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a multicenter study

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Introduction

Musculoskeletal pain is a common symptom experienced during the acute phase by individuals suffering from coronavirus 2, 2019 disease (COVID-19) with an estimated prevalence ranging from 15% to 20% [1,6]. Pain is also experienced after the acute phase of infection (i.e., post-COVID symptoms) [11,21]. A meta-analysis specifically focusing on musculoskeletal post-COVID pain reported an overall pooled prevalence ranging from 4.6% to 23.6% during the first six months after the infection [10]. Most studies included in this meta-analysis considered follow-ups between one and four months after SARS-CoV-2 infection, consisted of cross-sectional designs, included small samples and did not focus on pain symptom [10]. Interestingly, the prevalence of musculoskeletal pain reached 60% in studies specifically investigating this post-COVID symptom [2,3,17,30]. Again, these studies included small samples, recruited from single centers, and with follow-up periods less than three months after infection [2,3,17,30]. A multicenter study evaluating a large sample of previously hospitalized COVID-19 survivors reported a prevalence of musculoskeletal post-COVID pain of 45% at eight months after hospital discharge [9]. This study also found that female sex, history pre-existing musculoskeletal pain, presence of myalgia or headache as COVID-19 symptoms at hospital admission, and days at the hospital were risk factors associated with musculoskeletal post-COVID pain [9].

It should be considered that most studies specifically investigating musculoskeletal post-COVID pain symptoms are cross-sectional since they assessed the presence of pain symptoms just at one follow-up period [2,3,5,17,21,30]. Understanding the longitudinal evolution of post-COVID pain symptoms could have implications for optimizing patient treatment care, public health outcomes, and for informing patients. In fact, Yelin et al. have recently described a group of patients, called "pain-syndrome pattern" with post-COVID symptom mainly characterized by pain [33]. The current paper includes a longer follow-up period of our previous multicenter cohort study [9] and describes two approaches analyzing the recovery curve of musculoskeletal post-COVID pain. Accordingly, the objectives of the current study were: 1) to investigate the prevalence of musculoskeletal post-COVID pain symptoms during the first year after the infection by using mosaic plots; 2) to develop a bar plot model analyzing the trajectory curve of musculoskeletal post-COVID pain; and, 3) to investigate those risk factors associated with the development of musculoskeletal post-COVID pain one-year after hospitalization.

Methods

Participants

The current multicenter cohort study (LONG-COVID-EXP-CM) included individuals who were hospitalized during the first wave of the pandemic (from March 20 to June 30, 2020) due to acute SARS-CoV-2 infection from five urban hospitals in Madrid (Spain). The positive diagnosis of SARS-CoV-2 infection was based on real-time reverse transcription-polymerase chain reaction (PCR) assay of nasopharyngeal/oral swab samples and the presence of consistent clinical and radiological findings at hospital admission. As previously described, all hospitalized COVID-19 survivors discharged

from the participating hospitals (n=7,150) were included in an anonymous database and a random selection of 400 patients from each hospital was performed with an online randomization software [9]. The study was approved by all the Local Ethic Committees (URJC0907202015920, HCSC20/495E, HUFA20/126, HUIL/092-20, HSO25112020, HUF/EC1517). Participants provided informed consent before their inclusion and before collecting any data.

Collection Data

The procedures of this multicenter cohort study have been previously described [9]. Briefly, clinical and hospitalization data were collected from hospital medical records. Participants were scheduled for a telephone semi-structured interview by trained health care researchers at two follow-up periods with a 5-month period in between. They were asked for the presence of pain symptoms appearing after hospital discharge and whether the symptoms persisted at each time of assessment. We used the definition of chronic primary musculoskeletal pain proposed by the International Association for the Study of Pain (IASP) for defining musculoskeletal post-COVID pain [28]. Symptoms should have to be present for at least three consecutive months after hospital discharge. Participants were asked to describe the location of their symptoms (e.g., neck, shoulder, spine, lower extremity, upper extremity, or generalized) at each follow-up. We did not include head pain, due to the particular classification of headaches and need for a specific diagnosis. Participants were excluded if they presented any underlying medical conditions which could best explain their pain, e.g., arthritis.

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 used by telephone interview [15]. Both the anxiety (HADS-A, 7-items, 0-21 points) and depressive (HADS-D, 7-items, 0-21 points)

scales of the HADS were included [16]. The cut-off score recommended for the Spanish population (HADS-A≥12 points; HADS-D≥10 points) was used as indicative of anxiety/depressive symptoms [14]. The PSQI (0-21 points) was used to evaluate sleep quality for the previous month, and a score ≥8.0 points was indicative of poor sleeper [4].

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) or percentages as needed. Missing values (less than 1% in our sample) were imputed using median imputation. For the first aim, the mosaic plots were created with Python's library statsmodels 0.11.1. For the second aim, exponential bar plots were created with Matplotlib 3.3.4. The exponential curves were fitted to the data according to the formula $y = Ke^{ct}$, where y represents the modeled prevalence of the post-COVID symptom (musculoskeletal pain) at a time t (in months), and K and c are the parameters of the model. For the third aim, McNemar's chi-squared test and paired Student t-tests were used to first compare proportions and means between patients with/ without musculoskeletal post-COVID pain at one-year follow-up. Finally, univariate and multivariate logistic regressions were performed to identify variables collected at hospital admission and also the presence of musculoskeletal post-COVID pain at the first follow-up period associated with the development of musculoskeletal post-COVID pain at one-year follow-up period 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 patients randomly selected from the involved hospitals and invited to the study, data from 1,969 patients (46.5% women, mean age: 61, SD: 16 years) were collected at hospital admission (T0) and at the first assessment (T1 - mean: 8.0, SD: 1.5, range 6 to 10 months after hospitalization). These results have been previously published [9]. A total of 1,593 patients (44.6% women, mean age: 61, SD: 15 years) completed the second assessment (T2 - mean: 13.2, SD: 1.5, range 11 to 15 months after hospitalization) and their data are presented here.

Evolution of Musculoskeletal Post-COVID Pain Symptoms during the first year

At the time of the one-year assessment, 603 (37.8%) patients reported musculoskeletal post-COVID pain symptoms. **Table 1** details clinical and hospitalization data comparison between patients with and without musculoskeletal post-COVID pain one-year after the infection. Patients with musculoskeletal post-COVID pain one-year after hospitalization showed a greater number of COVID-19 symptoms at hospital admission (with a greater prevalence of myalgia and headache, $P<0.001$), and a longer stay of hospitalization than those not reporting musculoskeletal post-COVID pain one-year after hospital discharge. Further, individuals with musculoskeletal post-COVID pain one-year after also presented higher anxiety and depressive levels and poor sleep quality than those without symptoms ($P<0.001$, **Table 1**). **Figure 1** illustrates the main body locations of musculoskeletal post-COVID pain one-year after hospitalization. Pain in the lower extremity and widespread symptomatology were the most prevalent.

The prevalence of myalgia was 30.3% (n=483) at hospital admission (T0), whereas the prevalence of musculoskeletal post-COVID pain was 43.4% (n=692) at T1 and 37.8% (n=603) at T2. **Fig. 2** graphs mosaic plots comparing the prevalence of musculoskeletal pain between T0 to T1, T0 to T2, and T1 to T2. Comparing T0 vs. T1 at **Figure 2**, 46.8% of the subjects (n=226/483) experiencing pain symptoms (myalgias) at hospital admission

(T0) had recovered eight months after (T1), whereas 62.8% (n=435/692) of those with pain at T1, had developed this post-COVID symptom "de novo" (did not have myalgias as onset symptom at hospital admission). Comparing T1 vs. T2, 31.9% (n=221/692) of individuals with post-COVID pain symptoms at T1 had recovered at T2, whereas 21.8% (n=132/603) had developed "de novo" post-COVID symptom as they did not report pain at T1. Finally, comparing T0 vs. T2, we observed that 36.8% (n=222/603) of the patients reporting musculoskeletal pain at T2 also experienced pain (myalgias) as onset symptom at hospital admission (T0). The trajectory curve showing a slightly decreasing prevalence trend of musculoskeletal post-COVID pain can be found within **Figure 3**.

New-Onset Musculoskeletal Post-COVID Pain at one-year

The prevalence of pre-existing musculoskeletal pain symptoms before the infection was significantly higher ($P<0.001$) in those reporting musculoskeletal post-COVID pain at one-year follow-up (53.2%) than in those without musculoskeletal post-COVID pain (32.8%). Therefore, from 603 patients reporting musculoskeletal post-COVID pain one-year after hospital discharge, since 321 (53.2%) reported pain symptoms before infection, those 282 (46.8%) without previous symptoms should be considered as "new-onset" post-COVID related musculoskeletal pain. From those 321 individuals suffering from previous symptoms, 178 (29.1%) reported that the perceived post-COVID pain was different from their previous symptomatology (new-onset musculoskeletal post-COVID pain), whereas the remaining 143 (23.7%) subjects experienced an increase of their previous symptoms (exacerbated musculoskeletal post-COVID related-pain). Accordingly, the prevalence of new-onset post-COVID musculoskeletal pain one-year after hospital discharge in the total sample was up to 75.9%. The remaining 24.1% experienced an increase of their previous pain symptoms after SARS-CoV-2 infection.

Risk Factors associated with Musculoskeletal Post-COVID Pain

Table 2 details the results of univariate and multivariate analyses. The univariate analysis found that the presence of several medical comorbidities, e.g., obesity (P=0.03), hypertension (P=0.02), asthma (P=0.045), rheumatological diseases (P=0.006), chronic obstructive pulmonary disease (P=0.033), or other conditions (P=0.002); and the presence of some COVID-19 onset-symptoms at hospital admission such as diarrhoea (P=0.003), dyspnea (P=0.04) or dizziness (P=0.007) 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 (OR1.593, 95%CI 1.148-2.211, P=0.003), history of pre-existing musculoskeletal pain (OR1.591, 95%CI 1.211-2.074, P=0.001), presence of myalgia (OR1.371, 95%CI 1.032-1.821, P=0.03), or headache (OR2.278, 95%CI 1.622-3.199, P<0.001) at hospitalization, days at hospital (OR1.013, 95%CI 1.000-1.025, P=0.04) and the presence of post-COVID pain at T1 (OR11.02, 95% CI 8.493-14.305, P<0.001) were significantly associated with musculoskeletal post-COVID pain one-year after hospital discharge.

Discussion

To the best of our knowledge, this multicenter study describes the largest cohort to date investigating the trajectory of musculoskeletal post-COVID pain during the first year after hospitalization. The prevalence of musculoskeletal post-COVID pain ranged from 43.4% to 37.8% during the first year. In fact, “de novo” associated COVID-19 pain symptoms appear in most patients from the onset of infection (myalgia) and throughout the first year. Based on the presence of previous pain symptoms before infection, the prevalence of new-onset musculoskeletal post-COVID pain was 75.9%. The trajectory curve revealed a small decreasing prevalence trend of musculoskeletal post-COVID pain the following months (years) after hospitalization, suggesting that pain could be a long-

lasting post-COVID symptom. Female gender, previous history of musculoskeletal pain, the presence of myalgia or headache as symptoms at hospital admission, and suffering from post-COVID pain before were risk factors associated with musculoskeletal post-COVID pain at one-year follow-up.

Musculoskeletal Pain as a Long-Lasting Post-COVID Symptom

Two scenarios associated with SARS-CoV-2 infection and pain are supported by our findings [7]. The first one is the development of pain as a new post-COVID symptom. The prevalence of musculoskeletal post-COVID pain one-year after hospitalization in our study was 40%. This rate is higher than the prevalence found in other studies investigating general post-COVID symptoms, where the prevalence did not reach 25% during the first six months [10]. This meta-analysis suggests that pain could be an underestimated post-COVID symptom if not specifically investigated as those studies focused on different aspect such as fatigue, cognitive impairments, etc. In agreement with our results, previous studies (with smaller sample sizes) specifically investigating post-COVID pain reported a prevalence of 60% during the first three months after infection [2,3,17,30]. These data are supported by the trajectory curve estimated in this study showing a potentially but slightly decrease of pain symptoms with the passage of months/years.

The evolution of musculoskeletal pain during and after SARS-CoV-2 infection is more complicated than expected as shown in the mosaic plots. The fact that myalgia is one of the fifth most common symptoms experienced during the acute phase of infection is not new [31]. Importantly, almost 50% experiencing myalgia at hospital admission did not experience post-COVID pain eight months after. In fact, 63% of subjects experiencing musculoskeletal post-COVID pain eight months after infection did not exhibit myalgia (pain) as an onset symptom, developing “de novo” pain. A similar trend was observed

one-year after hospitalization, since 22% of subjects reporting pain attributed to COVID-19 developed this symptom on its "delayed" form, that is, post-COVID attributed-pain appeared several months after the infection. This form of analysis (mosaic plots) revealed that post-COVID pain is a complex condition which needs to be carefully monitored. In fact, mosaic plots confirm that post-COVID pain has a roller coaster manifestation, at least, during the first year after SARS-COV-2 infection.

The second scenario is an exacerbation of pain symptoms in individuals with pre-existing pain [7]. Our results also support that almost 25% of individuals self-reporting post-COVID pain after hospitalization described that their symptoms present before the infection have been exacerbated in heterogeneous way, e.g., intensity, duration, location, or frequency. In fact, they specifically reported that no new symptoms appeared after their hospitalization, but clearly their symptoms worsened after. A third potential scenario (not investigated in our study) would be an increase of symptoms in individuals with chronic pain, but not infected [7]. Evidence supports that non-infected people with chronic pain experienced an increase of their pain symptoms during the worldwide lockdown [18,24], probably associated with emotional and social factors (such as fear, catastrophism, social alarm, post-traumatic stress disorder, somatization, or uncertainty about their prognosis), surrounding the worldwide COVID-19 outbreak [5].

Widespread symptoms, pain in the lower extremities and in the chest were the most common locations of post-COVID pain of musculoskeletal origin (Fig. 1). These locations agree with previous studies reporting that widespread symptomatology [27,32] and pain in the lower extremity [26,30] are the most commonly areas. The presence of widespread pain and sensitization-associated symptoms [13] supports the hypothesis that post-COVID pain resembles features of a "nociplastic" condition [20].

Although discussing the underlying mechanisms behind post-COVID pain is out of the scope of this study, some hypothesis can explain the results [8]. We can hypothesize that SARS-CoV-2 cell-to-cell inflammatory mechanisms (i.e., cytokine and interleukin storms) provoke hyper-excitability of peripheral and central nervous systems throughout different pathways leading to development of de novo musculoskeletal post-COVID pain or, in predisposed individuals, to worsening of pre-existing pain symptoms, as it has been reported in the current study. Similarly, the SARS-CoV-2 virus can lead to an exaggerated immune response by inducing a hyper-activation of T cells, macrophages, and natural killer cells. An exacerbated immune response would promote facilitation of the central nervous system. A third hypothesis associated with the development of musculoskeletal post-COVID pain would be the high presence of ACE2 and TMPRSS-2 receptors in the muscle [8]. All these mechanisms could act in an individual who had survived to COVID-19 and contributing to the development of de novo or exacerbated musculoskeletal post-COVID pain.

Musculoskeletal Post-COVID Pain Associated Risk Factors

Female gender, previous history of musculoskeletal pain, the presence of myalgia, or headache as onset symptoms, days at hospital and the presence of post-COVID pain at the first follow-up were risk factors associated with musculoskeletal post-COVID pain one-year after. Most of these factors have been also identified in our previous report [9]. That female sex is a risk factor for developing post-COVID symptoms is now supported in former literature [22]. Similarly, the fact that women experience higher prevalence of musculoskeletal pain than men [25] would also lead to a higher risk of developing post-COVID pain symptoms. Therefore, management of post-COVID pain should be applied from a gender perspective.

Second, that history of pre-existing musculoskeletal pain before the infection and the presence of musculoskeletal post-COVID pain at a shorter follow-up were also highly associated with post-COVID pain at one-year suggests that monitoring of pain symptoms should be carefully considered into the initial (and follow-up) screening of COVID-19 patients to avoid chronification of such pain. In fact, the presence of myalgias at hospital admission and how early the pain begins can provide clinical guidance on the character and prognosis of post-COVID pain. We did not collect the location of myalgia symptoms at hospital admission (viral-induced myalgias are usually experienced as a generalized discomfort) but this hypothesis should be explored in future studies. This is an interesting finding, since the presence of pain as an onset symptom of SARS-CoV-2 infection at hospital admission is associated with good prognosis for hospitalization [29] and with a lower likelihood of ICU admission and death [19], but it is a risk factor for long-term musculoskeletal post-COVID pain [9]. Further, we also observed that not only myalgia but also headache at hospital admission were risk factors for developing musculoskeletal post-COVID pain one-year after. Accordingly, careful monitoring of painful COVID-19 onset symptoms may help to identify subjects at a risk of developing musculoskeletal post-COVID pain.

Limitations

Although this is the largest study with the longest follow-up period to date focusing on musculoskeletal post-COVID pain, it has some limitations. First, we do not have data from non-hospitalized subjects. Although some studies had included pain as post-COVID symptoms, specific and detailed data about post-COVID pain in non-hospitalized patients is scarce. Second, we did not collect serological biomarkers or estimation of COVID-19 severity at hospital admission in this large cohort of COVID-19 survivors. Nevertheless, it has been observed that the association between serological biomarkers at hospital

admission and development of long-term musculoskeletal post-COVID pain is small [12]. Third, data were collected over telephone, not face-to-face, a procedure with a potential bias in population-based survey studies, but used in COVID-19 research [11, 21]. Zuschlag et al seen that the use of open-questions could lead to an underestimation of post-COVID symptoms whereas closed-questions could lead to an overestimation of a particular symptom [34]. Since we specifically asked for pain symptomatology, the use of closed questions could have introduced a bias toward this post-COVID symptom [34]. With current data we were not able to differentiate between arthralgia or myalgia as musculoskeletal pain symptom. Further, some individuals could also exhibit neuropathic symptoms, which could lead to the presence of different subgroups. Studies phenotyping pain symptomatology are now needed. Fourth, although we longitudinally assessed our cohort of patients and used two analyses, it is difficult to exclusively attribute to SARS-CoV-2 the development of post-COVID pain several months after the infection. The lack of a control group would limit this assumption. It would be interesting to determine the development of pain in individuals without a confirmed diagnosis of SARS-CoV-2 since it has been suggested that some physical post-COVID symptoms may be associated more with a personal belief in having been infected rather than with having a laboratory-confirmed diagnosis [23]. Additionally, it is also possible that psychological factors (e.g., perceived stress) associated with COVID-19 outbreak and which were not evaluated in the current study also contribute to musculoskeletal post-COVID pain.

Conclusions

This multicenter cohort study found a prevalence of musculoskeletal post-COVID pain up to 40% during the first year after hospitalization. Pain appeared as a “de novo” associated COVID-19 symptom in most patients (almost 76%) from the onset of infection

(as myalgias) and throughout the first year. The trajectory analysis shows a slightly decreasing prevalence trend of musculoskeletal post-COVID pain the following months (years) after hospitalization. Female gender, previous history of musculoskeletal pain, the presence of myalgia or headache as onset symptoms, and suffering from post-COVID pain at a shorter follow-up were factors associated with musculoskeletal post-COVID pain one-year after hospitalization.

Legend of Figures

Figure 1: Location of musculoskeletal post-COVID pain symptoms one year after hospital discharge (n=603)

Figure 2: Mosaic plots of musculoskeletal pain symptoms (from left to right): T0 (hospital admission) vs T1 (8.4 months after hospital discharge), T1 vs T2 (13.2 months after hospital discharge), and T0 vs T2.

Figure 3: Recovery curve of musculoskeletal pain symptoms. The vertical bars represent the percentage of patients that have musculoskeletal post-COVID pain at any time (opacity approximately indicates the sample size at a given time). The mean values used for the development of the mosaic plots at T0, T1 and T2 follow-ups have been marked with asterisks in the graphs.

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Declaration of interests

No conflict of interest is declared by any of the authors

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