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Efficacy and safety of hyperbaric oxygen therapy for long COVID: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction There is still a lack of therapeutic options for long COVID. Several studies have shown the benefit of hyperbaric oxygen therapy (HBOT) on long COVID. However, the efficacy and safety of HBOT for long COVID remain unclear. Therefore, we will conduct this systematic review to assess the feasibility of HBOT as a primary or complemental therapy for long COVID.

Methods and analysis Databases such as Web of Science, PubMed, Embase, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, International Clinical Trials Registry Platform, Wanfang Database, China National Knowledge Infrastructure, SINOMED, VIP Database and the Chinese Clinical Trial Registry will be searched systematically from the establishment to 9 December 2023. All articles will be reviewed by two independent reviewers. Cochrane risk of bias tool will be used to assess the risk of bias in the study. We will evaluate heterogeneity using a visual inspection of the funnel plot. If an available number of studies are identified, we will perform a meta-analysis.

Ethics and dissemination No ethical approval is required since this study is based on published articles. The findings will be published in a peer-reviewed journal or disseminated through conference presentations.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A comprehensive literature search will be conducted without language limitation.
⇒ A thorough evaluation of bias will be carried out.
⇒ Detailed subgroup analysis will help us to better investigate the efficacy of hyperbaric oxygen therapy.
⇒ Lack of study restrictions may lead to low-quality evidence.

INTRODUCTION

Long COVID, also referred to as post-acute COVID-19 syndrome, is a multisystemic condition following COVID-19 infection. Preliminary reports have shown that at least 65 million individuals are estimated to suffer from long COVID, with cases increasing daily.[1 2] It is defined as the continuation or development of new symptoms 3 months after the initial COVID-19 infection, with these symptoms lasting for at least 2 months with no other explanation.[3] Most people with COVID-19 get better within a few days to a few weeks after infection, so at least 4 weeks after infection is the start of when long COVID could first be identified. A clinical study showed that even after 2 years, the risk of most sequelae of COVID-19 could be persistently increased.[4] The mechanism of long COVID remains unclear. Several hypotheses suggest that chronic inflammation, metabolic perturbations, endothelial dysfunction and gut dysbiosis may be involved.[5] Serotonin reduction, increased complement activation, thromboinflammation and tissue infiltration of amyloid-containing deposits in skeletal muscles can be observed in long COVID, informing the potential biomarkers for diagnosis and directions for treatment.[6–8]

Currently, available therapeutic choices for long COVID are largely insufficient.[9] Prompt multidisciplinary assessment is required in the management of long COVID.[10] Hyperbaric oxygen therapy (HBOT) is a non-invasive treatment based on the administration of 100% oxygen at raised pressure. HBOT has been shown a significant effect on improving the quality of life in some diseases with chronic fatigue.[11 12] Safety and effectiveness for several chronic inflammatory diseases have been verified.[13] Accumulating evidence does find a benefit of HBOT on long COVID.[14–16] However, to our knowledge, there is no relative review to evaluate the quality of these studies. Therefore, this systematic review and meta-analysis aim to better investigate the overall efficacy and safety of HBOT for long COVID.

METHODS

Protocol registration and reporting

The protocol for this systematic review and meta-analysis was registered on the

International Prospective Register of Systematic Reviews with registration number CRD42023482523. This review protocol is related to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocols 2015.[17] The findings of this review will be reported in accordance with the PRISMA 2020 statement.[18]

Information sources

The following databases Web of Science, PubMed, Embase, Cochrane Library, ClinicalTrials.gov, International Clinical Trials Registry Platform, Wanfang Database, China National Knowledge Infrastructure, SINOMED, VIP Database and the Chinese Clinical Trial Registry will be searched from inception to 9 December 2023. An update search will be conducted before we publish this systematic review. There will be no limitations on language.

Search strategy

The literature search will use the following terms: hyperbaric oxygen therapy, hyperbaric oxygenation, post-acute COVID-19 syndrome, long-haul COVID, long COVID, post acute sequelae of COVID-19, post-acute sequelae of SARS-Cov-2 infection, etc. A detailed search strategy can be found in online supplemental file 1.

Eligibility criteria

Types of studies

This study will include randomised controlled trials (RCTs), non-RCTs and controlled clinical trials, as well as prospective and retrospective cohort and case-control studies. We will include studies both published and unpublished without language restrictions.

Types of participants

Studies will be considered for inclusion if they included adults (aged 18 years and over) who suffered from the continuation or development of new symptoms 3 months after the initial SARS-Cov-2 infection.

Types of interventions

Studies that investigated the effect of HBOT on long COVID-19 are included.

Types of control

The comparison of interest will be conventional treatment (eg, nasal catheter oxygen inhalation), as defined by the original articles.

Types of outcomes

The primary outcome of interest will be health-related quality of life (HRQoL), including physical and cognitive function measurement. RAND 36-Item Health Survey (RAND-36) will be used to measure the quality of life. The secondary outcomes comprise lung function, depression, anxiety and adverse reactions. Follow-up times will be immediate term (≤6 weeks), short term (>6 weeks and ≤3 months), medium term (>3 months and ≤12 months) and long term (>12 months).

Exclusion criteria

We will exclude studies with any of the following criteria: (1) studies not related to long COVID; (2) studies lacking key safety and efficacy data on HBOT; (3) abstracts, reviews or letters; (4) duplicate studies.

Data management

Search results retrieved from the outlined databases will be assembled into a digital library using the reference management software EndNote V.17.0. Duplicate articles will be verified and eliminated.

Study selection

Two authors will independently screen the obtained articles through titles and abstracts. Any disagreement will be eliminated by discussion. A third author will participate and make a decision if an agreement cannot be made. The screen process will be shown using the PRISMA flow chart figure 1.

Data extraction

Using a standardised data extraction form, two authors will independently retrieve data from eligible studies. The following information will be extracted, including the study information, participant's characteristics, interventions, controls, outcome measures and adverse events. We will try to contact the original authors if the key information is missing.

Risk of bias assessment

The Cochrane Risk of Bias tool V.2 will be used to assess the risk of bias in each of the included randomised trials. Two authors will independently evaluate the methodological qualities of the eligible studies. We will assess the risk of bias through six domains: (D1) bias arising from the randomisation process; (D2) bias due to deviations from intended interventions; (D3) bias due to missing outcome data; (D4) bias in measurement of the outcome; (D5) bias in selection of the reported result and (D6) bias due to other risks. For non-RCTs, we will use the Newcastle-Ottawa Scale for case-control and cohort studies to investigate the study quality. All disagreements will be resolved by consensus.

Data analysis and synthesis

We will conduct data analysis using RevMan software (V.5.4.1) and R software (V.4.3.2). Dichotomous data will be performed as relative risk with 95% CI. The standardised mean difference with 95% CI will be used for continuous variables when the units are different. It is considered statistically significant when p<0.01.

Assessment of heterogeneity

Both the χ^2 test and I^2 statistics will be performed to investigate the heterogeneity. A fixed-effect model will be used when I^2 is <50% or p value is >0.1 representing no obvious heterogeneity. If I^2 is >50% or p value is <0.01, representing significant heterogeneity, a random-effects model will be used.

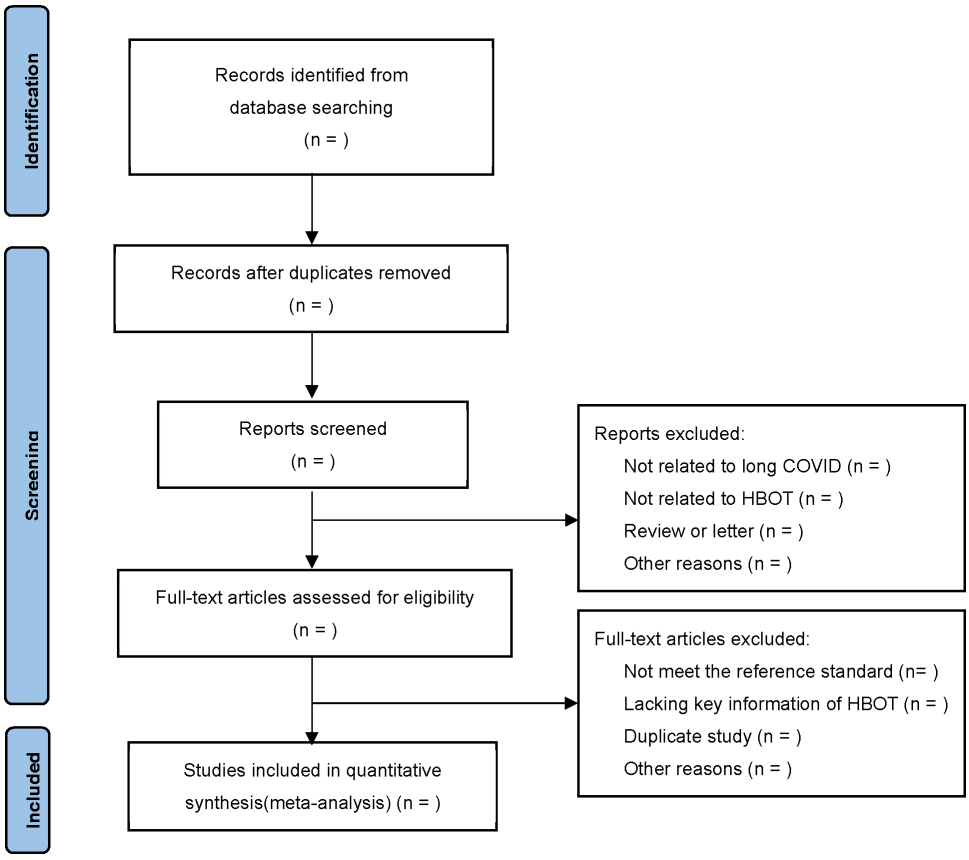

Figure 1 Flow diagram of the study selection process. HBOT, hyperbaric oxygen therapy.

Subgroup analysis and sensitivity analysis

If the data of studies are available and significant heterogeneity exists, subgroup analysis will be conducted based on the type of study design (eg, RCTs, non-RCTs and cohort studies), type of intervention (eg, different treatment programmes of HBOT), type of outcomes (eg, lung function, depression and anxiety) and disease severity determined by RAND-36 (mild, moderate and severe). A sensitivity analysis will be performed by excluding the studies with high or unclear risk of bias or using other statistical models.

Assessment of publication bias

Publication bias will be investigated by using funnel plots and Egger's test on asymmetry at an alpha level of 0.1 when there are 10 or greater studies available for meta-analysis. Meta-analysis will be limited to studies with >100 participants.[19] If necessary, a quality-effects model will be performed to ensure the robustness of the result. Larger studies and studies with high quality will be given greater weight.[20] Narrative analysis will be employed when a statistical aggregation is not feasible.

Grading the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation guidelines will be used to investigate the quality of eligible studies. The quality of evidence will be graded into high, moderate, low and very low levels.

Patient and public involvement

Patients nor the public will participate in the design or plans of our research.

DISCUSSION

Long COVID, with the typical symptoms including breathlessness, fatigue and brain fog, can be debilitating and affect the patients' daily work.[21–23] Thus, it is urgent to develop effective treatments.[21] HBOT is commonly involved in the treatment of inflammation, carbon monoxide poisoning, infections, ischaemia and chronic wounds.[24] HBOT can enhance the anti-inflammatory function of our immune systems.[25] It has been proposed in the management of autoimmune diseases due to its immunomodulatory effects.[26] In particular, HBOT has been shown to be safe and effective in the treatment of fibromyalgia, chronic fatigue syndrome and cognitive improvement.[11 27 28] Studies have shown that HBOT could alleviate fatigue and improve cognition function and HRQoL in long COVID.[14 29] HBOT can play an important role in the treatment of long COVID probably based on its anti-inflammatory, anticoagulant and tissue healing actions.[30] There is still a lack of therapeutic solutions and management for patients with long COVID.[7] Therefore, this systematic review will evaluate the safety and effectiveness of HBOT for long COVID and aims to provide

evidence for the guidance of HBOT in the management of long COVID.

ETHICS AND DISSEMINATION

No ethical committee approval is required in this systematic review. The results of the systematic review and meta-analysis will be published in a peer-reviewed journal.

Contributors YL(Yuxin Li) and ZZ conceived and planned the study. YL and JL completed literature search and drafted the first manuscript. JG and LT participated in designing the study. YL1(Yuntao Liu) took part in the critical revision of the manuscript. YL and JL contributed equally to this paper. All authors approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

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