

# BMJ Open Post-COVID pain and quality of life in COVID-19 patients: protocol for a meta-analysis and systematic review

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## ABSTRACT

**Introduction** During the COVID-19 pandemic, approximately 10%–35% of COVID-19 infected patients experience post-COVID sequelae. Among these sequelae, pain symptoms should not be neglected. In addition, the sequelae of COVID-19 also decrease the quality of life of these populations. However, meta-analyses that systematically evaluated post-COVID pain are sparse. **Methods and analysis** A comprehensive screening will be performed by searching MEDLINE and Embase without language restriction from inception to August 2021. Cohort studies, case-control studies, cross-sectional studies and case series will be included. Case report and interventional studies will be excluded. Studies with less than 20 participants will be also excluded. We aim to investigate the prevalence of pain-related symptoms in patients after the acute phase of COVID-19. The impact of COVID-19 on the quality of life and pain symptoms among these populations in the post-acute phase will also be evaluated. ROBINS-I tool will be used to assess the risk of bias of cohort studies. The risk of bias tool developed by Hoy *et al* will be used to assess the risk of bias of prevalence studies. Metaprop command in Stata will be used to estimate the pooled prevalence of pain symptoms. DerSimonian and Laird random-effects models will be used to calculate the pooled relative risks. All analyses will be calculated using Stata software (V.15.0; StataCorp) **Ethics and dissemination** Ethics approval is not required. Results of our study will be submitted to a peer-review journal.

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## INTRODUCTION

In December 2019, a disease caused by SARS-CoV-2 was first reported and subsequently named COVID-19 by the WHO.<sup>1</sup> According to reports, the incubation period of COVID-19 patients is generally 1–14 days, and symptoms generally appear 3–7 days after infection.<sup>2,3</sup> The clinical manifestations of COVID-19 patients are mostly respiratory symptoms, but many patients still have clinical manifestations of other systems, and the severity varies greatly, ranging from asymptomatic to death.<sup>1,4–6</sup>

## Strengths and limitations of this study

- ⇒ This meta-analysis will comprehensively evaluate the prevalence of post-COVID pain.
- ⇒ We will evaluate whether COVID-19 survivors after acute infection have a relatively higher risk of pain compared with controls, as controls are critical for characterising long COVID-19.
- ⇒ We will also assess the difference in the quality of life between COVID-19 survivors and controls.
- ⇒ Heterogeneity and risks of bias among included studies may influence the results of the meta-analysis.

It is worth noting that a considerable portion of COVID-19 patients still have various persistent symptoms or delayed complications after the acute phase of SARS-CoV-2 infection.<sup>7–9</sup> This phenomenon is defined as post-COVID syndrome or post-acute COVID-19 syndrome.<sup>9,10</sup> The prevalence of post-COVID syndrome varied with its definitions, study population, duration of follow-up. It is estimated that the prevalence of post-COVID syndrome is about 10%–35%, which is more prevalent in hospitalised patients, with a prevalence rate affecting up to 85%.<sup>9</sup> A prospective cohort study indicated that post-acute COVID-19 syndrome was present in 50.9% of COVID-19 survivors.<sup>11</sup> In a large Chinese study, up to 76% of discharged patients reported at least one symptom at 6 months after acute infection.<sup>12</sup>

In patients with the post-COVID syndrome, fatigue is the most common symptom, with a prevalence of 17.5%–72%,<sup>12–14</sup> followed by residual dyspnoea, with a prevalence between 10% and 40%.<sup>9,15</sup> The prevalence of mental problems, olfactory and gustatory dysfunctions are 26% and 11%, respectively.<sup>9,16</sup> Of note, among these sequelae, pain should also not be neglected. Increasing studies have reported that COVID-19 patients experience pain in different body regions such as myalgia, arthralgia, headache, chest pain

and abdominal pain.<sup>17-19</sup> To date, the prevalence of these disturbing experiences during the post-COVID period varied among related studies.

Meanwhile, a decline in quality of life is notable in the post-acute COVID-19 setting.<sup>16, 20</sup> In a study by Carfi *et al*, worsened quality of life, as measured by the EuroQol Visual Analogue Scale (VAS), was observed in 44.1% of discharged patients.<sup>16</sup> In another study, 56% of patients have a severe decrease in quality of life, defined as a decrease  $\geq 10$  in the EuroQol instrument.<sup>20</sup> A comprehensive understanding of the pain and the long-term impact on the quality of life is needed beyond the acute phase.

Although, previous meta-analyses focusing on post COVID-19 syndrome<sup>21-23</sup> and specific types of pain (such as headache) have been published,<sup>19</sup> up to now, systematic evaluation on pain in different body locations in recovered COVID-19 patients is sparse. In addition, COVID-19 infected patients who have severe illness during the acute phase are at high risk for post COVID-19 syndrome.<sup>10</sup> Duration of follow-up also has an impact on the data of the persisting symptom in post-acute COVID-19 setting.<sup>24</sup> Hence, it is reasonable to determine the prevalence of post-COVID pain stratified by severity of COVID-19 and follow-up period. However, these analyses are still limited. Moreover, one major limitation of previous studies is the lack of appropriate controls. Persistent physical symptoms after COVID-19 should not be automatically attributed to SARS-CoV-2,<sup>25</sup> and psychological factor may be associated with an increased risk of some persistent physical symptoms, including pain and dyspnea.<sup>26</sup> Hence, controls are vital for assessing long COVID-19.<sup>27</sup>

In this study, we will propose a meta-analysis and systematic review to comprehensively estimate the prevalence of post-COVID pain in different body regions and explore the impact on pain and quality of life in the postacute illness setting. Moreover, subgroup analysis will be performed stratified by disease severity and follow-up duration.

## METHODS

This protocol was developed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols (online supplemental files S1 and S2).<sup>28</sup> We plan to begin this meta-analysis in August 2021 and expect it to be completed within 1 year.

### Database and search strategy

In this systematic review and meta-analysis, we will search Medline via Ovid and Embase, databases for articles published from 2020 with no restrictions on language of publication. A full search strategy for MEDLINE via Ovid is presented (see online supplemental file S3). The search strategy will include a combination of subject terms and free-text terms. These terms will be combined by using 'OR' and 'AND' Boolean operators. Briefly, the search strategy will have these sets of terms: (1)

terms to search for "post-COVID" including post-acute COVID-19 syndrome, chronic COVID-19 syndrome, long COVID-19, post COVID-19, etc; (2) terms to search for "pain" including pain, arthralgia, headache, myalgia, muscle soreness, etc; (3) terms to search for "quality of life" including quality of life, QoL, HRQoL, etc. In addition, terms to search for post-COVID can also be a combination of "COVID-19" (including terms such as coronavirus disease 2019, COVID-19, COVID-2019, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, 2019nCoV, etc) and "sequelae" (including terms such as subacute, residual, persisting, persistent, long-term, etc). All subject terms will be exploded where appropriate. We will perform similar searches with a search strategy adapted to Embase database. The reference lists of full-text articles and other reviews retrieved during the search or known to the authors will also be manually searched for relevant articles.

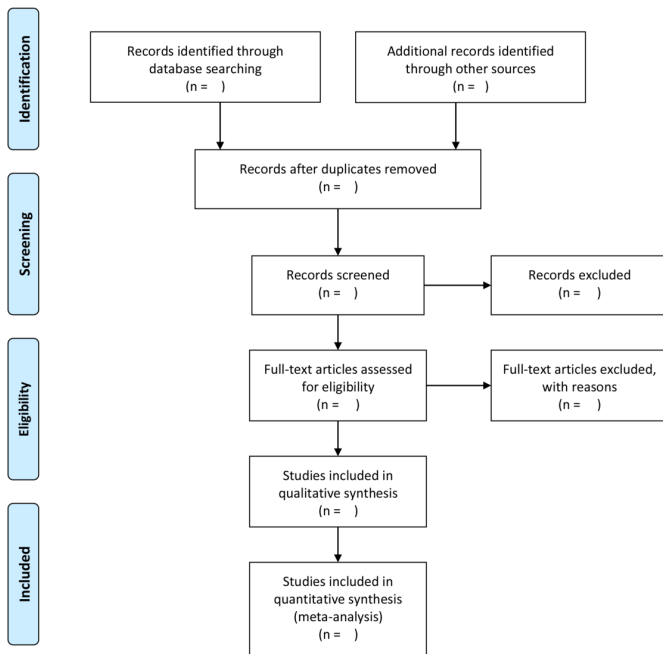
### Study selection and data extraction

This systematic review is to determine the prevalence of pain in different body regions (including arthralgia, myalgia, chest pain, abdominal pain, back pain, headache, sore throat and general pain) in COVID-19 patients after the acute phase. We will also assess the impact of COVID-19 on the pain symptoms and quality of life in the postacute phase compared with controls.

Prospective or retrospective cohort studies, case-control studies, cross-sectional studies, and case series, which reported the data concerning pain and/or quality of life in patients after acute COVID-19, will be included in this systematic review. The eligible instruments for pain include but are not limited to the following: Numerical Rating Scale and VAS. Meanwhile, the eligible instruments for quality of life include, but are not limited to the following: EuroQol five dimensions questionnaire, 36-Item Short Form Survey, Clinical COPD Questionnaire, Patient-Reported Outcomes Measurement Information System tool, St George's Respiratory Questionnaire. Case report and interventional studies will be excluded. We will also exclude studies with less than 20 participants.

We will export all citations identified by the above-mentioned search strategy to EndNote V.X9; duplicates will be removed by this bibliographic management software. The screening of citations will be conducted by this software. The first stage of screening involved screening the title and abstract. Two independent reviewers will assess the eligibility of studies according to inclusion and exclusion criteria. In the second stage of screening, full-text records retained from the first round of screening are then retrieved. Full-text records selected for inclusion by both authors will be included in the systematic review. When two or more studies included the same population and reported an overlapping sample, the study with the largest sample size will be considered.<sup>29-31</sup>

Any disagreements during this stage will be resolved through discussion. The citations in identified reports were also screened for relevant literature. In this case, if



**Figure 1** PRISMA flow chart for study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

non-English studies will be selected for inclusion in the review, Google Translate will be used to translate into English. A PRISMA flow will be constructed in [figure 1](#).

Two authors will independently extract data, including study characteristics, follow-up period, the prevalence of pain, instruments used to measure pain and quality of life, quality of life using a standardised excel sheet. If the studies report data from the same cohort but at different time points, the data at different time points are valuable and will be collected. To extract data in non-English studies, Google Translate will be used. If necessary, data were estimated from graphs with the GetData Graph Digitizer software.

### Assessment of the risk of bias

The risk of bias of the selected trials will be assessed independently by two reviewers. ROBINS-I tool will be used to assess the risk of bias of cohort and longitudinal studies.<sup>32</sup> The risk of bias tool developed by Hoy *et al*<sup>33</sup> will be used to assess the risk of bias of prevalence studies. We will resolve any disagreement through discussion.

### Statistical analysis

In this study, we will estimate the pooled prevalence of pain symptoms by using the Metaprop command in Stata with a random-effects model.<sup>34</sup> If investigators use multiple thresholds to create different levels of pain in the primary studies, these data will be dichotomised as present or absent, irrespective of the intensity.<sup>35</sup> Pain and quality of life may be often measured using different instruments. To combine continuous data from different measurement instruments for the same construct, the following approaches will be first considered: minimally

important difference (MID) approach.<sup>36–39</sup> If an MID has been established for all instruments, we will report the pooled results in MID units. That is, we standardise by dividing the mean difference by the MID.<sup>36–38</sup> As a result, we will obtain an estimate in MID units rather than obtaining an estimate in SD units. If MIDs have not been established for all instruments, we will undertake conversion to natural units the most popular instrument among included studies based on methods described by Thorlund *et al*.<sup>39</sup> Relative risks will be used to determine whether COVID-19 survivors after the acute phase have a relatively higher risk of pain and impaired quality of life compared with COVID-19-free populations. DerSimonian and Laird random-effects models will be used to calculate the pooled relative risks.<sup>40</sup> If adequate studies (three or more studies) are not available, we will undertake narrative syntheses. Heterogeneity will be reported as  $X^2$  test and  $I^2$  statistic.

Subgroup analyses will be undertaken based on evaluation instruments, the severity of COVID-19, age (adult vs children), follow-up periods, sample size, quality of included studies, and so on. Subgroup comparisons will be performed by Metaprop command.<sup>34</sup> The Instrument for assessing the Credibility of Effect Modification Analyses will be used to assess the credibility of effect modification analyses.<sup>41</sup> We also plan to assess the small-study effects using Egger's regression intercept and the skewness.<sup>42 43</sup> A two-sided  $p < 0.05$  will be regarded as significant for all analyses. All analyses will be calculated using Stata software (V.15.0; StataCorp).

### Patient and public involvement

Patients and the public will not be involved in the study.

### DISCUSSION

The current protocol reveals a clear plan to perform a meta-analysis and systematic review on post-COVID pain and residual effects of SARS-CoV-2 infection on quality of life, which provide pivotal information to make better decisions about prevention, treatment and management of post-COVID pain.

So far, some meta-analyses have reported the occurrence of pain caused by COVID-19.<sup>19 44</sup> However, these meta-analyses are focused on certain types of pain, such as headaches.<sup>19</sup> The scopes of researches are relatively narrow. Other than previous meta-analyses, this work will comprehensively evaluate pain symptoms in different body locations rather than a certain type of pain. Otherwise, prespecified subgroup analyses will be performed to explore the impact of disease severity and follow-up period on the outcome measures in this meta-analysis. In addition, as controls are vital when assessing the long COVID-19, we will evaluate whether COVID-19 survivors after the acute phase have a relatively higher risk of pain compared with COVID-19-free populations. Meanwhile, we will also assess the difference in the quality of life between COVID-19 survivors and controls. In short, this

systematic review will provide a better understanding of pain and quality of life in post-acute COVID-19 setting. Nevertheless, the following potential limitations should be noted: First, same as other meta-analysis, the quantity of included trials may influence the results of this study. Second, differences in patient characteristics, definitions of outcomes and methodological quality among included trials may cause considerable heterogeneity. Finally, due to the rapid updating of new studies regarding the issue, the latest research published during the submission process may not be included in the current work.

### Ethics and dissemination

For this type of study, ethics approval is unnecessary because data of individual patients will not be included and no privacy will be involved. The results of this review will be published in a peer-reviewed journal. Amendments of the basic protocol will be documented in the comprehensive review.

**Contributors** MM, YY, YX, JZ and JG conceptualised and designed the current study. YX, MM and YY drafted this protocol. The search strategy was designed by YX and MM and literature search will be performed by YY, PL, MJ, MY and ZW were involved in the methodological aspects and analysis sections of the protocol. JZ and JG are the guarantors of this review.

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**Competing interests** None declared.

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