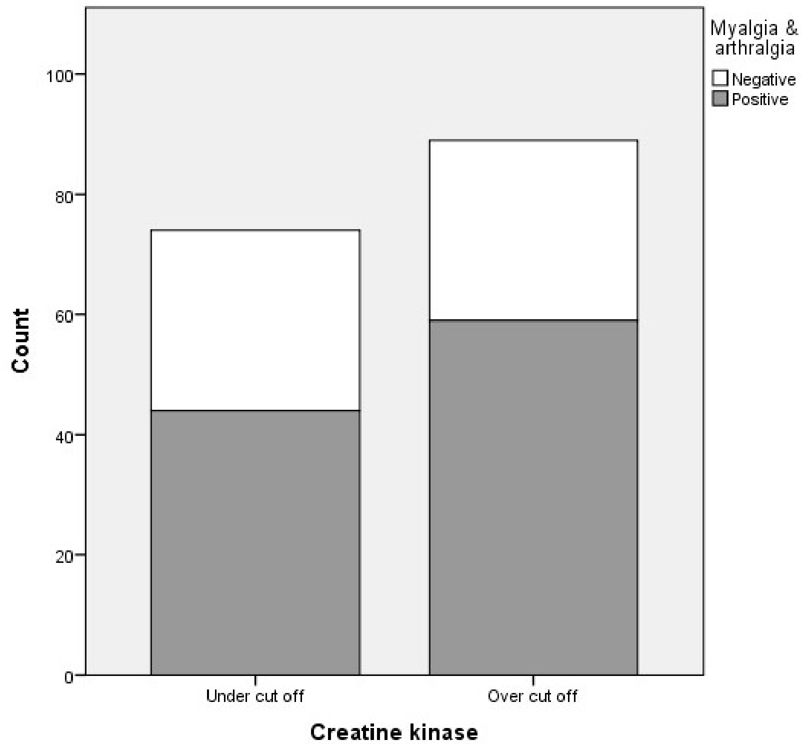
Myalgia & arthralgia
Negative
Positive
Count
0
20
40
60
80
100
Under cut off
Over cut off
Creatine kinase