

Peer-review Comments and Author Responses

Reviewer 1:

1. *The abstract is well-structured, concise, and comprehensive.*
2. *The introduction is very comprehensive. It highlighted the background and general information of the disease as well as disease pathology. Also, the author identified the existing gap in the literature that should be addressed however the aim of the study was not stated clearly as mentioned in the introduction of the abstract. Moreover, I think the global disease burden is relatively high. So, if the global magnitude of the disease and its morbidity were added to the introduction it will reflect strongly the importance of this study too.*

Corrected.

3. *The methodology addressed almost all the components of the rapid review however the author did not highlight one of the key steps in rapid reviews which is the Risk of Bias Assessment. Also, data synthesis and analysis were not well explained.*

Corrected, The quality assessment was conducted using the NIH Study Assessment Tools. Each study underwent evaluation based on a set of twelve to fourteen questions.

4. *The rapid review study design used in this study was not well justified from a public health urgent need perspective. The rapid review methodology is primarily carried out when timely evidence for decision-making is of high priority to address urgent and emergent health issues/questions. However, the research question of this article is important and it was worth having a systematic review to ensure the rigor of scientific evidence and methodology.*

This rapid review does not aim to substitute a comprehensive systematic review; instead, the aim is to complement it, by providing a temporary synthesis of the literature. This Rapid review offers a snapshot of the present understanding of the MS the current evidence and the research trends providing insights to guide subsequent comprehensive reviews, the main goal after doing this rapid review is to create a first step to create a systematic review and even think about a metaanalyses.

5. *Why snowball sampling was used? This sampling technique has a lot of disadvantages that can affect the study result and its validity.*

Due to the lack of accessibility of the databases we used this technique to increase the number of articles reviewed. Therefore, the limitations of this technique were mentioned.

6. *It is well known in the literature that gender plays critical roles in the development, progression, and treatment of MS. And females are more susceptible to MS than males, hence gender is a key risk in MS and should be included among the criteria. Also, the 4 clinical phenotypes and severity of the disease should be considered in the inclusion criteria e.g. adult patients (≥ 18 years of age) with a diagnosis of any MS phenotypes. Especially it is included in the table and part of the analysis.*

Any type of MS was included in the criteria. The gender was specified in the table, therefore even knowing that in the development, progression, and treatment of MS gender would play a relevant role, in every study both genders were included.

7. *How many researchers reviewed the database? For each article, how many researchers did the first and second screenings? The above information is so important to determine the quality and rigor of data as well as rolling out bias.*

The number of authors that did the screening was included.

8. *It is better to distinguish each section and have them separately as in the abstract and to streamline the structure. The general description of the study papers is comprehensive but nothing was mentioned about the distribution of study locations (countries). The table reveals that 40% of the studies were carried out in Iran while other papers were also limited to certain geographical areas. Therefore, we can not generalize the findings.*

Corrected.

9. *Having only 2 CTs and the bulk of the studies being observational, can negatively impact the validity of the result as the power of evidence from observational studies is not comparable with experimental studies. Especially, with the fact that given in the text and the table, 4/15 did not include a control group whereas the 2 clinical trials had no control group which makes the conclusions that came out of these studies questionable. That's why assessing the quality of papers and risks is a crucial step in rapid reviews.*

The quality assessment was conducted using the NIH Study Assessment Tools. Each study underwent evaluation based on a set of twelve to fourteen questions.

10. *Since animal studies were excluded in this review there is no need to include this in the opening as this will create confusion for readers, at first glance I thought the conclusions are related to studies carried out on animals. However, you can highlight there is a gap and limited studies in humans.*

Corrected.

11. *As the paper revealed that gene expression is a predictor for prognosis, this conclusion should be under “Inflammasomes as Prognostic Markers in Multiple Sclerosis” title and not under the “Therapeutic Targets”.*

Corrected.

12. *Since the MS has 4 categories why was the searching was limited to 2 types only?*

We incorporate the term "Chronic Progressive Multiple Sclerosis," which encompasses all the types of progressive forms including primary, progressive relapsing, and secondary progressive types.

Additionally, we acknowledge the "Clinically Isolated Syndrome" (CIS) type can be considered one of the four disease courses of multiple sclerosis. CIS represents the initial occurrence of neurological symptoms, and there is a possibility that it may not develop into MS. Furthermore, a person with CIS, by definition, is undergoing their first episode of symptoms caused by inflammation and demyelination in the central nervous system, whereas someone with MS has experienced multiple episodes.

13. *The limitation of the study should be specified and not kept generalized. e.g. “Although PubMed is one of the top research databases, other databases were excluded because of time and access constraints which increase the risk of missing articles” and “Therefore, a snowballing technique was implemented to improve retrieval. However, this technique limits the generalizability of the findings”.*

Corrected.

14. *Other limitations of this review can be: The quality of included studies was not screened as nothing was mentioned in the methodology regarding “Risk of Bias Assessment”.*

The quality assessment was conducted using the NIH Study Assessment Tools. Each study underwent evaluation based on a set of twelve to fourteen questions.

15. *Increased risk of bias in article selection as the author did not state how many authors screened the database.*

Corrected.

16. *Since it is well known in the literature that gender plays critical roles in development, progression and treatment of MS hence this review has a limitation because it did not involve gender in the inclusion criteria for searching strategy.*

The gender was specified in the table, therefore even knowing that in the development, progression, and treatment of MS gender would play a relevant role, in every study both genders were included.

17. *The author is using Harvard referencing style however in the initial submission checklist she affirmed to use APA style. Kindly amend the referencing to APA as indicated by the journal.*

Corrected we used APA 7th edition.

The comments on the table were assessed directly on the paper.

Reviewer 2:

18. *First paragraph – NLRP3 is misspelled due to the footnote reference misplacing – it's written NLRP⁴3 instead of NLRP3⁴*

Corrected.

19. *Review the many typos, including the frequent lack of spacing before or after parentheses – this difficults the reading.*

Corrected.

20. *Good table (columns synthesize very well the studies), though I couldn't guess to what logic the studies are ordered; not alphabetic by author, not by year, not by type of study; though the authors are relatively free to choose the ordering criteria, I'm positive there should be an obvious order, otherwise the table is chaotic. Ordering by study type would be a good choice, since it's how you present the results in the text!*

Corrected, the studies on the table were organized by alphabetic order by author.

21. *Overall you work with a lot of abbreviations, as many scientific papers do: these can be defined, in their first occurrence, either with the use of a footnote (as you indeed use) or by mentioning the entire term such as "... interferon-beta (INF-β) is..." - you should choose only one method and use it throughout your text (though you define most abbreviations with footnotes, it's not used for everyone.*

Corrected.

22. *The authors acknowledged your limitations very well and justified them.; lack of time to perform a systematic review, though, should not preclude the journals to seek systematic reviews instead of quick reviews; how do you defend your conclusions or, in other words, why should this be a valid review.*

This rapid review does not aim to substitute a comprehensive systematic review; instead, the aim is to complement it, by providing a temporary synthesis of the literature. This Rapid review offers a snapshot of the present understanding of the MS the current evidence and the research trends providing insights to guide subsequent comprehensive reviews.

Recommendation: Revisions Required

Reviewer 3:

23. *I couldn't find any information on tools used to assess the quality and bias of the articles that were used for the review. There are many you can use if you haven't used one like the CASP checklists.*

The quality assessment was conducted using the NIH Study Assessment Tools. Each study underwent evaluation based on a set of twelve to fourteen questions.

24. *If you find any risk or sources of bias in the articles you used, how would they be addressed?*

The quality assessment was conducted using the NIH Study Assessment Tools. Each study underwent evaluation based on a set of twelve to fourteen questions. And all of our articles were good to fair.

25. *In the limitations section, you mention certain aspects of the methodology that could affect the internal and external validity but you don't describe how it affects the article itself (does it decrease the external validity? How? Can it be a source of bias? How?*

Corrected.

26. *You describe there were 2 reviewers. I think it is important that you also describe how they evaluated the articles: did they both review all the articles blinded and then unblinded the decisions to see if they matched? Did they review half of each with no cross-review? Did you use any tools to help with this review?*

Corrected, this information was included in the methods.

Recommendation: Revisions Required

Reviewer 4:

27. *Keywords. PPCR Journal recommend providing 6 keywords or less, in this paper we can find 7 keywords.*

Corrected.

28. *Introduction. I think that the introduction provides adequate background, I would recommend defining the research question. In my opinion, some sentences should be re-write because they are difficult to understand (as for example This system is activated when PRRs recognize PAMPs, which are derived from invading pathogens, or DAMPs, induced by endogenous stress).*

Corrected.

29. *Check this reference sentence “Cotsapas et al., 2018; Dutta & Trapp, 2006) Duta et al., 2006” (probably a comma is missing and a parenthesis is left over).*

Corrected.

30. *Material and Methods. As you have used rapid review (Cochrane Guidelines), I think it should be referenced.*

Corrected, Cochrane Guidelines were cited.

31. *Eligibility Criteria. For exclusion criteria, I understand that patients < 18 years include pediatric patients. As in inclusion criteria you decide on articles published after 2010, I think that it’s not necessary to add the “negative form” (were published before 2010) as exclusion criteria.*

Corrected.

32. *Search strategy. As Cochrane Rapid Review recommends “Limit the publication language to English; add other languages only if justified”, I think it’s not necessary to use “Only studies in English, published between 2010 and 2022 were selected because of limited time, resources, and availability of researchers”.*

Corrected.

33. *Data extraction. Table 1, you mention that it includes a summary of study results, but what I understand is that in the table you include how researchers measure their outcomes, so it should be modified.*

Corrected.

34. *I miss in material and methods risk of bias assessment.*

The quality assessment was conducted using the NIH Study Assessment Tools. Each study underwent evaluation based on a set of twelve to fourteen questions. And all of our articles were good to fair.

35. *Results and Discussion - You mention that you have used surrogate measures to assess outcomes, we can assume that this is included in “intervention if the level of inflammasomes was evaluated” from inclusion criteria. If it’s not this, it should be specified in inclusion criteria.*

Corrected.

36. *Try to avoid discussing about other related publications and focus on your review’s papers.*

Corrected.

37. *Conclusions. I believe that part of the conclusion should be included in the discussion, you should not discuss your results in the conclusions (and avoid references in this section), so try to present a short conclusion of your rapid review.*

Corrected.

Recommendation: Revisions Required

Reviewer 5:

38. *Some sentences were hard to follow, and you should rewrite them. Also, I found that some pieces of information are not logically connected. Sometimes it seems that each author did the work separately and then merged, but without finding the connection between the sentences.*

Corrected.

39. *You should update the flowchart and table one. According to table 1, you found 15 articles, but you only cited 4 of those 15 articles. You have also cited some articles that should be*

included in table 1, but are not. In addition, you excluded review articles from your search, but you used information from review articles in the body of your systematic review.

Corrected, all the articles in the table were used to create the discussion.

40. *You will find more detailed information in the document that I uploaded. Don't take the comments negatively. These are suggestions to improve your paper. Overall, you have a great article that needs some improvement.*

The best.

41. *Since the abbreviation MS is defined in the text, I consider it redundant to add the footnote. Since every other abbreviation is explained only in the footnotes, I suggest leaving only MS in the text and keeping the footnote.*

Corrected.

42. *Though most people know what MRI is, I suggest adding a footnote.*

Corrected.

43. *“macrophage-colony stimulating factor” Again, you should define the abbreviation in the footnote, as in the text, in general.*

Corrected.

44. *“ Inflammasomes “ Why capitalizing?*

Corrected.

45. *“reactive oxygen species “ Again if you are defining the abbreviation in the text, you don't need to do it in the footnote.*

Corrected.

Recommendation: Revisions Required