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Systematic Review

Long haul COVID-19 and its associated risk factors: a systematic review and meta-analysis protocol

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ABSTRACT

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) first reported in December 2019 in Hubei province of Wuhan, China. Most people infected with COVID-19 disease experienced mild to moderate symptoms or even no symptoms at all, but growing body of evidence has shown that large number of COVID-19 survivors are experiencing multitude of long-lasting symptoms persisting for varied number of periods after the acute phase of infection. This condition is known as long COVID and since July 2021 has been added as a recognized condition that could result in a disability under the American with disability act (ADA). We will undertake a systematic search in PubMed, PubMed Central and Google scholar from December 2019 till June 2022. The study designs to be included will be cross-sectional, case-control, cohort, follow-up, observational studies. No ethical issues are anticipated. Dissemination will be done by submitting article to academic peer review journals. To add into the pool of knowledge of long COVID and provide evidence-based insight, this systematic review was planned to know about the prevalence of long COVID sequalae, commonly reported symptoms by COVID-19 survivors at an interval of 3, 6 and 12 months and possible risk factors attributable to the emergence of these symptoms. PROSPERO registration (CRD 42022340175).

Keywords: COVID-19, Long haul COVID, Long COVID, Prevalence, Post-COVID-19 symptoms

INTRODUCTION

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) first reported in December 2019 in Hubei province of Wuhan, China. It was acknowledged as a public health emergency of international concern (PHEIC) by World Health Organization (WHO) on 30 January 2020 and declared a "global pandemic" on 11 March 2020.[1,2] Most people infected with COVID-19 disease experienced mild to moderate symptom or even no symptoms at all, but growing body of evidence has shown that large number of COVID-19 survivors are experiencing multitude of long-lasting symptoms lasting for varied number of period after the acute phase of infection. This condition is known as long COVID and since July 2021 has been added as a recognized condition that could result in a disability under the American with disability act (ADA).[3,4] It has also been narrated using different words like 'post COVID-19 syndrome', 'post-acute COVID', 'chronic COVID-19' to name a few. A cohort study conducted among COVID-19 patients in Wuhan reported long COVID symptoms at 12 months in 49 percent.[5] Similarly study conducted by Groff et al on short and long-term rates reported proportion of COVID-19 survivors experiencing at least 1 PASC at more than 6 months in 54 percent.[6] Why some people get long COVID? What causes long COVID? What are the treatment modalities for long COVID? There are many

more questions pertaining to long COVID which still remain unanswered. Most of the data regarding long COVID have come from experiences and stories shared by COVID-19 survivors with some experiencing only 1 or 2 symptoms while others having an array of symptoms affecting different parts of their body like brain, kidney, heart, and joint. To add into the pool of knowledge of long COVID and provide evidence-based insight, this systematic review was planned to know about the prevalence of long COVID sequalae, commonly reported symptoms by COVID-19 survivors at an interval of 3, 6 and 12 months and possible risk factors attributable to the emergence of these symptoms.

Operational definition of long haul COVID-19

An interim definition of persistent symptoms and potential sequalae beyond 12 weeks from the onset of initial symptoms is used for the sake of this systematic review.

Research question

This systematic review will address the following research questions: what are the long haul COVID-19 sequalae? what are the associated risk factors of long haul COVID-19 sequalae?

METHODS

Prior to the onset of this project PROSPERO, MEDLINE and Cochrane data base were screen and no similar systematic reviews or meta-analysis were found pertaining to our research question. Following this, the study was registered on PROSPERO (CRD 42022340175). The items in this systematic review protocol are being reported as per the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidelines (Figure 1).

Inclusion criteria

Population/participants

Survivors of COVID-19 infection (either discharged from hospital or managed at home) were participants of the study.

Intervention/exposure

The patients were exposed to COVID-19 infection. Exposure: None.

Comparator/control

No control was used.

Outcome

Incidence rate of long haul COVID-19 infections (number of individuals with new symptoms following recovery from COVID-19), and proportion of organ specific long haul COVID-19 sequalae.

Phenomena of interest

For this systematic review, all the studies reporting post COVID-19 symptoms will be considered. It will focus on the most common system affected post COVID-19 among the survivors and identifying the risk factors pertaining to it.

Types of study

To address the research questions this systematic review will consider observational studies including follow up studies, cross-sectional study, prospective cohort, retrospective cohort or case-control studies. Studies with full text article and in English language published from December 2019 till June 2022 will be included in this review. Review articles, opinion articles randomized control trials, meta-analysis and articles written in language other than English will be excluded.

Search strategy

3 electronic data bases will be systematically searched for the relevant articles to be included in the present systematic review and meta-analysis. The database will be PubMed, PubMed Central (PMC) and Google scholar. The following MeSH heading will be used “post-acute COVID-19 syndromes”, “long haul COVID”, “chronic COVID-19 syndromes”, “post-acute sequalae of SARS-Cov-2 infection”. The details of search strategy are given in Table 1.

Table 1: Search strategy.

Search	Query	Records retrieved
#1	(((((((Long COVID) OR (Long haul COVID)) OR (Persistent COVID-19)) OR (Long hauler COVID)) OR (Chronic COVID syndrome)) OR (COVID, Long-Haul)) OR (Post-Acute COVID-19 Syndromes)) OR (Post-Acute Sequelae of SARS-CoV-2 Infection)	26,794
#2	"COVID-19"[All Fields] AND "syndrome"[All Fields]) OR ("Long"[All Fields] AND "covid"[All Fields]) OR "long covid"[All Fields] AND "COVID-19"[All Fields] AND "syndrome"[All Fields]) OR ("Long"[All Fields] AND "haul"[All Fields] AND "covid"[All Fields]) OR "long haul covid"[All Fields]) OR (("persist"[All Fields] OR "persistance"[All	1,412

Continued.

Search	Query	Records retrieved
	Fields] OR "persistant"[All Fields] OR "persisted"[All Fields] OR "persistence"[All Fields] OR "persistences"[All Fields] OR "persistencies"[All Fields] OR "persistency"[All Fields] OR "persistent"[All Fields] OR "persistently"[All Fields] OR "persistents"[All Fields] OR "persister"[All Fields] OR "persisters"[All Fields] OR "persisting"[All Fields] OR "persists"[All Fields]) AND ("COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19 vaccines"[All Fields] OR "COVID-19 vaccines"[MeSH Terms] OR "COVID-19 serotherapy"[All Fields] OR "COVID-19 serological testing"[All Fields] OR "COVID-19 serological testing"[MeSH Terms] OR "COVID-19 testing"[All Fields] OR "COVID-19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) OR ("Long"[All Fields] AND "hauler"[All Fields] AND ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "covid"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields])) OR (("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "covid"[All Fields] OR "COVID-19"[MeSH Terms] OR "COVID-19"[All Fields]) AND ("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "syndrome"[MeSH Terms]	

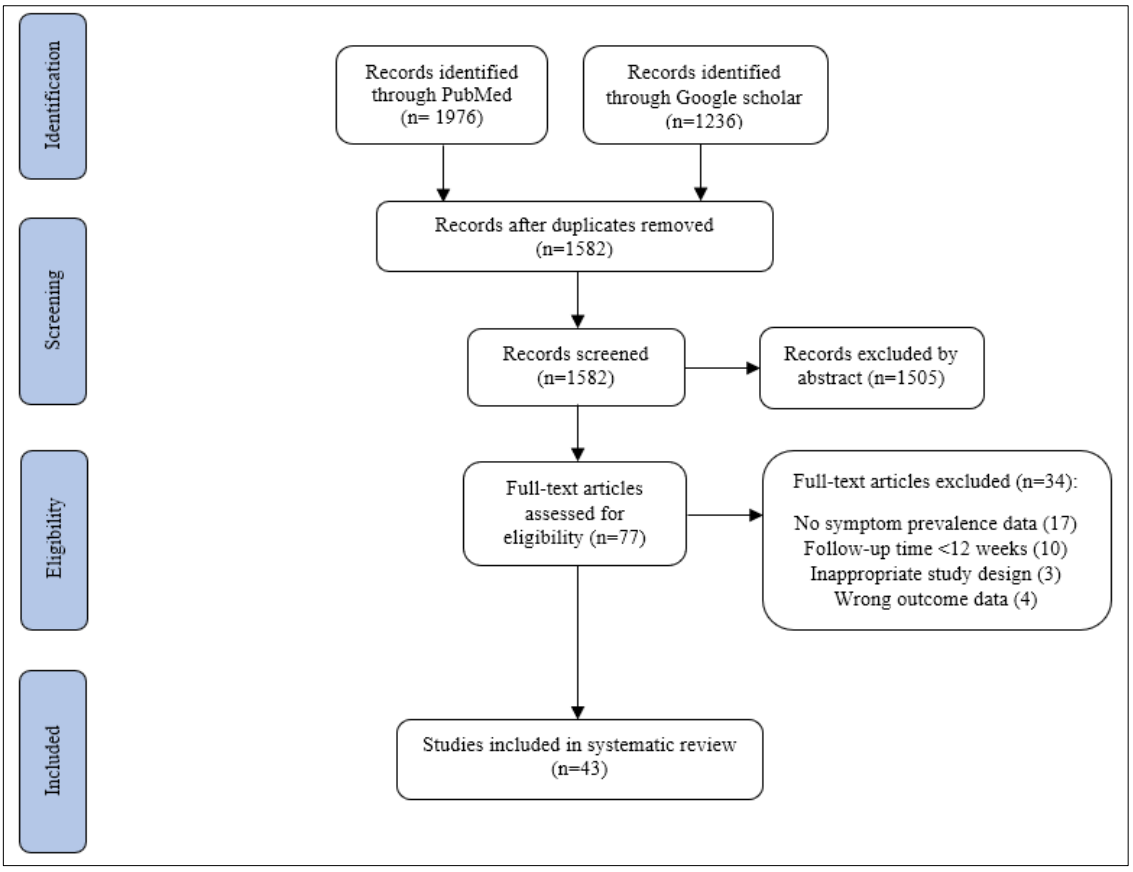

Figure 1: PRISMA flow diagram.

Selection of study

Following the search, all identified citations will be assembled and uploaded into EndNote, and duplicates will be removed. Titles and abstracts of all the selected studies will then be screened independently by 3 reviewers (PP, MK, SJ) for assessment against the inclusion and exclusion criteria for the review. For quality check, 50% of the abstracts will be independently assessed by supervisor (MA). Potentially relevant studies will be retrieved in full. The full text of selected citations will be again assessed in

detail against the inclusion criteria by two independent reviewers (PP, MK). Rationale for the exclusion of full-text studies that do not meet the adopted inclusion criteria will be recorded and addressed in the systematic review. Any conflict that will arise between the reviewers at any stage of the study's selection process will be resolved through dialogue or with a third reviewer (MA). The results of the search will be documented in full in the final systematic review and presented in a preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

Data extraction

First, all the databases will be searched independently by three reviewers (PP, MK, SJ) then the studies obtained from all the databases will be exported to End note version X8 software to remove the duplicates. The two authors will independently conduct a comprehensive screening of the title and abstracts including the eligibility criteria. Any disagreement between the two reviewers will be resolved by third reviewer/author (MA). After reaching at a good consensus, the full-text review will be performed. Finally, the reviewers (PP, MK) will independently extract data using a standardized data collection tool. The data will be extracted under the following headings i.e., author's name, year of study, study setting, study design, study participants and their age group, sample size, follow up period, symptoms reported, system affected and associated risk factors (if reported), etc. Any discrepancies during the selection and data collection will be resolved by discussion and consensus with other team members (SJ, SV, AS). Coding will be done by the team members only.

Assessment of methodological quality

Final selected studies will be critically appraised by three reviewers (PP, MK, SJ) independently for methodological quality in the review using New Newcastle-Ottawa scale (NOS), which is used to measure risk of bias in non-randomised studies.[7] Based on NOS criteria, a maximum of 4 stars for selection, 2 stars for comparability and 3 stars for exposure and outcome assessment were assigned. Studies with stars less than 5 were considered of low quality, with 5 to 7 stars of moderate quality and with more than 7 stars of high quality. Correspondents of papers, when required, will be contacted to request missing or additional data for clarification. Any disaccord that arises between the reviewers will be rectified by discussion or with a third reviewer (MA). The results of the critical appraisal will be reported in narrative as well as in table form. Ensuing critical appraisal, studies mot meeting the certain quality threshold will be excluded.

Strategy for data synthesis

Quantitative evaluation of the studies will be done in order to summarize the data and meta-analysis will be performed for the quantitative pooling of study findings. Pooled prevalence and its confidence intervals of specific post COVID-19 symptoms will be synthesized. Funnel plots and Egger's test will be conducted to look for the publication bias. Moreover, heterogeneity between the studies will be seen by means of forest plots as well as assessed using I^2 heterogeneity statistic. Meta-analysis will be conducted only for symptoms assessed by 2 or more studies, using random effects model and inverse variance weighting method will be used to calculate the pooled prevalence rate and effect size (OR) of each associated factor.

Statistical analysis will be performed using R core team (2022).

Confounding variables will be duly mentioned in the final systematic review and meta-analysis. Potential confounders expected to be there are: persistent symptoms of post intensive care syndrome (PICS), long term effects of treatment used during the acute illness of COVID-19 like corticosteroids. Also, long COVID carry a resemblance to chronic fatigue syndrome (CFS), another chronic condition that is often triggered by a viral infection.[8]

To adjust the effect of such confounders on the outcome variable meta regression will be performed and adjusted for the same in the analysis stage.

DISCUSSION

In this systematic review protocol, we have described in detail the study designs, population, interventions, and outcomes that will be considered in accordance with the objective and the data sources, search strategy, data extraction, risk of bias assessment and data synthesis.

CONCLUSION

This systematic review and meta-analysis will provide scientific evidence into the prevalence of long COVID sequelae among COVID-19 survivors, commonly involved organ systems and their potential risk factors. This in turn will help the policy makers and clinicians to build treatment and rehabilitation modalities to combat the rising number of people suffering from post-COVID syndrome.

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