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Prevalence, classification, risk factors and outcome impact of delirium in patients with COVID-19: a meta-analysis protocol for systematic review

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ABSTRACT

Introduction Previous studies have shown mixed results that delirium may result in a high risk of adverse clinical outcomes in patients with COVID-19. The aim of this meta-analysis is to summarise the evidence of prevalence, classification, risk factors and outcomes impact of delirium in adult patients with COVID-19.

Methods A systematic search will be performed in PubMed, EMBase, ISI Knowledge via Web of Science and preprint databases (MedRxiv and BioRxiv) (from inception until June 2021) to identify all cohort studies concerning delirium in adult patients with COVID-19. The primary outcome will be the prevalence of delirium with different classifications (hyperactive, hypoactive or mixed type). The secondary outcomes will include the association of risk factors and the association with all-cause mortality during hospitalisation. Univariable or multivariable meta-regression and subgroup analyses will be conducted for the study design and patient characteristics. Sensitivity analyses were used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of primary and secondary outcomes.

Ethics and dissemination Ethical approval is not an essential element for the systematic review protocol in accordance with the Institutional Review Board / Independent Ethics Committee of Beijing Hospital. This meta-analysis will be disseminated through a peer-reviewed journal for publication.

PROSPERO registration number CRD42020224871.

Strengths and limitations of this study

- ► Univariable or multivariable meta-regression and subgroup analyses for the association of delirium with all-cause mortality in patients with COVID-19 will be performed.
- ► Sensitivity analyses will be used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of prevalence of delirium, risk factors and all-cause mortality in patients with COVID-19.
- ► Whether different classifications of COVID-19 associated delirium possess different impact on outcomes merits further investigation.
- ► Most of the included studies will be retrospective in design, so the inherit bias cannot be ruled out.
- ► The sample size and the number of included studies may be small.

INTRODUCTION

Delirium is an organically caused acute and fluctuating state of deficit in attention and arousal in surgical patients or other critically ill patients.[1] In the intensive care unit (ICU), the estimated prevalence of delirium is 60%–80% of mechanically ventilated critically ill patients, while in non-mechanically ventilated patients, the prevalence remain as high as 20%–50%.[2] ICU delirium has been shown to be associated with prolonged ICU and hospital stays, and increased mortality risk.[3–5] Based on different assessment tools or clinical criteria, delirium can be classified into three motor subtypes: hyperactive (agitation, aggressive reaction, hallucinations and disorientation), hypoactive (sedation, bradykinesia, lethargy and withdrawal reaction) and mixed (coexistence of hypoactive and hyperactive subtypes).[6 7] More importantly, these three classifications have been shown to be associated with different prognoses, especially the hypoactive types.[8] Hence, the identification of different delirium classifications could lead to risk stratification, early intervention and improved prognosis for critically ill patient management.

Delirium in patients with COVID-19 has emerged as a major complication in clinical practice during the pandemic. The reported prevalence of delirium in COVID-19-infected patients admitted to the ICU is approximately 40%–80%.[9–11] What is worse, atypical syndrome onset with delirium after COVID-19 infection before hospitalisation has been shown to increase the risk of mortality.[12–14] The overall mortality risk of patients with COVID-19 remains stable at approximately

2.0% since the initial outbreak.[15] However, the critically ill patients admitted to the ICU exhibited a high mortality of up to 20%–50%.[16–18] Therefore, understanding risk factors and classifications for delirium following COVID-19 infection has critical clinical implications, including more precise targeting of interventions and the development of a sensitive risk screening tool for these outcomes. The use of a prediction tool for delirium following COVID-19 infection could lead to earlier intervention opportunities, better patient management and subsequent improved outcome. Additionally, whether different classifications of delirium possess different impacts on clinical outcomes remains unknown. However, there has been no related meta-analysis concerning this important issue. Therefore, we will conduct a comprehensive meta-analysis to quantitatively evaluate the prevalence, classification, risk factors and outcome impact of delirium in patients with COVID-19.

Objectives

The aim of this systematic review and meta-analysis is to summarise the evidence of prevalence, classification, risk factors and outcomes impact of delirium in patients with COVID-19.

METHODS AND ANALYSIS

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines will be used in this systematic review and meta-analysis.[19] A systematic search will be performed in PubMed, EMBase, ISI Knowledge via Web of Science and preprint databases (MedRxiv and BioRxiv) (from inception until June 2021) to select the related cohort studies concerning delirium in adult patients with COVID-19. The reference lists of the retrieved articles will also be searched. Figure 1 shows the searching process. Table 1 lists the related search strategy with keywords.

Type of participants

The study participants will include adult patients with COVID-19 infection.

Patient and public involvement

Patients and/or the public will not be involved in the design, conduct or reporting or dissemination plans for this research.

Type of studies

Both retrospective and prospective cohort studies concerning delirium in adult patients with COVID-19 will be included. The published language will be set as English. Studies reporting delirium in other coronavirus

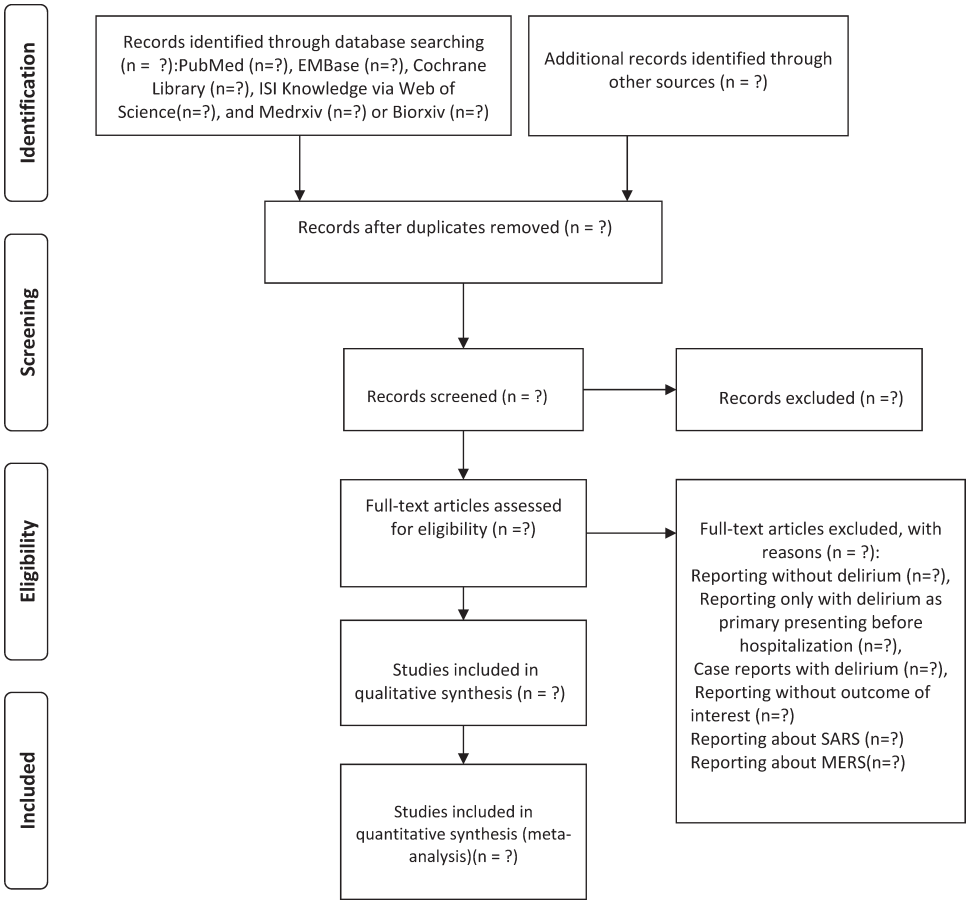

Figure 1 Eligible trial searching flowchart. MERS, middle east respiratory syndrome.

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Table 1 Search strategy for multiple databases including PubMed, EMBase, ISI Knowledge via Web of Science, MedRxiv and BioRxiv

Database	Search items
PubMed	
N	
# 1	(((((delirium) OR (delirious)) OR (neurologic)) OR (neurological)) OR (neurocovid)) OR (cognitive)
# 2	(COVID-19) OR (SARS-CoV-2)
# 3	# 1 and # 2
EMBase	
# 1	delirium OR delirious OR neurologic OR neurological OR neurocovid OR cognitive
# 2	'COVID-19 19' OR 'sars cov 2'
# 3	# 1 and # 2
ISI Knowledge via Web of Science	
# 1	TOPIC: (delirium) OR TOPIC: (delirious) OR TOPIC: (neurologic) OR TOPIC: (neurological) OR TOPIC: (cognitive) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 2	TOPIC: (COVID-19) OR TOPIC: (SARS-CoV-2) Timespan: All years. Databases: WOS, BIOSIS, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto
# 3	# 1 and # 2
MedRxiv	
# 1	((((delirium) OR (delirious)) OR (neurologic)) OR (neurological)) OR (cognitive)
# 2	(COVID-19) OR (SARS-CoV-2)
# 3	# 1 and # 2
BioRxiv	
# 1	((((delirium) OR (delirious)) OR (neurologic)) OR (neurological)) OR (cognitive)
# 2	(COVID-19) OR (SARS-CoV-2)
# 3	# 1 and # 2

infections (SARS or middle east respiratory syndrome) will be excluded. Studies that do not report the outcomes of interest will also be excluded.

Types of outcomes

The primary outcome will be the prevalence of delirium with different classifications (hyperactive, hypoactive or mixed type). The secondary outcomes will include the associated risk factors and the association with all-cause mortality during hospitalisation.

Data extraction

The data extraction will be completed by two independent authors (JG and YL). A third author (BL) will resolve any disagreements. The data extraction will include study design (author, publication year, country, retrospective or prospective and sample size), patient characteristics (age, male proportion, diabetes proportion, hypertension proportion, hyperlipidemia proportion, smoking proportion, coronary artery disease proportion, previous myocardial infarction proportion, chronic heart failure proportion, atrial fibrillation proportion, previous peripheral vascular disease proportion, previous stroke or transient ischaemic accident proportion, chronic kidney dysfunction proportion, previous lung disease proportion, beta-blocker usage, statin usage, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker usage, calcium channel blocker usage and aspirin usage), follow-up period, delirium definition and classification.

Risk of bias assessment

The Newcastle-Ottawa quality assessment scale will be used for the methodological quality evaluation of the studies.[20]

Data synthesis

The prevalence of delirium with different classifications (hypoactive, hyperactive and mixed subtypes) in each study will be calculated. The OR or HR and 95% CI in each study for the associated risk factors and association with all-cause mortality will be extracted. The DerSimonian and Laird random effects model will be used in the pooled analysis for potential clinical inconsistency. Univariable or multivariable metaregression and subgroup analyses will be conducted for the association of delirium with all-cause mortality. Sensitivity analyses will be used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates of prevalence of delirium, risk factors and all-cause mortality. Publication bias assessment will be performed by Begg's and Egger's tests. $P<0.05$ (two sided) will be considered to be statistically significant. All statistical analyses will be performed using Stata software (V.10.0, StataCorp., College Station, Texas, USA) and RevMan software (V.5.0, Cochrane Collaboration, Oxford, UK).

DISCUSSION

To date, the clinical presentation of delirium in adult patients with COVID-19 infection has not been extensively described. Some studies have reported the prevalence of delirium with a wide range of 40%–80%.[9–11] This difference among studies may result from some of the following reasons: (1) The definitions of delirium varied, and most of the studies did not use a systematic screening tool. (2) Delirium was not a primary endpoint in each study. (3) The COVID-19 patients were routinely isolated and the researchers were in a protective suit, resulting in inaccurate assessment, especially in patients with the hypoactive subtype.

The classification of delirium in COVID-19 is an intriguing issue in the clinical practice. Several studies divided COVID-19-associated delirium into hyperactive

and hypoactive types.[9–11 14] Only one study[9] reported the prevalence of mixed subtypes of delirium in COVID-19. Hyperactive subtypes can be a source of cross infection due to aerosol generation during coughing or other aggressive motions. On the other hand, patients with hypoactive subtypes are likely to be ignored for protective isolation, resulting in inadequate attention from medical staffs. Whether different classifications of delirium possess different impacts on outcomes merits further investigation.

The major strength of this systematic review and meta-analysis is that, for the first time, it comprehensively summarises the risk factors and impact on outcome of delirium in patients with COVID-19. Moreover, this meta-analysis will focus on the classification (hyperactive, hypoactive and mixed types) of delirium in patients with COVID-19. Limitations, on the other hand, also exist in our analysis. First, most of the included study will be retrospective in design and the inherent bias cannot be ruled out. Second, the sample size and the number of included studies may be small due to the resource-limited situation. Third, we could not rule out the potential influence of different definitions (with or without systematic screening tools) of delirium in COVID-19. Fourth, the impact of different classifications of COVID-19 associated delirium on clinical outcomes needs to be studied in future prospective studies.

ETHICS AND DISSEMINATION

Ethical approval is not an essential element for the systematic review protocol in accordance with the Institutional Review Board/Independent Ethics Committee of Beijing Hospital. This meta-analysis will be disseminated through a peer-reviewed journal for publication.

Contributors CZ and JS contributed to the conception and design of the study, and revision of the protocol. The manuscript of the protocol was drafted by BL. JG and YL will independently search and select the eligible studies and extract the data from the included studies. BL and CX will assess methodological quality and the risk of bias. All the authors approved the protocol publication.

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Competing interests None declared.

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

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

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