

Dear Editor,

Thank you for your great effort in handling our submission (Manuscript NO. 87014, entitled Risk factors, preventive interventions, overlapping symptoms, and clinical measures of delirium in elderly patients). We also thank the reviewer for his/her comments. In response to the comments and suggestions made by the referees, we have made a number of changes and additions to the manuscript. We believe that these changes, together with the detailed response to the reports given below, clarify all the points made by the referees. We would like to resubmit it. Thank you in advance for your further consideration of our contribution. We look forwards to your response in due course.

Sincerely yours,
Xi Mei

Round 1

Reviewer(s)' Comments to Author:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: I would like to thank you for the opportunity to review this paper. The authors review the syndrome of delirium, its predictors and known treatments. This is a very interesting paper; address the most important issues on this topic, and with interest to the journal readership. However, there are some issues that should be addressed: First, I don't understand if the authors address their paper as a systematic review. If so, the search terms and inclusion process must appear in the text. I don't think there is any change that only 76 papers exist for this very thoroughly studied subject. For example, just by searching "Delirium" AND "Treatment" in PubMed 6575 results appear. Please address this issue.

Response to Reviewer 1:

Thank you for your valuable advices. The search strategy focused on terms for “delirium AND risk factors AND epidemiology”, “delirium AND preventive interventions”, “delirium AND overlapping symptoms”, “delirium AND clinical measures”, and “delirium AND prevention and therapy” in ten years. Although there were 8,290 papers, not every paper was included in the study. We screened the papers further according to the following items: 1) The language of articles was restricted to English. 2) Trials with original data, published in English as full articles in peer-reviewed journals were included. 3) Meanwhile, studies representative of the general population, or of specific patient populations were included. 4) Where two or more articles reported data from the same study sample, only the most relevant article was considered. At last the search retrieved a total of 128 articles, which were manually examined for relevance and a total of 76 articles were identified for further assessment. We modified the sentences in

section of Methods.

Other issues: 1. The authors must add more data to support their findings. For example – in sections on predisposing or precipitating factors such as advanced age, history of delirium, and history of alcohol use, drug use – additional studies that found associations between these factors and delirium should be included.

Associations between these factors and delirium were described in relevant part of manuscript with yellow color in the revised manuscript.

1) Advanced age: “Delirium is very common among hospitalized older adults, but the reasons behind this phenomenon are need to be further studied (Marcantonio, 2017). As we age and our organs deteriorate, there is a decline in the brain and cerebrovascular functions even in the non-diseased state (Chan & Aneman, 2019). Neurons use glucose provided by the cerebral microvascular system to produce ATP via glycolysis as an energy uptake pathway (Winkler et al., 2015).” and “This can be dysfunctional in various ways, leading to delirium development in elderly (Wilson et al., 2020).”

2) History of delirium: “Patients who have experienced delirium are more likely to experience delirium again. Moreover, delirium maybe a predictor of cognitive decline and dementia (Wharton et al., 2018). History of delirium is common in Alzheimer’s disease dementia and dementia with Lewy bodies (Vardy et al., 2014).”

3) History of alcohol use: “The use of benzodiazepines in clinical management of alcohol withdrawal syndrome may associate with disrupted sleep patterns and delirium (Day & Daly, 2022).”

4) Drug use:

More relevant literatures were also included in the revised manuscript.

2. Some sub-sections do not seem to be relevant – as their connection to delirium is not presented. Examples – "brain function impairment" (just include 3 general lines), "acute somatic disorders" (why hypoglycemia or sepsis are examples for it?), pain and surgical anesthesia – you only include one study about its association with delirium while so many studies have been made on this topic.

According to your advice, we added more relevant studies in section of "brain function impairment", "acute somatic disorders" to discuss these topics.

1) Brain function impairment: “Delirium was affected by various factors of brain function” and “Excessive microglial activation, impaired endothelial barrier function, and blood-brain barrier dysfunction may associate with delirium and severe cognitive impairment (Gao & Hernandez, 2021).”

2) Acute somatic diseases: “Septicaemia-related encephalopathy is a common neurological complication of sepsis that is poorly understood, and it is associated with increased morbidity and mortality. The clinical manifestations of the disease ranged from mild confusion and delusion to severe cognitive impairment and deep coma (Gao & Hernandez, 2021). Recent popular theories such as the brain-gut axis, brain-kidney axis and brain-spleen axis suggested that physical health can affect brain function to a certain extent (Agirman & Yu, 2021; Chi et al., 2023).”

3) Pain and surgical anesthesia: “In a multicenter randomized clinical trial, in patients with fragile hip fractures over 65 years old, there was no significant difference in the incidence of delirium between general anesthesia and regional anesthesia within 7 days after surgery (Li et al., 2022).” More relevant literatures were also included in the revised manuscript.

3. I think one major way to prevent delirium is simply limiting the hospitalization duration as much as possible. Given that unfamiliar environment, no separation between day and night, and disorientation are frequent during admission and also major causes for delirium, early discharge once possible could be a key intervention. In this regard I recommend the authors to give examples for such interventions to shorten the hospital stay duration, and specifically the following recent example: <https://pubmed.ncbi.nlm.nih.gov/36645149/>

We added one paragraph in section of Discussion to describe the viewpoint. “One major way to prevent delirium is simply limiting the hospitalization duration as much as possible (Dechnik & Traube, 2020; Rieck et al., 2020). Given that unfamiliar environment, no separation between day and night, and disorientation are frequent during admission and also major causes for delirium, early discharge once possible could be a key intervention. Early discharge from the hospital is beneficial to the recovery if the health condition of patients is accurately assessed (Freund et al., 2023).” More relevant literatures were also included in the revised manuscript.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The study addresses an interesting topic, delirium syndrome, which tends to increase in function of the aging population. Discuss topics relevant to the approach of this syndrome. Alerts to the need for early diagnosis and timely taking of measures leading to avoid the appearance of this syndrome and minimize the adverse consequences of it. Thus, the study can impact on a better treatment of patients with delirium.

Response to Reviewer 2:

Thank you for your valuable advices. We modified the sentences and polished the words according to your suggestions with yellow color in the revised manuscript.

Round 2

Dear Editor,

Thank you for your great effort in handling our submission (Manuscript NO. 87014, entitled Risk factors, preventive interventions, overlapping symptoms, and clinical measures of delirium in elderly patients). We also thank the reviewer for his/her comments. In response to the comments and suggestions made by the referees, we have made a number of changes and additions to the

manuscript. We believe that these changes, together with the detailed response to the reports given below, clarify all the points made by the referees. We would like to resubmit it. Thank you in advance for your further consideration of our contribution. We look forwards to your response in due course.

Sincerely yours,
Xi Mei

Comments to Author:

Dear Dr. Mei,

Thank you for submitting your manuscript (NO.: 87014) to the World Journal of Psychiatry.

I am pleased to inform you that I have added an additional comment regarding your manuscript. The comment is as follows:

There are some issues need to be addressed.

1. We are very pleased to receive your revised manuscript (No. 87014). However, after our verification, we found that the language editing company mentioned in your submitted language certificate only polished the initial manuscript. Following the many changes that were introduced into the content of your manuscript during the revision process, some language problems exist in the revised manuscript. Further language polishing is required to fix all grammatical, syntactical, formatting and other related errors, in order to meet the publication requirement (Grade A). Now, you are requested to send the revised manuscript to a professional English language editing company or a native English-speaking expert to polish the language further. When you submit the subsequent polished manuscript to us, you must provide a new language certificate along with it. Once this step is completed, your manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

We sent the revised manuscript to a professional English language editing company. We provided a new language certificate.

2. Please further revise your manuscript according to comments of second-round review. "Thank you for the opportunity to review this paper once again. I would also like to thank and congratulate the authors for addressing all my comments and for significantly improving their paper. Currently I think there is only one issue remains for the authors to address. The authors answered my main comment on the amount of papers included. Still, there is no possibility that only 76 papers were found to fit with their search criteria. If the authors are correct and they have reviewed over 8000 papers, there are currently only 76 original papers on delirium, which is not possible in my view. The authors could state that they did a literature review and not a systematic review and add this issue in their limitations section. However, this must be stated as there are much more literature in my view. " -----Answer to reviewers: Please provide point to point answer to all reviewers. Authors should revise their article according to the reviewers' comments/suggestions and provide point-by-point responses to each in a letter that is to accompany their resubmission.

Thank you very much for your valuable advices. The search strategy focused on terms for “delirium AND risk factors AND epidemiology”, “delirium AND preventive interventions”, “delirium AND overlapping symptoms”, “delirium AND clinical measures”, and “delirium AND prevention and therapy” in ten years. Although there were 8,290 papers, not every paper was included in the study. We screened the papers further according to the following items: 1) The language of articles was restricted to English. 2) Trials with original data, published in English as full articles in peer-reviewed journals were included. 3) Meanwhile, studies representative of the general population, or of specific patient populations were included. 4) Where two or more articles reported data from the same study sample, only the most relevant article was considered. At last the search retrieved a total of 128 articles, which were manually examined for relevance and a total of 89 articles were identified for further assessment. We modified the sentences in section of Methods. More relevant literatures were also included in the revised manuscript.

3. Please provide the Table file in a ".doc or docx" document.

We provided the Table file in a "table.docx" document.

4. Please complete all the revisions based on the version of "0190-87014_Auto_Edited-v1", and upload above mentioned files in a ".zip" file.

We completed all the revisions based on the version of "0190-87014_Auto_Edited-v1", and uploaded above mentioned files in a "revision.zip" file.