

Prevalence of depression, anxiety, delirium, and post-traumatic stress disorder among COVID-19 patients: protocol for a living systematic review

Jiyuan Shi

Lanzhou University

Yuanyuan Li

Lanzhou University

Liang Zhao

Lanzhou University

Meili Yan

Lanzhou University

MingMing Niu

Lanzhou University

Yamin Chen

Lanzhou University

Ziwei Song

Lanzhou University

Gao Ya

Lanzhou University

Jinhui Tian (✉ 15038059737@163.com)

Lanzhou University

Protocol

Keywords: living systematic review (LSR), COVID-19, infection, mental health

Posted Date: August 10th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-48077/v2>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Systematic Reviews on November 6th, 2020. See the published version at <https://doi.org/10.1186/s13643-020-01507-2>.

Abstract

Background Previous studies on the impact of COVID-19 on the mental health of the patients has been limited by the lack of relevant data. With the rapid and sustained growth of the publications on COVID-19 research, we will perform a living systematic review (LSR) to provide comprehensive and continuously updated data to explore the prevalence of depression, anxiety, delirium, and post-traumatic stress disorder (PTSD) among COVID-19 patients.

Methods We will perform a comprehensive search of the following databases: Cochrane Library, PubMed, Web of Science, Embase, and Chinese Biomedicine Literature to identify relevant studies. We will utilize different tools to examine the bias risks (quality) regarding studies of varying design types, such as the revised Cochrane risk-of-bias tool (RoB 2) for randomized controlled trials (RCT), the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, etc. The literature searches would be updated every month. We will perform meta-analysis if any new eligible studies or data are obtained and resubmit an updated systematic review if any change in outcomes and heterogeneity is determined after the addition of the new studies. There will be no restrictions on language or year of publication.

Discussion This LSR would provide an in-depth and up-to-date summary of the psychological impact of COVID-19 diagnosis and treatment on the patients.

Systematic review registration PROSPERO CRD42020196610

Background

The global outbreak of the COVID-19 has been designated as a pandemic that has affected more than ten million people, with more than half a million fatalities [1, 2]. Previous research focusing on pandemics confirmed that individuals who had experienced public health emergencies reported varying degrees of psychological disorders even after the event ended or they were cured and discharged from the hospital [3-6]. Patients with confirmed and suspected infections may suffer from repeated psychiatric and neuropsychiatric incidences due to multiple reasons, such as progression of the disease, adverse drug reaction, social isolation, uncertainty, and physical discomfort [7-9].

A recently published systematic review and meta-analysis indicated the incidence of delirium as a common occurrence amongst patients hospitalized due to severe coronavirus infections (SARS-CoV and MERS-CoV), whereas, PTSD, anxiety, depression, and fatigue were observed in the subsequent months [3]. There exists some preliminary/unpublished data showing psychiatric and neuropsychiatric presentations in COVID-19 patients [3]. Since the spread of COVID-19, there has been extensive research on the topic globally, translating into an unprecedented number of publications, approximately 59 articles per day, probably higher than observed for any other disease [10]. It is essential to collect continuously updated data to provide convincing evidence for patients, healthcare workers, and policymakers. A living systematic review (LSR) retains the benefits of a systematic review and accepts continual updating of the relevant data without compromising the methodological rigor [11-14].

The aim of this study is to provide a living systematic review for synthesizing rapid and continual updating of data on whether the common neuropsychiatric conditions observed in patients hospitalized for severe SARS-CoV or MERS-CoV are also prevalent in a different stage of COVID-19 patients.

Methods/design

Study design

This systematic review has been designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement and has been registered on PROSPERO (CRD42020196610) [15].

Eligibility criteria

Population

Included are COVID-19 infection patients among adults (≥ 18 years of age) who are diagnosed with four types of psychiatric and neuropsychiatric syndromes (anxiety, depression, delirium, and post-traumatic stress disorder). We will use the author's definitions of psychiatric and neuropsychiatric syndromes, as well as diagnostic criteria for SARS-CoV-2 infection, with no age, gender or setting, location, or ethnicity restrictions.

Excluded are studies explored the indirect effects of SARS-CoV-2 on the mental health of family members, care providers, or isolated people who did not infect will be excluded. We also excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)), unless the trial authors provided subgroup data for people with COVID-19.

Type of outcomes

The primary outcomes are the prevalence of signs or symptoms (depression, anxiety, delirium, and PTSD). Secondary outcomes are the symptom severity (depression, anxiety, delirium, and PTSD), the incidence of mortality in COVID-19 patients with depression, anxiety, delirium or PTSD, and the measurement of health-related quality of life using a validated scale, such as the Short Form 36 Health Survey questionnaire. The outcome will be classified as examining the acute or post-illness psychiatric consequences of infection on the basis of whether the information is collected during the patient's illness or the period after the illness.

If a study met our criteria reports on COVID-19 infection that were not specified a priori as outcomes of interest for this review, the results will be noted in a narrative synthesis, but not necessarily pooled for meta-analyses nor reported in the summary of findings table.

Studies design

We will include only peer-reviewed RCT, cohort/case-control/cross-sectional studies, case reports, case series, and qualitative studies. Conference abstracts, commentaries, or opinion pieces will be excluded because they lack adequate information for meta-analysis. Only studies published in English and Chinese will be included in this review.

Search strategy

A senior investigator (Y.G.) would examine the published and gray literature sources to extract the studies reporting the prevalence of depression, PTSD, anxiety, or delirium in COVID-19 patients. An experienced medical information specialist (J.H.T.) would further check and approve the search methodology. We will conduct a comprehensive search of the Cochrane Library, PubMed, Web of Science, Embase, and Chinese Biomedicine Literature to extract articles/abstracts published between the inception of this disease (December 2019) until the completion of this review will be included. There will be no restrictions on language or year of publication. An additional file, which would describe the complete search strategy for PubMed as well as other electronic databases will be provided. We will also thoroughly search the reference lists of the relevant reviews and research trials. We have presented the search strategy using PubMed as an example in Table 1. The search strategy will be adapted to fit other online databases as well. Studies published before 12 December 2019 will be excluded.

Update plan

We will perform identical search operations at regular pre-defined intervals to identify newly published data. There are no robust standards for the update frequency based on current research; however, due to the unprecedented number of publications on COVID-19, we will update the literature searches every month, and perform meta-analysis if any new eligible studies or data are obtained. We will submit an updated systematic review if we observe any changes in the outcomes and heterogeneity after the addition of new studies or provide data on additional outcomes [11, 12]. We chose this updating frequency to allow quick updates and to highlight the most recent information to the researchers, clinicians, nurses, and policymakers [11, 14, 16].

Study selection

Original literature search records will be imported into Endnote X9 software tool (Thomson Reuters, New York, NY, USA) management software. Two authors (JYS and YG) will independently retrieve full-text of potential studies after deduplication to assess their eligibility according to the abovementioned inclusion criteria. Any disagreement will be resolved by the third reviewer (JHT).

Data extraction

Two independent reviewers (JYS and MMN) will be involved in data extraction; we will extract country of patients, population type (e.g., old people and children), age, study design (such as RCT/cohort/case-control), diagnostic criteria for the viral infection (such as WHO criteria), stage and severity of the disease, length of follow-up, sample size (such as number of cohort, number of cases), and gender.

Risk of bias (quality) assessment.

Two independent reviewers (JYS and YG) will use the following tools to examine the risk of bias in the included studies: Cochrane Collaboration RoB 2.0 tool for RCT [17], the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I Scale) for non-randomized controlled trials [18], the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies [19]. The 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ) will be used to assess the the quality of the cross-sectional studies that were included [20]. We will classify the methodological quality of each individual study as having a low, high, or unclear risk of bias as describing in Table 2. Any disagreement regarding inclusion of some studies will be resolved by discussion and consensus between the two reviewers. If this failed, it shall be resolved by the third reviewer (JHT).

Processing missing data

We will contact the corresponding or other primary authors to obtain missing data or insufficiently reported data after selecting the studies. Randomized controlled trials will be treated as cohort studies; all data from the control and experimental group will be extracted if they met our criteria. In addition, we will estimate missing data if they can be extracted from tables or figures. Trials with missing data that cannot be obtained will be excluded for reasons. Any significant deviations between the protocol and the final review will be reported clearly.

Differences between the protocol and the final review

Any significant deviations between the protocol and final review will be reported clearly.

Data analysis

The Stata (v13.0; StataCorp) and Revman 5 were used for statistical analysis. The statistical heterogeneity will be examined using the Cochran's Q and the I^2 statistic. An $I^2 > 50\%$, and a p -value < 0.05 will correspond to significant heterogeneity, and a random-effects model will be used for the subgroup analyses and pooled estimates. On the contrary, an $I^2 < 50\%$ and a p -value > 0.05 will correspond to insignificant heterogeneity, and the fixed-effect model shall be used for the subsequent meta-analysis. The effect size measures were mean difference with 95% CI (for the severity of the symptoms and degree of diagnoses) and prevalence with 95% CI (number of psychiatric diagnoses (depression, anxiety, delirium, and PTSD); severity of depression, anxiety, delirium, and PTSD). The heterogeneity/publication bias will be examined using the Egger's test or the symmetry of the funnel plot. In the Egger's test, bias will be significant when p -value < 0.05 .

Subgroup analysis

The following subgroup analyses will be planned for main outcomes if data are sufficient: Age (< 60 vs. ≥ 60 years), symptom severity (mild vs. severe vs. ICU patients), high and middle-high vs. middle-low and low-income countries, databases (data from Chinese databases vs. data from English databases), study design (RCT, cross-sectional, non-randomized control trials, cohort-study case-control trials, and qualitative studies), and follow-up time (1, 3, 6 months of acute and post-illness for COVID-19 patients).

Sensitivity analyses

We will perform sensitivity analyses by repeating meta-analysis with studies with an unclear or low risk for bias. Additional issues suitable for sensitivity analysis will be identified during the review process. We will report the sensitivity analysis by generating summary tables

Quality of the evidence assessment

The Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group method will be used to examine the quality of the evidence for each outcome. We will assess each

outcome based on each of the following five aspects: imprecision, inconsistency, limitations, indirectness, and publication bias. They will be rated as very-low, low, moderate, or high level [21].

Discussion

Coronaviruses have resulted in two severe outbreaks of severe acute respiratory syndrome (SARS); however, before SARS-CoV-2. Previous coronaviruses have been associated with delirium signs in the acute stage and fatigue, depression, PTSD, and anxiety in the post-illness stage [3]. However, the lack of adequate data on COVID-19 patients limited the previous study to investigate and conclude the effects of the SARS-CoV-2 infection on patients' mental health. Given that the rapid and sustained growth of publication of COVID-19 research, we will perform a LSR to comprehensive and continuous synthesis updated data to explore the prevalence of depression, anxiety, delirium, and PTSD in COVID-19 patients.

Declarations

Ethics approval and consent to participate

All authors are accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study will not involve any patients and/or the public. No ethical approve or informed consent is required for the purposes of the present study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding: none

Authors' contributions

(I) Conception and design: JYS and JHT; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: YYL, LZ and YMC; (V) Data analysis and interpretation: YG, MMN and MLY; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Acknowledgments

The authors are grateful to Dr. Peng Wang who provided valuable feedback on the draft version of the protocol.

References

1. Sahu KK, Mishra AK, Lal A. Trajectory of the COVID-19 pandemic: chasing a moving target. *Ann Transl Med.* 2020;8(11):694.
2. Available online. <https://covid19.who.int>.
3. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiat.* 2020;7(7):611–27.
4. Greenberg N, Docherty M, Gnanapragasam S, Wessely S. Managing mental health challenges faced by healthcare workers during covid-19 pandemic. *BMJ.* 2020;368:m1211.
5. Xiang YT, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. *Lancet Psychiat.* 2020;7(3):228–9.
6. Strahan EH, Brown RJ. A qualitative study of the experiences of patients following transfer from intensive care. *Intens Crit Care Nur.* 2005;21(3):160–71.
7. Talevi D, Socci V, Carai M, Carnaghi G, Faleri S, Trebbi E, et al. Mental health outcomes of the CoViD-19 pandemic. *Riv Psichiatr.* 2020;55(3):137–44.
8. Park SC, Park YC. Mental Health Care Measures in Response to the 2019 Novel Coronavirus Outbreak in Korea. *Psychiat Invest.* 2020;17(2):85–6.
9. Mak IW, Chu CM, Pan PC, Yiu MG, Ho SC, Chan VL. Risk factors for chronic post-traumatic stress disorder (PTSD) in SARS survivors. *Gen Hosp Psychiat.* 2010;32(6):590–8.
10. Tao Z, Zhou S, Yao R, Wen K, Da W, Meng Y, et al. COVID-19 will stimulate a new coronavirus research breakthrough: a 20-year bibliometric analysis. *Ann Transl Med.* 2020;8(8):528.
11. Garner P, Hopewell S, Chandler J, MacLehose H, Schünemann HJ, Akl EA, et al. When and how to update systematic reviews: consensus and checklist. *BMJ.* 2016;354:i3507.
12. Schünemann HJ, Khabsa J, Solo K, Khamis AM, Brignardello-Petersen R, El-Harakeh A, et al. Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19: A Living Systematic Review of Multiple Streams of Evidence. *Ann Intern Med* 2020.
13. Thombs BD, Bonardi O, Rice DB, Boruff JT, Azar M, He C, et al. Curating evidence on mental health during COVID-19: A living systematic review. *J Psychosom Res.* 2020;133:110113.
14. Créquit P, Martin-Montoya T, Attiche N, Trinquart L, Vivot A, Ravaud P. Living network meta-analysis was feasible when considering the pace of evidence generation. *J Clin Epidemiol.* 2019;108:10–6.
15. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.*

2015;350:g7647.

16. Badgett RG, Vindhya M, Stirnaman JT, Gibson CM, Halaby R. A Living Systematic Review of Nebulized Hypertonic Saline for Acute Bronchiolitis in Infants. *JAMA Pediatr.* 2015;169(8):788–9.
17. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
18. Ge L, Sadeghirad B, Ball GDC, da Costa BR, Hitchcock CL, Svendrovski A, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. *BMJ.* 2020;369:m696.

Tables

Table 1 Search strategy of PubMed database

#1 "Stress Disorders, Post-Traumatic"[Mesh] OR "Post Traumatic Stress Disorder*"[Title/Abstract] OR "Post traumatic Neuroses"[Title/Abstract] OR "Post traumatic Stress Disorder*"[Title/Abstract] OR "Post Traumatic Neuroses"[Title/Abstract] OR "Post-Traumatic Neuroses"[Title/Abstract] OR "Post-Traumatic Stress Disorder*"[Title/Abstract] OR "Post Traumatic Stress Disorder*"[Title/Abstract] OR "Moral Injur*"[Title/Abstract] OR "Delayed Onset Post-Traumatic Stress Disorder"[Title/Abstract] OR "Delayed Onset Post Traumatic Stress Disorder"[Title/Abstract] OR "Chronic Post-Traumatic Stress Disorder*"[Title/Abstract] OR "Chronic Post Traumatic Stress Disorder*"[Title/Abstract]

#2 "Depressive Disorder"[Mesh] OR "Depression"[Mesh] OR "Depression*"[Title/Abstract] OR "Depressive Symptom*"[Title/Abstract] OR "Emotional Depression*"[Title/Abstract] OR "Depressive Disorder*"[Title/Abstract] OR "Depressive Neuroses"[Title/Abstract] OR "Depressive Neurosis"[Title/Abstract] OR "Endogenous Depression*"[Title/Abstract] OR "Depressive Syndrome*"[Title/Abstract] OR "Neurotic Depression*"[Title/Abstract] OR "Melancholia*"[Title/Abstract] OR "Unipolar Depression*"[Title/Abstract]

#3 "Delirium"[Mesh] OR "Delirium"[Title/Abstract] OR "Subacute Delirium*"[Title/Abstract] OR "Delirium of Mixed Origin"[Title/Abstract] OR "Mixed Origin Delirium*"[Title/Abstract]

#4 "Anxiety"[Mesh] OR "Anxiet*"[Title/Abstract] OR "Hypervigilance"[Title/Abstract] OR "Nervousness"[Title/Abstract] OR "Social Anxiet*"[Title/Abstract]

#5 "COVID-19" [Supplementary Concept]

#6 "2019 novel coronavirus disease"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "COVID-19 pandemic"[Title/Abstract] OR "SARS-CoV-2 infection"[Title/Abstract] OR "COVID-19 virus disease"[Title/Abstract] OR "2019 novel coronavirus infection"[Title/Abstract] OR "2019-nCoV infection"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "coronavirus disease-19"[Title/Abstract] OR "2019-nCoV disease"[Title/Abstract] OR "COVID-19 virus infection"[Title/Abstract]

#7 #1 OR #2 OR #3 OR #4

#8 #5 OR #6

#9 #7 AND #8

Table2. Risk of bias assessment for included studies.			
Study design	Tool	Domains/Checklist	Overall risk of bias judgement
RCT	RoB 2.0 tool	<ol style="list-style-type: none"> 1. Bias arising from the randomisation process; 2. Bias due to deviations from intended interventions; 3. Bias due to missing outcome data; 4. Bias in measurement of the outcome; 5. Bias in selection of the reported result. 	<p>Low risk of bias – the study is judged to be at low risk of bias for all domains for this result</p> <p>Some concerns: the study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.</p> <p>High risk of bias: (1) the study is judged to be at high risk of bias in at least one domain for this result; (2) the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.</p>
Non-randomized controlled trials	ROBINS-I-tool	<ol style="list-style-type: none"> 1. Confounding 2. Selection bias 3. Bias in measurement classification of interventions 4. Bias due to deviations from intended interventions 5. Bias due to missing data 6. Bias in measurement of outcomes 7. Bias in measurement of outcomes 	<p>Low risk of bias – the study is judged to be at low risk of bias for all domains for this result.</p> <p>Some concerns: the study is judged to be at some concerns in at least one domain for this result.</p> <p>High risk of bias: (1) the study is judged to be at high risk of bias in at least one domain for this result; (2) the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.</p>
Cross-sectional studies	AHRQ checklist	<ol style="list-style-type: none"> 1. Define the source of information (survey, record review) 2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications 3. Indicate time period used for identifying patients 4. Indicate whether or not subjects were consecutive if not population-based 5. Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants 6. Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements) 7. Explain any patient exclusions from analysis 8. Describe how confounding was assessed and/or controlled. 9. If applicable, explain how missing data were handled in the analysis 10. Summarize patient response rates and completeness of data collection 	<p>An item would be scored “0” if it was answered “No” or “Unclear”; if it was answered “Yes”, then the item scored “1”.</p> <p>Article quality was assessed as follows: low quality = 0-3; moderate quality = 4-7; high quality = 8-11.</p>

		11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	
Cohort and case-control studies	NOS	<ol style="list-style-type: none"> 1. Was selection of exposed and non-exposed cohorts drawn from the same population? 2. Can we be confident in the assessment of exposure? 3. Can we be confident that the outcome of interest was not present at start of study? 4. Did the statistical analysis adjust for all confounders? 5. Can we be confident in the assessment of the presence or absence of potential confounders? 6. Can we be confident in the assessment of outcome? 7. Was the follow up of cohorts adequate? 	<p>An item would be scored "0" if it was answered "No" or "Unclear"; if it was answered "Yes", then the item scored "1".</p> <p>Article quality was assessed as follows: low risk of bias: total score \leq 5; high risk of bias: total score $>$ 5.</p>

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [searchstrategy.docx](#)
- [PRISMAPchecklist.docx](#)
- [1.docx](#)