Risk factors associated with cognitive impairment in patients with COVID-19: a protocol of systematic review and meta-analysis

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ABSTRACT

Introduction COVID-19 infections have become a global public health emergency. Although COVID-19 is primarily a respiratory disease, some of hospitalised patients exhibit cognitive impairment-related neurological damage. Using a systematic review and meta-analysis, we aim to investigate the risk factors for cognitive impairment in patients with COVID-19.

Methods and analysis This meta-analysis has been registered with the International Prospective Register of Systematic Reviews. From inception to 5 August 2022, we will search PubMed, Web of Science, Embase via Ovid, the Chinese Biological Medical Database and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies. We will also look for additional studies in the reference lists of selected articles. To ensure data quality and accuracy, only researches published in English and Chinese will be included. Fixed or random-effects model will be used to calculate the relative risk (RR) or odds ratio (OR) and 95% CIs for pooled data about dichotomous outcomes. We will also assess heterogeneity using Cochrane’s Q and I² tests. Cognitive impairment RR or OR is the primary outcome.

Ethics and dissemination Data will be extracted from published studies, so ethical approval is not required. The outcomes of this meta-analysis will be published in a journal with peer review.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This meta-analysis applies multiple quality assessment tools that ensure the study is conducted in a rigorous manner, reducing the risk of bias and increasing the validity of the findings.
⇒ This study has a comprehensive search strategy that can include as many relevant studies as possible to enhance the reliability of conclusions.
⇒ The limited number of original studies may reduce the quality of the obtained evidence.

INTRODUCTION

Since the 2019 outbreak of novel coronavirus pneumonia, COVID-19 has been a significant public health threat.1 COVID-19 may cause severe harm to various organ functions, including pulmonary function, gastrointestinal function.2,3 In addition, the harm described above could have adverse effects on psychosocial and neurological manifestations, including cognitive impairment.4

Cognitive decline is the primary symptom of damage to the central nervous system. Specifically, the following function domains were impaired: information processing speed, fundamental attention, performance functions, memory and language skills.5 Cognitive impairment is a risk factor for dementia and a significant burden on the medical expenditures of the elderly, as demonstrated by a previous study.6 Certain factors in patients not infected with the novel coronavirus have been confirmed to increase the risk of developing cognitive function disorders, including advancing age, low educational attainment, diabetes and hypertension.7 Furthermore, the novel coronavirus could not only directly cause neuronal injury that impairs cognitive function but also affect coagulation function and the production of inflammatory cytokines, thereby contributing to nervous system damage.8,9 Therefore, it is necessary to investigate the risk factors associated with cognitive impairment in patients with novel coronavirus pneumonia. By getting more details about the related risk factors, physicians might be able to take specific preventive strategies to help reduce the incidence of cognitive impairment. And for more understandable interpretation, these factors are grouped into the following categories: sociodemographic, clinical risk, lifestyle, personal history and illness-related factors.

To our knowledge, no systematic review or meta-analysis has been conducted on the
risk factors for cognitive decline in COVID-19 patients. Consequently, the purpose of this study was to analyse the existing literature and identify the associated risk factors. Lastly, it was anticipated that this study would yield evidence that could assist physicians in adopting treatment and prevention measures to reduce cognitive impairment in this population.

METHODS

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols, \(^{10, 11}\) this systematic review and meta-analysis study protocol was conducted. The PROSPERO registration number is CRD42022351011. Because all data will be obtained from published sources, informed consent and patient ethical approval are unnecessary.

**Literature search**

Two reviewers will independently search PubMed, Web of Science, Embase via Ovid, the Chinese Biological Medical Database and the Cochrane Central Register of Controlled Trials (CENTRAL) to access all relevant research since its inception to 5 August 2022. In addition, the relevant literature was also searched by hand. This meta-analysis will include randomised controlled trials (RCTs), controlled clinical trials (CCTs), prospective and retrospective comparative cohort studies, cross-sectional research and observational research on cognitive impairment in adult patients with COVID-19. The search terms included “cognitive impairment” or “cognitive decline” or “cognitive dysfunction”, as well as “SARS-CoV-2” or “COVID-19” or “SARS-CoV-2 pneumonia”, and the PubMed search strategy is outlined in table 1. And the complete strategies of all database were presented in online supplemental file 1. To ensure data quality and accuracy, only researches published in English and Chinese will be included, while researches published in other languages will be excluded.

**Eligibility criteria**

**Study design type**

This meta-analysis will include all relevant studies, including RCTs, CCTs, prospective and retrospective comparative cohort studies, and cross-sectional and observational research. Due to the lack of original trials, we strive to locate as many pertinent studies as possible. Studies not reporting incidence or prevalence rate of cognitive impairment will be excluded.

**Table 1** The PubMed search strategy

<table>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>“covid 19”[MeSH Terms]</td>
</tr>
<tr>
<td>#3</td>
<td>#1 or #2</td>
</tr>
<tr>
<td>#4</td>
<td>“cognitive dysfunction”[MeSH Terms]</td>
</tr>
<tr>
<td>#6</td>
<td>#4 or #5</td>
</tr>
<tr>
<td>#7</td>
<td>#3 and #6</td>
</tr>
</tbody>
</table>
Participants
Patients (age $\geq 18$ years old) with COVID-19 and who have developed cognitive impairment will be involved. Regarding the restrictions on the number of original studies, there are no racial or national restrictions. Therefore, the studies from various nations will be included in the global compilation.

Exposures
All factors that can cause cognitive impairment in patients will be considered exposures. Consequently, no separate exposure will be restricted.

Outcomes
Cognitive impairment relative risk (RR) or OR is the primary outcome. This meta-analysis examines the risk factors for cognitive impairment in COVID-19-infected patients. Therefore, it is unnecessary to present alternative results.

Study selection and data collection
Two researchers will select the studies independently. If discrepancies exist between the searchers, a senior reviewer will be consulted to resolve the issue. After removing duplicates, the quality of studies will be evaluated based on their titles and abstracts. Then, we will...
conduct the final evaluation by reading the entire text. The selection flow diagram is shown in figure 1. Two reviewers will extract the data independently using a standardised collection form. Meanwhile, discrepancies will be resolved by another senior reviewer. The extracted data consists of a journal, first author, publication date, sample size, study type, patient characteristics, cognitive impairment, degree of cognitive impairment, laboratory results, length of hospitalisation and any cognitive impairment-related factors. For the missing information, we will contact the author.

Risk-of-bias assessment and quality assessed
Two instruments will be used to assess the quality of the included studies. Cochrane’s risk-of-bias tool evaluates the RCTs based on the following domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; discrimination from the measurement of the outcome; bias from the selection of the reported result. Meanwhile, for non-randomised studies, we will employ the Newcastle-Ottawa Scale to assess bias, including subject selection, study comparability and outcome measurement. According to the tool for assessing the risk of bias, the decisions may have a ‘low’, ‘high’ or ‘some concerns’ risk of bias. The risk of bias will be evaluated independently by two researchers. In addition, the Grading of Recommendations, Assessment, Development and Evaluation criteria are used to evaluate the quality of the evidence in the included studies.

Data synthesis and statistical analysis
We will use Stata V.17 (StataCorp) for data synthesis and meta-analysis. Weight mean differences (WMD, 95% CI) and RR or ORs (95% CI) represent continuous and dichotomous outcomes, respectively. Data from multivariable analyses on risk factors will be compiled in a tabular format to facilitate qualitative inferences regarding cognitive impairment risk factors. Using the I² index, heterogeneity will be evaluated (I²>50% indicates significant heterogeneity). If the data are highly heterogeneous, a random-effect model will be employed. In the absence of apparent heterogeneity, a fixed-effect model will be used.

Subgroup and sensitivity analysis, and publication bias assessment
With high heterogeneity, the subgroup analysis will be performed, according to the age. The sensitivity analysis will consist of repeatedly removing one study at a time. The meta-analysis will be considered reliable and stable if removing one study does not alter the final pooled results. In addition, funnel plot asymmetry and Egger’s test will be used to detect publication bias.

Ethics and dissemination
Because the data are obtained from published reports, ethical approval is not necessary. The findings of this systematic review will be published in an academic journal.

Patient and public involvement
None.

DISCUSSION
To our knowledge, this is the first meta-analysis to investigate cognitive impairment risk factors in COVID-19 patients. Cognitive impairment can increase hospitalisation length, medical expenses and mortality, especially for COVID-19-infected patients. COVID-19 is a complex infectious disease associated with an increased risk of cognitive impairment. However, there is no extant evidence pooled on cognitive impairment mediated by some risk factors in COVID-19 patients. Therefore, a meta-analysis must determine the specific risk factors for cognitive impairment in COVID-19 patients. The findings of this study will guide physicians in adopting preventative measures against cognitive impairment in patients with COVID-19, and improve patient survival rate. This meta-analysis can also serve as a research foundation for future high-quality trials aimed at improving neuropsychiatric symptoms in COVID-19-infected patients. Nevertheless, this meta-analysis has a few limitations. For one, the limited number of original studies may diminish the quality of the obtained evidence. Due to the limitations of the original studies, it may be challenging to identify all risk factors in this meta-analysis.

CONCLUSION
This meta-analysis is expected to investigate the risk factors associated with cognitive impairment in patients with COVID-19.

Contributors BJ and CC designed this review and made the search strategy. BJ and MC completed the literature search and data collection. BJ will perform the data synthesis and analysis. BJ and MC were the major contributors to writing the protocol draft writing. SL and YJ edited the English expression. TZ and CC revised the manuscript critically. All authors have read and approved the final version.

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Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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