

OPEN PEER REVIEW

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- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
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Middle East Journal of Rehabilitation and Health Studies

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Peer Review Report for "Botulinum toxin injection for treating spasticity in multiple sclerosis patients: a systematic review and meta-analysis"

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Review Timeline:

Submit Date:	2 Oct 2024
Revised Date:	28 Dec 2024
Accepted Date:	25 Dec 2024

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFeree : Reviewer

23 Oct 2024

Dear Editor

Thank you for the opportunity to review the manuscript. The authors should revise the manuscript and explain the innovation of their work to be suitable for publication.

The comments to the authors are given below:

Abstract and Introduction

It is suggested that the search strategy and screening of articles be based on the "PICO." However, the main and secondary outcomes of the research are not clear in

the introduction and text of the article.

Line 15 and 21: What were the investigated outcomes? EDSS, Ashworth?

In lines 53-61, the side effects of BT are reported. Lines 62-68 also mentioned the unknown effects of adjunctive treatments. Are the authors going to examine these cases as outcomes? If not, shorten the introduction by reducing them.

The authors must specify the main research question in the introduction. What are the primary and secondary outcomes of the research? Didn't previous meta-analyses seek to find the effect of BT on spasticity in MS patients?

Methods

Line 85: The authors stated: "No restrictions were applied regarding language". But in line 94, it is said that "articles in languages other than English were excluded from the study".

Line 97-103:

The main study outcome was Spasticity, but in line 98-100, there is no mention of the data extraction related to it. The authors should specify the primary and secondary outcomes.

Results

Table 1: What F/M stands for?

Table 2: What HRB, URB, LRB, and URL stand for?

Table 3: What QA stands for? What are the range of scores and their interpretations?

Discussion

Line 225: Considering that a similar meta-analysis was conducted in 2021, what is the innovation of this meta-analysis? The studies included in this meta-analysis are from 2021 and earlier and overlap with Mariano's study.

Line 236: Please add a reference.

The authors should rewrite the discussion in line with the purpose of the study and its findings. The aim of the study was not to investigate the BT's injection dose, side effects, or its effects on functional mobility.

REFeree : Reviewer

1 Nov 2024

Thank you for the opportunity to review the manuscript. The manuscript needs minor revision. In general, an interesting and important topic. The comments to the authors are given below:

Keywords:

- Keywords should be chosen by using MeSH.

Abstract

- Specify the exact time period of the search.

Introduction

- Some sentences are lengthy, and breaking them into shorter sentences may improve clarity. Increasing coherence helps maintain a cohesive narrative by seamlessly connecting different aspects of the discussion.

- When discussing the variability of patient responses and the adjunctive therapies (occupational therapy, physical therapy, and...) could strengthen the argument and provide a clearer picture of the current research landscape.

- Addressing the variability in patient responses and the need for a comprehensive evaluation signals an awareness of ongoing challenges in the field, justifying the need for a systematic review and meta-analysis.

Discussion

- The discussion would be improved with increased organization and perhaps subheadings.
- Address potential biases and study limitations.

Table:

- Tables should adhere to APA style.
- Please upload the filled PRISMA Statement provides.

REFeree : Associate Editor

1 Nov 2024

Dear EIC

Based on the reviewers' comments, this manuscript needs major revisions. the authors should be apply the reviewers' comments carefully in the manuscript.

Thanks

Fatemeh Ehsani : EIC

2 Nov 2024

Dear Authors

According to the reviewers and associate editor's comments, your article needs to be revised majorly. When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and submit the required files up two months.

Best Regards

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reviewers' Comments:

Reviewer 1:

Dear Editor

Thank you for the opportunity to review the manuscript. The authors should revise the manuscript and explain the innovation of their work to be suitable for publication.

The comments to the authors are given below:

Abstract and Introduction

1- It is suggested that the search strategy and screening of articles be based on the "PICO." However, the main and secondary outcomes of the research are not clear in the introduction and text of the article.

We appreciate your valuable feedback regarding the need for clarity in the research outcomes and the application of the PICO framework. In response to your suggestion, we have revised the introduction to explicitly outline our main and secondary outcomes.

The PICO framework for our study is as follows:

- **P (Population): Patients with Multiple Sclerosis experiencing spasticity**
- **I (Intervention): Botulinum toxin (BT) injections**
- **C (Comparison): Various standard treatments or control groups**
- **O (Outcomes):**
 - **Main Outcomes: Changes in spasticity measured by the Modified Ashworth Scale (MAS) and overall quality of life.**
 - **Secondary Outcomes: Changes in the Expanded Disability Status Scale (EDSS) and any reported side effects.**

We believe that these revisions provide a clearer understanding of the research objectives and the outcomes we aim to measure, thereby improving the overall quality of the manuscript.

2- Line 15 and 21: What were the investigated outcomes? EDSS, Ashworth?

Thank you for your valuable comment. We have revised the abstract for greater clarity to specify that the investigated outcomes in this study included the Expanded Disability Status Scale (EDSS) and the Modified Ashworth Scale (MAS). This change explicitly highlights

the criteria assessed in this systematic review and meta-analysis. The revisions have been highlighted and are visible in the updated version of the manuscript.

3- In lines 53-61, the side effects of BT are reported. Lines 62-68 also mentioned the unknown effects of adjunctive treatments. Are the authors going to examine these cases as outcomes? If not, shorten the introduction by reducing them.

Thank you for your valuable feedback. We have revised the introduction to clarify the main and secondary outcomes of our research as per the PICO framework. The main outcomes are specified as changes in spasticity measured by the Modified Ashworth Scale (MAS) and overall quality of life, while the secondary outcomes include changes in the Expanded Disability Status Scale (EDSS) and reported side effects.

Additionally, we have shortened the part on side effects and adjunctive treatments, indicating that our review will primarily focus on the efficacy of botulinum toxin (BT) in reducing spasticity, rather than examining the unknown effects of adjunctive treatments. This should enhance the clarity and focus of the introduction.

4- The authors must specify the main research question in the introduction. What are the primary and secondary outcomes of the research? Didn't previous meta-analyses seek to find the effect of BT on spasticity in MS patients?

Thank you for your insightful comment. We mentioned the main research question and the primary and secondary outcomes in the revised introduction as you mentioned. Also, we appreciate your attention to the existing body of literature. Indeed, previous meta-analyses have investigated the effect of botulinum toxin (BT) on spasticity in patients with multiple sclerosis (MS). In our revised introduction, we have specified this point and acknowledged the findings of earlier studies. We also highlight the gaps in these studies, such as variability in treatment protocols, follow-up durations, and patient populations, which justify the need for our updated systematic review and meta-analysis to provide a more definitive and comprehensive assessment of BT's efficacy.

Methods

5- Line 85: The authors stated: "No restrictions were applied regarding language". But in line 94, it is said that "articles in languages other than English were excluded from the study".

Thank you for pointing out this discrepancy. You are correct; there was an inconsistency in our description of the language restriction. We initially intended to include studies without

language restrictions. However, during the screening process, it was decided to exclude articles in languages other than English due to limited resources for translation and verification. We have clarified this in the Method section and adjusted the text to accurately reflect our approach.

6- Line 97-103: The main study outcome was Spasticity, but in line 98-100, there is no mention of the data extraction related to it. The authors should specify the primary and secondary outcomes.

We appreciate your observation. We have revised the Method section to explicitly specify the primary and secondary outcomes and ensure clarity regarding data extraction related to spasticity.

Results

7- Table 1: What F/M stands for?

8- Table 2: What HRB, URB, LRB, and URL stand for?

9- Table 3: What QA stands for? What are the range of scores and their interpretations?

Thank you for your insightful comment about the abbreviations. We added the explanation under each table. Also, we wrote a detailed explanation of the Quality Assessment (QA) scores. The scores ranges from 0 to 10, where 0-3 denotes low quality, 4-6 represents moderate quality, and 7-10 indicates high quality. This addition aims to provide better clarity on the assessment and interpretation of the quality of included observational studies. We believe this enhancement will help readers better understand the methodological rigor of each study included in our review.

Discussion

10- Line 225: Considering that a similar meta-analysis was conducted in 2021, what is the innovation of this meta-analysis? The studies included in this meta-analysis are from 2021 and earlier and overlap with Mariano's study.

Thank you for your valuable feedback. We would like to clarify that the study by Marinaro et al. (2021) titled "Synergic use of botulinum toxin injection and radial extracorporeal shockwave therapy in Multiple Sclerosis spasticity" is not a meta-analysis, but rather a randomized controlled trial (RCT) examining the combined effects of botulinum toxin (BT) and shockwave therapy on spasticity in MS patients. This study is distinct from our meta-

analysis, which aims to synthesize and assess the pooled efficacy of BT for spasticity in MS patients across various studies.

Our study is innovative in that it provides a comprehensive meta-analysis of existing data, whereas Marinaro's study focuses on a specific intervention (combination therapy) and is limited to a single trial. Additionally, our work includes a broader scope of studies from different methodologies, providing more robust and generalizable insights into the effectiveness of BT in managing spasticity in MS patients.

11- Line 236: Please add a reference.

The reference has been added.

12- The authors should rewrite the discussion in line with the purpose of the study and its findings. The aim of the study was not to investigate the BT's injection dose, side effects, or its effects on functional mobility.

We appreciate the reviewer's observation. We have revised the discussion section to better align with the primary objectives and findings of our study, which focused on evaluating the effects of botulinum toxin (BT) injections on reducing spasticity as measured by the Modified Ashworth Scale (MAS) and assessing disability changes via the Expanded Disability Status Scale (EDSS) in multiple sclerosis (MS) patients.

To address this, we have shortened the content related to BT injection dosage, side effects, and its influence on functional mobility, as these were not the main objectives of our systematic review. Instead, the revised discussion now more emphasizes the therapeutic impact of BT on reducing spasticity (MAS scores) and improving disability status (EDSS scores), in line with the purpose of our study.

We believe these changes enhance the focus of the discussion and align it more closely with the intended goals and outcomes of the research.

Reviewer 2:

Thank you for the opportunity to review the manuscript. The manuscript needs minor revision. In general, an interesting and important topic. The comments to the authors are given below:

Keywords:

- Keywords should be chosen by using MeSH.

Thank you for your insightful comment regarding the selection of keywords. In response, we have carefully revised the keywords to ensure they align with MeSH terms. The updated keywords now include: Multiple Sclerosis, Muscle Spasticity, Botulinum Toxin, treatment efficacy

We appreciate your suggestion, as it enhances the clarity and relevance of our article within the medical literature.

Abstract

- Specify the exact time period of the search.

Thank you for your comment. We have revised the abstract to specify the exact time period of the search. The updated version now clearly states that the literature search was conducted from January 2000 up to April 2023. This addition ensures the time frame of the search is transparent to readers. The change has been highlighted in the abstract for easy identification.

Introduction

- Some sentences are lengthy, and breaking them into shorter sentences may improve clarity. Increasing coherence helps maintain a cohesive narrative by seamlessly connecting different aspects of the discussion.

Thank you for your valuable feedback. We appreciate your suggestion regarding the improvement of clarity and coherence in the introduction.

We have revised the introduction by breaking down longer sentences into shorter ones and adjusting the structure to enhance the flow of information. These changes were made with the goal of improving the clarity and readability of the text while maintaining a cohesive narrative. We believe that the revised version better communicates the study's background and the necessity of this systematic review and meta-analysis.

We hope the changes meet your expectations and contribute to a clearer presentation of the research focus.

- When discussing the variability of patient responses and the adjunctive therapies (occupational therapy, physical therapy,

and...) could strengthen the argument and provide a clearer picture of the current research landscape.

Thank you for your insightful comment regarding the discussion on the variability of patient responses and the adjunctive therapies. While we understand that adding more context about these aspects could strengthen the introduction and provide a more comprehensive overview of the current research landscape, we have decided to focus the introduction specifically on the primary scope of our study (the effects of botulinum toxin (BT) injections on reducing spasticity as measured by the Modified Ashworth Scale (MAS) and assessing disability changes via the Expanded Disability Status Scale (EDSS) in multiple sclerosis (MS) patients) to maintain clarity and relevance. As such, we have streamlined the content by reducing discussions on adjunctive treatments to ensure that the introduction remains directly aligned with our main research objectives. We hope this approach maintains the balance between providing background context and staying focused on the study's goals.

- Addressing the variability in patient responses and the need for a comprehensive evaluation signals an awareness of ongoing challenges in the field, justifying the need for a systematic review and meta-analysis.

Thank you for your insightful comment. We appreciate your suggestion to address the variability in patient responses and the importance of a comprehensive evaluation to highlight current challenges in the field. However, we opted to streamline the introduction by rewriting the section related to variability in patient responses in order to more focus on the main study aims and outcomes. That said, we agree with the importance of justifying the necessity of our systematic review and meta-analysis. To strengthen this aspect, we will add a statement in the introduction explaining the need for a comprehensive review of current evidence to address these ongoing challenges and support clinical decision-making.

Discussion

- The discussion would be improved with increased organization and perhaps subheadings.

Thank you for the suggestion. We agree that adding subheadings can enhance the clarity and organization of the discussion section. We have revised the discussion by structuring it into clear subheadings, including:

1. Summary of Key Findings
2. Comparison with Previous Studies
3. Clinical Implications
4. Limitations of the Study

5. Recommendations for Future Research

This restructuring aims to provide a more cohesive flow and allow readers to easily follow the main arguments and conclusions of our study. We hope this change improves the readability and coherence of the discussion section.

- Address potential biases and study limitations.

We thank the reviewer for the suggestion to address potential biases and study limitations. In response, we have added a section in the discussion to highlight the limitations and biases present in the included studies.

Table:

- Tables should adhere to APA style.

Thank you for your feedback regarding the formatting of the tables. We have revised the tables to adhere to APA style guidelines, including adjustments to the title, column headings, alignment, and spacing. Additionally, we have included a notes section where necessary to clarify abbreviations and provide further explanations. We believe these changes improve the clarity and presentation of the tables in accordance with the APA format.

- Please upload the filled PRISMA Statement provides.

It has been completed and uploaded in the journal site.

Reviewer Assistant Recommendations:

1. Enhance Methodology: Provide more detailed descriptions of the search strategy, including keywords and software used.

Thank you for your valuable suggestion. We have enhanced the Method section by providing a more detailed description of the search strategy, including the specific keywords used and the software employed for the process.

2. Include Flow Diagram: Add a flow diagram to illustrate the study selection process.

Thanks for your comment. We had uploaded a PRISMA flow-chart for study selection as a figure file during our primary submission. It can be seen at the end of the manuscript PDF file.

3. Discuss Limitations: Include a thorough discussion of the limitations of both the included studies and the review process itself.

Thank you for your valuable feedback. We have revised the discussion to thoroughly address the limitations of both the included studies and the review process itself. We acknowledge the variability in study designs, sample sizes, treatment protocols, and follow-up periods, which may impact the generalizability and robustness of our findings. Additionally, we discuss potential biases, such as the inclusion of grey literature, publication bias and data extraction bias.

4. Clarify Data Collection: Specify how data were collected and any tools used in the process.

Thank you for your feedback. We have added a more detailed description of the data collection process and the tools used in this review. The data were primarily collected through a systematic literature search in multiple academic databases, including PubMed, Scopus, and Web of Science. We employed predefined inclusion and exclusion criteria to select relevant studies. Data extraction was carried out using a standardized form to ensure consistency across studies, focusing on key outcome measures such as spasticity levels (measured by the Modified Ashworth Scale, MAS) and functional outcomes (such as the EDSS). The quality of the studies was assessed using established appraisal tools, including the Cochrane Risk of Bias tool for randomized controlled trials. This systematic approach was crucial in minimizing bias and ensuring that only the most reliable data were included in the review.

OPEN PEER REVIEW

Revision (1)

REFEREE : Reviewer

20 Nov 2024

no comments.

REFEREE : Associate Editor

8 Dec 2024

The manuscript is suitable for publication.

Fatemeh Ehsani : EIC

10 Dec 2024

Dear Authors

According to the bellow comments, your article needs to be revised minor. When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and submit the required files up to one month.

Enhance Methodology: Provide more detailed descriptions of the search strategy, including keywords and software used.

Include Flow Diagram: Add a flow diagram to illustrate the study selection process.

Discuss Limitations: Include a thorough discussion of the limitations of both the included studies and the review process itself.

Clarify Data Collection: Specify how data were collected and any tools used in the process.

This review could benefit from addressing these areas to improve adherence to the MOOSE and PRISMA guidelines, thereby enhancing the clarity and reliability of the findings.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

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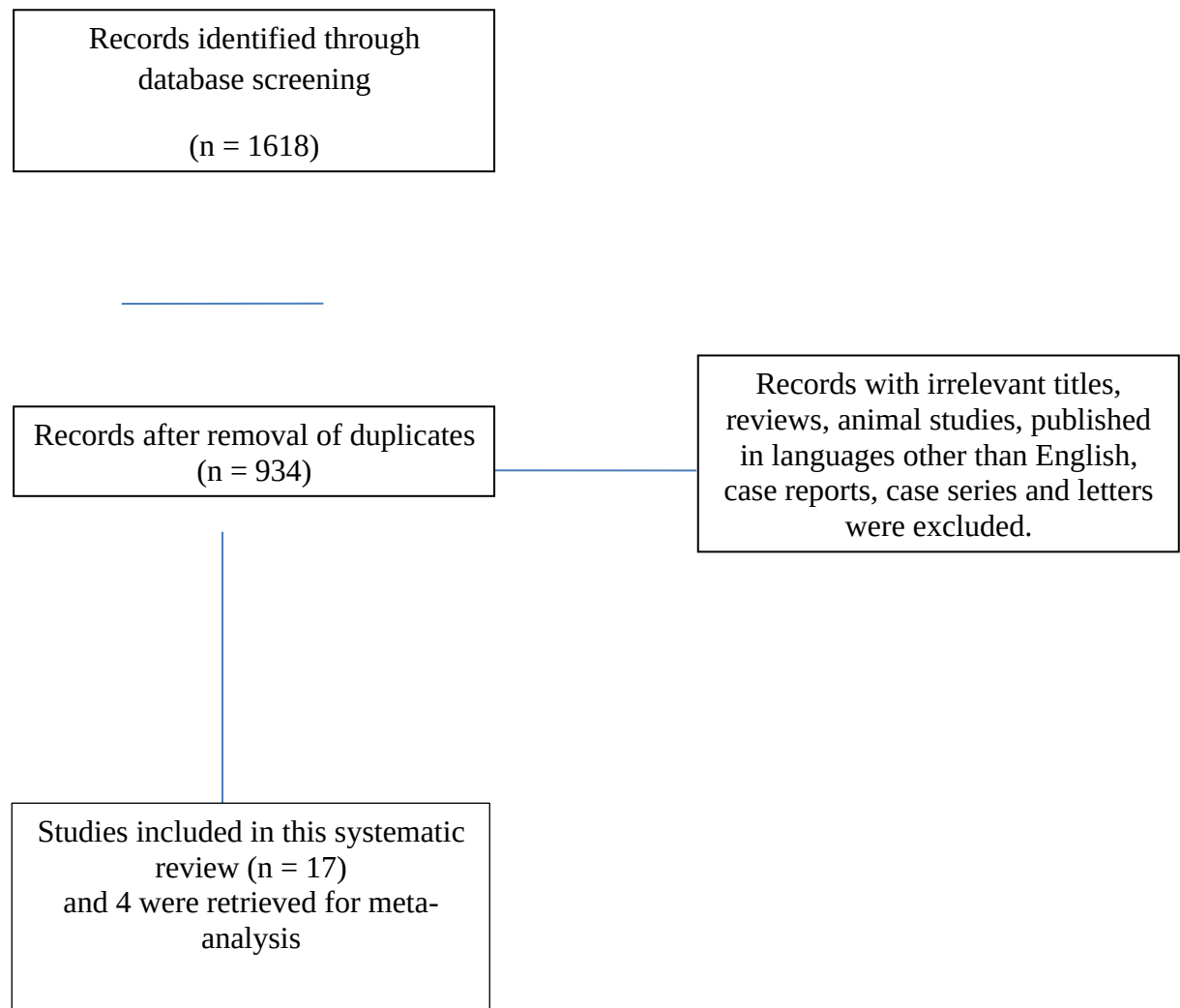


Figure 1. PRISMA flow diagram of study selection process.

3. Discuss Limitations: Include a thorough discussion of the limitations of both the included studies and the review process itself.

Thank you for your valuable feedback. We have revised the discussion to thoroughly address the limitations of both the included studies and the review process itself. We acknowledge the variability in study designs, sample sizes, treatment protocols, and follow-up periods, which may impact the generalizability and robustness of our findings. Additionally, we discuss potential biases, such as the inclusion of grey literature, publication bias and data extraction bias.

4. Clarify Data Collection: Specify how data were collected and any tools used in the process.

Thank you for your feedback. We have added a more detailed description of the data collection process and the tools used in this review. The data were primarily collected through a systematic literature search in multiple academic databases, including PubMed, Scopus, and Web of Science. We employed predefined inclusion and exclusion criteria to select relevant studies. Data extraction was carried out using a standardized form to ensure consistency across studies, focusing on key outcome measures such as spasticity levels (measured by the Modified Ashworth Scale, MAS) and functional outcomes (such as the EDSS). The quality of the studies was assessed using established appraisal tools, including the Cochrane Risk of Bias tool for randomized controlled trials. This systematic approach was crucial in minimizing bias and ensuring that only the most reliable data were included in the review.

OPEN PEER REVIEW

Revision (2)

Fatemeh Ehsani : EIC

23 Dec 2024

Dear Authors

According to the reviewers and associated editor's comments, your article needs to be revised minor. When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and submit the required files up to one month.

Moreover, please consider these recommendations during revision:

Enhance Methodology: Provide more detailed descriptions of the search strategy, including keywords and software used.

Include Flow Diagram: Add a flow diagram to illustrate the study selection process.

Discuss Limitations: Include a thorough discussion of the limitations of both the included studies and the review process itself.

Clarify Data Collection: Specify how data were collected and any tools used in the process.

OPEN PEER REVIEW

Revision (3)

Reply to Reviewers

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You can read the authors' responses to the reviewers' comments in the next page.

Reviewers' Comments:

Associate Editor's Comments:

Associate Editor 1:

Please revise and add the flow diagram of study selection according to the latest version of PRISMA in the text.

Thanks for your valuable comment. The flow diagram of study selection was revised according to latest PRISMA flow-chart sample (2020) and also added through the text as you mentioned.

EIC Decision:

Dear Authors

According to the reviewers and associated editor's comments, your article needs to be revised minor. When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and submit the required files up to one month.

Moreover, please consider these recommendations during revision:

Enhance Methodology: Provide more detailed descriptions of the search strategy, including keywords and software used.

Include Flow Diagram: Add a flow diagram to illustrate the study selection process.

Discuss Limitations: Include a thorough discussion of the limitations of both the included studies and the review process itself.

Clarify Data Collection: Specify how data were collected and any tools used in the process.

Thanks again. All the AI recommendations were considered in the last version of the manuscript and also highlighted in this version.

We enhance the methodology by adding more details in this part (in different aspects such as data collection, search strategy and software used). We also included the latest version of PRISMA flow-chart for study selection in the text. Moreover, we discuss limitations in details at the end of the manuscript.

OPEN PEER REVIEW

Revision (3)

Fatemeh Ehsani : EIC

25 Dec 2024

Dear Authors

We are pleased to inform you that your article is accepted for publication in the MEJRHS. We hope to receive the other qualified articles from your group.