MUSCULOSKELETAL PAIN IN PATIENTS WITH COVID-19

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Abstract. Introduction: *The end of 2019 marked the beginning of a new disease for the mankind, which changed the lives of people all over the world. Almost 3 years have passed from the declaration of a global pandemic till today, but despite this, our knowledge of the disease COVID-19 caused by SARS CoV-2 is still the object of many studies. The reasons are the heterogeneous manifestation of the disease and the involvement of multiple organs and systems in the clinical presentation. The spectrum of rheumatological manifestations that directly concern the rheumatologist is also very miscellaneous. Most common are musculoskeletal pain phenomena as a rheumatic manifestation of the disease.* ***Objective:*** *The aim of the study was to assess the intensity of pain of musculoskeletal origin – joint (arthralgias) and muscle (myalgias), and its relationship with anxiety and depressive attitudes among a Bulgarian cohort of patients with moderate and severe COVID-19, hospitalized in Rheumatology Clinic – Varna.* ***Material and methods:*** *A single-center, observational study including patients diagnosed with COVID-19 and hospitalized in the Rheumatology Clinic, „St. Marina" UMBAL – Varna, took place. The etiological diagnosis was accepted with a positive result of polymerase chain reaction (PCR) test or rapid antigen test for SARS-CoV-2. An inclusion criterion was new-onset musculoskeletal pain during the acute phase of COVID-19. Visual analogue scales (VAS) to assess pain intensity (muscular and joint) and Zung self-report scales for depression (SDS) and anxiety (SAS) were used. Laboratory acute phase indicators and thrombotic biomarkers were investigated, and chest imaging was performed in all patients. Descriptive statistics, one-Sample T-test, correlation and linear regression analyses were used. A significance level of $p < 0.05$ was accepted.* ***Results:*** *226 inpatients with moderate and severe COVID19, with new onset of musculoskeletal pain, were included. The average age of the study population was 65.5 years (from 26-91). Of them, 46.5% (n = 105) were women, 53.5% (n = 121) were men. The intensity of pain (VAS-muscular and joint) and the degree of anxiety and depression (SAS and SDS) show a strong directly proportional correlation dependence (VASm and SDS $r = 0.666$, $p < 0.001$; VASm and SAS $r = 0.644$, $p < 0.001$; VASa and SDS $r = 0.698$, $p < 0.001$; VASa and SAS $r = 0.680$, $p < 0.001$, respectively). 51% of the changes in joint pain intensity and 45% of the changes in muscle pain intensity could be determined by changes in the anxiety and depression of the COVID 19 patients. No correlation was found between pain intensity and inflammatory markers, nor with thrombogenic markers in patients with SARS-CoV-2.* ***Conclusion:*** *Musculoskeletal pain is one of the most common clinical presentations of COVID-19. The intensity of the pain correlates with anxiety and depressive symptoms in these patients and does not correlate with the levels of inflammation and thrombotic biomarkers.*

Key words: *Musculoskeletal pain, COVID-19, anxiety and depressive symptoms*

Introduction

In 2020, the modern humanity was faced with an infection that caused a global threat, classified as a pandemic by the World Health Organization (WHO). The new pandemic, the coronavirus disease (COVID-19), is caused by the SARS-CoV-2 virus, which was first registered at the end of November 2019 in Wuhan, central China. This happens when people develop pneumonia that does not respond to known treatments [1]. Taxonomically, SARS-CoV-2 is part of the coronavirus family and is a variant (strain) of the Severe acute respiratory syndrome-related coronavirus, also known as SARS-CoV-2 [2]. The name „coronavirus" has Latin origin, from „corona", which means „halo" or „wreath", which comes from the Ancient Greek – κορώνη (korṓnē), which means „garland, wreath". It refers to the characteristic appearance of viral particles (virions): they have fringes reminiscent of a royal crown or the sun's corona. Strains of the coronavirus family are pathogenic to birds and mammals, including humans. Human coronaviruses are quite diverse in the diseases they can cause. In some, the mortality can reach more than 30% of the infected patients (such as MERS-CoV), while others are relatively harmless and the diseases resemble an acute viral infection like com-

mon cold. The majority of representatives of the coronavirus family cause acute infections with the main symptoms – fever and sore throat (angina), mainly during the winter and early spring season. Coronaviruses can cause pneumonia (direct viral pneumonia or secondary bacterial pneumonia) as well as bronchitis (direct viral bronchitis or secondary bacterial bronchitis). The human coronavirus SARS-CoV, discovered in 2003, which causes severe acute respiratory syndrome (SARS), has a unique pathogenesis because it causes upper and lower respiratory tract infections, and the disease is characterized by high mortality [3]. Other members of the coronavirus family can also cause severe illnesses such as Middle East Respiratory Syndrome (MERS). Only 7 representatives of the coronavirus family are known to be pathogenic to humans [4].

The concept of the disease COVID-19, initially considered a flu-like disease, has undergone a radical change. Currently, the disease is perceived as a polysyndromic inflammatory disease involving not only the respiratory system, but also the musculoskeletal system cardiovascular system, skin, urinary and nervous systems, and is associated by a number of hematological, gastrohepatoenterological and endocrine disorders [5]. Tissue damage in COVID-19 is immune-mediated, resembling exacerbations of advanced rheumatologic disease.

Various pain phenomena also appear in the clinic of the disease, often as a single manifestation or in combination with symptoms from different organs and systems. Most observed pain symptoms are headache, sore throat (angina), arthralgia, myalgia, chest pain (including pleurodynia), abdominal pain, neuropathic pain and others [6, 7, 8, 9, 10, 11, 12]. According to the International Association for the Study of Pain (IASP), pain is „an unpleasant sensory and emotional experience associated with actual or potential tissue damage“. Pain is the result of complex biochemical processes and is influenced to varying degrees by biological, physiological and social factors. It is a subjective experience, experienced only in the solitude of our individual minds, and the perception of pain is not always proportional to the intensity of tissue damage or the unwanted stimulus. Many studies have been done to establish the correlation of pain and various factors such as inflammation, severity of the disease, duration of symptoms. Pain can also lead to psycho-emotional manifestations in patients, as it is known that acute pain often causes anxiety, while chronic pain is more likely to lead to depression. This can lead to disturbances in the quality of life and cause various functional deficits in these patients.

Objectives

The aim of the study was to evaluate the frequency and intensity of musculoskeletal pain – joint pain (arthralgia) and muscle pain (myalgia), in patients with COVID-19 and their relationship with anxiety and depression in these patients, the inflammation rates and activity (determined by measuring inflammatory markers) and with thrombotic biomarkers.

Material and methods

With the permission No. 116/ 28/04/2022. of the Committee on Ethics of Scientific Research (CESR) of Medical University – Varna, in the Rheumatology Clinic – Varna, restructured as a sector for the treatment of patients with COVID-19, was conducted a single-center observational follow-up study during the last COVID wave (continuing from October 2021 to March 2022).

The subjects of the study were 226 hospitalized patients diagnosed with COVID-19.

The diagnosis was confirmed with a positive result of polymerase chain reaction (PCR) test or rapid antigen test (RAT) for SARS-CoV-2, carried out before hospitalization in University Multiprofile Hospital for Active Treatment „Sv. Marina“.

An inclusion criterion for participation in the study was new-onset musculoskeletal pain during the acute phase of the disease.

The study did not include patients with known prior to the current hospitalization:

- Inflammatory, degenerative or metabolic joint diseases, as well as autoimmune vascular-connective tissue diseases, for which patients take medication (NSAIDs, corticosteroids or disease-modifying agents).
- Mental disorders.

Socio-demographic characteristics of the studied patient population were analyzed.

A detailed history of the onset and duration of complaints was taken and all patients were examined by a rheumatologist. All patients underwent chest imaging including conventional radiography or computed tomography (CT) of the chest, and only patients with established interstitial pneumonia and/or initial inflammatory infiltrates were included. Blood tests were taken including inflammation markers such as erythrocyte sedimentation rate (ESR),

C-reactive protein (CRP), fibrinogen, ferritin, lactate dehydrogenase (LDH), as well as thrombotic biomarkers (D dimer), as a specific end product of fibrinolysis. The following reference values of the investigated indicators were used: ESR (3-46 mm), CRP (0-5 mg/l), fibrinogen (2.38-4.98 g/l), LDH (150-480 U/L), ferritin (women 13-150 ng/mL and men 30-400 ng/mL), D dimer (< 0.5 mcg/mL).

A 100 mm visual analogue scale was used to assess the intensity of pain, which for the purposes of the study was coded VAS-m – for muscle pain, and VAS-a for joint pain.

Two self-report measures of depression and anxiety were used: Zung's Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS):

- 20-49 normal range
- 50-59 mild depression
- 60-69 moderately depressed
- 70 and over-severe depression [13].

The Zung Self-Rating Depression Scale is a short self-administered survey to quantify a patient's depressed state. The scale has 20 items that assess the four general characteristics of depression: comprehensive affect, physiological equivalents, other disturbances, and psychomotor activities. There are ten positively worded and ten negatively worded questions. Each question is rated on a scale of 1-4 (a little of the time, some of the time, good part of the time, most of the time). Scores range from 20-80.

The SAS is a 20-item self-report instrument designed to measure anxiety levels based on scoring in 4 clusters of manifestations: cognitive, autonomic, motor, and central nervous system symptoms. In responding to the statements, a person must indicate how much each statement applies to him or her within one or two weeks before taking the test. Each question is rated on a 1-4 Likert scale (based on these responses: „a little of the time," „some of the time," „a good deal of the time," „most of the time"). Some questions are worded negatively to avoid the fixed-response problem. The overall assessment is done through a total score. Total raw scores range from 20-80. The raw score should then be converted to an „Anxiety Index" score using the chart on the paper version of the test, which can be found at the link below. The Anxiety Index score can be used on the scale below to determine the clinical interpretation of the level of anxiety:

- 20-44 normal range
- 45-59 Mild to moderate levels of anxiety
- 60-74 Marked to severe levels of anxiety
- 75 and higher levels of extreme anxiety [14].

In order to avoid interference from the treatment on the indicators of interest, they were taken on the day of hospitalization, before the start of the treatment.

Statistical data processing was performed with SPSS for iOs on Mac and included descriptive statistics, one simple T test and correlation analysis. In order to establish a linear correlation between the strength of muscle and joint pain (VAS 0-100 mm) and the degree of anxiety and depression (SAS 20-80; SDS 20-80), a linear regression analysis was performed. A value of $p < 0.05$ was accepted as a level of significance for exceeding the null hypothesis.

Results

In the study were included 226 hospitalized patients with COVID-19 (mean 56.5 ± SD). No difference was found in the gender distribution (women 46.5% (n = 105) vs. men 53.5% (n = 121, $p > 0.05$) (Tabl. 1, Fig. 1).

The mean age of the studied population of patients was 65.5 years as a significant part of the patients with COVID-19 is over 60 years of age (63.27%, $p < 0.05$).

The average values for the investigated indicators of inflammation and thrombogenic biomarkers (measured with the specific degradation products of fibrinolysis) in hospitalized patients with COVID-19 are significantly higher than the upper limit of the norm and are presented in Table 1.

The mean values of VASm and VASa for the entire group were in the range of "mild pain" for both muscle and joint pain, which was significantly increased pain than the generally accepted norm of < 4 mm ((44.23 and 43.23, respectively, ($p < 0.001$). Distributed by gender, women were found to experience significantly increased pain than men, with their VAS pain intensity defined as „moderate pain" for both muscle and joint (VASfm – 49.5, VASfa – 48.5 vs VASmm – 39.32 VASma – 38.62, $p < 0.001$).

In COVID-19 patients were found moderate depression and anxiety. The mean value of the levels of anxiety and depressed attitude were greater than the normal range), which defines patients with mild to moderate anxiety and mild depression (SAS = 45.22, SDS = 49.52).

A very strong directly proportional correlation was found between VAS values (for muscle and joint pain)

(r = 0.867, p < 0.001). The intensity of pain (VAS – muscle and joint) and the degree of anxiety and depression (SAS and SDS) show a strong directly proportional correlation dependence (VASm and SDS r = 0.666, p < 0.001; VASm and SDS r = 0.644, p < 0.001; VASa and SDS r = 0.698, p < 0.001; VASa and SAS r = 0.680, p < 0.001 respectively)

The equations found for the relationship between the scales are:

- VASm = -38.36 + 1.04* SDS + 0.68 SAS
- VASa = -42.50 +1.02*SDS + 0.77*SAS

The value of the adjusted coefficients of determination (adjusted R2) of joint and muscle pain are 0.51 and 0.45. Therefore, 51% of the changes in joint pain and 45% of the changes in muscle pain can be explained by the degree of anxiety and depression of the COVID-19 patients (Tabl. 2).

On the other hand, no correlation was found between the level of inflammation indicators, thrombogenic markers and the two studied pain phenomena – arthralgias and myalgias (Tabl. 3).

These indicators determine only about 2% of the variation of muscle pain (adjusted R square 0.018) and about 1% of the variation of joint pain (adjusted R square 0.011) (Tabl. 4).

Table 1. Clinico-demographic characteristics of the patients

Indicator	Patients with COVID – 19 and musculoskeletal pain (n = 226)	P value
Age years (mean, min-max)	65.6 (26-91 yrs.)	
Patients over 60 years (n, %)	143 (63.27)	< 0,05
Gender – female (n,%)	105 (46.5)	> 0,05
EST (3-37 mm/h) (mean ± SD)	78.26 ± 30.24	< 0,05
CRP (0-5.0 mg/l) (mean ± SD)	96.09 ± 78.95	< 0,001
Fibrinogen (2.38 - 4.98 g/L) (mean ± SD)	7.45 ± 26.32	< 0,001
Ferritin (females 13-150 ng/mL, males 30-400 ng/mL) (mean ± SD)	1129.12 ± 2474.59	< 0,001
Lactate dehydrogenase, LDH (150-480 U/l) (mean ± SD)	683.56 ± 512.36	< 0,001
D-dimer (< 0.5 mcg/mL) (mean ± SD)	6.97 ± 85.31	< 0.001
VASm (mm, mean ± SD)	44.06 ± 27.84	
VASm – female (n = 105)	49.52 ± 27.16	p < 0.001
VASm –male (n = 121)	39.32 ± 28.32	
VASa (mm, mean ± SD)	43.23 ± 28.19	
VASa – female (n = 105)	48.53 ± 27.29	p < 0,001
VASa – male (n = 121)	38.62 ± 27.59	
SDS (range 20-80) (mean ± SD)	49.52 ± 11.96	
SAS (range 20-80) mean ± SD)	45.22 ± 10.58	

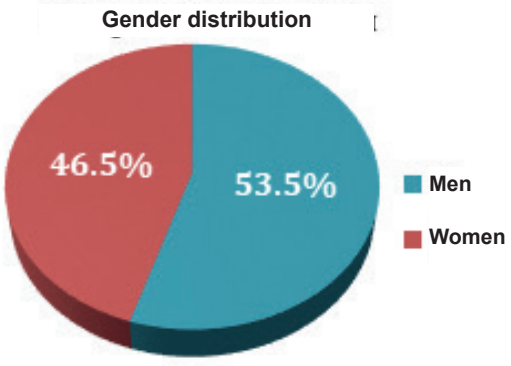

Fig. 1. Gender distribution of the patients

Table 2. Predictive value of depression and anxiety for musculoskeletal pain

Joint pain (VAS 100 mm)				
Model	R	R Square	Adjusted R Square	Std. Error of the estimate
1	.712	.508	.508	19.62
a. Predictors (constants), SAS Sum, SDS Sum				
Muscule pain (VAS 100 mm)				
Model	R	R Square	Adjusted R Square	Std. Error of the estimate
1	.678	.459	.454	20.82
a. Predictors (constants), SAS Sum, SDS Sum				

Table 3. Inflammatory indicators and thrombogenic biomarkers and musculoskeletal pain in COVID-19 patients

Joint pain					
Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	40.290	3.551		11.346	.000
CRP	.046	.0.26	.130	1.805	.072
Fibrinogen	-.092	.068	-.090	-1.361	.175
Ferritin	.001	.001	.062	.880	.380
Lactate dehydrogenase	-.002	.004	-.042	-.598	.550
D-dimer	-.024	.022	-0.76	-1.113	.267
Dependent Variable: Joint pain					
Muscle pain					
Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	39.214	3.584		10.941	.000
CRP	.055	.026	.152	2.120	.035
Fibrinogen	-.099	.068	-.096	-1.447	.149
Ferritin	.001	.001	.046	.661	.509
Lactate dehydrogenase	.000	.004	-.006	-.093	.926
D-dimer	-.021	.022	-0.66	-.972	.332
Dependent Variable: Muscle pain					

Table 4. Predictive value of inflammation and thrombogenic biomarkers on musculoskeletal pain

Muscule pain (VAS 100 mm)				
Model	R	R Square	Adjusted R Square	Std. Error of the estimate
1	.198	.039	.018	27.94
a. Predictors (constants), D-dimer, LDH, Fibrinogen, CRP, ferritin				
Joint pain (VAS 100 mm)				
Model	R	R Square	Adjusted R Square	Std. Error of the estimate
1	.181	.033	.011	27.6877
a. Predictors (constants), D-dimer, LDH, fibrinogen, CRP, ferritin				

Discussion

Musculoskeletal pain symptoms are the most frequent clinical manifestations of COVID-19. They can be observed as an individual manifestation of the disease or in the context of symptoms from other organs and systems. They are often one of the first manifestations of the disease. Pain is the overall result of complex biochemical processes and is influenced to varying degrees by biological, physiological and social factors. The perception of pain is not always proportional to the intensity of tissue damage or the unwanted stimulus.

The results of this study clearly show that patients with moderate to severe COVID-19 experience joint and muscle pain. The established strength of muscle and joint pain, through average VAS values, is significantly above the generally accepted norm of up to 4 mm and can be defined as „mild" pain. Musculoskeletal pain in patients with COVID-19 is largely determined by the psycho-emotional attitudes of the patients, as the degree of anxiety (anxiety) and depression directly and significantly correlate with the intensity of the pain. The combination of the two indicators – anxiety and depression, largely determine the variation of muscle-joint pain, respectively 50.8% of the joint pain and 45.9% of the variation of muscle pain. These results are similar to previous research on the influence of mood disorders on pain intensity [15, 16, 17].

On the other hand, the degree of systemic inflammation is not always a reliable marker of pain symptom severity in patients with musculoskeletal involvement in COVID-19. Our results also show no association between the level of acute phase indicators and the severity of musculoskeletal pain in patients with moderate or severe COVID-19.

Another important factor influencing the perception of pain is the age of the patients [18]. It is known that with aging, the risk of depression and anxiety increases, which leads to a decrease in the pain threshold and changes its perception [19]. When interpreting the results obtained by us, it is necessary to take into account that patients over the age of 60 represent a significantly larger proportion than the younger patients in the studied group (63.3%). This fact alone could explain the higher level of anxiety and depression, even without the presence of the COVID-19 disease.

An important factor is also the gender difference, which has an impact both on the perception and severity of pain, as well as on the effect of the ongoing therapy with analgesic medications [20, 21, 22]. Sex hormones and the distribution of their receptors in peripheral and central nervous system areas involved in nociceptive transmission influence patients' sensitivity to pain, with women's pain threshold and pain tolerance varying with estrogen levels and stage of the menstrual cycle. In women, there is increased sensitivity to the majority of pain modalities (including skeletal) during the luteal phase of the menstrual cycle, relative to the follicular phase [23]. Brain imaging studies have been performed that show differences between men and women in the spatial pattern and intensity of the acute pain response [24]. The female sex hormones estradiol and progesterone exert a dual effect (pronociceptive and antinociceptive) on pain sensitivity [25], while the male sex hormone testosterone is more antinociceptive in nature [26, 27]. Decreased androgen concentrations are associated with the presence of chronic pain [28], with women more likely to report pain and also more likely to suffer from chronic pain [29, 30].

Although no gender predominance was found in the study group of COVID 19 patients, women reported significantly more pain than men. A significant difference was found between the mean values of VASm and VASa in males and females (10.2 mm and 9.9 mm, respectively).

At this stage, the data on whether women or men are more sensitive to pain, i.e., whether there is a difference in the interpretation of pain intensity, remain controversial. A meta-analysis of medical records of > 11,000 patients who reported new-onset pain indicated that women rated their pain higher than men [31].

An additional factor that affects the perception and experience of pain is fear and stress [32]. Fear is a predictor that increases the occurrence and intensity of pain in predisposed individuals and its correlation is higher for acute pain [33, 34]. Fear and stress can be discussed as factors in COVID-19 patients, especially those with moderate to severe disease. We could discuss the role of COVID-19 as a disease with a high mortality rate (about 3.4%), leading to possible complications, which may cause fear in patients of a potential adverse outcome. This, in turn, could be related to the pronounced pain symptomatology in them and have an effect on the intensity of the pain.

The study has its flaws. Data on co-morbidities of COVID 19 in the study population were not analyzed. They could influence both the intensity of the pain and the psycho-emotional status of the patients. Another shortcoming that we report is that the predictive value of gender and age and their influence

on both the level of depression and anxiety and the intensity of musculoskeletal pain in these patients have not been investigated. Also, the study was only conducted among patients with COVID-19, which is also a shortcoming. In order to establish the significance of this disease for the associations found, it is planned to deepen the study by making the same interrelationships in a control group. This will differentiate the importance of COVID-19 for anxiety and depression, and from there for pain. All these weaknesses of the current scientific work give grounds for future scientific research that would illuminate in greater depth and give greater clarity about the role of the psycho-emotional state and the feeling of pain, as well as various other factors (age, gender, accompanying diseases, etc.).

Conclusion

Musculoskeletal pain is one of the most common clinical manifestations of COVID-19 patients. The intensity of joint-muscle pain in them is associated with the degree of manifestation of anxiety and depressive symptoms, and not with the values of acute-phase indicators of inflammation and thrombotic biomarkers. A beneficial impact on the musculoskeletal manifestations of patients with COVID-19 can be achieved by a multidisciplinary team including a rheumatologist and a psychiatrist.

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