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ARAŞTIRMA MAKALESİ/ORIGINAL ARTICLE

The Relationship Between COVID-19 and Secondary Chronic Musculoskeletal Pain

COVID-19 ve Sekonder Kronik Kas-iskelet Ağrısı İlişkisi

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Abstract

Objective: To evaluate the development of secondary chronic musculoskeletal pain in patients with COVID-19 with and without pulmonary involvement and to determine the areas of pain.

Methods: The cross-sectional study included a total of 150 patients aged 18 years and over, who presented to the emergency department with COVID-19 symptoms and were diagnosed with COVID-19 within 2020. Eighty-four of these patients had pulmonary involvement and 66 had no pulmonary involvement. Data were obtained through communication with the patients face-to-face during the diagnosis process and in the three months period afterwards, or via video calls over the Skype application on smartphones by contacting them through the information given in their files. The participants were asked to mark the areas of pain on the "Collaborative Health Outcomes Information Registry" body map and rate their pain intensity on a scale of 1-10 using the Visual Analog Scale.

Results: It was observed that the maximum degree of acute musculoskeletal pain indicated on the Visual Analog Scale was statistically significantly lower in patients with lung involvement compared to those without lung involvement. The patients with pulmonary involvement also had lower rates of acute pain and chronic pain, except for the abdomen area, compared to those without pulmonary involvement.

Conclusion: In patients with COVID-19 with pulmonary involvement, the degree of chronic pain of the musculoskeletal system may be lower due to the development of stress analgesia secondary to stress and inflammatory response. Further extensive studies are needed on this subject.

Keywords: COVID-19, Chronic Musculoskeletal Pain, Visual Analog Scale

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Öz

Amaç: Bu çalışmanın amacı, akciğer tutulumu olan ve olmayan COVID-19 hastalarında sekonder kronik kas-iskelet ağrısı gelişimini değerlendirmek ve ağrı alanlarını belirlemektir.

Yöntem: Kesitsel olarak dizayn edilen bu çalışmaya 2020 yılı içerisinde, acil servise COVID-19 semptomları ile başvuran ve COVID-19 tanısı konan 18 yaş ve üzeri toplam 150 hasta dahil edildi. Bu hastaların 84'ünde akciğer tutulumu varken, 66'sında akciğer tutulumu yoktu. Tanı sürecinde ve sonrasındaki üç aylık süreçte hastalarla yüz yüze iletişim kurularak ya da akıllı telefonlardan Skype uygulaması üzerinden görüntülü görüşme yoluyla dosyalarına kaydedilen verilere ulaşıldı. Katılımcılardan, "İşbirlikçi Sağlık Sonuçları Bilgi Kaydı" vücut haritasında ağrı alanlarını işaretlemeleri ve Vizüel Analog Skala kullanarak ağrı yoğunluklarını 1-10 arasında derecelendirmeleri istendi.

Bulgular: Vizüel Analog Skala 'da belirtilen maksimum akut kas-iskelet ağrısı derecesinin akciğer tutulumu olan hastalarda akciğer tutulumu olmayanlara göre istatistiksel olarak anlamlı derecede daha düşük olduğu görüldü. Akciğer tutulumu olan hastalarda karın bölgesi dışında akut ağrı ve kronik ağrı oranları da akciğer tutulumu olmayanlara göre istatistiksel olarak anlamlı derecede daha düşüktü.

Sonuç: Akciğer tutulumu olan COVID-19 hastalarında, stres ve inflamatuar yanıta sekonder stres analjezi gelişmesi nedeniyle kronik kas-iskelet sistemi ağrı derecesi daha düşük olabilir. Bu konuda daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Kronik Kas-iskelet Ağrısı, Vizüel Analog Skala

INTRODUCTION

Chronic musculoskeletal pain refers to persistent or recurrent pain in one or more musculoskeletal regions for at least three months, and many patients present to hospitals due to chronic musculoskeletal pain (1,2). For better pain management, the World Health Organization (WHO) recommends classifying chronic musculoskeletal pain as primary and secondary. It has been accepted that primary chronic musculoskeletal pain is associated with conditions affecting the musculoskeletal system, including muscles, bones and joints (3). The basis of chronic secondary musculoskeletal pain is considered to be permanent inflammation (4,5).

It is known that the infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has increasing prevalence across the world, causes chronic musculoskeletal pain, especially through inflammation (6). Respiratory system infection caused by SARS-CoV-2 induces systemic inflammation, which can affect the musculoskeletal system. Although it is known that the angiotensin-converting enzyme 2 (ACE-2) and transmembrane protease, serine 2 (TMPRSS2) genes, which cause direct viral infection, affect different types of muscle cells, it is not yet known whether the virus has direct mechanical effects on the musculoskeletal system (7,8). The proteolytic cleavage of the viral S protein by TMPRSS2 leads to the stimulation of peptides in cell membranes of the viral RNA in the cytoplasm (9). In addition, the infection induced by cytokines and proinflammatory signaling molecules can lead to pathological changes in skeletal muscles. IFN-g, IL-1b, IL-6, IL-17 and TNF-a can directly induce muscle fiber proteolysis and decrease protein synthesis (10). IL-1b and IL-6 induce muscle fibroblast activity and cause fibrosis, leading to the disruption of skeletal muscle regeneration and increased sensitivity to pain (11). In an article by Shanthanna et al. presenting the recommendations of an international panel on COVID-19, it was

noted that COVID-19 infection suppressed the immune system and increased chronic musculoskeletal pain and if the treatment of patients with pain due to the pandemic process continued to be delayed, major problems could occur in future, especially in emergency services (12).

The Visual Analog Scale (VAS), developed by Fredy in 1923, is one of the important measurement tools used in the subjective evaluation of patients' pain and can be applied easily (13,14).

The aim of this study was to assess the musculoskeletal areas of pain and pain severity described at baseline and three months later in patients aged 18 years and older, who were laboratory or radiologically confirmed to have COVID-19 according to the WHO guideline (15,16), and to compare the findings between the patients with and without pulmonary involvement.

METHODS

Study design and participants

This study cross-sectional was conducted between April 2020 and February 2021 with a total of 150 patients aged over 18 years and over, who presented to the emergency service with COVID-19 symptoms. Based on laboratory and radiological results, 84 of these patients were confirmed to have COVID-19 with pulmonary involvement (35 female, 49 male), and 66 had COVID-19 without pulmonary involvement (48 female, 18 male). Two groups with and without pulmonary involvement were randomized to assess the development of secondary chronic musculoskeletal pain and to identify areas of pain.

For this study, permission from the Ministry of Health and local ethics committee approval were obtained (date: May 20, 2021/number: 81-1417).

Data Collection

The patients were contacted through their information in their files, and they were invited to the physical therapy and rehabilitation polyclinic of a training and research hospital affiliated with a university to conduct face-to-face interviews. Those that were not able to visit the hospital were interviewed through video calls made over the Skype application on their smartphones. The participants were asked to mark their pain areas on the Collaborative Health Outcomes Information Registry (CHOIR) body map (17) and score their pain intensity using VAS.

Inclusion criteria

1) Being diagnosed with COVID-19 with or without pulmonary involvement based on laboratory and imaging methods.

2) Having no previous diagnosis of chronic musculoskeletal pain .

Exclusion criteria

1) Age under 18 years

2) Pregnancy

Statistical Analysis

The pain areas marked on the CHOIR body map and the data obtained through the VAS pain scoring made on this image were analyzed using SPSS v. 21. Results on continuous data were presented as mean ± standard deviation. The Kolmogorov-Smirnov test was applied to confirm whether continuous variables showed a normal distribution. The t-test was used for continuous variables with a normal distribution in dependent samples and the Mann-Whitney U test for continuous variables with a non-normal distribution. The difference between the baseline and third-month values within the groups was tested with the Wilcoxon signed-rank test. P values of <0.05 were considered statistically significant.

RESULTS

Gender, age, weight, height, and body mass index (BMI) averages differed between the patients with and without pulmonary involvement ($p < 0.05$).

The degree of maximum acute pain was observed to be significantly lower in the patients with pulmonary involvement compared to those without pulmonary involvement ($p < 0.001$). (Table 2)

The degrees of acute headache, acute thigh pain, and acute calf pain were observed to be lower in the patients with pulmonary involvement compared to those without pulmonary involvement ($p = 0.003$, $p = 0.007$, and $p = 0.004$, respectively). The degrees of acute abdominal pain and chronic abdominal pain were higher in the patients with pulmonary involvement compared to those without pulmonary involvement ($p = 0.033$ and $p = 0.010$). (Table 3)

Table 1. Distribution of Sociodemographic Data by Groups

		Pulmonary involvement (+)		Pulmonary involvement (-)		
		Mean ± SD	Min-Max	Mean ± SD	Min-Max	p
Gender n (%)	Female	35	41.7	48	72.7	**<0.001**
	Male	49	58.3	18	27.3	
Age		52.39 ± 13.83	26-82	40.44 ± 9.97	20-67	**<0.001**
Weight		80.15 ± 16.21	50-119	70.55 ± 12.39	50-105	**<0.001**
Height		1.69 ± 0.11	1.5-1.9	1.65 ± 0.08	1.5-1.86	**0.038**
BMI		28.24 ± 5.55	18.42-46.22	25.91 ± 4.86	19-46.67	**0.008**

Table 2. Degree of Acute and Chronic Pain by Groups

	Pulmonary involvement (+)			Pulmonary involvement (-)			
	Mean ± SD	Median [IQR]	Min-Max	Mean ± SD	Median [IQR]	Min-Max	p
Maximum acute pain	5.32 ± 2.79	5 [3.25-7.75]	0-10	7.42 ± 2.68	8 [5.75-10]	0-10	<0.001
Maximum chronic pain	1.05 ± 1.62	0 [0-2]	0-7	1.53 ± 1.87	1 [0-3]	0-7	0.066

Table 3. Comparison of Acute and Chronic Pain Values Between the Groups

Pain	Acute					Chronic				
	Pulmonary involvement (+)		Pulmonary involvement (-)			Pulmonary involvement (+)		Pulmonary involvement (-)		
Localization	Mean ± SD	Min-Max	Mean ± SD	Min-Max	p	Mean ± SD	Min-Max	Mean ± SD	Min-Max	p
Head	1.32 ± 2.71	0-10	3.68 ± 4.49	0-10	**0.003**	0.15 ± 0.81	0-7	0.39 ± 1.15	0-6	0.103
Throat	0.85 ± 2.48	0-10	1.33 ± 3.2	0-10	0.363	0.05 ± 0.26	0-2	0.11 ± 0.47	0-3	0.465
Neck	1.18 ± 2.83	0-10	1.08 ± 3	0-10	0.425	0.19 ± 0.7	0-5	0.15 ± 0.90	0-7	0.256
Shoulder	0.93 ± 2.7	0-10	1.33 ± 3.12	0-10	0.407	0.30 ± 1.20	0-7	0.24 ± 0.82	0-4	0.695
Shoulder joint	1.07 ± 2.87	0-10	1.23 ± 3.05	0-10	0.720	0.31 ± 1.19	0-7	0.24 ± 0.82	0-4	0.859
Elbow	0.38 ± 1.78	0-10	0.61 ± 2.4	0-10	0.697	0.01 ± 0.11	0-1	0 ± 0	0-0	0.375
Wrist	0.38 ± 1.78	0-10	0.3 ± 1.73	0-10	0.608	0.01 ± 0.11	0-1	0 ± 0	0-0	0.375
Upper arm	0.32 ± 1.7	0-10	0.62 ± 2.4	0-10	0.278	0.01 ± 0.11	0-1	0 ± 0	0-0	0.375
Forearm	0.32 ± 1.7	0-10	0.62 ± 2.4	0-10	0.278	0.01 ± 0.11	0-1	0 ± 0	0-0	0.375
Breast	1.55 ± 3.26	0-10	1.73 ± 3.44	0-10	0.952	0.26 ± 1.02	0-7	0.21 ± 0.67	0-4	0.504
Abdomen	2.23 ± 3.42	0-10	1.41 ± 3.11	0-10	**0.033**	0.37 ± 1.20	0-7	0.06 ± 0.49	0-4	**0.010**
Ridge	3.82 ± 3.58	0-10	3.29 ± 4.11	0-10	0.139	0.81 ± 1.56	0-7	0.82 ± 1.52	0-7	0.927
Waist	3.94 ± 3.69	0-10	4.17 ± 4.24	0-10	0.830	0.92 ± 1.6	0-7	0.82 ± 1.56	0-7	0.537
Buttocks (Right)	2.63 ± 3.82	0-10	3.02 ± 4.17	0-10	0.755	0.68 ± 1.53	0-7	0.82 ± 1.63	0-7	0.512
Femur	1.72 ± 3.48	0-10	3.5 ± 4.33	0-10	**0.007**	0.52 ± 1.44	0-7	0.52 ± 1.18	0-6	0.450
Calf	1.64 ± 3.39	0-10	3.62 ± 4.42	0-10	**0.004**	0.51 ± 1.44	0-7	0.48 ± 1.11	0-6	0.281
Knee	1.69 ± 3.4	0-10	2.76 ± 4.09	0-10	0.119	0.49 ± 1.43	0-7	0.35 ± 1.06	0-6	0.982
Foot	1.33 ± 3.13	0-10	1.59 ± 3.43	0-10	0.623	0.44 ± 1.37	0-7	0.17 ± 0.69	0-4	0.210
Ankle	1.46 ± 3.22	0-10	1.62 ± 3.43	0-10	0.873	0.49 ± 1.43	0-7	0.17 ± 0.67	0-4	0.239
Buttocks (Left)	1.4 ± 3.16	0-10	0.68 ± 2.43	0-10	0.080	0.45 ± 1.38	0-7	0.12 ± 0.57	0-3	0.103

Table 4. Evaluation of Chronicity of Pain by Groups

		Pulmonary involvement				Total		
		(+)		(-)				
	Pain	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Head	None	62	73.8	38	57.6	100	66.7	0.091
	Acute	16	19.0	18	27.3	34	22.7	
	Chronic	6	7.1	10	15.2	16	10.7	
Throat	None	74	88.1	55	83.3	129	86.0	0.673
	Acute	7	8.3	7	10.6	14	9.3	
	Chronic	3	3.6	4	6.1	7	4.7	
Neck	None	69	82.1	58	87.9	127	84.7	0.492
	Acute	7	8.3	5	7.6	12	8.0	
	Chronic	8	9.5	3	4.5	11	7.3	
Shoulder	None	74	88.1	55	83.3	129	86.0	0.673
	Acute	3	3.6	4	6.1	7	4.7	
	Chronic	7	8.3	7	10.6	14	9.3	
Shoulder joint	None	73	86.9	56	84.8	129	86.0	0.928
	Acute	3	3.6	3	4.5	6	4.0	
	Chronic	8	9.5	7	10.6	15	10.0	
Elbow	None	80	95.2	62	93.9	142	94.7	0.526
	Acute	3	3.6	4	6.1	7	4.7	
	Chronic	1	1.2	0	0.0	1	0.7	
Wrist	None	80	95.2	64	97.0	144	96.0	0.660
	Acute	3	3.6	2	3.0	5	3.3	
	Chronic	1	1.2	0	0.0	1	0.7	
Upper arm	None	81	96.4	61	92.4	142	94.7	0.225
	Acute	2	2.4	5	7.6	7	4.7	
	Chronic	1	1.2	0	0.0	1	0.7	
Forearm	None	81	96.4	61	92.4	142	94.7	0.225
	Acute	2	2.4	5	7.6	7	4.7	
	Chronic	1	1.2	0	0.0	1	0.7	
Chest	None	65	77.4	51	77.3	116	77.3	0.584
	Acute	11	13.1	6	9.1	17	11.3	
	Chronic	8	9.5	9	13.6	17	11.3	
Abdomen	None	53	63.1	54	81.8*	107	71.3	**0.012**
	Acute	20	23.8	11	16.7	31	20.7	
	Chronic	11	13.1*	1	1.5	12	8.0	
Ridge	None	27	32.1	38	57.6*	65	43.3	**<0.001**
	Acute	31	36.9*	7	10.6	38	25.3	
	Chronic	26	31.0	21	31.8	47	31.3	
Waist	None	32	38.1	31	47.0	63	42.0	0.550
	Acute	22	26.2	15	22.7	37	24.7	
	Chronic	30	35.7	20	30.3	50	33.3	
Buttocks (Right)	None	53	63.1	42	63.6	95	63.3	0.561
	Acute	12	14.3	6	9.1	18	12.0	
	Chronic	19	22.6	18	27.3	37	24.7	

Table 4. Evaluation of Chronicity of Pain by Groups

Femur	None	66	78.6*	38	57.6	104	69.3	**0.007**
	Acute	5	6.0	14	21.2*	19	12.7	
	Chronic	13	15.5	14	21.2	27	18.0	
Calf	None	66	78.6*	38	57.6	104	69.3	**0.015**
	Acute	6	7.1	13	19.7*	19	12.7	
	Chronic	12	14.3	15	22.7	27	18.0	
Knee	None	65	77.4	44	66.7	109	72.7	0.190
	Acute	8	9.5	13	19.7	21	14.0	
	Chronic	11	13.1	9	13.6	20	13.3	
Foot	None	70	83.3	53	80.3	123	82.0	0.093
	Acute	4	4.8	9	13.6	13	8.7	
	Chronic	10	11.9	4	6.1	14	9.3	
Ankle	None	68	81.0	53	80.3	121	80.7	0.262
	Acute	5	6.0	8	12.1	13	8.7	
	Chronic	11	13.1	5	7.6	16	10.7	
Buttocks (Left)	None	69	82.1	61	92.4	130	86.7	0.179
	Acute	5	6.0	2	3.0	7	4.7	
	Chronic	10	11.9	3	4.5	13	8.7	

*refers to the higher rate ($p < 0.005$)

The type of pain in the abdomen, back, thigh, and calf significantly differed according to the presence of pulmonary involvement ($p = 0.012$, $p < 0.001$, $p = 0.007$, and $p = 0.015$, respectively). The rates of chronic abdominal and back pain were significantly lower and the rates of chronic thigh and calf pain were significantly higher in the patients with pulmonary involvement compared to those without pulmonary involvement ($p < 0.05$ for all). (Table 4)

Table 5. Distribution of Drug Use by Groups

		Pulmonary Involvement				Total		
		(+)		(-)				
		n	%	n	%	n	%	p
Drug utilization	Present	84	100.0	62	93.9	146	97.3	**0.036**
	Not Present	0	0.0	4	6.1	4	2.7	
Favipiravir	Present	84	100.0	59	89.4	143	95.3	**0.003**
	Not Present	0	0.0	7	10.6	7	4.7	
Hydroxychloroquine sulfate	Present	7	8.3	1	1.5	8	5.3	0.079
	Not Present	77	91.7	65	98.5	142	94.7	
Enoxaparin sodium	Present	83	98.8	41	62.1	124	82.7	**<0.001**
	Not Present	1	1.2	25	37.9	26	17.3	
Acetylsalicylic acid	Present	12	14.3	19	28.8	31	20.7	**0.029**
	Not Present	72	85.7	47	71.2	119	79.3	
Methylprednisolone	Present	46	54.8	0	0.0	46	30.7	**<0.001**
	Not Present	38	45.2	66	100.0	104	69.3	

Table 5. Distribution of Drug Use by Groups

Antibiotic	Present	35	41.7	0	0.0	35	23.3	**<0.001**
	Not Present	49	58.3	66	100.0	115	76.7	
Multivitamin	Present	81	96.4	28	42.4	109	72.7	**<0.001**
	Not Present	3	3.6	38	57.6	41	27.3	

Concerning drug use, the rates of favipiravir, enoxaparin sodium, acetylsalicylic acid, methylprednisolone, antibiotic, and multivitamin use significantly differed between the patients with and without pulmonary involvement. While all the patients with pulmonary involvement used favipiravir, 93.9% of those without pulmonary involvement used favipiravir. Enoxaparin sodium was used by 98.8% of the patients with pulmonary involvement and 62.2% of those without pulmonary involvement. Antibiotic use was only present in the group with pulmonary involvement. The use of multivitamins was found to be significantly higher in the group with pulmonary involvement (96.4%). (Table 5)

While 58.3% of the patients with pulmonary involvement were male, 72.2% of those without pulmonary involvement were female.

DISCUSSION

A review of the literature indicates that there are only limited studies on the effect of SARS-CoV-2 the musculoskeletal system (18,19,20). This study differs from other studies in that it compared the development of secondary chronic musculoskeletal system pain status and areas of pain in patients with COVID-19 between those with and without pulmonary involvement.

In a meta-analysis study covering 40 studies including a total of 2,459 severe and critical COVID-19 cases, Zhong et al. determined that 62.3% of the patients were male. In our study, 58.3% of the patients with pulmonary involvement were male, and 72.7% of those without involvement were female. Based on these results, it can be suggested that pulmonary involvement is higher in male patients than in female patients (21).

In a study by Zhou et al. including 191 severely hospitalized COVID-19 cases, it was reported that 62% of the patients were male, and the mean age was 56 years. In our study, the mean age was determined as 52.39 years for the patient with pulmonary involvement and 40.44 years for those without pulmonary involvement. These results suggest that the severity of the disease increases with age (22).

In a study by Tüzün et al. conducted with 103 patients with severe and non-severe COVID-19 treated in hospital due to pulmonary involvement, muscle involvement was associated with functional deterioration rather than true tissue damage, and it was stated that myalgia was not correlated with disease severity (23). In our study, the degree of pain in all the musculoskeletal areas except the abdomen was found to be statistically significantly lower in the patients with pulmonary involvement compared to those without pulmonary involvement.

In a study by Lechien et al. including 1,420 patients, it was determined that 62.5% of the patients had myalgia and 66.6% had loss of smell, with the latter being an important symptom of mild to moderate COVID-19. In our study, we found that the rate of myalgia was significantly higher in patients who did not have pulmonary involvement and had a mild course of the disease, compared to those with pulmonary involvement, which is consistent with the literature (24).

In COVID-19 patients with lung involvement, the organism is in a state of alarm, with enkephalin secretion increasing, especially from the anterior pituitary and adrenal medulla in response to the increase in the corticotropin-releasing hormone, cytokine, chemokine, and catecholamines as a result of stress. In addition, it is considered that the excitability of sensory nerves and the release of excitatory neuropeptides are inhibited as stress analgesia as a result of the increase in the opioid release from leukocytes in the event of inflammation, thus leading to the activation of peripheral opioid receptors (25).

In COVID-19, ACE-2 receptors, which are used by the virus for cell entry, are expressed in the epithelium of the respiratory tract and gastrointestinal tract (26). It has been

reported that abdominal pain is associated with the severity of the disease (27). In our study, abdominal pain was found to be statistically significantly higher in the patients with pulmonary involvement, which is in agreement with the literature.

In conclusion, it is considered that stress analgesia develops secondary to stress and inflammation response in patients with pulmonary involvement in COVID-19 and abdominal pain can be used in predicting the prognosis of the disease.

Abbreviations

ACE-2: Angiotensin-Converting Enzyme 2

CHOIR: Collaborative Health Outcomes Information Registry

SARS-CoV-2: Acute Respiratory Syndrome Coronavirus 2

TMPRSS 2: Transmembrane Protease, Serine 2

VAS: Visual Analog Scale

WHO: World Health Organization

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Conflict of Interest

The authors declare that they have no conflict of interest.

Support Resources

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Ethical Declaration

For this study, permission from the Ministry of Health, Adana City Training and Research Hospital and local ethics committee approval were obtained (date: May 20, 2021/number: 81-1417).

Authorship Contributions

Study design: GYO, Data collection and entry: GYO, Statistical analysis: IB, Literature search: GYO, IB, Writing: IB

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