# Time course prevalence of post-COVID pain symptoms of musculoskeletal origin in patients who had survived severe acute respiratory syndrome coronavirus 2 infection

*a systematic review and meta-analysis*

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# Time course prevalence of post-COVID pain symptoms of musculoskeletal origin in patients who had survived to SARS-CoV-2 infection: a systematic review and meta-analysis

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Abstract

The aim of this review/meta-analysis is to synthesize the prevalence of post-COVID pain symptoms of musculoskeletal origin in hospitalized/non-hospitalized patients recovered from SARS-CoV-2 infection. MEDLINE, CINAHL, PubMed, EMBASE, and Web of Science databases, as well as medRxiv and bioRxiv preprint servers were searched up to May 1, 2021. Studies or preprints reporting data on post-COVID pain symptoms such as myalgias, arthralgias, or chest pain after SARS-CoV-2 infection and collected by personal, telephonic, or electronical interview were included. The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale. Random-effects models were used for meta-analytical pooled prevalence of each post-COVID musculoskeletal pain symptom. Data synthesis was categorized at onset or hospital admission, and at 30, 60, and 90, and ≥180 days after. From a total of 12,123 studies identified, 27 peer-reviewed studies and 6 preprints were included. The sample included 14,639 hospitalized and 11,070 non-hospitalized COVID-19 patients. The methodological quality of almost 70% studies was fair. The overall prevalence of post-COVID myalgia, joint pain, and chest pain ranged from 5.65% to 18.15%, 4.6% to 12.1%, and 7.8% to 23.6% respectively at different follow-up periods during the first year post-infection. Time trend analysis showed a decrease prevalence of musculoskeletal post-COVID pain from the symptom's onset to 30 days after, an increase 60 days after, but with a second decrease ≥180 days after. This meta-analysis has shown that almost 10% of individuals infected by SARS-CoV-2 will suffer from musculoskeletal post-COVID pain symptomatology at some time during the first year after the infection.

Keywords: COVID-19, pain, myalgia, arthralgia, meta-analysis, prevalence.

## Introduction

The rapid spread of the coronavirus disease 2019 (COVID-19) caused by the pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a worldwide sanitary and humanitarian crisis. Symptoms associated with SARS-CoV-2 infection seem to be highly heterogeneous and can affect respiratory, musculoskeletal, gastrointestinal, cardiovascular or neurological systems. Symptoms in the musculoskeletal system include myalgias, arthralgias, and chest pain, although this latest symptom can be also related to respiratory problems. The World Health Organization (WHO) has recognized that around 15% of patients experience myalgias and arthralgias as COVID-19 associated symptoms. [55] Two meta-analyses have reported an overall prevalence of 19% for myalgias as an acute COVID-19 symptom,[1,8] but so far no systematic attempts have been made to specifically estimate post-COVID pain sequela. In fact, the Cochrane review concluded that myalgia and arthralgia are the fifth most prevalent symptom during the COVID-19 acute phase and may be also considered red flags for COVID-19 because their specificity (in addition to fever, fatigue, and headache) was over 90%.[48]

Importantly, many of the heterogeneous symptoms experienced by COVID-19 patients can persist after the acute phase of infection, leading to post-COVID or long COVID.[36] An increasing number of studies describing the presence of post-COVID symptoms have recently been conducted. In fact, two meta-analyses,[5,24] one narrative review,[44] one rapid review,[18] and one living systematic review[29] had been already published. All previous reviews pooled prevalence rates of post-COVID

symptoms without considering follow-up periods after the infection.[5,18,24,29,44] Only Michelen et al. differentiated between hospitalized and non-hospitalized patients but without pooling prevalence data. [29] Differentiation between hospitalized and non-hospitalized patients is important since most severe COVID-19 cases are hospitalized whereas mild, moderate or asymptomatic cases are non-hospitalized and, it would be expected that post-COVID symptoms would be different. Additionally, factors associated with hospitalization such as immobilization during hospitalization, intensive care unit (ICU) admission, pharmacological treatment, and hospital environment could promote development of post-hospitalization symptoms. Similarly, specific definition of follow-up periods when post-COVID symptoms appear are relevant to properly define post-COVID spectrum. [11] Finally, pooled specific data on post-COVID pain of musculoskeletal origin is scarce since only the meta-analysis by Lopez-Leon et al[24] reported post-COVID data of joint pain.

This study presents the first systematic meta-analysis pooling prevalence data of post-COVID pain symptoms of musculoskeletal origin, i.e., myalgia, arthralgia or chest pain, differentiating between hospitalized or non-hospitalized COVID-19 survivors and grouping post-COVID symptoms at different timepoints. The research questions of the current systematic review and meta-analysis were: 1, what is the prevalence of post-COVID myalgia, arthralgia (joint pain) or chest pain in hospitalized and non-hospitalized patients recovered from SARS-CoV-2 infection? 2, what is the time course and trajectory of these pain symptoms from the onset of the infection to different post-COVID follow-up periods?

## Methods

This systematic review and metanalysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and it was prospectively registered in the OSF database https://doi.org/10.17605/OSF.IO/2HRNZ

### Literature Search

Electronic literature searches were conducted with the assistance of an experienced health science librarian on PubMed, MEDLINE, CINAHL, EMBASE, and Web of Science databases, as well as on medRxiv and bioRxiv preprint servers, for published studies up to May 1, 2021. We screened the reference list of the identified papers for identifying other studies. The following terms were used: "long COVID", "long COVID symptoms", "long haulers", "chronic post-COVID symptoms", "post-COVID symptoms", "persistent post-COVID", "post-COVID pain" OR "long COVID pain". The inclusion and exclusion criteria were formulated using the Population, Concept, Context (PCC) mnemonic:

Population: Adults (>18 years), positively diagnosed of SARS-CoV-2 infection with real-time reverse transcription-polymerase chain reaction (PCR-RT). Both hospitalized and non-hospitalized patients were considered.

Concept: Collection of pain symptoms of musculoskeletal origin such as myalgia, chest pain, or arthralgia developed after the SARS-CoV-2 infection by personal, telephonic, or electronical interview.

Context: Monitorization of any post-COVID pain symptom of musculoskeletal origin after the acute phase. Studies monitoring just changes in immunological, serological, or radiological outcomes without the assessment of post-COVID pain were excluded.

Type of studies: Cohort or case-control studies where a sample of COVID-19 survivors, either hospitalized or non-hospitalized, were followed for the presence of post-COVID

myalgia, arthralgia, or chest pain for more than two weeks after infection were included. Editorials, opinion, case series, case reports, and correspondence articles were excluded. Language: No restriction in language was applied.

**Screening Process, Study Selection and Data Extraction**

Title of publications identified in the databases were reviewed by two authors in a blinded fashion before meeting. After removing duplicates, abstracts of the articles were screened for potential eligibility and posterior full-read text by the same two authors independently. For screening process and extraction, data were managed by sing Endnote and Covidence software (www.covidence.org). Data including author, country, sample size, clinical data, settings (hospitalization/no hospitalization), pain symptoms at onset, and post-COVID pain symptoms at different follow-up periods were extracted from each study. Both authors had to achieve a consensus on data-extraction. Discrepancies at any stage of the screening process were resolved by asking a third author, when needed.

**Methodological Quality**

The Newcastle-Ottawa Scale, a star rating system that evaluates the risk of bias of case -control and cohort studies was used for assessing methodological quality of the studies [54]. This scale includes three main sections: case selection (i.e., representativeness of cohort, selection of non-exposed cohort, ascertainment of exposure/case definition, and outcome of interest no present at start), comparability (i.e., analysis of between-groups comparison controlled for age, gender, or other factors), and exposure (i.e., outcome assessment, long enough and adequate follow-up period). In longitudinal cohort studies or case-control studies, a maximum of 9 stars can

be awarded. Studies scoring ≥ 7 stars are considered of good quality; those scoring 5 or 6 are of fair quality and studies scoring 0-4 are of poor quality. In cross-sectional studies, a maximum of 3 stars can be awarded. Studies scoring 3 are considered of good quality, those scoring 2 are of fair quality and studies scoring 1 star are of poor quality [54]. Two authors independently evaluated the methodological quality of the studies, and the differences, if existed, were discussed. If disagreement existed, a third researcher arbitrated a consensus decision.

**Data Synthesis and Analysis**

The meta-analysis was conducted with the R software 4.0.0 using *meta* and *dmetar* packages. Percentages and frequencies of each pain symptom at the acute phase of COVID-19 and each post-COVID pain symptom were extracted from each isolated study and an overall proportion was calculated reporting a single proportion using the *metaprop* function. We used a random-effects model because potential heterogeneity was expected. An $I^2$ value ≥75% was considered to indicate serious heterogeneity. We were not able to assess funnel plot asymmetry due to insufficient number of studies assessing the same post-COVID pain symptom at any particular follow-up. We calculated sample size-weighted mean scores for each study reporting data with their 95% confidence intervals (95%CI) in addition to potential meta-analytical summary effect on the pooled prevalence data for each symptom. Data synthesis was categorized at the acute phase (onset) and at 30 days, 60 days, 90 days and ≥180 days after onset/hospital discharge.

To determine the evolution of post-COVID pain symptoms over time (from onset to ≥180 days after), Freeman-Tukey double arcsine transformation was conducted using the *escalc* function in the *metafor package*. The *rma.mv* (meta-analytic multilevel random effect model with moderators via linear mixed-effect models) was used to carry

out a multilevel metanalysis with three levels to identify time and time*subgroup effect. For meta-analyses of studies reporting outcomes at multiple time points, it may be reasonable to assume that the true effects are correlated over time according to an autoregressive structure; hence, a heteroscedastic autoregressive (HAR) model was adopted. Grouping by gender was not possible due to lack of data in the available studies.

For quantitative data (age, days at hospital), overall means and standard deviations (SD) were calculated using the *pool.groups* function from the *dmetar* package. Median and interquartile range (IQR) were converted to mean and SD.[25] If necessary, data were estimated from graphs with the GetData Graph Digitizer v.2.26.0.20 software.

**Role of the Funding Source**

No funds were received. CFdlP and MSN had access to the raw data. The corresponding author had full access to all data and had final responsibility for the decision to submit.

**Patient and Public Involvement**

Patients were not involved in the study since this was a meta-analysis of the literature.

**Results**

**Study Selection**

The electronic search identified 12,123 potential peer-reviewed studies and preprints. After removing duplicates and papers not related to post-COVID pain symptoms, fifty-three studies remained. Nineteen (n=19) were excluded after title/abstract examination, leaving 34 articles for full-text analysis. Therefore, 27

published studies [2,6,7,12-17,19–23,26,32,33,42,46,47,49,50,52,53,56,57,59] and seven preprints [4,9,35,39,40,51,59] were initially included. One preprint [51] was excluded because the study was posteriorly published in a peer-reviewed journal.[50] A total of 27 peer-reviewed studies [2,6,7,12-17,19-23,26,32,33,42,46,47,49,50,52,53,56,57,59] and six preprints [4,9,35,39,40,60] (total n=33) were finally included in the meta-analysis **(Figure 1)**.

Eighteen studies were conducted in European countries including France [7,13,49,56], Italy [4,6,19,53], Spain [12,33], United Kingdom [2,52,60], Denmark [22], Sweden [15], Norway [47],The Netherlands [14], and Faroe Islands. [42] The remaining fifteen were conducted in China [16,57,59], USA [9,20,23,39,40] , Egypt [21], Russia [35], India [26], Iran [32], Brazil, [46], Pakistan [17], and multi-country (including UK, USA and Sweden) [50].

**Sample Characteristics**

The features of the COVID-19 samples of the included studies are shown in **Table 1.** Twenty-two studies included hospitalized patients [2,6,7,12,13,16,19-22,26,32,33,35, 40,46,49,52,53,56,57,59], whereas twelve included non-hospitalized patients [4,9,14,15, 17,20,23,39,42,47,50,60]. The total sample included 25,709 COVID-19 survivors (56.2% female; mean age: 47.25, SD: 15.8 years); 14,639 were hospitalized (42.74% female; age: 49.0, SD 16.9) whereas 11,070 (75% female; age: 45, SD: 13.9) were non-hospitalized. The prevalence of post-COVID pain symptoms of musculoskeletal origin was assessed in different follow-up periods after onset or hospital discharge: 30days after in ten studies (n=7 hospitalized [15,19,22,26,32,39,59], n=3 non-hospitalized [9,17,39]), 60days after in seven (n=5 hospitalized [6,7,15,21,33], n=2 non-hospitalized [9,50]), 90 days after in fifteen (n=10 hospitalized, [2,13,20,22,46,49,52,53,56,57], n=5 non-hospitalized [9,14, 20,42,47]), and ≥180 days

after in eight (n=4 hospitalized [12,15,16,35], n=4 non-hospitalized [4,23,39,60]) studies.

Overall, hypertension (23.8%, 95%CI 17.6-31.2%) and obesity (22.2%, 95%CI 13.7-34.0%) were the comorbidities more prevalent. Pre-existing comorbidities were, in general, more prevalent in hospitalized patients than in non-hospitalized patients, being statistically significant for obesity, hypertension, diabetes, heart and kidney diseases (all, $P<0.01$). **Table 2** summarizes pooled age, gender, pre-existing medical co-morbidities and hospitalization data of COVID-19 survivors included in the studies.

A supplementary table (available at http://links.lww.com/PAIN/B512) summarizes which study assessed myalgias, arthralgias or chest pain as associated COVID-19 symptom at each moment. Pooled prevalence data of myalgias, arthralgias or chest pain at the acute phase and at each post-COVID follow-up period experienced by the total sample, including both hospitalized and non-hospitalized patients and by group are detailed in **Table 3**.

**Methodological Quality**

Twenty-four (72.7%) were cross-sectional, 22 were considered of fair quality (2/3 stars), and two of poor quality (1/3 stars). Six were longitudinal cohort studies with high methodological quality (≥7/9 stars), whereas three were case-control studies, one of poor quality (5/9 stars) and two of high quality (7/9 stars). No disagreement between authors was observed. **Table 4** presents the Newcastle-Ottawa Scale scores for each study and a summary of every item.

**Time Course of Myalgias as an associated COVID-19 Pain Symptom**

In the total sample, the prevalence of myalgia was 44.5%, 5.65%, 10.3%, 18.1%, and 10.9% as symptom at onset/hospital admission, and 30days, 60days, 90days and ≥ 180days after onset/hospital discharge, respectively (Table 3). All pooled data showed

high heterogeneity ($I^2 \geq 75\%$). No significant differences between hospitalized and non-hospitalized patients were observed except for myalgias as an onset symptom where non-hospitalized patients experienced higher prevalence than those hospitalized.

**Figure 2** graphs the evolution of myalgias at onset/hospitalization to 30, 60, 90, and ≥180 days. The random effect model revealed a significant effect for time ($P<0.001$) showing that the prevalence of myalgia dropped from the symptom's onset to 30days, but increased 60days after, with a second decrease ≥180days after. No significant group*time effect was observed showing that this tendency was similar in both hospitalized and non-hospitalized patients.

**Time Course of Arthralgias as an associated COVID-19 Pain Symptom**

The overall prevalence of joint pain was 33.2%, 4.6%, 12.0%, 12.1%, and 7.7% as symptom at onset/hospital admission, and 30days, 60days, 90days and ≥ 180days after onset/hospitalization, respectively (Table 3). All pooled data showed high heterogeneity ($I^2 \geq 75\%$). No significant differences between hospitalized and non-hospitalized patients were seen except for joint pain as post-COVID symptom 60days after symptoms' onset where hospitalized patients experienced higher prevalence than that non-hospitalized.

The random effect model again revealed a significant effect for time ($P<0.001$), but not group*time, showing that the prevalence of joint pain dropped from symptom's onset to 30days, but increased 60days after, with a second decrease ≥180days after in a similar way in both hospitalized and non-hospitalized COVID-19 survivors (**Figure 2**).

**Time Course of Chest Pain as an associated COVID-19 Symptom**

The overall prevalence of chest pain was 18.1%, 7.9%, 23.6%, 11.6%, and 7.8% as symptom at onset/hospital admission, and 30days, 60days, 90days and ≥ 180days after onset/hospital discharge respectively (Table 3). Most data have shown high

heterogeneity ($I^2 \geq 75\%$). No significant differences between hospitalized and non-hospitalized patients were observed except for chest pain as an onset symptom where non-hospitalized patients experienced higher prevalence than those hospitalized.

Again, the prevalence of chest pain dropped from symptom's onset to 30days, but increased 60days after, with a second decrease ≥90days after (P<0.001, **Figure 2)**.

## Discussion

### Findings

This systematic review/meta-analysis is the first one investigating the prevalence of post-COVID pain symptoms of musculoskeletal origin considering different follow-up periods and if patients were hospitalized or not. We found that the overall prevalence of post-COVID myalgia, joint pain, and chest pain ranged from 5.65% to 18.15%, 4.6% to 12.1%, and 7.8% to 23.6% respectively at different follow-up periods during the first year after the infection. In fact, we were able to identify 27 peer-reviewed studies and six preprints; however, most studies were of fair methodological quality and showed high heterogeneity in their results.

Previous meta-analyses did not differentiate between hospitalized/non-hospitalized patients and did not separate between follow-up periods [5,24], therefore, the comparison between current and previous data should be conducted with caution. Lopez-Leon et al reported an overall prevalence of 19% (95%CI 7-34%, n=4 studies) for joint pain and of 16% (95%CI 10-22%, n=6 studies) for chest pain, no data on myalgia was reported [24]. Cares-Marambio et al focused their meta-analysis on respiratory post-COVID symptoms and reported a pooled prevalence of post-COVID chest pain of 16% (95%CI 10-23%, n=5 studies) [5]. Both meta-analyses provided overall prevalence data without distinction between hospitalized/non-hospitalized

patients nor considering follow-up periods after the infection.[5,24] Additionally, studies included in previous meta-analyses included short-term follow-ups ranging from 3 weeks and 3 months.[5,24]

The prevalence of persistent pain after suffering a viral disease has been also found in Severe Acute Respiratory Syndrome (SARS) where almost 20% of the patients exhibit persistent pain the first year after the infection.[3,31] These data are similar to the general trend observed in the current study for post-COVID pain of musculoskeletal origin; However, it should be recognized that SARS outbreak led to a lower number of infected people worldwide than COVID-19, making current results more relevant from a public health perspective.

An important information provided by the current meta-analysis was the time course analysis of post-COVID pain-related symptoms of musculoskeletal origin. The time trend analysis revealed a decrease in prevalence of musculoskeletal post-COVID pain from the acute onset/hospital admission to 30days after, with an increase 60days after, but with a second decrease ≥180days after (Fig. 2). This time course of post-COVID pain symptoms of musculoskeletal origin confirms a fluctuating nature of post-COVID symptomatology and the relevance of determining the follow-up period when the symptoms are assessed [11]. This fluctuating pattern could be explained by current hypotheses suggested for the development of post-COVID musculoskeletal pain symptoms. The most expanded theory is the potential effects of the prolonged pro-inflammatory response (i.e., cytokine storm) associated to SARS-CoV-2 infection on the immune system[34]. The overproduction of inflammatory mediators may promote several processes associated with muscular pain, such as increase of inflammatory interleukin-6 (IL-6)[10] and of angiotensin-converting enzyme 2 (ACE2) at the central and peripheral nervous systems[27,45]. It is possible that these responses could lead to

hyper-excitability of the central nervous system throughout different pathways promoting musculoskeletal pain as long-term post-COVID sequalae. If the development of post-COVID pain symptoms is related to changes into the immune system affected by the prolonged effect of the SARS-CoV-2 infection, it is probably that these changes need time to be manifested explaining the decrease of pain symptoms from the acute onset (where the immune system hardly fight against the infection) to 30days after (where the infection could seem to be solved), with a posterior increase 60days after (where a potential reactivation of the process would occur again). No available data exists explaining the fluctuating pattern of post-COVID symptomatology.

Another relevant finding was that this time trend was similar in hospitalized and non-hospitalized patients supporting that the time course of post-COVID pain symptoms of musculoskeletal origin seems to be similar in severe COVID-19 patients (hospitalized) and moderate to mild COVID-19 patients (non-hospitalized). These results would suggest that the presence of post-COVID pain symptoms of musculoskeletal origin may be more related to the fact of suffering from COVID-19 and not as much to hospitalization factors. This hypothesis would agree with current proposal that symptoms load, i.e., the number of symptoms at the acute phase of COVID-19, but not the severity of the disease, is a risk factor associated with the presence of post-COVID symptoms [58].

Interestingly, the prevalence of myalgia as an onset symptom at the acute phase of the infection was higher in non-hospitalized patients. One potential explanation would be related to the topic that myalgia is not considered as bothersome symptom if compared with other onset COVID-19 related-symptoms such as dyspnea, or fever. It is possible that pain symptoms are underreported by patients at hospital admission. This hypothesis agrees with a clustering study showing that individuals experiencing pain

symptoms, e.g., arthromyalgia and headache, as onset at hospital admission showed good prognosis for hospitalization by COVID-19[43]. No study has directly compared post-COVID pain of musculoskeletal origin between cases requiring hospitalization and those recovering at home (non-hospitalized) to better understand these differences.

The prevalence of arthralgias and chest pain was similar in both hospitalized and non-hospitalized patients at all follow-up periods. It should be noted that differentiating myalgias and arthralgias can be difficult for both patients and clinicians. Patients usually describe COVID-19 associated-myalgia as generalized diffuse muscular pain, whereas joint pain is mostly described as regional pain surrounding different joints. Differentiation between these post-COVID symptoms of musculoskeletal origin needs further studies. Similarly, chest pain may be also a post-COVID symptom associated with cardiovascular complications such as myocardial infarction, arrhythmia or cardiomyopathies resembling STEMI presentations seen in COVID-19 patients. No effort in the literature included in the current meta-analysis has been done to differentiate the origin of chest pain symptoms.

**Strengths and Weaknesses**

Although this is the first meta-analysis summarizing prevalence rates of post-COVID pain symptoms of musculoskeletal origin, its results should be considered according to its strengths and weaknesses. The rigorous methodology applied on the review process, the methodological quality assessment, and the inclusion of more than 30 studies can be considered as strengths of the review. Nevertheless, some weaknesses should be also recognized. First, a meta-regression could not be conducted because the heterogeneity between studies. Second, the small number of studies in some comparisons limit the generality of current results. For instance, the number of patients requiring ICU admission was small for pooling specific data. Similarly, no study

provided prevalence data of post-COVID symptoms by gender or age; therefore, it was not possible to analyze gender or age effects. Although a small number of studies reported that females tend to report more post-COVID symptomatology [58], data stratified by gender was not provided. This will be highly important for future studies due to the higher prevalence of musculoskeletal pain in females.[28,30,38] Fourth, most studies included Caucasian subjects, with just four studies including Chinese people and none including African people; hence, racial influence on the presence of post-COVID musculoskeletal pain symptoms is not known. Finally, post-COVID symptoms were cross-sectionally obtained and mostly self-reported by the patients. Future longitudinal studies investigating the time course of the symptoms in the same cohort of patients will help to elucidate this question.

**Future Research Directions**

The current review and meta-analysis analyzing prevalence rates of post-COVID pain symptoms of musculoskeletal origin opens several questions for future studies. First, due to the relapsing and remitting nature of post-COVID symptoms in general, it would be highly relevant to determine the time frame where a particular post-COVID symptom should be considered as an acute post-acute COVID symptom or as a long-term post-COVID symptom[37]. In fact, results from this meta-analysis support the remitting nature of post-COVID pain symptoms of musculoskeletal origin based on the time trend.

Second, identification of risk factors associated with post-COVID pain is crucial for future research. The heterogeneity in the methodology of the studies included in this meta-analysis did not permit to identify any risk factor associated with post-COVID pain. Only one study identified that the presence of myalgias as an onset symptom at the acute phase was associated with a higher risk of post-COVID musculoskeletal pain.[12]

Studies investigating risk factors associated with post-COVID pain symptoms are clearly needed. An important factor to be considered as a risk factor in future studies is the presence of musculoskeletal pain conditions before infection since it is not the same the development of pain as a new post-COVID symptom or experiencing a post-COVID exacerbation of previous pain symptoms. This consideration would lead to differentiate between presence of new-onset musculoskeletal post-COVID pain (compatible with a diagnosis of chronic primary musculoskeletal pain, defined by the International Association for the Study of Pain[41], and exacerbated post-COVID pain symptoms (related to the presence of pre-existing musculoskeletal pain). Only one study described pain conditions suffered before COVID-19 infection by patients.[12] Finally, studies investigating potential underlying mechanisms explaining post-COVID pain and the time trend seen in this meta-analysis would help for management of this group of individuals.

## Conclusions

This meta-analysis revealed that almost 10% of individuals infected by SARS-CoV-2 will exhibit musculoskeletal post-COVID pain symptomatology at some time during the first year after the infection. The time course of the symptoms supports a fluctuating pattern since the prevalence of post-COVID pain symptoms decreased from the symptom onset at the acute infection to 30days after, increased 60days after, but again decrease ≥180days after. Early identification of post-COVID pain symptoms of musculoskeletal origin will ensure immediate action and counselling of long haulers who may otherwise struggle with unrecognized and unmanaged symptoms.

## Legend of Figures

**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow diagram

**Figure 2**: Time course trend of the musculoskeletal post-COVID pain symptoms from the symptoms' onset/hospital admission to 30days, 60days, 90days and ≥180 days after.

* Statistically significant effect (P<0.001) showing a time trend during the different follow-up periods

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**Author contributions**

All authors contributed to the study concept and design. CFdlP, DMP, GPM and MNS conducted literature review. CFdlP, MNS, and LLF did the statistical analysis. All authors contributed to interpretation of the data. CFdlP, VGM, LLF and LAN drafted the paper. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

**Conflict of Interest**

No conflict of interest is declared by any of the authors

**Role of the Funding Source**

No funds were received for this study

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**Table 1:** Characteristics of the included studies investigating musculoskeletal post-COVID Pain Symptoms

| Study | Country | Participants (Male/Female) | Hospitalization | Age Mean (SD) | Days of follow -up (median) |
|---|---|---|---|---|---|
| **Carvalho-Schneider et al.**[7] | France | 150 (66 / 84) | YES | 49 (15) | 30-60 |
| **Jacobs et al.**[19] | Italy | 183 (112 / 71) | YES | 57 IQR 48-68 | 35 |
| **Carfi et al.**[6] | Italy | 143 (90 / 53) | YES | 56.5 (14.6) | 60 |
| **Kamal et al.**[21] | Egypt | 287 (103 /184) | YES | 32.3 (8.5) | 60 |
| **Moreno-Pérez et al.**[33] | Spain | 277 (146 /131) | YES | 56 (42 – 67.5) | 77 |
| **#Perlis et al.**[40] | USA | 5,437 (3,189 / 2,248) | YES | 37.87 (11.92) | 60 |
| **Garrigues et al.**[13] | France | 120 (73 / 47) | YES | 63.2 (15.7) | 100 |
| **Arnold et al.**[2] | UK | 110 (68 / 42) | YES | 60 IQR 46-73 | 90 |
| **Xiong et al.**[57] | China | 538 (245 / 293) | YES | 52 IQR 41-62 | 97 |
| **Huang et al.**[16] | China | 1,733 (897 / 836) | YES | 57 IQR 47-65 | 186 |
| **Jacobson et al.**[20] | USA | 22 (14 /8) | YES | 50.6 (15.1) | 138 |
| **Sykes et al.**[52] | UK | 134 (88 / 46) | YES | 59.6 (14) | 113 |
| **Zhou et al.**[59] | China | 89 (46 / 43) | YES | 43 (31-52) | 21 |
| **Venturelli et al.**[53] | Italy | 767 (515/ 252) | YES | 63 (13.6) | 81 |
| **Suarez-Robles et al.**[49] | France | 134 (515 / 252) | YES | 58.5 (18.5) | 90 |

| | | | | | |
|---|---|---|---|---|---|
| **COMEBAC Study Group et al.**[56] | France | 478 (277 / 201) | YES | 60.9 (16.1) | 113 |
| #**Munblit et al.**[35] | Russia | 2,649 (1,296 / 1,353) | YES | 56 (46-66) | 217.5 |
| **Mahmud et al.**[26] | India | 355 (207 / 148) | YES | 39.8 (13.4) | 30 |
| **Leth et al.**[22] | Denmark | 49 (21 / 28) | YES | 58 (48-73) | 40-90 |
| **Moradian et al.**[32] | Iran | 200 (160 / 40) | YES | 55.6 (13.5) | 36 |
| **Fernández-de-las-Peñas et al.**[12] | Spain | 738 (352 / 386) | YES | 60 (15) | 210 |
| **Carvalho Soares et al.**[46] | Brazil | 46 (21 / 25) | YES | 56.3 (15) | 113 |
| ***Jacobson et al.**[20] | USA | 96 (49 / 47) | NO | 41.6 (12.5) | 115 |
| #**Cirulli et al.**[9] | USA | 357 (NR) | NO | 56 IQR 18-89 | 30-60-90 |
| **Goertz et al.**[14] | Netherland | 2113 (310 / 1,803) | NO | 47 IQR 39-54.0 | 80 |
| **Stavem et al.**[47] | Norway | 451 (198 / 253) | NO | 49.8 (15.2) | 95 |
| **Petersen et al.**[42] | Faroe Islands | 180 (82 / 98) | NO | 39.9 (19.4) | 120 |
| **Sudre et al.**[50] | Multi-country | 4,182 (1,192 / 2,990) | NO | 42 (32-53) | 30-60 |
| **Logue et al.**[23] | USA | 177 (76 /101) | NO | 48 (15.2) | 169 |
| **Iqbal et al.**[17] | Pakistan | 158 (71 / 87) | NO | 32.1 (12.4) | 38 |
| #**Peluso et al.**[39] | USA | 135 (100 / 79) | NO | 48 (37-57) | 3-36 weeks |
| **Havervall et al.**[15] | Sweden | 323 (55 / 268) | NO | 43 (33-52) | 30-60-180 |
| #**Boscolo-Rizzo et al.**[4] | Italy | 304 (119 / 185) | NO | 47 (18-76) | 365 |
| #**Ziauddeen et al.**[60] | UK | 2,550 (413 / 2,108) | NO | 46.5 (11) | 220 |

SD: standard deviation; IQR: Interquartile range; NR: Not Reported

* Jacobson et al included both hospitalized and non-hospitalized patients

# These articles are preprint and not peer-reviewed papers.



**Table 2:** Pooled means of demographic and clinical data of the total sample (n=25,709), hospitalized (n=14,639) and non-hospitalized (n=11,070) COVID-19 patients

| | **Total** | **Hospitalized** | **Non-Hospitalized** |
|---|---|---|---|
| **Age, mean (SD), years** | 47.25 (15.8)<br>N=25,709 - 32 studies | 49.0 (16.9)<br>N=14,639 - 22 studies | 45.0 (13.9)<br>N=11,070 - 12 studies |
| **Gender, male/female n (%)** | 11,386 (43.8%) /<br>14,608 (56.2%) | 9,189 (57.53%) /<br>6,791 (42.74%) | 2,665 (24.95%) /<br>8,019 (75.05%) |
| **Medical co-morbidities** | | | |
| Obesity | 22.2% [13.7; 34.0]<br>N = 2,005 / 8,860<br>$I^2$ = 95% - 8 studies | 23.8% [13.0; 39.6]<br>N = 869 / 4,374<br>$I^2$ = 98% - 6 studies | 18.3 [10.2; 30.8]<br>N = 1,136 / 4,486<br>$I^2$ = 97% - 2 studies |
| Hypertension* | 23.8% [17.6; 31.2]<br>N = 3,024 / 9,809<br>$I^2$ = 97% - 21 studies | 29.4% [22.9; 36.9]<br>N = 2,864 / 8,664<br>$I^2$ = 97% - 16 studies | 10.7% [5.5; 19.7]<br>N = 160 / 1,145<br>$I^2$ = 82% - 5 studies |
| Diabetes* | 11.0% [8.0; 15.0]<br>N = 1,357 / 13,665 | 14.5% [11.1; 18.6]<br>N = 1,195 / 8,664 | 4.2% [2.75; 6.25]<br>N = 162 / 5,001 |

| | | | |
|---|---|---|---|
| | $I^2$ = 96% - 21 studies | $I^2$ = 92% - 16 studies | $I^2$ = 82% - 5 studies |
| Heart Disease* | 8.0% [5.3; 12.0]<br>N = 1,054 / 12,310<br>$I^2$ = 97% - 18 studies | 11.45% [8.25; 15.75]<br>N = 934 / 7,307<br>$I^2$ = 94% - 13 studies | 2.9% [1.25; 6.5]<br>N = 120 / 5,003<br>$I^2$ = 93% - 5 studies |
| Asthma | 8.7% [6.2; 12.15]<br>N = 881 / 10,027<br>$I^2$ = 93% - 12 studies | 8.0% [4.6; 13.3]<br>N = 379 / 5,056<br>$I^2$ = 95% - 8 studies | 10.1% [9.3; 11.0]<br>N = 502 / 4,971<br>$I^2$ = 0% - 4 studies |
| COPD | 5.6% [3.9; 8.0]<br>N = 467 / 7,889<br>$I^2$ = 92% - 14 studies | 5.95% [4.0; 8.6]<br>N = 443 / 7,889<br>$I^2$ = 93% - 12 studies | 3.8% [1.4; 10.1]<br>N = 24 / 484<br>$I^2$ = 82% - 2 studies |
| Cancer | 3.2% [2.25; 4.55]<br>N = 269 / 8,275<br>$I^2$ = 80% - 14 studies | 3.7% [2.5; 5.4]<br>N = 258 / 7,612<br>$I^2$ = 82% - 11 studies | 1.65% [0.9; 3.0]<br>N = 11 / 663<br>$I^2$ = 0% - 3 studies |
| Kidney disease* | 2.7% [1.5; 4.8]<br>N = 274 / 10,975<br>$I^2$ = 98% - 11 studies | 3.5% [2.1; 5.9]<br>N = 247 / 6,635<br>$I^2$ = 92% - 9 studies | 0.6% [0.4; 0.9]<br>N = 27 / 4,340<br>$I^2$ = 5% - 2 studies |
| Immune Disorders | 4.2% [3.0; 6.0]<br>N = 101 / 2,441<br>$I^2$ = 71% - 8 studies | 4.1% [2.5; 7.3]<br>N = 77 / 1,958<br>$I^2$ = 78% - 6 studies | 5.0% [3.3; 7.3]<br>N = 24 / 483<br>$I^2$ = 35% - 2 studies |
| **Stay at the hospital, mean (SD), days** | | 12.9 (7.9)<br>N=7,671 - 16 studies | |
| **Intensive Care Unit (ICU) admission**<br>Yes/No, n (%)<br>Stay at ICU, mean (SD), days | | <br><br>469 - 12 studies<br>16.0 (14.5)<br>N= 415 - 7 studies | |

COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; SD: Standard Deviation

* Significant differences in the presence of pre-existing medical comorbidities between non-hospitalized and hospitalized COVID-19 patients

**Table 3:** Pooled prevalence of symptoms at onset, and post-COVID Symptoms 30, 60, and ≥90 days after onset/hospitalization

| | Onset | | | 30 days after | | | 60 days after | | | 90 days dafter | | | ≥180 days dafter | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **T** | **H** | **NH** | **T** | **H** | **NH** | **T** | **H** | **NH** | **T** | **H** | **NH** | **T** | **H** | **NH** |
| **Myalgia** | **44.55%** | **32.6%** | **58.3%*** | **5.65%** | **5.5%** | **5.7%** | **10.3%** | **8.1%** | **13.0%** | **18.15%** | **22.0%** | **14.0%** | **10.9%** | **9.8%** | **12.5%** |
| 95%CI | 35.5; 54.0 | 22.6; 44.5 | 53.2; 63.2 | 2.5; 12.2 | 1.6; 17.3 | 2.4; 12.9 | 3.3; 27.9 | 3.55; 17.3 | 1.6; 58.1 | 10.2; 30.25 | 9.2; 44.0 | 7.85; 23.9 | 6.7; 17.7 | 3.9; 22.0 | 7.9; 19.9 |
| $I^2$ | 98% | 97% | 92% | 90% | 91% | 87% | 100% | 98% | 99% | 98% | 98% | 98% | 99% | 98% | 97% |
| Event/Total | 4,536/8,747 | 823/2,436 | 3,713/6,311 | 110/1,585 | 67/876 | 43/709 | 665/6,898 | 286/5,857 | 379/1,041 | 1,040/4,626 | 199/1,666 | 841/2,960 | 1,198/5,286 | 191/5,826 | 878/3,312 |
| Studies | 17 | 9 | 8 | 8 | 5 | 3 | 6 | 3 | 3 | 12 | 7 | 5 | 14 | 7 | 7 |
| **Joint Pain** | **33.2%** | **32.05%** | **33.6%** | **4.6%** | **4.1%** | **5.2%** | **12.0%** | **22.9%** | **4.13%*** | **12.1%** | **10.6%** | **13.3%** | **7.7%** | **8.4%** | **7.1%** |
| 95%CI | 23.5; 44.5 | 19.0; 48.7 | 21.4; 48.5 | 1.6; 12.85 | 1.4; 11.7 | 0.8; 27.3 | 4.5; 28.5 | 13.0; 37.4 | 1.0; 15.0 | 8.2; 17.5 | 4.8; 21.8 | 9.0; 19.2 | 2.5; 21.3 | 2.0; 30.85 | 1.4; 29.6 |
| $I^2$ | 95 | 94 | 96 | 96% | 91% | 98% | 95% | 91% | 93% | 94% | 94% | 94% | 100% | 100% | 99% |
| Event/Total | 2,419/6,570 | 145/436 | 2,274/6,134 | 142/1,644 | 44/777 | 98/867 | 173/1,037 | 152/560 | 21/477 | 620/3,641 | 80/782 | 540/2,859 | 1,618/8,370 | 452/5,016 | 1,166/3,354 |
| Studies | 10 | 3 | 7 | 8 | 4 | 4 | 5 | 3 | 2 | 7 | 3 | 4 | 7 | 3 | 4 |
| **Chest Pain** | **18.1%** | **11.3%** | **29.5%*** | **7.9%** | **5.6%** | **10.9%** | **23.6%** | **21.0%** | **28.5%** | **11.6%** | **10.1%** | **16.7%** | **7.8%** | **4.4%** | **11.25%** |
| 95%CI | 10.1; 30.1 | 5.0; 23.4 | 17.2; 45.6 | 2.9; 19.8 | 1.2; 22.9 | 3.3; 30.6 | 11.9; 41.5 | 14.4; 29.7 | 5.8; 72.2 | 8.2; 16.2 | 6.7; 15.0 | 10.8; 25.0 | 3.25; 17.5 | 3.9; 5.1 | 3.2; 32.8 |
| $I^2$ | 99 | 97 | 99 | 95% | 93% | 97% | 98% | 84% | 99% | 95% | 88% | 86% | 99% | 0% | 98% |
| Event/Total | 2,571/6,843 | 135/1,345 | 2,426/5,498 | 114/1,105 | 35/554 | 79/551 | 481/1,278 | 131/560 | 350/718 | 721/4,547 | 187/2,218 | 534/2,329 | 218/7,311 | 190/4,278 | 919/3,033 |
| Studies | 11 | 6 | 5 | 6 | 3 | 3 | 5 | 3 | 2 | 11 | 8 | 3 | 5 | 3 | 3 |

T: Total sample, H: Hospitalized COVID-19 patients; NH: Non-hospitalized COVID-19 patients; CI: Confidence interval

* Statistically significant differences between hospitalized and non-hospitalized patients; # No heterogeneity between studies ($I^2$<75%)

**Table 4:** Newcastle-Ottawa Quality Assessment Scale: Quality appraisal cohort/cross-sectional studies

| | Selection | | | | Comparability | | Exposure | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Cohort Study** | **Representativeness of exposed cohort** | **Selection of non-exposed cohort** | **Ascertainment of exposure** | **Outcome of interest nor present at start** | **Study controls for age/gender** | **Study controls for additional factor** | **Assessment of outcome** | **Long enough follow-up** | **Adequate follow-up** | **Score** |
| **Carvalho-Schneider et al.**[7] | ★ | | ★ | | | | | | | 2/3 |
| **Jacobs et al.**[19] | ★ | | ★ | | | | | | | 2/3 |
| **Carfi et al.**[6] | ★ | | ★ | | | | | | | 2/3 |
| **Kamal et al.**[21] | | | ★ | | | | | | | 1/3 |
| **Moreno-Pérez et al.**[33] | ★ | | ★ | | | | | | | 2/3 |
| **#Perlis et al.**[40] | ★ | | ★ | | | | | | | 2/3 |
| **Garrigues et al.**[13] | ★ | | ★ | | | | | | | 2/3 |
| **Arnold et al.**[2] | ★ | | ★ | | | | | | | 2/3 |
| **Xiong et al.**[57] | ★ | | ★ | | | | | | | 2/3 |
| **Huang et al.**[16] | ★ | | ★ | | | | | | | 2/3 |
| **Jacobson et al.**[20] | ★ | | ★ | | | | | | | 2/3 |
| **Sykes et al.**[52] | ★ | | ★ | | | | | | | 2/3 |
| **Zhou et al.**[59] | ★ | | ★ | | | | | | | 2/3 |
| **Venturelli et al.**[53] | ★ | | ★ | | | | | | | 2/3 |
| **Suarez-Robles et al.**[49] | ★ | | ★ | | | | | | | 2/3 |
| **COMEBAC Study Group et al.**[56] | ★ | | ★ | | | | | | | 2/3 |
| **#Munblit et al.**[35] | ★ | | ★ | | | | | | | 2/3 |
| **Mahmud et al.**[26] | ★ | | ★ | ★ | ★ | ★ | | ★ | ★ | 7/9 |
| **Leth et al.**[22] | ★ | | ★ | ★ | ★ | ★ | | ★ | ★ | 7/9 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Moradian et al.**[32] | | ★ | | ★ | ★ | | ★ | ★ | | | ★ | ★ | | 7/9 |
| **#Cirulli et al.**[9] | | ★ | ★ | ★ | ★ | | ★ | ★ | | | ★ | ★ | | 8/9 |
| **Goertz et al.**[14] | | ★ | | | | | | | | | | | | 1/3 |
| **Stavem et al.**[47] | | ★ | | ★ | | | | | | | | | | 2/3 |
| **Petersen et al.**[42] | | ★ | | ★ | | | | | | | | | | 2/3 |
| **Iqbal et al.**[17] | | ★ | | ★ | | | | | | | | | | 2/3 |
| **#Peluso et al.**[39] | | ★ | | ★ | | | | | | | | | | 2/3 |
| **Sudre et al.** [50] | | ★ | | ★ | | | | | | | | | | 2/3 |
| **Havervall et al.**[15] | | ★ | | ★ | ★ | | ★ | ★ | | | ★ | ★ | | 7/9 |
| **#Boscolo-Rizzo et al.**[4] | | ★ | | ★ | ★ | | ★ | ★ | | | ★ | ★ | | 7/9 |
| **#Ziauddeen et al.**[60] | | ★ | | ★ | | | | | | | | | | 2/3 |
| **Case-Control Study** | | **Adequate case definitions** | **Representativeness of cases** | **Selection of controls** | **Definitions of controls** | | **Controlled for age** | **Controlled for additional factors** | | **Ascertainment of exposure** | **Same method for cases and controls** | **Non-response rate** | | **Score** |
| **Logue et al.**[23] | | ★ | ★ | ★ | ★ | | | | | | ★ | | | 5/9 |
| **Fernández-de-las-Peñas et al.**[12] | | ★ | ★ | ★ | ★ | | ★ | ★ | | | ★ | | | 7/9 |
| **Carvalho Soares et al.**[46] | | ★ | ★ | ★ | ★ | | ★ | ★ | | | ★ | | | 7/9 |

# These articles are preprint and not peer-reviewed papers.