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Prevalence and risk factors of musculoskeletal pain symptoms as long-term post-COVID sequelae in hospitalized COVID-19 survivors: a multicenter study

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This study investigated the prevalence of long-term musculoskeletal post-COVID pain and their risk factors in a large cohort of COVID-19 survivors. A multicenter cohort study including patients hospitalised due to COVID-19 in five hospitals of Madrid (Spain) during the first wave of the pandemic was conducted. Hospitalisation and clinical data were collected from medical records. Patients were scheduled for a telephone interview after hospital discharge for collecting data about the musculoskeletal post-COVID pain. Anxiety/depressive levels and sleep quality were likewise assessed. From 2,000 patients recruited, a total of 1,969 (46.4% women, age: 61, SD: 16 years) were assessed on average at 8.4 (SD 1.5) months after discharge. At the time of the study, 887 (45% women) reported musculoskeletal post-COVID pain. According to the presence of previous pain symptoms, the prevalence of "de novo" (new-onset) musculoskeletal post-COVID pain was 74.9%, whereas 25.1% experienced an increase of previous symptoms (exacerbated COVID-related pain). Female gender (OR1.349, 95%CI 1.059-1.720), previous history of musculoskeletal pain (OR1.553,

95%CI 1.271-1.898), the presence of myalgia (OR1.546, 95%CI 1.155-2.070) and headache (1.866, 95%CI 1.349-2.580) as COVID-19 associated onset symptoms, and days at hospital (OR1.013, 95%CI 1.004-1.022) were risk factors associated musculoskeletal post-COVID pain. In conclusion, musculoskeletal post-COVID pain is present in 45.1% of COVID-19 survivors at eight months after hospital discharge with most patients developing "de novo" post-COVID pain. Female gender, history of musculoskeletal pain, presence of myalgias and headache as COVID-19 symptoms at the acute phase, and days at hospital were risk factors associated with musculoskeletal post-COVID pain.

Key words: COVID-19, musculoskeletal pain, post-COVID, risk factors, prevalence.

Introduction

Clinical manifestation of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) are heterogeneous and affect respiratory, gastrointestinal, cardiovascular, neurological, or musculoskeletal systems [46]. Generalized pain (myalgia) is a common symptom suffered by patients with the coronavirus 2, 2019 disease (COVID-19) during the acute phase with an estimated prevalence ranging from 15% to 20% [1,14,45]. The potential implications of musculoskeletal pain symptoms associated with COVID-19 are not properly understood and suggests a heterogeneous physiological process [31].

Due to the worldwide COVID-19 outbreak, the incidence of musculoskeletal pain would be expected to raise by three different ways: 1) by increasing the number of people developing de novo musculoskeletal pain as a post-COVID sequelae; 2) by exacerbating pain in infected individuals with pre-existing conditions; and also, 3) by increasing pain symptoms in non-infected people with musculoskeletal pain conditions

due to COVID-19 surrounding factors (e.g., lockdown, isolation, or stress) [15]. In fact, current literature supports that patients with chronic pain (but not infected) reported an increase of their symptoms and their pain interference during the main lockdown [18,28,33]. Additionally, female gender, people with lower education, worse disability and higher catastrophizing have shown to be at a higher risk of social isolation during COVID-19 outbreak [25].

Data about the first two assumptions is less clear to date. Different meta-analyses reported that almost 60% of COVID-19 survivors will develop post-COVID symptoms (i.e., long COVID) in the following months after the infection [3,10,30]. Although these texts described the presence of several post-COVID symptoms, specific data on pain is scarce [3,10,30]. One meta-analysis focusing just on musculoskeletal post-COVID pain symptoms identified 33 studies [19]. These authors found that most studies investigated follow-up periods between one and four months after infection [19]. A remarkable finding of this meta-analysis was that, despite including 33 papers investigating post-COVID pain, large epidemiological studies specifically focusing on post-COVID pain symptoms are missing [5,19].

Alizadeh and Aghsaeifard described eight patients with previous history of chronic pain where COVID-19 triggered their previous pain symptoms [4]. Two small cohort studies reported that the prevalence of musculoskeletal pain can reach up to 60.7% in COVID-19 survivors one month after infection [7,27]. However, both studies included small sample sizes, did not differentiate if pain symptoms were present before the infection or not, and included short-term follow-up periods [7,27]. Soares et al observed that almost 65.2% of COVID-19 survivors developed “de novo” post-COVID pain symptoms [44]. Again, this study included a small sample of patients, just recruited from a single center, and included a follow-up period less than three months after [44].

The current multicenter study includes a large cohort of previously hospitalized COVID-19 survivors with a long-term follow-up period. The aims of the current study were: 1) to investigate the prevalence of musculoskeletal post-COVID pain symptoms in a large cohort of hospitalized COVID-19 survivors; 2) to determine if musculoskeletal post-COVID pain is a new-onset ("de novo") or an exacerbated symptom of pre-existing musculoskeletal pain conditions; 3) to investigate potential risk factors associated with the development of musculoskeletal post-COVID pain.

Methods

Participants

This multicenter cohort study included individuals who had recovered from acute SARS-CoV-2 infection during the first wave of the pandemic (from March 20 to June 30, 2020) from five urban hospitals in Madrid (Spain). Participants were hospitalized because SARS-CoV-2 infection diagnosed with real-time reverse transcription-polymerase chain reaction (PCR) assay of nasopharyngeal/oral swab samples and the presence of consistent clinical and radiological findings. All hospitalized COVID-19 survivors discharged from the participating hospitals (n=7,150) during the first wave of the pandemic were included in an anonymous database and a random selection of 400 patients from each hospital was performed with an online randomization software. The study was approved by all Local Ethic Committees (URJC0907202015920, HCSC20/495E, HUFA20/126, HUIL/092-20, HSO25112020, HUF/EC1517). Participants were informed of the study and all provided informed consent before their inclusion and before collecting any data.

Procedure

Clinical data (age, gender, height, weight, COVID-19 associated symptoms at hospital admission, pre-existing medical comorbidities, intensive care unit [ICU] admission, days at hospital) were collected from hospital records. Participants who agreed to participate in the current study were scheduled for a telephone semi-structured interview by trained healthcare researchers. A questionnaire focusing on musculoskeletal pain symptoms was developed by a multidisciplinary research team. Participants were asked for the presence of pain symptoms appearing after hospital discharge and whether the reported symptoms persisted at the time of the study. Particular attention was paid to the development of musculoskeletal post-COVID pain symptoms differentiating from headache, particularly migraine-like pain. We defined musculoskeletal post-COVID pain as: 1) pain symptoms compatible with diagnosis of chronic primary musculoskeletal pain, as defined by the International Association for the Study of Pain (IASP) [39]; 2) symptoms experienced for at least three consecutive months after hospital discharge, and 3) absence of any underlying medical condition which could best explain pain, e.g., arthritis. Finally, participants were asked to describe the location of their pain symptoms (e.g., neck, shoulder, spine, lower extremity, upper extremity, generalized) and to differentiate these symptoms from any pain condition that they suffered from before being infected by SARS-CoV-2. We did not include headache symptoms, due to the particular classification of headaches and need for a proper diagnosis according to the classification.

Anxiety/depressive symptoms and sleep quality were assessed with the Hospital Anxiety and Depression Scale (HADS) and the Pittsburgh Sleep Quality Index (PSQI), respectively, since both can be properly evaluated by telephone interview [22]. From HADS, we included the scale assessing anxiety symptoms (HADS-A, 7-items, 0-21 points) and the scale assessing depressive symptoms (HADS-D, 7-items, 0-21 points).

Higher scores suggest more anxiety/depressive levels, with a cut-off of score >8 points being suggestive of anxiety/depressive disorder [23]. In the current study, we considered the cut-off scores recommended for Spanish population (HADS-A ≥12 points; HADS-D ≥10 points) indicative of anxiety and depressive symptoms, respectively [21]. The PSQI (0-21 points) evaluates sleep quality by including 19 self-rated questions assessing different aspects of sleep during the previous month [8]. Higher scores indicate worse sleep quality, and a score ≥8.0 points is indicative of poor sleep [8]. The PSQI has shown good internal consistency and test-retest reliability [11].

Statistical Analysis

The STATA 16.1 program (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP. USA) was used for consolidation of the multicenter records. Data are presented as means (standard deviation, SD) and/or percentages as appropriate. McNemar's chi-squared test and paired Student t-tests were conducted to compare proportions and means between patients with and without musculoskeletal post-COVID pain. Missing values were imputed using median imputation due to their small numbers. Univariate and multivariate logistic regressions were conducted to identify the association of the development of musculoskeletal post-COVID pain with COVID-19 associated variables collected at hospital admission (age, gender, height, weight, COVID-19 onset symptoms at hospital admission, pre-existing medical comorbidities, intensive care unit [ICU] admission, days at hospital) by using Python's library statsmodels 0.11.1. Adjusted odds ratio (OR) and confidence intervals (95%CI) were calculated. A priori, the level of significance was set at 0.05.

Results

From 2,000 participants randomly selected from the involved hospitals and invited to participate, six refused to participate, eleven could not be contacted after three attempts, and 14 had deceased after hospital discharge. Finally, a total of 1,969 (46.4% women, age: 61, SD: 16 years) were included.

Prevalence of Post-COVID Musculoskeletal Pain

Participants were assessed from 6 to 10 (mean: 8.4, SD 1.5) months after hospital discharge. At the time of the evaluation, 887 (45.1%) patients reported musculoskeletal post-COVID pain symptoms. The main locations of musculoskeletal post-COVID pain are illustrated in **Figure 1**, being widespread and lower extremity pain the most prevalent.

Table 1 compares clinical and hospitalization data between individuals developing and not developing musculoskeletal post-COVID pain symptoms. Individuals reporting musculoskeletal post-COVID pain showed a greater number of COVID-19 symptoms at hospital admission, with a greater prevalence of myalgias and headache (both, $P<0.001$); longer stay of hospitalization, and higher incidence of ICU admission than those not reporting long-term musculoskeletal post-COVID pain. Individuals with musculoskeletal post-COVID pain also exhibited higher anxiety and depression scores and poor sleep quality ($P<0.001$, **Table 1**).

New-Onset (de novo) or Exacerbated Musculoskeletal Post-COVID Pain

The prevalence of pre-existing musculoskeletal pain symptoms before the infection was significantly higher ($P<0.001$) in those reporting musculoskeletal post-COVID pain (49.8%) than in those without post-COVID pain (33.6%). No significant differences were seen in body location of previous pain symptoms between individuals developing or not developing musculoskeletal post-COVID pain (**Figure 2**). From 887

patients reporting musculoskeletal post-COVID pain, almost 50% (n=442) reported musculoskeletal pain symptoms before infection. Accordingly, the remaining 445 (50.1%) developed new-onset musculoskeletal post-COVID related pain, since they did not suffer from symptoms before the infection. Additionally, from those 442 individuals suffering from previous symptoms, 220 (24.8%) reported that post-COVID pain symptoms were different from previous symptomatology (new-onset musculoskeletal post-COVID pain), whereas the remaining 222 (25.1%) patients experienced an increase of the previous symptoms (exacerbated musculoskeletal post-COVID related-pain) on their intensity (n=89, 40.1%), the extension (n=42, 18.9%), frequency (n=55, 24.8%) and both intensity and extension (n= 36, 16.2%): the prevalence of new-onset post-COVID musculoskeletal pain in the total sample was up to 74.9%.

Risk Factors associated with Musculoskeletal Post-COVID Pain

Table 2 details the results of univariate and multivariate analyses. The univariate analysis revealed that age (P=0.001); weight (P=0.001); ICU admission (P=0.015); the presence of several medical comorbidities, e.g., diabetes (P=0.04), cardiovascular disease (P=0.024), asthma (P=0.02), obesity (P=0.044), or chronic obstructive pulmonary disease (P=0.045); and the presence of some COVID-19 onset symptoms at hospital admission such as dyspnoea (P=0.04), cough (P=0.03), anosmia (P=0.025), or throat pain (P=0.03) were associated with musculoskeletal post-COVID pain; however, these variables were not significant in the multivariate analysis.

The multivariate analysis revealed that, after adjusting by all variables, female gender (OR 1.349, 95%CI 1.059-1.720, P=0.01), previous history of musculoskeletal pain (OR 1.553, 95%CI 1.271-1.898, P<0.001), the presence of myalgia (OR 1.546, 95%CI 1.155-2.070, P=0.003) and headache (OR 1.866, 95%CI 1.349-2.580, P<0.001) as COVID-19 associated symptoms at the acute phase, and days at hospital (OR 1.013,

95%CI 1.004-1.022, P=0.006) were associated with the presence of long-term musculoskeletal post-COVID pain symptoms.

Discussion

This multicenter study found a prevalence of musculoskeletal post-COVID pain of 45.1% eight months after hospital discharge. Based on the presence of previous symptoms the prevalence of "de novo" musculoskeletal post-COVID pain was 74.9%. Female sex, history of musculoskeletal pain, the presence of myalgia and headache as COVID-19 associated symptoms and days at hospital were risk factors.

Post-COVID Musculoskeletal Pain

We reported a prevalence of musculoskeletal post-COVID pain of 45.1% eight months after hospitalization. Our results reveal higher prevalence rate than those reported in a recent meta-analysis, which observed a prevalence of 10.9% and 7.7% for myalgias and arthralgias 6-months after hospital discharge [19]. Differences in age, gender, pre-existing comorbidities - particularly history of musculoskeletal pain (data not considered in most studies) - or severity of the disease could explain discrepancies. On the contrary, our results fall slightly below from those reported by three small cohort studies providing prevalence rates of musculoskeletal post-COVID pain up to 60% at one [7,27] and three [44] months after. Only one study considered the presence of previous musculoskeletal pain [44]. Our study is the largest multicenter study providing prevalence data of long-term musculoskeletal post-COVID pain in hospitalized survivors.

We found that widespread pain and lower extremity pain were the most common forms of musculoskeletal post-COVID pain. Soares et al [44] and Numan [37] also found that lower extremity was the most affected location. Similarly, subjects who had

survived to SARS also exhibit widespread pain as a sequela one year after [35]. Current evidence suggests that musculoskeletal post-COVID pain tend to be heterogeneous, but a tendency to widespread symptoms seems to be present. Such widespread pain symptomatology, as commonly observed in, e.g., fibromyalgia, has been suggested to be related to deficient immune regulatory mechanisms [41] and could indicate a prolonged immune system impact in post-COVID pain sufferers.

It is also possible that location of musculoskeletal post-COVID pain is related to the location of symptoms (e.g., myalgias) experienced at the acute phase. Şahin et al. seen that pain symptoms in the extremities were highly prevalent during the acute phase [42]. Pain at the acute phase of the infection may be widespread (viral-induced myalgias) and in some cases it could be the main complaint. The presence of pain at hospital admission and how early the pain begins can provide guidance on the prognosis of post-COVID pain. We did not collect the area of symptoms at hospital admission in our cohort, but this hypothesis should be explored in future studies.

De Novo or Exacerbated Musculoskeletal Post-COVID Pain

We hypothesized that the existence of musculoskeletal pain prior to COVID-19 may predispose to the development of de novo (new-onset) pain but also to an exacerbation of preexisting pain, possibly due to the cytokine storm. Our results support both hypotheses, since 49.75% (n=220/442) of patients developed “de novo” musculoskeletal post-COVID pain and 50.2% (n=222/442) experienced an increase of previous symptoms (exacerbated musculoskeletal post-COVID-related pain). In agreement with our results, Soares et al reported that 60% of COVID-19 survivors developed “de novo” post-COVID pain [44].

Risk Factors

Identification of patients at risk of developing musculoskeletal post-COVID pain is important [29]. Our study revealed that female gender, history of musculoskeletal pain, the presence of myalgia and headache as COVID-19 onset symptoms and days at hospital were risk factors associated with musculoskeletal post-COVID pain.

Female sex has been previously suggested as a risk factor for post-COVID symptoms [26]. Our study supports that females are at a higher risk of musculoskeletal post-COVID pain than males. This could be expected since musculoskeletal pain is more prevalent in females [32,34]. Another explanation can be biological gender differences on expression of angiotensin-converting enzyme-2 (ACE2) and also transmembrane protease serine 2 (TMPRSS2) receptors [9].

An important risk factor was a history of pre-existing musculoskeletal pain before the infection. Accordingly, the presence of pre-existing musculoskeletal pain should be considered into the initial screening of COVID-19 patients to avoid a confusion in the characterization of such pain. This would be highly relevant in individuals experiencing viral-induced myalgia as an onset symptom, since these patients were also more prone to develop musculoskeletal post-COVID pain symptom. This is an interesting finding, since the presence of pain at onset is associated with good prognosis for hospitalization [40], yet it is associated with musculoskeletal post-COVID pain in our study. The hypothesis that suffering myalgia as an onset symptom is a risk factor for post-COVID pain has been recently supported by a case-control study [20]. The current study increases evidence on the hypothesis that not only myalgia, but also the presence of headache at the acute phase is also a risk factor for musculoskeletal post-COVID pain. It is important to consider that these two COVID-19 pain symptoms are not considered as bothersome symptoms when compared with others, e.g., fever or

dyspnea. Accordingly, monitoring of musculoskeletal symptoms, COVID-19 associated-onset myalgia or headache, and musculoskeletal post-COVID pain would be carefully needed.

Finally, we also observed that a longer hospital stay was a risk factor, but showing a smaller influence, for musculoskeletal post-COVID pain, in agreement with a previous study [7]. It is possible that hospitalization factors such as physical inactivity or treatment received for managing the infection could promote future musculoskeletal post-COVID pain.

Underlying Mechanisms of Musculoskeletal Post-COVID Pain

Several hypotheses explaining musculoskeletal post-COVID pain are suggested. The first step would be the prolonged pro-inflammatory responses (cytokine and interleukin storms) associated to SARS-CoV-2 infection could lead to an exuberant immune response by inducing a hyper-activation of T cells, macrophages, and natural killer cells [16,36]. This response could promote different mechanisms associated with musculoskeletal pain, e.g., an atypical response of the mast cells [2] and an over-expression of ACE2 receptors [31,43]. The presence of ACE2 and TMPRSS-2 receptors is higher in the muscle [17], which would explain the development of widespread post-COVID pain. Accordingly, SARS-CoV-2 infection could trigger "nociplastic pain" by altering balance between the neuromodulation systems of nociception [12]. We hypothesize that SARS-CoV-2 cytokine/interleukin associated-storms may lead to hyper-excitability of peripheral and central nervous systems throughout different pathways and, in predisposed individuals, lead to development of new-onset musculoskeletal post-COVID pain or to a worsening of pre-existing pain symptoms.

It is also important to consider that emotional and social factors surrounding the COVID-19 outbreak, e.g., catastrophic social alarm, post-traumatic stress disorder, fear,

somatization, or uncertainty about prognosis, may also play a role in the development of musculoskeletal post-COVID pain [13]. We see that people developing musculoskeletal post-COVID pain exhibited higher levels of anxiety or depression and worse sleep quality than those not developing post-COVID pain. Nevertheless, we did not assess the presence of anxiety/depressive levels at hospital admission or during hospital stay, factors which could contribute to the development of long-term musculoskeletal post-COVID pain.

It seems that musculoskeletal post-COVID pain has a multifactorial genesis, where factors related to the pathogen (SARS-CoV-2 associated-factors) intersect with the host response to the infection (within-individual factors), as well as with external factors related to therapies used (hospitalization-related factors) and also emotional factors (COVID-19 outbreak surrounding elements) [12].

Limitations

First, current data can be only applicable to hospitalized COVID-19 survivors. Specific data on musculoskeletal post-COVID pain in non-hospitalized patients remain lacking. Thus, our cohort included Caucasian participants; hence, ethnic differences could not be investigated. Second, we did not collect laboratory measures, e.g., estimation of infection severity or inflammatory biomarkers which could help to elucidate if these parameters are risk factors for musculoskeletal post-COVID pain. Interestingly, Hickie et al observed that individuals suffering viral and non-viral infections exhibited similar post-infectious pain symptoms than post-COVID patients, but these symptoms were not related to the inflammatory response at the acute phase [24]. Additionally, we did not evaluate COVID-19 severity and the number of individuals requiring ICU admission was small. Similarly, hospitalization treatments, e.g., medication intake received for management of the acute infection or use of

analgesics during the hospital stay, or used of analgesic drugs at the time of the interview were not collected. Third, data were collected over telephone, a procedure with a potential bias in population-based survey studies. It should be noted that most studies investigating post-COVID symptoms had used similar methods for data collection [19]. Fourth, the cross-sectional design does not allow to further determine the evolution of musculoskeletal post-COVID pain during all the follow-up period. In fact, it is difficult to exclusively attribute to SARS-CoV-2 infection the presence of post-COVID pain eight months after hospital, since no medical examination was conducted. Therefore, we cannot completely rule out the development of "de novo" medical diseases explaining the development of musculoskeletal pain. Further, not only musculoskeletal, but also neuropathic, pain has been described as post-COVID sequelae [6], although the role of ACE2 receptors on peripheral small-fiber sensory neurons is still unknown [37]. It is possible that some of the subjects also experienced neuropathic post-COVID pain. Finally, we did not collect the severity, e.g., intensity and related-disability, of musculoskeletal post-COVID pain.

Conclusions

This multicenter cohort study found a 45.1% prevalence of musculoskeletal post-COVID pain eight months after hospital discharge. Female gender, previous history of musculoskeletal pain, the presence of myalgia and headache as COVID-19

symptoms and the number of days at hospital were risk factors associated with musculoskeletal post-COVID pain.

Legend of Figures

Figure 1: Location of musculoskeletal post-COVID pain symptoms eight months after hospital discharge (n=887)

Figure 2: Location of previous musculoskeletal pain symptoms before infection in those suffering from musculoskeletal post-COVID pain (n=442, left side) or non-suffering from musculoskeletal post-COVID pain (n=364, right side)

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Declaration of interests

No conflict of interest is declared by any of the authors

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Table 1: Demographic, hospitalisation and clinical data of COVID-19 patients according to the presence or absence of musculoskeletal (MSK) post-COVID pain

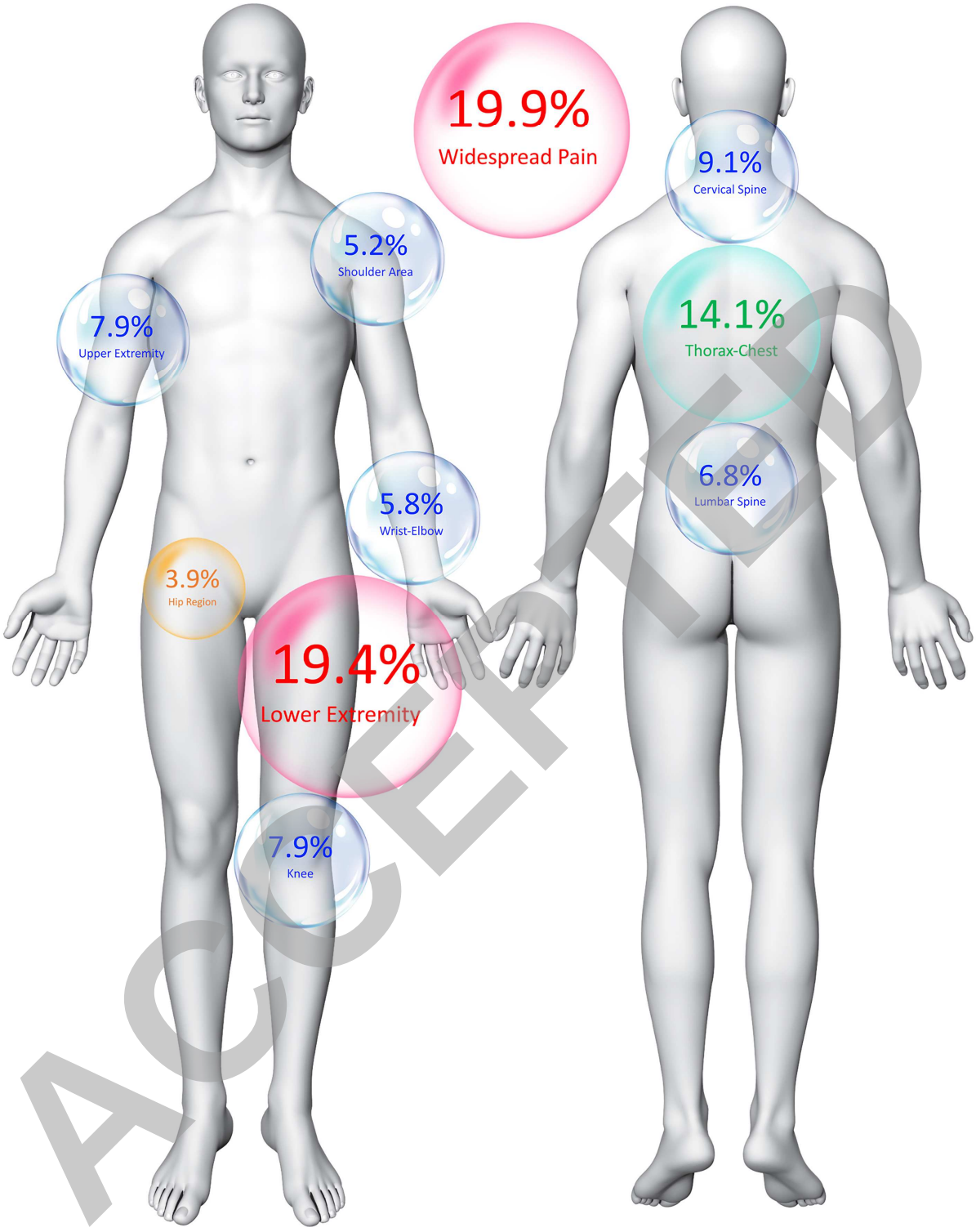
	MSK Post-COVID Pain (n=887)	**No MSK Post-COVID Pain (n=1,082)**	**Missing (%)**
Age, mean (SD), years	60.5 (15.0)	61.5 (17.0)	0.15%
Gender, male/female (%)*	426 (48%) / 461 (52%)	628 (45%) / 454 (42%)	0%
Weight, mean (SD), kg.*	76.2 (16.3)	73.8 (14.1)	1.93%
Height, mean (SD), cm.	165 (9.5)	166 (9)	1.88%
Number of medical comorbidities	0.9 (0.9)	0.8 (0.85)	0%
Medical co-morbidities			0%
Hypertension	256 (28.9%)	258 (23.8%)	
Diabetes	102 (11.5%)	134 (12.4%)	
Cardiovascular Diseases	117 (13.2%)	117 (10.8%)	
Asthma	73 (8.2%)	53 (4.9%)	
Obesity	54 (6.1%)	34 (3.1%)	
Chronic Obstructive Pulmonary Disease	39 (4.4%)	38 (3.5%)	
Rheumatological Diseases	19 (2.1%)	12 (1.1%)	
Migraine	32 (3.6%)	25 (2.4%)	
Other (Cancer, Kidney Disease)	171 (19.3%)	161 (14.9%)	
Previous Musculoskeletal Pain, n (%)*	442 (49.8%)	364 (33.6%)	0%
Number of COVID-19 symptoms at hospital admission, mean (SD)*	2.4 (0.8)	2.0 (0.8)	0%
Symptoms at hospital admission, n (%)			0%
Fever	643 (72.5%)	826 (76.3%)	
Dyspnoea	303 (34.1%)	317 (25.5%)	
Cough	249 (28.1%)	300 (27.7%)	
Myalgias*	328 (37%)	276 (25.5%)	
Headache*	199 (22.4%)	133 (12.3%)	
Diarrhoea	113 (12.7%)	97 (9%)	
Anosmia	69 (7.8%)	98 (9.1%)	
Ageusia	66 (7.5%)	79 (7.3%)	
Throat Pain	59 (6.6%)	43 (4%)	
Vomiting	28 (3.1%)	27 (2.5%)	
Dizziness	37 (4.2%)	29 (2.7%)	
Stay at the hospital, mean (SD), days*	12.5 (11.5)	10.2 (11.0)	0.20%
Intensive Care Unit (ICU) admission			0%
Yes/No, n (%)*	79 (8.9%) / 806 (91.1%)	51 (4.7%) / 1,029 (95.3%)	
Stay at ICU, mean (SD), days	13.0 (12.5)	12.5 (16.5)	
HADS-D (0-21), mean (SD)*	5.7 (5.0)	3.8 (4.5)	0.05%
Depressive Symptoms (HADS-D≥10 points), n (%)	223 (25.1%)	150 (13.8%)	
HADS-A (0-21), mean (SD)*	5.8 (5.2)	4.1 (5.1)	0.05%
Anxiety Symptoms (HADS-A≥12 points), n (%)	156 (17.6%)	152 (14.05%)	
PSQI (0-21), mean (SD)*	7.6 (5.0)	5.6 (3.5)	0.05%
Poor Sleep Quality (SQI≥8 points), n (%)	408 (46.0%)	266 (24.6%)	

n: number; SD: Standard Deviation; HADS: Hospital Anxiety and Depression Scale (A: Anxiety; D: Depression); PSQI: Pittsburgh Sleep Quality Index

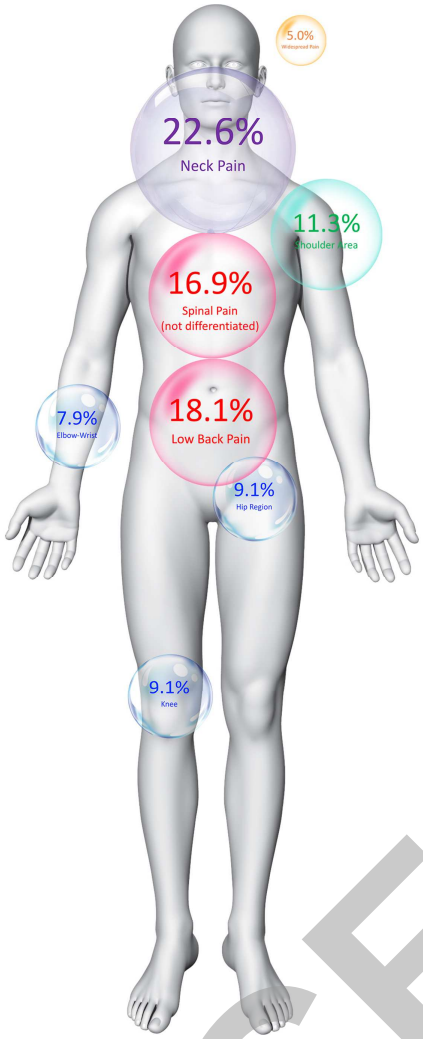
* Statistically significant differences between groups (P<0.01)

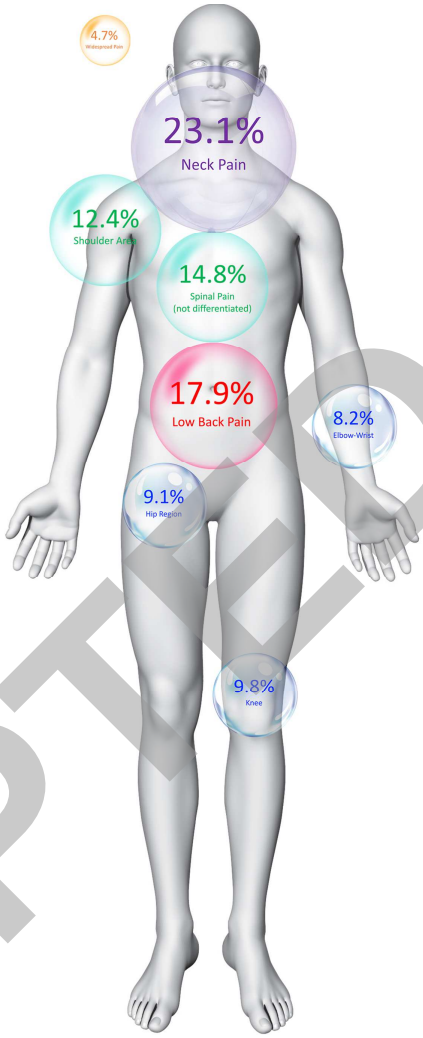
Table 2: Adjusted odd ratio (95% confidence interval) of the univariate and multivariate regression analyses

	Multivariate	Univariate
Age	0.995 (0.988, 1.002)	0.997 (0.995, 0.998) *
Female Sex	1.349 (1.059, 1.720) *	1.015 (0.892, 1.156)
Weight	1.010 (1.002, 1.019) *	0.998 (0.997, 0.999) *
Height	0.992 (0,978, 1.005)	0.999 (0.998, 1.000)
Number of medical comorbidities	0.562 (0.273, 1.156)	1.008 (0.939, 1.082)
Medical co-morbidities		
Hypertension	0.992 (0.835, 1.180)	2.016 (0.954, 4.259)
Diabetes	1.414 (0.654, 3.057)	0.761 (0.588, 0.985) *
Cardiovascular Diseases	1.000 (0.774, 1.292)	2.478 (1.126, 5.453) *
Asthma	1.377 (0.967, 1.962)	2.720 (1.196, 6.189) *
Obesity	1.588 (0.998, 2.439)	2.489 (1.026, 6.039) *
Chronic Obstructive Pulmonary Disease	1.026 (0.657, 1.604)	2.395 (1.010, 5.677) *
Rheumatological Diseases	1.583 (0.769, 3.262)	2.722 (0.921, 8.040)
Other (Cancer, Kidney Disease)	1.062 (0.856, 1.317)	2.078 (0.962, 4.490)
Previous Musculoskeletal Pain	1.553 (1.271, 1.898) *	1.214 (1.057, 1.395) *
Number of symptoms at hospital admission	1.172 (0.936, 1.476)	0.977 (0.941, 1.014)
Symptoms at hospital admission		
Dyspnoea	0.956 (0.817, 1.119)	1.351 (1.018, 1,793) *
Cough	1.054 (0.789, 1.408)	0.830 (0.702, 0.982) *
Myalgias*	1.546 (1.155, 2.070) *	1.188 (1.013, 1.395) *
Headache*	1.866 (1.349, 2.580) *	1.496 (1.201, 1.864) *
Diarrhoea	1.359 (0.943, 1.959)	1.165 (0.888, 1.528)
Anosmia	0.850 (0.564, 1.281)	0.704 (0.517, 0.958) *
Ageusia	1.163 (0.757, 1.785)	0.835 (0.603, 1.158)
Throat Pain	1.372 (0.926, 2.033)	1.707 (1.058, 2.756) *
Vomiting	1.118 (0.610, 2.050)	1.037 (0.611, 1.759)
Dizziness	1.349 (0.778, 2.336)	1.276 (0.785, 2.074)
Days at the hospital	1.013 (1.004, 1.022) *	1000 (0.994, 1.005)
Intensive Care Unit (ICU) admission	1.477 (0.981, 2.224)	1.549 (1.089, 2.203) *



MSK Post-COVID Pain(n=442)





Non-MSK Post-COVID Pain (n=364)