Myalgia as a symptom at hospital admission by severe acute respiratory syndrome coronavirus 2 infection is associated with persistent musculoskeletal pain as long-term post-COVID sequelae

a case-control study

Fernández-de-Las-Peñas, César; Rodríguez-Jiménez, Jorge; Fuensalida-Novo, Stella; Palacios-Ceña, María; Gómez-Mayordomo, Víctor; Florencio, Lidiane L; Hernández-Barrera, Valentín; Arendt-Nielsen, Lars

Published in:
Pain

DOI (link to publication from Publisher):
10.1097/j.pain.0000000000002306

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000002306

Myalgia as a symptom at hospital admission by SARS-CoV-2 infection is associated to persistent musculoskeletal pain as long-term post-COVID sequelae: a case-control study

César Fernández-de-las-Peñas, Dr. Med, PhD[1,2]; Jorge Rodríguez-Jiménez, PT; MSc[1]; Stella Fuensalida-Novo, PT, MSc[1]; María Palacios-Ceña, PT, PhD[1]; Víctor Gómez-Mayordomo, MD[3]; Lidiane L Florencio, PhD[1]; Valentín Hernández-Barrera, PhD[4]; Lars Arendt-Nielsen, Dr. Med, PhD[2]

[1]Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Madrid. Spain.

[2]Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark

[3]Department of Neurology, Hospital Clínico San Carlos. Madrid, Spain

[4]Department of Public Health, Universidad Rey Juan Carlos (URJC), Madrid. Spain.

Corresponding author: César Fernández-de-las-Peñas, Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Avenida de Atenas s/n, 28922 Alcorcón, Madrid, SPAIN, Email: cesar.fernandez@urjc.es , Telephone number: + 34 91 488 88 84, Fax number: +34 91 488 89 57

Conflict of interest statement: None to declare.

Abstract

This study investigated the association between COVID-related myalgia experienced by patients at hospital admission and the presence of post-COVID symptoms. A case-control study including patients hospitalised due to COVID-19 between February 20 and May 31, 2020 was conducted. Patients reporting myalgia and patients without myalgia at hospital admission were scheduled for a telephone interview 7 months after hospital discharge. Hospitalisation and clinical data were collected from medical records. A list of post-COVID symptoms with attention to musculoskeletal pain was evaluated. Anxiety and depressive symptoms, and sleep quality were likewise assessed. From a total 1,200 hospitalised COVID-19 patients, 369 with and 369 without myalgia at hospital admission were assessed 7.2 months (SD 0.6) after hospital discharge. A greater proportion (P=0.03) of patients with myalgia at hospital admission (20%) showed ≥3 post-COVID symptoms when compared with individuals without myalgia (13%). A higher proportion of patients presenting myalgia (OR1.41, 95%CI 1.04-1.90) exhibited musculoskeletal post-COVID pain when compared to those without myalgia. The prevalence of musculoskeletal post-COVID pain in the total sample was 38%. Fifty percent of individuals with pre-existing musculoskeletal pain experienced a worsening of their symptoms after COVID-19. No differences in fatigue, dyspnoea, anxiety/depressive levels or sleep quality were observed between myalgia and non-myalgia groups. The presence of myalgia at hospital admission was associated with pre-existing history of musculoskeletal pain (OR1.62, 95%CI 1.10-2.40). In conclusion, myalgia at the acute phase was associated with musculoskeletal pain as long-term post-COVID sequelae. Additionally, half of patients with pre-existing pain conditions experienced a persistent exacerbation of their previous syndromes.

Key words: Myalgia, COVID-19, musculoskeletal pain, post-COVID, sleep, anxiety, depression, pain sequelae.

Introduction

Patients affected by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) can present with heterogeneous respiratory (dyspnoea, cough), gastrointestinal (diarrhoea, vomiting) or neurological (headache, anosmia) symptoms [18]. In addition, the presence of generalised myalgia (viral-induced myalgia) is also a common symptom of the acute phase of coronavirus 2, 2019 disease (COVID-19) [41]. The World Health Organization (WHO) recognized that 15% of patients with COVID-19 experience viral-induced myalgia as an associated symptom [43]. Two meta-analyses have also shown that myalgia has a pooled prevalence of 19% as a symptom during the acute phase of the infection [1,11]. In fact, myalgia and arthralgia are the fifth most prevalent symptoms during the COVID-19 acute phase [42]. The presence of myalgia at the acute phase has so far not been associated with worse prognosis [38], disease severity [30] or mortality [29]. However, Zhang et al. [44] found that myalgia was a predictive factor for the severity of the overall disease in individuals with abnormal computed tomographic or radiographic imaging of the lungs.

Due to the COVID-19 outbreak, an increase in the incidence of musculoskeletal pain could be expected, either by increasing the number of people developing new onset chronic pain as a result of COVID-19, or by an exacerbation of pre-existing pain [12]. An increase in the severity of symptoms of chronic musculoskeletal pain conditions has been observed during the COVID-19 lockdown [24,39]. Importantly, in the face of a second pandemic due to COVID-19 sequelae, the characteristics of pain in “long-haulers” [37] need to be better investigated and understood to ensure proper approach

among healthcare professionals. Evidence suggests that around 75% of previously hospitalised patients with COVID-19 can exhibit post-COVID symptoms; however, specific data on pain is scarce [32]. Further, the prevalence rates of this symptom are heterogeneous depending on the follow-up period: 50% of persistent pain one-month after the acute infection [26], 15% two months after [9], 25% three months after [5]; and 3% at six months since the infection [25]. Musculoskeletal pain during the acute infection by SARS-CoV-2 translates a heterogeneous pathophysiological process of COVID-19 [31]. It is uncertain whether these mechanisms may contribute to post-COVID pain sequelae.

The aims of this study were to investigate: 1) if the presence of myalgia at hospital admission during the acute phase could be associated with the development of long-term post-COVID pain, and 2) if previous musculoskeletal pain may worsen after COVID-19. We hypothesized that the presence of myalgia as a symptom during the SARS-CoV-2 infection might be a predictor for the development of persistent post-COVID pain at long-term and exacerbate pre-existence musculoskeletal pain problems.

Methods

Participants

A case-control study including individuals who had recovered from acute SARS-CoV-2 infection during the first wave of the pandemic (from February 20 to May 31, 2020) from one urban hospital in Madrid (Spain), was conducted. All participants were attended at the hospital due to COVID-19 symptoms and were positively diagnosed at the time of hospitalisation of SARS-CoV-2 infection with real-time reverse transcription-polymerase chain reaction (PCR) assay of nasopharyngeal and/or oral swab samples and the presence of consistent clinical and radiological findings.

Individuals with a medical diagnosis of dementia, delirium, or psychotic pathology e.g., schizophrenia (or otherwise unable to conduct the interview) were excluded. The study design was approved by the Ethics Committee of Hospital Universitario Clínico San Carlos (URJC0907202015920, HCSC20/495E). Participants were informed of the study and provided verbal informed consent before their inclusion.

Clinical and hospitalisation data including age, gender, height, weight, pre-existing comorbidities (including musculoskeletal pain), intensive care unit (ICU) admission and symptoms at hospital admission were collected from medical records. Due to the critical situation at the first outbreak and the huge and quick increase of hospital admissions due to COVID-19, a list of primary COVID-19 related symptoms including fever, dyspnoea, cough, myalgia, ageusia and anosmia was systematically used, but patients were free to report any symptom that they presented. From all patients hospitalised due to SARS-CoV-2 infection from February 20 to May 31, 2020 at Hospital Universitario Clínico San Carlos, we selected all patients reporting myalgia as a symptom during the acute phase of COVID-19 at hospital admission as cases. Myalgia is a common symptom experienced by 50% of patients with respiratory infections, e.g., influenza [16]. The term myalgia in the current study refers to generalized viral-induced muscle pain that was self-reported by the patients during the acute phase of the infection. Additionally, from all patients hospitalised due to COVID-19 from February 20 to May 31, 2020, we randomly selected age- and sex-matched individuals not reporting myalgia at hospital admission.

Procedure

Participants who agreed to participate were scheduled for a telephonic semi-structured interview by trained researchers. Interviews were conducted by specialised healthcare professionals. Patients reporting the presence of viral-induced myalgia as

acute COVID-19 symptom at hospital admission were asked for its qualitative description. Additionally, participants were asked to report the presence of symptoms appearing after hospitalisation and whether the symptoms persisted at the time of the study. It was emphasized to the participants that symptoms should have appeared after hospital discharge (i.e., post-COVID symptoms). A predefined list of general post-COVID symptoms (i.e., dyspnoea, fatigue, anosmia, ageusia, diarrhoea, cough, palpitations, brain fog, hair loss, skin rashes, loss of concentration) was systematically used, but patients were free to report any symptom that they considered relevant. Particular attention was paid to development of new onset musculoskeletal post-COVID pain. Patients were asked for the location of this musculoskeletal pain (e.g., neck, shoulder, spine, extremities) and to differentiate it from any pain condition that they suffered from before being infected by SARS-CoV-2.

Mood disorders including anxiety/depressive symptoms and sleep quality were assessed with the Hospital Anxiety and Depression Scale (HADS) and Pittsburgh Sleep Quality Index (PSQI) respectively. The HADS includes one subscale assessing anxiety symptoms (HADS-A, 7-items) and one assessing depressive symptoms (HADS-D, 7-items). Each item is scored on a 4-point Likert scale (0-3) providing a maximum score of 21 points, where higher scores suggest more symptoms [22]. Although a cut-off score of ≥8 points on each subscale has shown good sensitivity and specificity [35], 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 [20]. The HADS has shown good validity and reliability in the general population [7] and it has been previously used in patients with COVID-19 [15].

The PSQI evaluates sleep quality by including 19 self-rated questions assessing the usual bedtime, usual wake time, number of hours slept, and number of minutes to

fall asleep [8]. Questions are answered on a 4-point Likert-type scale (0-3). All answers are summed and transformed into a global score of a maximum of 21 points, where higher scores indicate worse sleep quality. A score ≥8.0 points is indicative of poor sleep quality [8]. The PSQI has shown good internal consistency and test-retest reliability [10]. These questionnaires were selected because both can be evaluated by telephone interview [21].

Statistical Analysis

The STATA 16.1 program (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP. USA) was used for statistical analysis. Data were presented as mean (standard deviation, SD) or percentages as appropriate. The McNemar test and paired Student t-tests were conducted to compare proportions and means between patients with and without myalgia as a symptom at hospital admission. Multivariable conditional logistic regression models were constructed to identify those variables related to hospitalization (number of symptoms at hospitalization, days at hospital, pre-existing comorbidities, ICU admission or not) and post-COVID symptoms independently associated with the presence of myalgia as an onset symptom. Adjusted Odd Ratio (OR) with 95% confidence intervals (95%CI) were calculated. A priori the level of significance was set at 0.05.

Results

From 1,200 hospitalised patients due to SARS-CoV-2 infection from February 20 to May 31, 2020, a total of 369 (30.7%) reporting myalgia as a symptom during the acute phase of the infection and at hospital admission, and 369 age- and sex-matched patients without reporting myalgia during the acute phase of the disease were included.

All were Caucasian. **Figure 1** shows a flow diagram summarizing the hospitalization patients, the number of deaths at hospital and follow-up, and excluded patients.

COVID-19 Related Symptoms at Hospital Admission

The most common symptoms at hospital admission due to COVID-19 infection were fever, dyspnoea, cough, and headache. Dyspnoea and cough were less frequent in patients presenting with myalgia (22.5% and 20.5%, compared to 38.5% and 27.5%, respectively, P<0.01). No other significant differences in symptoms at onset were observed (**Table 1**). Almost 90% of patients reporting myalgia at hospital admission described this symptom as generalized muscle diffuse pain. Three hundred (40.5%) patients had no comorbidity, 393 (53.5%) had one or two comorbidities, and the remaining 45 (6%) reported ≥3 comorbidities. Patients reporting previous history of musculoskeletal pain were more prone to suffer from viral-induced myalgia at hospital admission (24% versus. 15%, respectively; OR 1.79, 95%CI 1.23-2.60, P=0.023). Neck and low back pain were the most prevalent pre-exiting musculoskeletal pain conditions reported by patients before infection, without differences between myalgia and non-myalgia groups. Clinical and hospitalisation data of both groups are summarized in **Table 1**.

Post-COVID Symptoms

Participants were assessed a mean of 7.2 months (SD 0.6) after hospital discharge. At the time of the evaluation, only 257 (35%) were completely free of any post-COVID symptom, 357 (48.5%) had one or two symptoms, and the remaining 123 (16.5%) had 3 or more post-COVID symptoms. A significantly greater proportion (X^2: 10.651, P=0.03) of patients reporting viral-induced myalgia during the acute phase experienced ≥3 post-COVID symptoms when compared to those without viral-induced myalgia. However, no significant differences in the total number of general post-

COVID symptoms (OR 1.09, 95%CI 0.98-1.20, P=0.1) between individuals with (mean: 2.2, SD 1.5) and without (mean: 2.0, SD 1.4) myalgia at hospital admission were found.

Figure 2 graphs the distribution of the six most prevalent post-COVID symptoms in patients with and without myalgia during the acute phase of the disease at seven months after hospitalisation. The most prevalent long-term post-COVID symptoms were fatigue, dyspnoea on exertion, musculoskeletal pain, dyspnoea at rest, hair loss, and memory loss. No significant differences in the presence of persistent fatigue (OR 1.05, 95%CI 0.77-1.42, P=0.74), dyspnoea on exertion (OR 0.98, 95%CI 0.73-1.31, P=0.88) or dyspnoea at rest (OR 0.83, 95%CI 0.59-1.17, P=0.322) were found based on the presence or absence of myalgia at hospital admission (**Table** 2).

A significantly greater proportion (OR 1.41 95%CI 1.04-1.904, P=0.02) of patients suffering from myalgia at hospital admission developed musculoskeletal post-COVID pain (42.5%) as compared to those not reporting myalgia at hospital admission (34.5%). Overall, the prevalence of musculoskeletal post-COVID pain in the sample was 38.4% (n=284/738). From 284 individuals suffering musculoskeletal post-COVID pain (Table 2), 143 (50.3%) reported pre-existing history of musculoskeletal pain conditions. Among these, 76/143 (53.1%) patients suffering from pre-existing musculoskeletal pain condition before infection experienced an increase of their symptoms in intensity (53%), extension (25-27%) or frequency (17-21%), without differences regarding the presence of myalgia at hospital admission (Table 2). Therefore, a total of 208 individuals (67/143 patients with pre-existing musculoskeletal pain and 141 patients without a pre-existing musculoskeletal pain) developed new onset musculoskeletal post-COVID pain. Hence, the prevalence of new onset post-COVID musculoskeletal pain was up to 73.2%. The location of persistent musculoskeletal post-

COVID pain was similar in both groups, being the spinal region the most prevalent (**Table 2**).

No significant differences in HADS-A (P=0.388), HADS-D (P=0.825), and PSQI (P=0.291) scores were observed between both groups. In fact, no significant association between the presence of myalgia at hospital admission with depressive symptoms (OR 1.06, 95%CI 0.72-1.55, P=0.77), anxiety symptoms (OR 1.13, 95%CI 0.80-1.60, P=0.479) and poor sleep quality (OR 1.02 95%CI 0.76-1.38, P=0.770) was either found (**Table 2**).

The multivariate analysis revealed that, after adjusting by all variables, individuals with viral-induced myalgia at the acute COVID-19 phase had a more frequent pre-existing history of musculoskeletal pain conditions (OR1.62, 95%CI 1.10-2.40, P=0.015).

Discussion

This study describes the prevalence of long-term post-COVID symptoms depending on the presence of myalgia as a symptom at hospital admission. We found that this acute symptom was associated with the presence of pre-existing musculoskeletal pain and also with the development of musculoskeletal pain as post-COVID sequelae. The prevalence of persistent musculoskeletal pain after COVID-19 reached 38%. No differences in persistent fatigue, dyspnoea, anxiety/depressive levels, or sleep quality between patients experiencing or not myalgia at hospital admission were found.

Myalgia as COVID-19 Related Symptom at Onset of the Infection

Evidence supports that clinical presentation of SARS-CoV-2 infection is heterogeneous since these patients exhibit a plethora of symptoms at onset, being fever,

cough, fatigue, and dyspnoea the most prevalent [4]. Rubio-Rivas et al identified four clusters of COVID-19 patients, where individuals presenting with myalgia, arthralgia or headache at the acute phase presented lower rates of hospital mortality [38]. The association of pain at the acute phase of COVID-19 with a decrease in mortality has been also recently observed by Knox et al [29].

We found that the presence of myalgia as a symptom at hospital admission was more prevalent in individuals with pre-existing musculoskeletal pain conditions, but this was not exclusive, since 15% of patients not suffering myalgia at hospital admission also reported previous history of musculoskeletal pain before the infection. The location of pre-existing musculoskeletal pain conditions should be considered during the screening of acute COVID-19 patients, and they must be differentiated from the location of the new viral-related pain symptoms. Erçalık et al [19] observed that spinal pain was the most frequent painful location experienced by patients before COVID-19, whereas headache and more generalized pain, including the extremities, were the most prevalent during the infection. In our study, we also observed that spinal pain was the most frequent painful location experienced by patients before infection, but also the most common location of post-COVID musculoskeletal pain. In contrast, most patients of our research reported that myalgia experienced as a symptom of SARS-CoV-2 infection at hospital admission was perceived as generalized diffuse muscle pain and clearly different from their pre-existing musculoskeletal pain symptoms.

Musculoskeletal Pain as Post-COVID Sequelae

We reported an overall prevalence of musculoskeletal post-COVID pain of 38% of patients, seven months after hospitalisation. Current data are much higher than those previously reported six months after hospital discharge (3%) [25]. Most of other studies providing prevalence data of post-COVID pain included shorter follow-up periods [5,9,

26]; therefore, comparisons should not be made. Also, differences in populations, pre-existing comorbidities, pre-existing history of musculoskeletal pain (data not reported in previous studies), follow-up periods, or clinical course of the disease could explain these discrepancies. Our study is the first focussing on persistent post-COVID pain, considering the presence of pre-existing musculoskeletal pain before hospitalisation and the presence of myalgia at the acute phase.

Identification of patients at risk of developing post-COVID musculoskeletal pain could lead to better therapeutic strategies [28]. Our findings have clinical implications, since pre-existing musculoskeletal pain may predispose to exacerbation of pre-existing conditions or also to the development of new pain conditions [6]. Our results support both assumptions, since 50% of individuals with pre-existing musculoskeletal pain reported an exacerbation of their pre-existing symptoms seven months after infection (exacerbated COVID-19 related-pain), and the remaining 50% developed new musculoskeletal post-COVID pain (new onset COVID-19 related-pain). The results from this study support that musculoskeletal pain can appear as new long-term post-COVID sequalae or could be also an exacerbated post-COVID pain sequalae. Further studies are needed to characterize the nature of post-COVID musculoskeletal pain.

In addition, the development of musculoskeletal post-COVID pain was associated with the presence of myalgia as a symptom at the onset of the SARS-CoV-2 infection and hospital admission. It is possible that early consideration of myalgia at onset may help clinicians identify subjects at risk of developing musculoskeletal post-COVID pain. This is a relevant topic since myalgia is not considered one of the most bothersome symptoms by COVID-19, when compared with other related-symptoms such as dyspnoea, fever or chest pain. Therefore, it is possible that this symptom is underreported by some patients at hospital admission. Our results support the relevance

of properly identify this symptom at onset infection since it was associated to a higher risk of developing musculoskeletal post-COVID pain.

Mechanisms of Musculoskeletal Pain as Post-COVID Sequelae

The main hypothesis explaining the association between musculoskeletal pain and SARS-CoV-2 infection is the prolonged pro-inflammatory response associated to COVID-19. This cytokine storm leads to a rapid hyper-activation of T cells, macrophages and natural killer cells, stimulating the overproduction of pro-inflammatory mediators [33]. These events could promote mechanisms associated with muscle pain, e.g., atypical responses of the mast cells [3], increase of inflammatory interleukin-6 (IL-6) [14], and an over-expression of angiotensin-converting enzyme 2 (ACE2) at central and peripheral nervous systems [40]. Current hypotheses suggest that pain may result from viral neurotropic properties, the activation of nociceptive neurons, involvement of peripheral nervous system and muscle and autoimmune reactions, having the potential to increase the incidence of chronic pain [31]. However, no evidence of a direct association between these mechanisms, e.g., ACE2 overexpression, and COVID-19 is still confirmed [34]. It is possible that these cytokine-mediated responses lead to a hyper-excitability of the peripheral and central nervous systems, promoting the development of post-COVID pain symptoms [13]. In fact, it is possible that cytokine storm could lead to the ability of SARS-CoV-2 infection for triggering nociplastic pain [12]. In such a scenario, the presence of viral-induced myalgia as a symptom at the acute phase could active a cascade of events that, in predisposing subjects, may lead to development of new musculoskeletal post-COVID pain symptoms or to a worsening of a pre-existing pain symptom, as it was observed in our study.

Additionally, emotional and social factors related to COVID-19 can also promote the development of musculoskeletal post-COVID pain or the exacerbation of

pre-existing painful conditions [27], exacerbated by the barriers encountered in accessing adequate medical care for patients with chronic pain during the worldwide COVID-19 lockdown [17]. Surprisingly, we did not observe differences in the presence of anxiety/depressive levels and sleep quality depending on the presence or absence of myalgia as a symptom at infection. In addition, anxiety and depressive levels or sleep quality was not either associated to the presence of pre-existing musculoskeletal pain or the development of musculoskeletal post-COVID pain (data not shown). The fact that the anxiety/depressive levels were small in our sample could explain these results. Further, other psychosocial mechanisms including catastrophic social alarm, hospitalization-related post-traumatic stress disorder or uncertainty about prognosis, may also play a role since these factors also interplay with central mechanisms that contribute to chronic pain [2]. For instance, it has been previously found that those patients recalling higher pain and distress during ICU admission are at higher risk of developing chronic pain after hospital discharge [36]. Our sample of patients requiring ICU admission was small to make conclusions. Future studies determining the association between emotional factors and the development of musculoskeletal post-COVID pain are needed.

Limitations

Although this is the largest study with the longest follow-up period to date focussing on musculoskeletal post-COVID pain and also considering the presence of viral-induced myalgia at hospital admission, potential limitations should be recognized. First, we just included hospitalised COVID-19 survivors; therefore, we cannot extrapolate these results to non-hospitalised patients. Second, we only included Caucasian participants; therefore, ethnic differences could not be investigated. Further, since musculoskeletal pain exhibits a female predominance, future studies assessing

gender differences are needed. Third, we did not collect laboratory measures, e.g., biomarkers of inflammation, or estimations of severity of the infection, e.g., cycle thresholds of the PCR, which could help to further characterize musculoskeletal post-COVID pain. Nevertheless, Hickie et al observed that post-infectious symptoms are not related to the inflammatory response at the acute phase, but rather by the intensity of these symptoms at baseline [23]. Similarly, we did not collect data about the intensity or severity of musculoskeletal pain; therefore, we were not able to determine the proportion of patients showing disabling pain symptoms. Future studies characterising the severity of musculoskeletal post-COVID pain are now needed. Fourth, data were collected over the telephone, a procedure with a well-known potential bias in survey studies. Nevertheless, it should be noted that previous studies investigating post-COVID symptoms have also used similar methods for the recruitment of data [5,9,25,26]. Finally, the cross-sectional design of the study does not allow to determine the evolution of musculoskeletal post-COVID pain during the follow-up period after hospital discharge making it difficult to exclusively attribute to SARS-CoV-2 its development seven months after the infection and hospitalisation. Longitudinal studies investigating the evolution of post-COVID sequelae are needed. Finally, it should be noted that differentiating myalgias and arthralgias can be difficult for both patients and clinicians; therefore, the it is possible that the term myalgias and arthralgias would have been more appropriate.

In conclusion, this study reported that 65% of COVID-19 survivors exhibited long-term post-COVID symptoms. The prevalence of musculoskeletal post-COVID pain was 38%. Myalgia as a symptom at the acute phase was more frequent in individuals with pre-existing musculoskeletal pain conditions. The presence of viral-induced myalgia at hospital admission was associated with the development of

musculoskeletal post-COVID pain. Overall, 50% of patients with pre-existing musculoskeletal pain conditions showed exacerbation of their symptoms and the remaining 50% developed new musculoskeletal post-COVID pain. No differences in dyspnoea, anxiety/depressive levels, or sleep quality were found between patients with and without myalgia at the acute phase of the infection.

Acknowledgements

The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). Authors declare that they have no conflict of interest.

Conflict of Interest

None declared

Legend of Figures

Figure 1: Flow chart showing of the number of patients throughout the study.

Figure 2: Distribution of the most prevalent post-COVID symptoms (fatigue, dyspnoea on exertion, musculoskeletal pain, dyspnoea at rest, hair loss, and memory loss) in patients with and without viral-induce myalgia at the acute phase of infection.

References

1. Abdullahi A, Candan SA, Abba MA, Bello AH, Alshehri MA, Afamefuna Victor E, Umar NA, Kundakci B Neurological and musculoskeletal features of COVID-19: A systematic review and meta-analysis. Front Neurol 2020; 11: 687.
2. Adams LM, Turk DC. Psychosocial factors and central sensitivity syndromes. Curr Rheumatol Rev 2015; 11: 96-108.

3. Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis 2020; 100: 327-332.
4. Alimohamadi Y, Sepandi M, Taghdir M, Hosamirudsari H. Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis. J Prev Med Hyg. 2020; 61: E304.
5. Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, Noel A, Gunning S, Hatrick J, Hamilton S, Elvers KT, Hyams C, Bibby A, Moran E, Adamali HI, Dodd JW, Maskell NA, Barratt SL. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax. 2020 Dec 3: thoraxjnl-2020-216086.
6. Baumbach P, G€otz T, Günther A, Weiss T, Meissner W. Prevalence and characteristics of chronic intensive care-related pain: the role of severe sepsis and septic shock. Crit Care Med 2016; 44: 1129-1137.
7. Bjelland I, Dahl AA, Haug T, Neckelman D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002; 52: 69-77.
8. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28: 193-213.
9. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA 2020; 324: 603-605.
10. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res. 1998; 45: 5-13.

11. Ciaffi J, Meliconi R, Ruscitti P, Berardicurti O, Giacomelli R, Ursini F. Rheumatic manifestations of COVID-19: a systematic review and meta-analysis. BMC Rheumatol 2020; 4: 65.
12. Clauw DJ, Häuser W, Cohen SP, Fitzcharles MA Considering the potential for an increase in chronic pain after the COVID-19 pandemic. Pain 2020; 161: 1694-1697.
13. Cohen SP, Baber ZB, Buvanendran A, McLean BC, Chen Y, Hooten WM, Laker SR, Wasan AD, Kennedy DJ, Sandbrink F, King SA, Fowler IM, Stojanovic MP, Hayek SM, Phillips CR. Pain management best practices from multispecialty organizations during the COVID-19 pandemic and public health crises. Pain Med 2020; 21: 1331-1346.
14. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: A systematic review and meta-analysis. Rev Med Virol 2020; 30: 1-9.
15. Deng J, Zhou F, Hou W, Silver Z, Wong CY, Chang O, Huang E, Zuo Q. The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis. Ann N Y Acad Sci 2020 Oct 2:10.1111/nyas.14506.
16. Eccles R. Understanding the symptoms of the common cold and influenza. Lancet Infect Dis 2005; 5: 718-725
17. Eccleston C, Blyth FM, Dear BF, Fisher EA, Keefe FJ, Lynch ME, Palermo TM, Reid MC, Williams ACC. Managing patients with chronic pain during the COVID-19 outbreak: considerations for the rapid introduction of remotely supported (eHealth) pain management services. Pain 2020; 161: 889-893.
18. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. Lancet Neurol 2020; 19: 767-783.

19. Erçalık T, Ayyıldız A, Gencer-Atalay K, Akgün C, Özdemir HM, Kuran B Pain symptoms in COVID-19. Am J Phys Med Rehabil. 2021 Feb 1. doi: 10.1097/PHM.0000000000001699.
20. Grupo de Trabajo de la Guía de Práctica Clínica para el Manejo de Pacientes con Trastornos de Ansiedad en Atención Primaria 2008. Guías de Práctica Clínica en el SNS - UETS Nº 2006/10. Madrid: Plan Nacional para el SNS del MSC, Unidad de Evaluación de Tecnologías Sanitarias, Agencia Laín Entralgo, Comunidad de Madrid.
21. Hedman E, Ljótsson B, Blom K, El Alaoui S, Kraepelien M, Rück C, Andersson G, Svanborg C, Lindefors N, Kaldo V. Telephone versus internet administration of self-report measures of social anxiety, depressive symptoms, and insomnia: psychometric evaluation of a method to reduce the impact of missing data. J Med Internet Res 2013; 15: e229.
22. Herrmann-Lingen C, Buss U, Snaith RP. Hospital Anxiety and Depression Scale – Deutsche Version (HADS-D) Verlag Hans Huber, Bern; 2011.
23. Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, Reeves WC, Lloyd A; Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ 2006; 333: 575.
24. Hruschak V, Flowers KM, Azizoddin DR, Jamison RN, Edwards RR, Schreiber KL. Cross-sectional study of psychosocial and pain-related variables among patients with chronic pain during a time of social distancing imposed by the coronavirus disease 2019 pandemic. Pain 2021; 162: 619-629.

25. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220-232.

26. Jacobs LG, Gourna Paleoudis E, Lesky-Di Bari D, Nyirenda T, Friedman T, Gupta A, et al. Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. PLoS One. 2020; 15: e0243882.

27. Karos K, McParland JL, Bunzli S, Devan H, Hirsh A, Kapos FP, Keogh E, Moore D, Tracy LM, Ashton-James CE. The social threats of COVID-19 for people with chronic pain. Pain 2020; 161: 2229-2235.

28. Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: implications for rehabilitation. Br J Anaesth. 2020; 125: 436-440.

29. Knox N, Lee CS, Moon JY, Cohen SP. Pain manifestations of COVID-19 and their association with mortality: A multi-center prospective observational study. Mayo Clinic Proceedings 2021. doi: https://doi.org/10.1016/j.mayocp.2020.12.014.

30. Lippi G, Wong J, Brandon MH. Myalgia may not be associated with severity of coronavirus disease 2019. World J Emerg Med 2020;11: 193-194.

31. McFarland AJ, Yousuf MS, Shiers S, Price TJ. Neurobiology of SARS-CoV-2 interactions with the peripheral nervous system: implications for COVID-19 and pain. Pain Rep 2021; 6: e885

32. Meyer-Frießem CH, Gierthmühlen J, Baron R, Sommer C, Üçeyler N, Enax-Krumova EK. Pain during and after COVID-19 in Germany and worldwide: a narrative review of current knowledge. Pain Rep 2021; 6: e893

33. Mulchandani R, Lyngdoh T, Kakkar AK. Deciphering the COVID-19 cytokine storm: Systematic review and meta-analysis. Eur J Clin Invest 2021; 51: e13429.

34. Oaklander AL. Clinical significance of angiotensin-converting enzyme 2 receptors for severe acute respiratory syndrome coronavirus 2 (COVID-19) on peripheral small-fiber sensory neurons is unknown today. Pain 2020; 161: 2431-2433.

35. Olssøn I, Mykletun A, Dahl AA. The Hospital Anxiety and Depression Rating Scale: a cross-sectional study of psychometrics and case finding abilities in general practice. BMC Psychiatry. 2005; 5: 46.

36. Puntillo KA, Max A, Chaize M, Chanques G, Azoulay E. Patient recollection of ICU procedural pain and post ICU burden: the Memory Study. Crit Care Med 2016; 44: 1988-1995.

37. Rubin R. As their numbers grow, COVID-19 "Long Haulers" stump experts. JAMA 2020 Sep 23. doi: 10.1001/jama.2020.17709

38. Rubio-Rivas M, Corbella X, Mora-Luján JM, Loureiro-Amigo J, López Sampalo A, Yera Bergua C, Esteve Atiénzar PJ, Díez García LF, Gonzalez Ferrer R, Plaza Canteli S, Pérez Piñeiro A, Cortés Rodríguez B, Jorquer Vidal L, Pérez Catalán I, León Téllez M, Martín Oterino JÁ, Martín González MC, Serrano Carrillo de Albornoz JL, García Sardon E, Alcalá Pedrajas JN, Martin-Urda Diez-Canseco A, Esteban Giner MJ, Tellería Gómez P, Ramos-Rincón JM, Gómez-Huelgas R. Predicting clinical outcome with phenotypic clusters in COVID-19 pneumonia: An analysis of 12,066 hospitalized patients from the Spanish Registry SEMI-COVID-19. J Clin Med. 2020; 9: 3488.

39. Serrano-Ibáñez ER, Esteve R, Ramírez-Maestre C, Ruiz-Párraga GT, López-Martínez AE. Chronic pain in the time of COVID-19: Stress aftermath and central sensitization. Br J Health Psychol. 2020 Oct 25. doi: 10.1111/bjhp.12483

40. Shiers S, Ray PR, Wangzhou A, Sankaranarayanan I, Tatsui CE, Rhines LD, Li Y, Uhelski ML, Dougherty PM, Price TJ. ACE2 and SCARF expression in human dorsal root ganglion nociceptors: implications for SARS-CoV-2 virus neurological effects. Pain 2020; 161: 2494-2501.
41. Song XJ, Xiong DL, Wang ZY, Yang D, Zhou L, Li RC. Pain management during the COVID-19 pandemic in China: lessons learned. Pain Med 2020; 21: 1319-1323.
42. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, Spijker R, Hooft L, Emperador D, Dittrich S, Domen J, Horn SRA, Van den Bruel A; Cochrane COVID-19 Diagnostic Test Accuracy Group. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. Cochrane Database Syst Rev 2020;7: CD013665.
43. World Health Organization (WHO). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19); World Health Organization: Geneva, Switzerland, 2020.
44. Zhang X, Cai H, Hu J, Lian J, Gu J, Zhang S, Ye C, Lu Y, Jin C, Yu G, Jia H, Zhang Y,Sheng J, Li L, Yang Y. Epidemiological, clinical characteristics of cases of SARS-CoV- 2 infection with abnormal imaging findings. Int J Infect Dis 2020; 94: 81-87.

Table 1: Demographic and hospitalisation data of COVID-19 patients with myalgias (cases) and without myalgia (controls) at hospital admission

	Cases (n=369)	**Controls (n=369)**
Age, mean (SD), years	60 (15.5)	60 (15.0)
Gender, male/female (%)	176 (48%) / 193 (52%)	176 (48%) / 193 (52%)
Weight, mean (SD), kg.	75.0 (16.5)	73.5 (14.5)
Height, mean (SD), cm.	165.0 (11)	165 (9.5)
Body Mass Index, mean (SD), kg/cm^2	27.5 (6.0)	27.0 (4.5)
Smoking status, n (%)		
Active	27 (7.5%)	28 (8%)
None or Former	342 (92.5%)	341 (92%)
Number of medical comorbidities, n (%)		
None	148 (40%)	152 (41%)
1 or 2	191 (52%)	202 (55%)
3 or more	30 (8%)	15 (4%)
Medical co-morbidities		
Hypertension	92 (25%)	86 (23.5%)
History of Musculoskeletal Pain*	88 (24%)	55 (15%)
Diabetes	52 (14%)	45 (12%)
Cardiovascular Diseases	40 (11%)	37 (10%)
Asthma	28 (7.5%)	20 (5.5%)
Obesity	16 (4.5%)	19 (5%)
Rheumatological Diseases	10 (2.5%)	10 (2.5%)
Chronic Obstructive Pulmonary Disease	12 (3%)	18 (5%)
Stroke	7 (2%)	9 (2.5%)
Migraine	13 (3.5%)	9 (2.5%)
Other (Cancer, Kidney Disease)	55 (15%)	52 (14%)
Musculoskeletal Pain History		
Neck Pain	30/88 (34%)	17/55 (31%)
Low Back Pain	20/88 (23%)	12/55 (22%)
Shoulder Area	15/88 (17%)	8/55 (14.5%)
Elbow-Wrist	5/88 (5.5%)	3/55 (5.5%)
Hip Region	8/88 (9.5%)	6/55 (11%)
Knee	10/88 (11%)	9/55 (10%)
Symptoms at hospital admission, n (%)		
Myalgia	369 (100%)	0 (0%)
Fever	248 (67%)	271 (73.5%)
Dyspnoea*	83 (22.5%)	142 (38.5%)
Cough*	76 (20.5%)	102 (27.5%)
Headache	75 (20%)	71 (19%)
Diarrhoea	42 (11.5%)	49 (13%)
Anosmia	29 (8%)	36 (10%)
Ageusia	26 (7%)	32 (8.5%)
Throat Pain	18 (5%)	21 (5.5%)
Vomiting	7 (2%)	8 (2%)
Stay at the hospital, mean (SD), days	13.5 (12.0)	14.0 (12.0)
Intensive Care Unit (ICU) admission		
Yes/No, n (%)	26 (7%) / 343 (93%)	30 (8%) / 339 (92%)
Stay at ICU, mean (SD), days	17.5 (15)	12 (11)

n: number; SD: Standard Deviation

* Statistically significant differences between cases and controls (P<0.05)

Table 2: Prevalence of Post-COVID Symptoms in COVID-19 survivors with and without myalgias at hospital admission

	Cases (n=369)	Controls (n=369)
Number of post-COVID symptoms, n (%)*		
None	124 (34%)	133 (36%)
1 or 2	171 (46%)	186 (50.5%)
3 or more	73 (20%)	50 (13.5%)
Total number of post-COVID symptoms - mean (SD)	2.2 (1.5)	2.0 (1.4)
Post-COVID symptoms, n (%)		
Fatigue	240 (65%)	235 (64%)
Dyspnoea on exertion	217 (59%)	219 (59.5%)
Musculoskeletal Pain*	157 (42.5%)	127 (34.5%)
Dyspnoea rest	83 (22.5%)	95 (26%)
Loss hair	77 (21%)	80 (21.5%)
Loss memory	72 (19.5%)	64 (17.5%)
Tension-Type Like Headache	40 (11%)	40 (11%)
Skin rashes	43 (11.5%)	36 (10%)
Gastrointestinal Disorders - Diarrhoea	40 (11%)	35 (9.5%)
Cognitive Blunting - Brain fog	35 (9.5%)	31 (8.5%)
Tachycardia-Palpitations*	35 (9.5%)	18 (5%)
Ageusia/Hypogeusia	16 (4.5%)	10 (2.5%)
Ocular/Vision Disorders	13 (3.5%)	10 (2.5%)
Anosmia/Hyposmia	11 (3%)	14 (4%)
Cough	7 (2%)	8 (2%)
Dizziness	6 (1.5%)	8 (2%)
Migraine Like Headache	8 (2%)	6 (1.5%)
Worsening of Previous Musculoskeletal Pain		
Yes/No, n (%)	47 (53.4%) / 41 (45.6%)	29 (52.7%) / 26 (47.3%)
Pain Intensity Increase	25/47 (53%)	16/29 (55%)
Pain Extension Increase	12/47 (25.5%)	8/29 (27.5%)
Pain Frequency Increase	10/47 (21.5%)	5/29 (17.5%)
Location of post-COVID Musculoskeletal Pain		
Cervical Spine	22/157 (14%)	17/127 (13.5%)
Thorax-Chest	18/157 (11.5%)	13/127 (10%)
Lumbar Spine	20/157 (13%)	18/127 (14%)
Widespread Pain	24/157 (15.5%)	19/127 (15%)
Upper Extremity	13/157 (8%)	13/127 (10%)
Shoulder Area	9/157 (6%)	6/127 (6%)
Wrist-Elbow	7/157 (4.5%)	4/127 (3%)
Lower Extremity	26/157 (16.5%)	22/127 (17%)
Hip Region	6/157 (3.5%)	4/127 (3%)
Knee	12/157 (7.5%)	11/127 (8.5%)
HADS-D (0-21), mean (SD)	5.5 (4.7)	5.3 (4.8)
Depressive Symptoms (HADS-D ≥10 points), n (%)	86 (23.5%)	78 (21.0%)
HADS-A (0-21), mean (SD)	5.6 (5.5)	5.3 (5.0)
Anxiety Symptoms (HADS-A ≥12 points), n (%)	65 (17.5%)	62 (17.0%)
PSQI (0-21), mean (SD)	7.0 (4.0)	6.5 (4.0)
Poor Sleep Quality (PSQI ≥8 points), n (%)	138 (37.5%)	136 (37.0%)

HADS: Hospital Anxiety and Depression Scale (A: Anxiety; D: Depression);
PSQI: Pittsburgh Sleep Quality Index; SD: Standard Deviation
* Statistically significant differences between cases and controls (P<0.05)

Figure 1: Flow diagram of patients throughout the course of the study

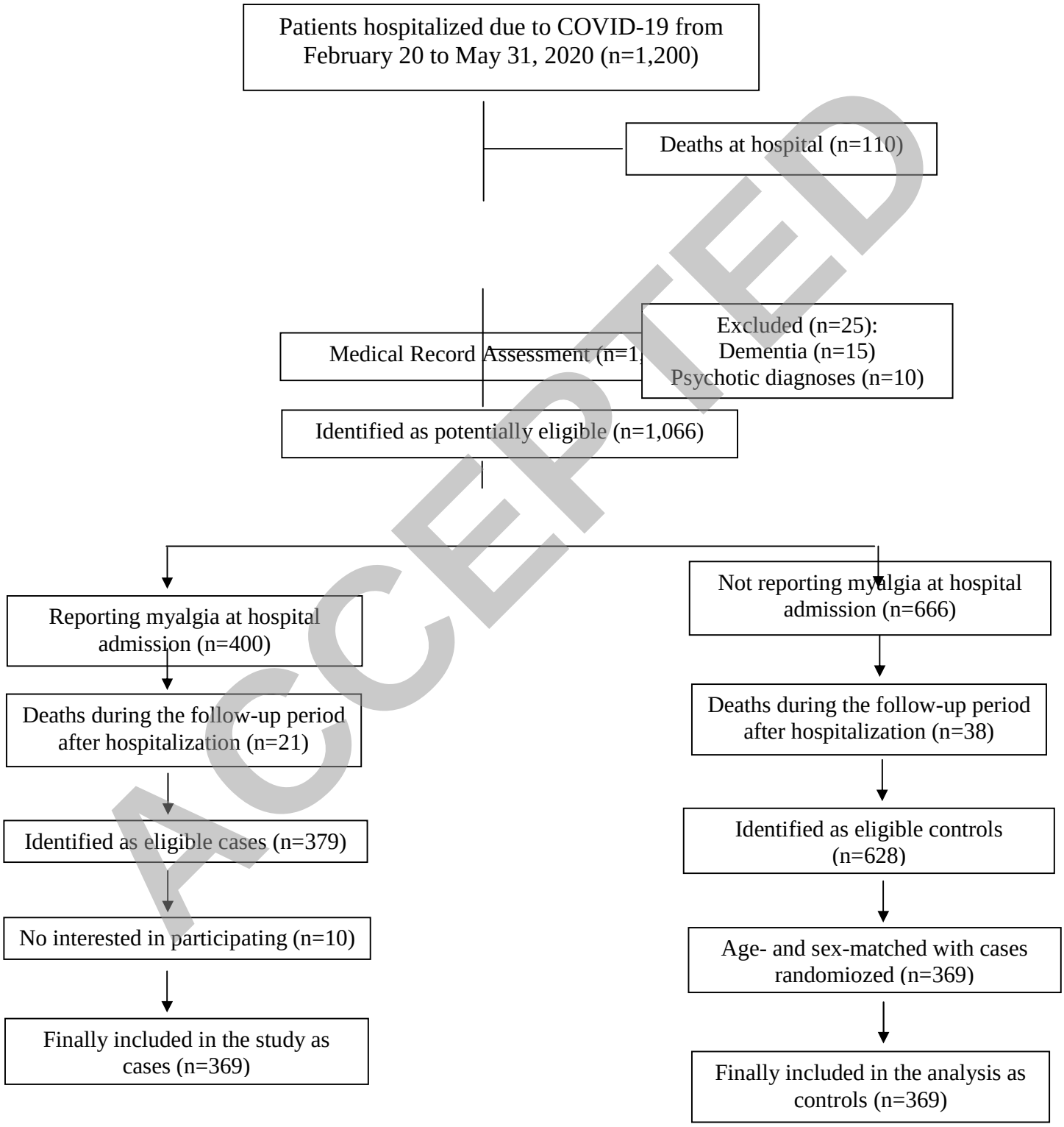

Figure 1