Original Article

COVID-19-Related Neurological and Musculoskeletal Pain Symptoms- A Cross-Sectional Study

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Abstract

Background: The neurological and musculoskeletal pain symptoms should be taken seriously when dealing with the acute phase of COVID-19 patients. This study aims to explore the neurological and musculoskeletal pain symptoms among confirmed COVID-19 patients.

Methods: A cross-sectional study was conducted from 1st July to 30th August at the Baquba teaching hospital, Diyala province, Iraq. Medical records of one hundred and twenty-three hospitalized COVID-19 patients have been investigated for neurological and musculoskeletal pain symptoms. Descriptive, bivariate, and multiple logistic regression were performed to predict the prevalence of pain symptoms. SPSS version 16 was recruited to analyze the data, and the statistically significant was considered at less than 0.05.

Results: The mean age of respondents was 46.38 (+ 12.37). Most of the patients were males (60.2%), with mild severity of COVID-19 (59.3%), had not been vaccinated yet (78.0%), tobacco smokers (38.2%), and had a history of DM (43.3%) and HT (25.4%), respectively. More than half of patients (66, 53.7%) developed at least one pain symptom after confirming the diagnosis of COVID-19 infection. The highest Prevalence of pain symptoms was headache (43.9%), neuropathic pain (34.8%), generalized myalgia (31.8%), polyarthralgia (25.7%), and low back pain (22.7%). In multiple logistic regression, the patients aged 50 years and above (odds ratio (OR) = 10.577, 95% CI: 2.867 to 9.029, P <0.001), males (OR = 3.769, 95% CI: 2.826 to 8.593, P=0.027), presence of comorbidities (OR = 6.407, 95% CI: 1.820 to 3.557, P = 0.004), the severity of COVID-19 (moderate to severe) (OR = 10.229, 95% CI: 2.450 to 6.714, P=0.001), and tobacco smoking (OR = 4.225, 95% CI: 1.160 to 5.390, P=0.029), were significantly associated with the presence of neurological and musculoskeletal pain symptoms (p < 0.001).

Conclusion: Much evidence suggests the emergence of neuropathic and musculoskeletal pain symptoms in the acute phase of COVID-19 infection. Therefore, priority should be given to such symptoms when clinicians tried to diagnose COVID-19 patients.

Keywords: COVID-19, Myalgia, Arthralgia, Neuropathic, Pain Symptoms, Prevalence, Iraq.

INTRODUCTION

The World Health Organization (WHO) announced that the COVID-19 epidemic had turned into a pandemic in March 2020 [1]. The world struggles to address successive waves that carry several variants of the coronavirus SARS-CoV-2 [2]. The pandemic quickly penetrated the borders to reach most of the world's countries. The global health system was shocked by a simultaneously tremendous increase in morbidity and mortality rates [3]. Non-specific pathological symptoms start from the 2-14 days after contracting COVID-19 infection. Clinically, the condition might dramatically progress from mild or moderate symptoms including "fever, dry cough, headache, shortness of breath, muscle and joint pains, temporary loss of smell and taste" to be more severe and even fatal respiratory tract infection [4]. Since the emergence of the SARS-CoV-2 pandemic at the end of 2019, much evidence has increasingly confirmed various painful symptoms during and after COVID-19 infection. The Covid-19 - related neurological, muscular, and skeletal symptoms were among the interests of researchers worldwide intending to reduce the risk of illness [5-18]. The most common experienced muscle pain is skeletal muscle or musculoskeletal pain when the level of "serum creatinine kinase" exceeds 200 U/L [14].

Additionally, the immune system and the inflammatory process may be indirectly encouraging the development of myalgia and arthralgia [15]. Joint discomfort, or arthralgia, has been listed among the early signs of COVID-19 infection in various investigations [16]. Muscle discomfort and arthralgia have frequently been observed combined, especially in moderate and severe cases. When multiple joints are affected at once, the condition is known as polyarthralgia. Patients with Covid-19 frequently experience inexplicable headaches following the onset of infection. The COVID-19 virus' direct infiltration and

subsequent injury to the central nervous system, including the trigeminal nerve at the nose and oral cavities, leading to headaches, is the most popular idea for cause of headaches [17,18]. Several investigations were undertaken in the Republic of Iraq to evaluate the general public's and healthcare professionals' knowledge, attitudes, and practices about COVID-19 and immunization [19–21]. The discussion of the neurological and musculoskeletal pain symptoms, however, has received little attention. Between February and March 2020, Kuser et al. [22] attempted to characterize the neurological symptoms of 177 verified Covid-19 patients in Iraq. According to the researchers, 36.40% of patients experienced brain injuries, and 19.30% suffered musculoskeletal ones. Furthermore, 45.50% of the patients who were in critical condition had neurologic symptoms. In this study, a sample of the Iraqi population was examined for neurological and musculoskeletal pain complaints linked to COVID-19.

Methods

Study design and sampling

A prospective cross-sectional study was conducted at the Baquba Teaching Hospital, Diyala province, Iraq. The data were collected from hospitalized patients from 1st July to 10th August 2022.

Inclusion and exclusion criteria

All confirmed cases of SARS-COV-2, aged 18 years and above, of both genders, who signed the consent form and are willing to participate, are included in the study. The known cases of chronic pain disorders other than COVID-19 or concurrent comorbidities that significantly inhibit participation, psychiatric illness, unconsciousness, and unwillingness to participate were excluded from the study. Regardless of clinical signs and symptoms, Real-time reverse transcription–polymerase chain reaction (RT-PCR) has been adopted to confirm the COVID-19 infection.

Sample size

Based on the 61.5% prevalence rate reported by Jena et al. [23], 95% confidence level, and a 7% margin of error, the minimum sample size recorded by the online “Raosoft” sample size calculator [24] was 184 + 18 (10% non-response) =202.

Data Collection

Medical records pertaining to patients have all been carefully reviewed. Age, gender, height, weight, COVID-19 severity, cigarette use, and concurrent comorbidities data have all been reported. The severity of confirmed COVID-19 infections has been categorized into "mild, moderate, or severe" according to WHO criteria [25]. After learning that their COVID-19 test results were positive, the patients' musculoskeletal (MSK) and neurological pain complaints have been documented. The place, intensity, and nature of the pain were decided by the researcher. The central and peripheral nerve systems' manifestations have each been evaluated individually. To validate the presence of neuropathic pain, the reliable Arabic DN4 Questionnaire (Douleur Neuropathique 4 Questions) has been used [26]. To rate headaches and MSK pain, the reliable Arabic version of the Numeric Rating Scale (NRS) was used. The NRS is a well-known "zero to 10 scale" that rates the intensity of pain. When there is no pain, the patient has a score of 0, and a score of 10 indicates that the patient is in the most discomfort. The patient who participated in our study and had two or more scores has been included [27]. Depending on where the pain existed, it was divided into anatomical categories. Because most patients have trouble describing the shoulder and neck separately, we treated them as a single unit. Some people may experience widespread muscular pain and pains (generalized myalgia), whereas others may experience joint pain (polyarthralgia).

Dependent variable

In this study, the dependent variable was the "presence of pain symptoms or not", depending on the patient's answer to the question, "Have you experienced musculoskeletal or neurological pain after diagnosis of COVID-19?"

Independent variables

The age of respondents was categorized into two age groups: "<50" or " > 50", and. The gender was either "Male" or "Female". The severity of COVID-19 was categorized as "Mild" or "Moderate to Sever". The received COVID-19 vaccination was categorized as “Vaccinated)” for those who received at least one dose and "None" for those who did not receive any dose yet. The history of chronic diseases (comorbidities) and (tobacco smoking) was categorized as "present" or "absent ." The Body Mass Index (BMI) was calculated by dividing the weight (kg) by the square of height (m2). BMI was categorized into “Normal” or “Overweight and Obese”.

Ethics approval and consent to participate

We conducted the research following the Declaration of Helsinki. Ethical permission was granted by the Ethics Committee of the Faculty of Medicine, University of Diyala, Iraq (Ref No.09222103069 /1445/2022/June/07) on 28th June 2022. All patients

gave written informed consent.

Statistical analysis

The mean ± standard deviation (SD) and numbers and percentages were used to describe the continuous and categorical variables. In multivariate analysis, we recruited the binary logistic regression to find out the predictor variables of pain symptoms that emerged after confirming the diagnosis of the COVID-19 infection. The Statistical analysis was performed using SPSS 16.0 software. p-value < 0.05 was considered statistically significant.

Results

The data of 123 in-ward COVID-19 patients were examined in this study. The mean age was 46.38 (+ 12.37) in the range of 25-69 years and mostly aged less than 50 years old (70, 56.9%). Most of the respondents were males (60.2%), overweight (37.4), mild severity of COVID-19 (59.3%), had not been vaccinated yet (78.0%), tobacco smokers (38.2%), and had a history of DM (43.3%) and HT (25.4%), respectively.

Tables 1: Demographic and clinical characteristics of patients (N = 123)

Variable	**Categories**	**N (%)**
Age	Mean ($\pm$ SD)	46.38 ($\pm$ 12.37)
	< 50	70 (56.9)
	$\geq$ 50	53 (43.1)
Gender	Female	49 (39.8)
	Male	74 (60.2)
BMI (kg/m^2)	Normal (18.5 – 25 kg/m^2)	69 (56.1)
	Overweight (25 – 30 kg/m^2)	77 (37.4)
	Obese (> 30 kg/m^2)	8 (6.5)
Severity	Mild	73 (59.3)
	Moderate	43 (35.0)
	Severe	7 (5.7)
COVID-19 vaccination	None	96 (78.0)
	Vaccinated -one dose	21 (17.1)
	Vaccinated -two doses and more	6 (4.9)
Tobacco smoking	None	76 (61.8)
	Yes	47 (38.2)
Comorbidities	None	56 (45.5)
	Yes	67 (54.5)
	Diabetes mellitus	29 (43.3)
	High blood pressure	17(25.4)
	Ischemic heart diseases	9 (13.4)
	Chronic lung diseases	7(10.4)
	Immune suppressing diseases	3(4.5)
	Others	2(3.0)

Prevalence of pain symptoms

Out of the total respondents, 66 (53.7%) declared that they developed at least one pain symptom just after confirming the diagnosis of COVID-19 infection compared to 57 (46.3%) who had no pain symptoms. The highest Prevalence of pain symptoms was headache (29, 43.9%), neuropathic pain (23, 34.8%), generalized myalgia (21, 31.8%), polyarthralgia (17, 25.7%), and low back pain (15, 22.7%).

Table 2. Distribution of pain and associated symptoms among the participants (N = 123)

Pain symptoms	Categories	N (%)
No pain symptoms	-	57 (46.3)
Pain symptoms	-	66(53.7)
Neurological pain symptoms (n=66)	Headache	29 (43.9)
	Neuropathic pain	23(34.8)
	a. Lower limbs	9 (39.1)
	b. Upper limbs	12 (52.2)
	c. Diffuse	2 (8.7)
Musculoskeletal pain symptoms (n=66)	Generalized myalgia	21 (31.8)
	Polyarthralgia	17 (25.7)
	Low back pain	15 (22.7)
	Neck/shoulder pain	13 (19.7)
	Leg pain	11 (16.6)
	Knee pain	9 (13.6)
	Hand pain	8 (12.1)
	Foot pain	8 (12.1)

Factors associated with neurological and musculoskeletal pain symptoms in multiple logistic regression

Multiple logistic regression was performed to predict neurological and musculoskeletal pain symptoms after the diagnosis of COVID-19 (Table 3). The patients aged 50 years and above (odds ratio (OR) = 10.577, 95% CI: 2.867 to 9.029, P <0.001), male (OR = 3.769, 95% CI: 2.826 to 8.593, P=0.027), presence of comorbidities (OR = 6.407, 95% CI: 1.820 to 3.557, P = 0.004), the severity of COVID-19 (moderate to severe) (OR = 10.229, 95% CI: 2.450 to 6.714, P=0.001), and history of tobacco smoking (OR = 4.225, 95% CI: 1.160 to 5.390, P=0.029), were associated significantly with the presence of neurological and musculoskeletal pain symptoms ($p < 0.0001$). The Hosmer and Lemeshow test indicated a good fit ($p = 0.431$). The total model was significant ($p = 0.001$) and accounted for 70.6% of the variance (Nagelkerke R square = 0.706).

Table 3. Factors associated with neurological and musculoskeletal pain symptoms in multiple logistic regression

Variables	B	S.E.	Wald	Sig.	Exp(B)	95.0% C.I. for Exp(B) Lower-Upper
≥ 50 years	2.359	0.666	12.538	<0.001	10.577	2.867-9.029
< 50 years					Reference	
Male	1.327	0.599	4.899	0.027	3.769	2.826-8.593
Female					Reference	
Comorbidities (Yes)	1.827	0.642	8.366	0.004	6.407	1.820-3.557
Comorbidities (No)					Reference	

Severity (Moderate to severe)	2.3.25	0.729	10.167	0.001	10.229	2.450-6.714
Severity (Mild)					Reference	
Smoking (Yes)	1.441	0.660	4.774	0.029	4.225	1.160-5.390
Smoking (No)					Reference	
Constant	4.435	0.863	6.432	0.000	0.012	-

Discussion

In this study more than half of the patients (66, 53.7%) developed "neurological and musculoskeletal pain symptoms" in the form of headache (43.9%), generalized myalgia (31.8%), and polyarthralgia (25.7%). Demirel et al. [28] reported that among 154 COVID-19 hospitalized Turkish patients, 71.4% developed myalgia (71.4%) and 55.8% arthralgia, respectively. Similarly, Jena et al. [23] reported pain symptoms among 61.5% of COVID-19 patients. The authors found that about 33.0% of patients developed generalized myalgia, 27.5% had a headache, and 22.5% had low back pain. Knox N et al. [9] reported active pain among 38.5% of patients. Authors found that 30.1% of patients complained from headache, 24.7% (spinal pain), 17.8% (myalgia), 15.1% (arthralgia), and 12.3% (generalized pain), respectively. In their systematic review and meta-analysis, Abdullahi et al. [10] reported a 12.0% prevalence rate for headaches, 19.0 % for myalgia, and 10.0% for back pain. Two meta-analysis studies conducted in 2020 by Nascimento et al. [11], and Zhu et al. [12], reported muscle pain in 36.0% and 21.9% of COVID-19 patients, respectively. Unlike in several previously published articles, the Prevalence of headache in our study was higher than that reported by Divella et al. [5] (1.7–33.9%), Abdullahi et al. [10] (12.0%), and Jena et al. [23] (27.5%). The incidence rates were different depending on the category of pain, location of pain (sore throat, myalgia, arthralgia, headache, chest pain, and abdominal pain), the severity of infection, long-standing disease, patients-related memory bias, demographic characteristics, and the stages of COVID-19 pandemic development such as emerging of new variants [6-8]. For example, Şahin et al. [13] found that the prevalence of pain symptoms rose to 82.5% after the diagnosis of COVID-19 infection compare to 40.7% just before the infection.

In multiple logistic regression, older patients (> 50) were 10.577 times more likely to have neurological and musculoskeletal pain than younger people. Persistent and multisite musculoskeletal pain affects the healthy lives of more than half of older adults [Redfield RR] [29]. Older people suffer more health problems than young people. The immune system's weakness made them more vulnerable to COVID-19 infection [Gómez-Belda AB] [30]. Therefore, the quarantine during the pandemic exacerbated the already known social, psychological, and physical health problems, including physical inactivity [Ali Jadoo SA] [31]. Patients presented with the severity of COVID-19 (moderate to severe) were 10.229 times to complain of neurological and musculoskeletal pain symptoms than those in mild cases. Similarly, Mao et al. [Mao L] [32] found that the more severe Covid-19 infection had neurologic manifestations and skeletal muscle injury. The storm of cytokines is associated with the severity of the disease and the emergence of pain during the acute phase of Covid-19 infection. Unlike the fact that old age females are more prone to develop musculoskeletal health problems than males, our findings showed that males were 3.769 times more likely to have neurological and musculoskeletal disorders than females. Moreover, Kirmizi et al. [33] concluded that during the COVID-19 pandemic, female patients had more musculoskeletal symptoms than males. Generally, the Prevalence of COVID-19 infection among the male population is higher than in females. The pain tolerance among females was frequently reported to be lower than their counterparts [34]. However, the efficient immune system among females and the angiotensin-converting enzyme 2 (ACE-2) location on x- chromosomes enhance females' protective role [35,36] and might explain the gender difference. Patients who presented with comorbidities were 6.407 times like to have neurological and musculoskeletal than others. Chronic diseases, especially diabetes mellitus, as in this study, are often accompanied by neuromusculoskeletal sequelae. COVID-19 infection attacks multiple organs, including the immune system. Therefore, the patients with non-communicable were vulnerable to unwanted consequences [37]. Tobacco smokers were 4.225 times more likely to develop neurological and musculoskeletal than none- smokers. Clift et al. [38] reported that the higher the number of cigarettes smoked, the higher the risk of infection, hospitalization, and death, indicating the causal effect of smoking on the severity of Covid-19 infection. Moreover, Tarakji et al. [39] indicated that the effect of cigarette smoking on the musculoskeletal system is evident. Smoking decreases tissue oxygenation and causes harmful effects on bone metabolism [40]. Postmenopausal smoking has been proven to exacerbate the development of osteoporosis [41]. Although BMI and the COVID-19 vaccination status were not statistically significant in multivariate analysis, much evidence suggests their indirect effect on neurological and musculoskeletal pain symptoms. Gao et al. [42] found that patients with BMI > 23 kg/m2 had a higher risk for severe COVID-19, higher admission, and mortality rate. Notarte et al. [43], in their systematic review, assured the role of vaccination

in reducing the risk of COVID-19 infection, suggesting a higher possibility of minimizing the long-COVID symptoms when the received vaccination exceeded one dose. In addition to the cross-sectional design, which does not allow for causative, our study complained of other limitations. Our study is not generalizable because it is conducted in one tertiary hospital. Also, we investigated only confirmed and admitted patients to the government sector; however, many patients contacting the private sector are out of our research. Furthermore, we could not confirm the possible exacerbating or calming effect on pain symptoms of some medications used to treat COVID-19.

Conclusion

In conclusion, the Prevalence of neurological and musculoskeletal pain symptoms was 53.7%. The symptom of headache topped the list (43.9%), followed by neuropathic pain (34.8%), generalized myalgia (31.8%), and polyarthralgia (25.7%), respectively. The male patients aged fifty years or older with comorbidities, moderate to severe covid-19 infection, and tobacco smokers were significantly associated with the emergence of at least one neurological and musculoskeletal pain symptom. The results of this study can direct physicians and healthcare providers to put neurological and musculoskeletal pain symptoms within the diagnostic priorities when searching for the suspected Covid-19 infection.

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