Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.899515
J Health Sci Med 2021; 4(3): 300-305

A relationship between musculoskeletal pain and prognosis in hospitalized COVID-19 patients

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Cite this article as: Demirel E, Şahin A, Utlu M, Çepni Ş, Veizi E, Yavuz Veizi BG. A relationship between musculoskeletal pain and prognosis in hospitalized COVID-19 patients. J Health Sci Med 2021; 4(3): 300-305.

ABSTRACT

Introduction: Musculoskeletal system complaints are often encountered in patients with COVID-19. The aim of this study was to evaluate the frequency of symptoms such as arthralgia, myalgia, and arthritis in hospitalized patients and their relationship with the final prognosis.

Material and Method: Complaints related to myalgia, arthralgia, arthritis-like symptoms, laboratory parameters, VAS scores and localized painful areas of 154 hospitalized patients who were treated with a COVID-19 diagnosis were recorded on admission and during their hospitalization period. The relationship between these clinical and laboratory data and the duration of hospital stays, need for intensive care and death-recovery states was evaluated.

Results: Of 154 cases, 45.5% (n=70) were female, 71.4% (n=110) had myalgia while 55.8% (n=86) had arthralgia. Mean VAS value was 6.39±2.04. The most commonly reported painful locations were dorsum in 68.2% (n=75) and chest in 63.6% (n=70) of the patients. The death rate was significantly higher in patients with dorsum pain. 25-0H-Vitamin D levels did not have a significant effect on the prognosis and in terms of needing intensive care.

Conclusion: Myalgia and arthralgia are present in a significant part of patients with a diagnosis of COVID-19. Pain localized in the chest and dorsum area is associated with bad prognosis.

Keywords: COVID-19, myalgia, arthralgia, pain area, prognosis

INTRODUCTION

Since November 2019, the world has been struggling against the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), which was firstly detected in Wuhan, China. Shortly after the outbreak, the World Health Organization (WHO) announced a pandemic, and the disease has now become a global health problem (1).

Symptoms are often non-specific, and the condition appears with changing severity from asymptomatic infection to severe and sometimes fatal respiratory tract infections (2-5). Another feature of COVID-19 is its mild onset which tends to progress to severe stages. The increase in hospitalization rates has brought healthcare systems close to breaking point in many countries. It is extremely important to have early diagnosis and treatment plans in order to shorten the duration of hospital stay (4).

The most common symptoms experienced by COVID-19 patients are fever, dry cough, dyspnea, muscle-joint pains, headache, smell-taste disorders, diarrhea followed by less common conjunctivitis and dermatitis (6). Though its spike protein, the virus attaches to the transmembrane protease serine 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) receptors in the human organism. Pathological changes in the musculoskeletal system occur with the exposure of the muscle, synovium and bone cells containing these receptors to the viral infection or due to the effects of cytokines and proinflammatory agents (1,4).

Musculoskeletal symptoms such as fatigue, myalgia and arthralgia are common COVID-19 symptoms but the prevalence of these are yet to be examined systematically (7,8). Additionally, chronic pains such as headache and

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Received: 19.03.2021 **Accepted:** 24.04.2021

neck, back, orofacial and cervical/lumbar pain tends to get worse with disease progression and these patients might need additional care and support as their need for analgesic will increase (9).

This study examines the prevalence of myalgia, arthralgia, and arthritis-like symptoms in hospitalized patients diagnosed with COVID-19 and the relationship between musculoskeletal pains and COVID-19 prognosis.

MATERIAL AND METHOD

The study was carried out with the permission of Erzurum Regional Training and Development Hospital Clinical Researches Ethics Committee (Date: 02.11.2020, Decision No: 2020/20-194)

Patient Selection

This prospective longitudinal study was performed at the Erzurum Regional Training and Development Hospital and included consecutive hospitalized patients diagnosed with COVID-19 between December 2020 and January 2021. Inclusion criteria were patients older than 18, with a confirmed diagnosis of PCR (+) COVID-19 and who were treated as an inpatient case. Pregnant women, patients with active malignity, those with a history of inflammatory disease or fibromyalgia prior to admission, those with chronic liver and kidney disorders, patients with known vertebral and disc pathologies, and patients on antidepressant medicaments were excluded from the study. A total of 154 patients who met these criteria and volunteered to participate were included in the final analyses.

Data Gathering

The hospitalization indications for patients with a diagnosis of COVID-19 in the emergency service and outpatient clinic were pneumonia symptoms and with consistent X-ray or tomography findings, patients with a SpO_2 level lower than 90%, patients with severe coughing associated with severe musculoskeletal pain, and patients who could not continue outpatient treatment. Vital signs, white blood cell (WBC), c-reactive protein (CRP), ferritin, D-dimer, and 25 hydroxy vitamin D (vit-D) values were recorded for all patients upon admission. A clinician made a detailed explanation to all patients during hospitalization and patients were asked to grade their pain from 1 to 10 according to the visual analog scale (VAS). Myalgia, arthralgia and arthritis-like complaints and symptoms were evaluated. The pain diagram (**Figure**), which was defined by Margolis (10,11) and divides the body into 45 separate areas, was simplified into eight areas (neck, arm, chest, dorsum, back, thigh, leg and foot) and presented to patients who defined myalgia. They were asked to specify painful areas.

Transfer to the intensive care unit (ICU) was performed after consulting with the intensive care unit physician and it was reserved for patients who developed dyspnea and tachypnea, those with a respiratory rate of ≥30/min or PaO_2/FiO_2<300, those with an increased oxygen need during the follow-up whose SpO_2 was <90% or PaO_2 was <70 mmHg (despite 5 L/min oxygen treatment), those who developed hypotension (systolic blood pressure<90mmHg and average artery pressure <65 mmHg), patients with an acute organ dysfunction (such as acute kidney damage, acute liver dysfunction, confusion, acute hemorrhagic diathesis), patients who developed arrhythmia and had an increased troponin level and those with a lactate level of >4 mmol. The total duration of hospital stays, the need for intensive care and deceased patients were recorded.

Statistical Analyses

Number Cruncher Statistical System (NCSS) program was used for statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the data. The conformity of quantitative data with the normal distribution was tested with the Shapiro-Wilk test and graphic examinations. The Student-t test was used for the binary intergroup comparisons of the quantitative variables with normal distribution while Mann-Whitney U test was used for the binary inter-group comparisons of the quantitative variables without normal distribution. The Pearson chi-square test, Fisher's exact test and Fisher-Freeman-Halton exact test were used for the comparison of qualitative data. The Spearman correlation test was used to evaluate the relationships between the qualitative data. The statistical significance was $p<0.05$.

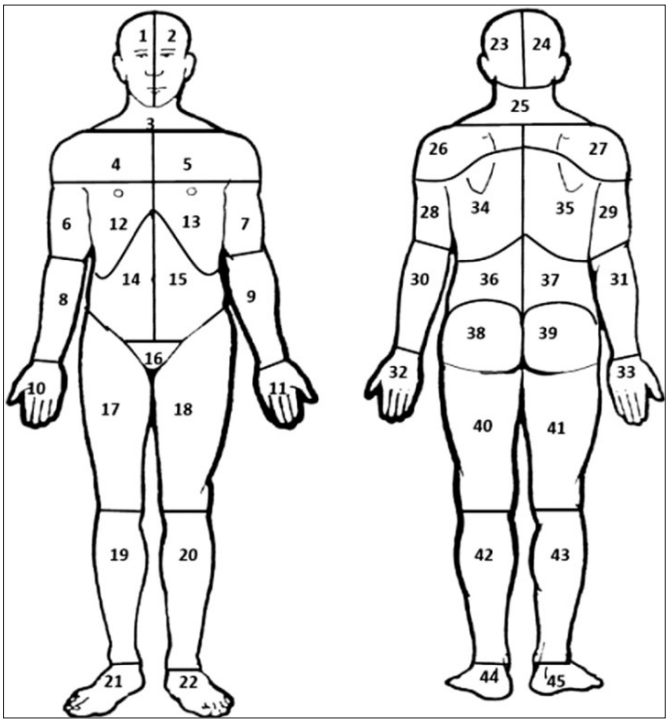

Figure. Template for identifying painful areas

RESULTS

The study was conducted with 154 cases of whom 45.5% (n=70) were female. Mean age was 63.66 (range 21-89) years. Of the cases included in the study, 71.4% (n=110) had myalgia, 55.8% (n=86) had arthralgia. Mean VAS value on admission was 6.39±2.04. The mean duration of hospital stay of patients was 12.83±7.08 (4-35) days. Data on all demographic and descriptive variables are shown on **Table 1**.

The most common painful regions reported by the patients were dorsum (68.2%; n=75) and chest (63.6%; n=70). A strong correlation was found between the need for intensive care and back and chest pain on admission (p=0.015 and p=0.001 respectively). There was no significant correlation between other localizations of pain and the need for intensive care (**Table 2**).

Table 1. Demographic and descriptive variable distribution

Age	
Min-Max (Median)	21-89 (65)
Mean±SD	63.66±13.33
Sex	
Female	70 (45.5%)
Male	84 (54.5%)
Myalgia	
Yes	110 (71.4%)
No	44 (28.6%9
Arthralgia	
Yes	86 (55.8%)
No	68 (44.2%)
VAS	
Min-Max (Median)	0-10 (6)
Mean±SD	6.39±2.04
Painful region*	
Feet	18 (16.4%)
Hip	16 (14.5%)
Chest	70 (63.6%)
Leg	54 (49.1%)
Dorsum	75 (68.2%)
Back	28 (25.5%)
Neck	22 (20.0%)
Arms	21 (19.1%)
Hospitalization period (days)	
Min-Max (Median)	4-35 (11%)
Mean±SD	12.83±7.08
ICU admission	
Yes	132 (85.7%)
No	22 (14.3%)
Days in the ICU	
Min-Max (Median)	1-12 (4)
Mean±SD	5.44±3.50
Final state	
Discharged	142 (92.2%)
Died	12 (7.8%)

*Patient reported more than one painful region

There was a significant positive correlation between high CRP, WBC, and D-dimer values and the need for intensive care (p<0.05). No significant differences and correlations were found between the other parameters. All data is shown on **Table 3**.

Table 2. Relationship between need for ICU and region of pain

	Need for ICU		P value
	No	Yes	
VAS			[a]0.280
Min-Max (Median)	0-10 (6)	4-10 (6)	
Mean±SD	6.42±2.04	6.18±2.08	
Pain localization			
Feet			[b]0.076
No	108 (83.1)	22 (16.9)	
Yes	18 (100.0)	0 (0.0)	
Hip			[b]0.130
No	110 (83.3)	22 (16.7)	
Yes	16 (100.0)	0 (0.0)	
Chest			[c]0.001
No	74 (94.9)	4 (5.1)	
Yes	52 (74.3)	18 (25.7)	
Leg			[c]0.990
No	80 (85.1)	14 (14.9)	
Yes	46 (85.2)	8 (14.8)	
Dorsum			[c]0.945
No	62 (49.2)	11 (50.0)	
Yes	64 (50.8)	11 (50.0)	
Back			[b]0.015
No	98 (81.7)	22 (18.3)	
Yes	28 (100.0)	0 (0.0)	
Neck			[b]0.745
No	108 (85.7)	18 (14.3)	
Yes	18 (81.8)	4 (18.2)	
Arms			[b]0.741
No	107 (84.3)	20 (15.7)	
Yes	19 (90.5)	2 (9.5)	

[a]Mann Whitney U test, [b]Fisher's exact test, [c]Pearson Chi-square test

Table 3. Relationship between need for ICU and laboratory findings

	Need for ICU		P value
	No	Yes	
WBC			[d]0.010
Min-Max (Median)	2.4-23.5 (7.2)	6.1-14.3 (10.5)	
Mean±SD	8.12±3.68	10.25±2.57	
CRP			[a]0.005
Min-Max (Median)	0.5-215 (41)	0.5-248 (97)	
Mean±SD	55.58±50.24	108.25±80.95	
Ferritin			[a]0.869
Min-Max (Median)	30-1650 (330.5)	97-917 (351)	
Mean±SD	473.94±457.5	383.82±243.83	
25-OH-Vitamin D			[a]0.156
Min-Max (Median)	4.4-67.5 (12.9)	9.2-25 (17.5)	
Mean±SD	16.26±10.79	17.43±6.44	
D-Dimer			[a]0.013
Min-Max (Median)	0.2-4261 (715)	190-4170 (1230)	
Mean±SD	987.26±961.45	1668.73±1273.02	

[a]Mann Whitney U test, [d]Student-t test

The fatality rate of cases with chest pain was significantly higher than those without (p<0.01). Similarly, the fatality rate of cases with dorsum pain was also significantly higher than those without (p<0.05) (**Table 4**).

High WBC and D-dimer values during the hospitalization were associated with high fatality risk. Vitamin D levels of deceased patients were significantly higher compared to those who recovered (p<0.05). There was no statistical correlation between ferritin and CRP values and death rate (**Table 5**).

A significant positive correlation was found between high VAS values on admission and the duration of hospital stay (p<0.05). There also was a significant positive correlation between CRP, ferritin and D-dimer values of the cases and their duration of hospital stay (p<0.05). Higher CRP, ferritin and D-dimer values on admission were correlated to a longer hospital stay. All relative data is presented on **Table 6**.

Table 4. Relationship between end-result and pain localization

	End-result		p value
	Discharge	Death	
Pain localization			
Feet			[b]0.362
No	118 (90.8)	12 (9.2)	
Yes	18 (100.0)	0 (0.0)	
Hip			[b]0.364
No	120 (90.9)	12 (9.1)	
Yes	16 (100.0)	0 (0.0)	
Chest			[c]0.009
No	76 (97.4)	2 (2.6)	
Yes	60 (85.7)	10 (14.3)	
Leg			[b]0.356
No	88 (93.6)	6 (6.4)	
Yes	48 (88.9)	6 (11.1)	
Dorsum			[c]0.014
No	73 (97.3)	2 (2.7)	
Yes	63 (86.3)	10 (13.7)	
Back			[b]0.124
No	108 (90.0)	12 (10.0)	
Yes	28 (100.0)	0 (0.0)	
Neck			[b]0.081
No	118 (93.7)	8 (6.3)	
Yes	18 (81.8)	4 (18.2)	
Arms			[b]0.680
No	117 (92.1)	10 (7.9)	
Yes	19 (90.5)	2 (9.5)	

[a]Mann Whitney U test, [b]Fisher's exact test, [c]Pearson Chi-square test

Table 5. Relationship between end-result and laboratory findings

	End-result		p value
	Discharge (n=142)	Death (n=12)	
WBC			[a]0.020*
Min-Max (Median)	2.4-23.5 (7.5)	6.1-14.3 (11.5)	
Mean±SD	8.25±3.61	10.53±3.08	
CRP			[a]0.157
Min-Max (Median)	0.5-248 (43)	1.3-152 (94.5)	
Mean±SD	61.69±58.92	79.88±49.91	
Ferritin			[a]0.112
Min-Max (Median)	30-1650 (324)	97-917 (590)	
Mean±SD	453.01±442.47	556.33±315.87	
25-OH-Vitamin D			[a]0.04
Min-Max (Median)	4.4-67.5 (12.9)	10.7-25 (22)	
Mean±SD	16.17±10.53	19.38±6.11	
D-Dimer			[a]0.003
Min-Max (Median)	0.2-4261 (697.5)	630-3288 (1889)	
Mean±SD	1015.76±1013.22	1913.67±990.67	

[a]Mann Whitney U test

Table 6. Effect of variables on hospitalization time

	Hospitalization time	
	r	p
VAS	0.205	0.011
WBC	-0.040	0.624
CRP	0.177	0.028
Ferritin	0.161	0.046
25-OH Vitamin D	0.109	0.227
D-dimer	0.231	0.005

r=Spearman's correlation coefficient

DISCUSSION

The results of our study clearly show a high incidence of musculoskeletal pain in COVID patients with chest and dorsum being the most prominent ones. Pain in these regions was strongly correlated with need for ICU and fatality rate. A high VAS score on admission was also an indicator of longer hospital stay.

Myalgia, arthralgia, fatigue and rarely arthritis-like symptoms can be seen in individuals infected with COVID-19 (12). Although musculoskeletal system symptoms in general were evaluated in many studies (4,5,12,13), the systematic prevalence studies primarily focused on this subject are not yet sufficient. Musculoskeletal symptoms are most probably evaluated behind severe clinical tables such as severe respiratory symptoms, cardiovascular involvements and multiple organ failures. The role of the musculoskeletal system has not been examined in detail during this pandemic (14). Generally, indirect effects due to inflammatory and/or immune response are regarded as the cause of arthralgia and myalgia (4). This study found that myalgia (71.4%) and arthralgia (55.8%) are common symptoms in hospitalized COVID-19 patients. This is in accordance with what other

previous studies have shown in this regard (13-16). In addition to the emergence of new painful regions due to the disease itself, chronic painful conditions may also worsen and symptoms like myalgia and arthralgia might affect the patient's ability to perform their daily life activities (17,18). Pain management should be considered an important part of the treatment algorithm.

The most common risk factors for mortality in the prognosis of the COVID-19 are multilobular infiltration in the lungs, lymphopenia, the existence of bacterial coinfection, the history of smoking, hypertension and age parameters (19,20). The existence of myalgia in the early period of the disease with high ALT and high hemoglobin levels was shown as a predictive indicator of severe SARS-CoV-2 infection (21). There are studies which assert that myalgia is not associated with the severity and death rate of the disease (22,23). In this study we found the most common painful regions related to myalgia to be the dorsum area (68.2%; n=75) and chest (63.6%; n=70). The results of this study comply with the study by Uz et al. (24) where the symptom of back pain was the second most common symptom after fatigue with a ratio of 50.5%.

This study also tried to determine the effect of myalgic localizations on the prognosis and final end-result. Pain localized in the chest and dorsum areas was associated with bad prognosis. This was not a surprising result. Hyperfunction of intercostal muscles to compensate for oxygen deficiency due to pneumonia may explain pain in these areas (14,22). Moreover, pneumonia with peripheral involvement may spread to the parental pleura and stimulate the intercostal nerves resulting in pleuritic chest pain and back pain through related dermatomes (25). Back pain was also associated with relatively good prognosis. However, this might be due to the fact that patient back pain was overshadowed by their painful dorsum.

Vitamin D is responsible for the maintenance of a healthy skeleton through regulation of calcium and phosphate metabolism. It is also an immunomodulatory hormone. Experimental studies have shown that the active form of vit-D, exerts immunologic activities on the innate and adaptive immune system. Many immune-related diseases and conditions such as psoriasis, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, tuberculosis, sepsis, respiratory infection, and COVID-19 have been associated with low levels of serum 25-hydroxyvitamin D (26). While vit-D deficiency has been associated with reduced ambulation after hip fracture surgery (27) and it also pre-disposes patients to decreased odds of remission to inflammation (28). The effect of vit-D on hospitalization and fatality rate in SARS-CoV-2 infection has often been discussed in the literature. Many studies assert that vit-D deficiency has a negative effect on the prognosis of pneumonia due to COVID-19 or other reasons (29-31). However, this hypothesis contradicts the high case and death rates in equatorial countries that are advantageous in terms of benefiting from the sunlight such as Brazil. Some studies assert that low vit-D values does not have any effect on pneumonia prognosis or is associated with low mortality (32,33). This study found no risk in terms of ICU admission rates with regard to vit-D values. The vit-D values of deceased patients were slightly higher than those who recovered but this could have been influenced by our small number of patients. Although the effects of vit-D on the musculoskeletal system are known, its effect on the immune system needs further research. A drawback on this subject is that COVID-19 patients may experience secondary vit-D deficiency as a result of them remaining still for a long time and being devoid of sunlight due to isolation. Therefore, the researchers are of the opinion that patients may face increased risk of fracture in the following period. Further research is required on this topic.

This study has some limitations. Firstly, the study included only adults of 18 years of age and higher. There might be differences in the expression of pain in lower age populations and so our results are only valid for the adult age groups. The second limitation is that the small sample size of patients who needed intensive care (n=22) and deceased patients (n=12). Because of this, the study might be insufficient in showing the relationship between musculoskeletal system pains and laboratory findings in the COVID-19 patients. More studies will be needed to reveal the uncertainties on this subject.

CONCLUSION

The majority of hospitalized patients in this study who were diagnosed with COVID-19, had musculoskeletal system pain. The study revealed that the probability of patients with chest and dorsum pain to have a worse prognosis is relatively high. This information might help clinicians in predicting the prognosis during treatment. Additionally, even though the pains in other areas are not specifically associated with the prognosis, they are among the problems that must be solved at the treatment stage.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erzurum Regional Training and Development Hospital Clinical Researches Ethics Committee (Date: 02.11.2020, Decision No: 2020/20-194).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study had received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and approved the final version.

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