Peer-review Comments and Author Responses

Reviewer 1

1. *Regarding the abstract: Changing the sentence "this mini review provides an overview of these clinical scales, discussing their strengths and limitations." The review doesn't discuss the strengths and limitations of the scales used. I would consider changing it to "This review provides an overview of the clinical scales most often used when studying spasticity in Multiple Sclerosis."*

Well noted. In fact, after reviewing we agreed to change the title to “An Overview of Clinical Scales for Assessment of Spasticity in Multiple Sclerosis”. The change was also included in the abstract/objective [Page 3].

2. *Regarding the discussion, it is great that you included a brief description of the MAS, AS and MTA scales. I suggest you to also provide a description of the MSSS 88 scale. For example, the MSSS 88 scale focuses on describing the impact of spasticity on a patient. It considers subscales related to spasticity symptoms, physical and social functioning, and emotional health.*

Thank you for pointing this out. We agreed with this recommendation and included the sentence in the discussion [Page 8].

Reviewer 2

3. *I appreciate the authors' efforts and dedication to address a topic that is interesting and relevant to the field. Nevertheless, I would like to suggest that they explain their research question and PICOS more clearly, and also provide more context to show the novelty of their study.*

Thank you for this suggestion. Accordingly, we modified the final paragraphs of the introduction as follows:

“Hugos et al.'s review describes the tools available for measuring spasticity in multiple sclerosis. However, the current literature lacks a standardized approach for addressing spasticity in this population.

We conducted this systematic review to explore the tools that are used to evaluate spasticity in MS. Our main objective is to identify the most commonly used scales for the assessment of spasticity in MS, and to examine their applications in recent studies published in the literature.” [Page 5].

4. *Abstract: include subheadings, instead of keeping as a continuous text.*

We considered this an excellent suggestion. We modified the abstract accordingly [Page 3].

5. *Make the gap in the literature more clear in the text.*

We have added the suggested content to the introduction as mentioned in the comment before [Page 5].

6. *The authors describe: "Modified Ashworth Scale and Ashworth Scale as the most frequently used (38.4% each), with approximately 30% of studies employing multiple scales for assessment." Nevertheless, this information is not highlighted in the main text. I suggest reviewing that.*

Thank you for this observation. We included this information in the results section [Page 6].

7. *Introduction: in the third paragraph, the authors describe details about the different types of spasticity assessments and why this assessment is relevant, but I missed the novelty of the study here. In other words: where is the gap in literature that they are trying to address with this study? For example: are there previous reviews on this topic? If so, how is their study different and how is it going to add to the body of existing knowledge? If not, then I suggest emphasizing this, so that it could justify the novelty of the study*

Thank you for your suggestion. As mentioned before, this was included in the last paragraphs of the Introduction [Page 5]. The only previous review on this topic was cited including the difference between that one (description of the scales) and our review “identify the most commonly used scales for the assessment of spasticity in MS, and to examine their applications in recent studies published in the literature.”

8. *Introduction: It would be beneficial to provide more context on the different types of spasticity scales.*

We appreciate the reviewer's feedback, but we respectfully disagree. While we understand the value of providing more context on each scale, our main goal was to examine the use of these scales in recent studies.

9. *I also suggest reviewing the last paragraph of Introduction and provide more details on the purpose of the study and state more clearly if it was a systematic review.*

We have added this suggestion [Page 5].

10. *Introduction: The spasticity scales are not specific for the studied condition (multiple sclerosis). So it is not clear why the authors are assessing those scales in this condition, since they can be used in other conditions with spasticity as a symptom. In other words: the research question is not clear. Do the authors want to evaluate/describe the psychometric properties of the scales used in the context of*

multiple sclerosis? or to assess/describe which scales are most used in MS? I suggest making this point more clear.

Thank you for mentioning this question. Our goal was focused on scales to measure spasticity specifically in the context of MS. Hence, we emphasized it in the introduction. [Page 5].

11. *Introduction: the last paragraph is supposed to be all about the study design and PICOS. The sentence "We aim to equip researchers with insights for proper muscle spasticity assessment in MS, enhancing accuracy in clinical evaluations and personalized treatment strategies" is not the purpose of the present study and says more about justification and relevance. So I suggest moving the sentence to previous paragraphs and providing more details about the study design and PICOS in this last paragraph.*

We appreciate this comment and deleted the sentence "We aim to equip researchers with insights for proper muscle spasticity assessment in MS, enhancing accuracy in clinical evaluations and personalized treatment strategies".

12. *Methods: if they believe one database is enough, please then explain here why their methodology was enough to capture all papers. If they think one database is not enough to find all articles, then they need to add other databases.*

Thank you for this observation. The search was run in one database because we considered that Pubmed is the most important and large Database in the US, they have most of the articles in English and it has a more straightforward search engine. However, it can be seen as a limitation of our study, as we might have missed other valuable articles, which could introduce publication bias in the study.

13. *Methods: why the restriction of the dates to the period of 2003 to 2023?*

The decision was made to identify the current trend of authors in the field who studied spasticity assessment in Multiple Sclerosis.

14. *Methods: did they apply any language restrictions?*

Thank you for raising this concern. Yes, only studies in English were considered. Accordingly, we acknowledged this in the Material and Methods section as follows: "Given the nature of this mini-review, our search was confined to the MEDLINE database (accessed through PubMed) exclusively, focusing on articles published in English, between 2003 and 2023 to ensure that our bibliography is recent and up-to-date." [Page 5]. We also included it in our limitations: "Language restrictions and the possibility of unpublished data could be considered as additional limitations." [Page 8].

15. *Methods: I miss more details on the inclusion and exclusion criteria of the studies: Did the authors specify the design of the included studies? Which specific characteristics of the spasticity scales needed to be reported to warrant inclusion in the study? Were there any exclusion criteria? If the population of the study was heterogeneous (not only MS but also other neurological disorders), could it be included?*

The design of the studies was not specified in the initial search but after reviewing the articles obtained, those without patients with MS, case reports, and review articles were excluded. We included articles with heterogeneous populations. However, not including patients with MS was an exclusion criterion.

We have added the following modification regarding these points. In Method and Materials:: “Study inclusion criteria required a focus on MS-related muscle spasticity indicated by specific MeSH terms within the title or abstract. Additionally, studies had to employ scales to assess muscle spasticity in this population excluding spasticity related to other diseases. Non-English publications and studies in which spasticity is not measured through clinical scales are excluded.” [Page 5]. Also in the results: “The initial search retrieved 29 studies. Upon title review, six articles were clearly unrelated and thus were primarily excluded. Ten more articles were omitted after an abstract review. The main reasons for exclusion were the absence of MS patients or an unclear patient cohort (n=3), study protocols (n=1), case reports (n=3), and review articles (n=3). The final analysis included 13 articles; in 10 of them scales are used as outcome measure while in 3 of them the studies assess the scales accuracy and psychometric properties (Table 1,Table 2). Six focused on the assessment of spasticity scales. The remaining articles involved interventions and observational studies (Figure 1). [Page 6].

16. *Results: please, insert a reference to Table 1 in the text.*

Thank you for this suggestion. Reference was added. [Page 6].

17. *Results: The column about "Comparison" in the table seems confusing and heterogeneous, since in some studies it is the "comparison" for some intervention and in others the comparison is to other diseases or other types of information. I suggest reviewing that and deciding whether it makes sense to include this column or make adaptations.*

Thank you for your close reading of the table. After analyzing this concern, we agreed that the column “Comparison” could be confusing. Accordingly, we deleted it.

18. *Results: I suggest organizing the text in sections using subheadings. It could be in accordance with the scale evaluated or the type of studies (diagnostic studies X studies in which the scales were outcome measures).*

We agreed that the table could be improved. For this reason, we decided to divide it into two tables as follows: “Table 1. Description of the studies in which the scales were used

as outcome measures. Table 2. Description of the studies assessing the scales accuracy and psychometric properties". Both tables are attached.

19. *Results: the authors report excluded articles, but in the Methods section they did not specify clearly the exclusion criteria.*

We have made this modification in the previous comment.

20. *Results: The authors mixed studies in which the scales were used as outcome measures with studies assessing the scales accuracy and psychometric properties. If the authors want to keep this way, I suggest organizing the text and the table in a way to group similar studies together. For example, one table for the studies that analyzed the properties and another one to describe the ones that used the scales as outcome measures.*

We agreed on this approach and decided to divide the table as mentioned in the previous comment.

21. *Results: I am not sure on the relevance of the risk of bias assessment in this study, since some papers were included only because they used the scales as outcome measures (and do not evaluate the accuracy and other properties of the scales). If the authors decide to keep this section, I suggest providing a table with the description of the assessment of each study.*

Thank you for raising this concern. After discussing this section, we decided to delete this section since the articles selected did not directly compare the scales, but we aimed to review the most used scales and their characteristics.

22. *Discussion: the first paragraph of this section should summarize and highlight the main findings of the study. I suggest the authors write again this paragraph with this purpose in mind. In the following paragraphs, when the authors contextualize their findings, I suggest searching for previous similar studies describing these kinds of scales, contrasting the results with the present study.*

Thank you for this observation. Although we consider it valid, we consider that the discussion is written contextualizing our findings with existing literature. For instance: "In the studies selected for this review, there was significant variability in the spasticity measure scales utilized. The MAS and AS, independently used or combined with other tools, were the most prevalent choices. They both grade muscle tone escalation on a scale from zero to four. The MAS incorporates a +1 increment to augment sensitivity (Meseguer-Henarejos et al., 2018). The AS was initially designed to assess the spasticity and effectiveness of antispastic drugs in MS patients. However, the MAS, a revised version of the AS, addresses limitations with better reliability and validity (MohanaSundaram et al., s. f.; Petek Balci, 2018). Both scales have been featured

prominently in neurological literature and have gained widespread recognition and clinical acceptance within the field." [Page 8-9].

23. *Discussion: please, provide a reference for the Multiple Sclerosis Spasticity Scale-88 (MSSS-88), in the third paragraph.*

Reference was included in the revised manuscript as follows: "Remarkably, specific well-established spasticity assessment scales, such as the Multiple Sclerosis Spasticity Scale-88 (MSSS-88), remained absent from the scales employed in the selected papers (Hugos et al., 2019)." [Page 8].

24. *Discussion: in the paragraph about limitations, I missed comments about the use of only 1 database, language restrictions and the possibility of unpublished data.*

Thank you for highlighting this. The following sentence was added to the manuscript "Language restrictions and the possibility of unpublished data could be considered as additional limitations." [Page 8].

25. Conclusion: In this paragraph, I can see the generalization and recommendations for the field, but I missed a more clear statement about which were the main study findings and how they are linked with those recommendations.

Thank you for this suggestion. The following statement was added to the manuscript: "In this brief review there was significant variability in the spasticity measure scales utilized. The MAS and AS, independently used or combined with other tools, were the most prevalent choices. This provides insight into scale selection for assessing MS-related spasticity. Nevertheless, the scale selection must depend on expertise and resources available, and even though there is no agreement on the best tool, the combination of them, especially with objective methods, could offer a more reliable assessment of this clinical presentation. This integrated approach may provide researchers with a more comprehensive evaluation of spasticity, improving the overall management of multiple sclerosis." [Page 9].

Reviewer 3

26. *Introduction: first paragraph - a. Lines 106-107 – "causing substantial disability in the young population, ages 15-45, with progression over 20-30 years." Please reword this sentence for clarity.*

As suggested we modified the sentence accordingly "It commonly affects individuals between the ages of 15 and 45, with progression over 20 to 30 years, causing substantial disability" Introduction [Page 4].

27. *Introduction: first paragraph - b. Lines 111-113 - "Spasticity's impact extends to various body parts, including legs, groin, buttocks, back, arms, hands, and even speech, resulting in difficulty in extending or flexing the limbs due to either flexor or extensor spasticity." It sounds like the second part refers to the speech. I suggest breaking this sentence into two sentences for clarity.*

Thanks for mentioning this. We adjusted it as follows: " Spasticity's impact extends to various body parts, including legs, arms and hands resulting in difficulty in extending or flexing the limbs due to either flexor or extensor spasticity." Introduction [Page 4].

28. *Overall, the introduction reflects the current state of the spasticity in multiple sclerosis. However, it needs to be clarified why this review is important; what motivated the authors to conduct this review?*

After careful consideration and analysis, we agreed that a better statement related to the current gap in the literature and the novelty of our review was missing. Hence, we modified the final paragraphs of the introduction as follows:

" Hugos et al.'s review describes the tools available for measuring spasticity in multiple sclerosis. However, the current literature lacks a standardized approach for addressing spasticity in this population.

We conducted this systematic review to explore the tools that are used to evaluate spasticity in MS. Our main objective is to identify the most commonly used scales for the assessment of spasticity in MS, and to examine their applications in recent studies published in the literature." [Page 5].

29. *Material and methods: first paragraph - a. Lines 133-134 – "We conducted an extensive search on the MEDLINE (PubMed) database." I suggest rewording this sentence as: "We conducted an extensive search on the MEDLINE database (accessed through Pubmed)."*

Well noted. We modified this sentence as follows: "Given the nature of this mini-review, our search was confined to the MEDLINE database (accessed through PubMed) exclusively, focusing on articles published in English, between 2003 and 2023 to ensure that our bibliography is recent and up-to-date." [Page 5].

30. *Material and methods: first paragraph - b. Lines 136-137 – This part should be better written. Some parentheses and brackets open and do not close or close twice.*

Thank you for mentioning this. It was modified accordingly: "The search was performed using the keywords (Muscle spasticity [Title/Abstract][Mesh]) AND (multiple sclerosis[Title/Abstract][Mesh]) AND ((assessment[Title/Abstract]) OR (scale[Title/Abstract]) OR (scales[Title/Abstract]))." [Page 5].

31. *Material and methods: second and third paragraph - In the inclusion criteria, it is important to detail the characteristics of the studies included, such as the language - Did the authors include only studies published in English?*

That is correct. We only included studies in English. This was mentioned in the modifications related to “Lines 133-134” in our previous comment.

32. *Material and methods: second and third paragraph - The authors did not mention what their exclusion criteria were – Please specify.*

Thank you for highlighting this. We have added the following modification regarding inclusion/exclusion criteria. In the Method and Materials section: “Study inclusion criteria required a focus on MS-related muscle spasticity indicated by specific MeSH terms within the title or abstract. Additionally, studies had to employ scales to assess muscle spasticity in this population excluding spasticity related to other diseases. Non-English publications and studies in which spasticity is not measured through clinical scales are excluded.” [Page 5].

Also in the Results section: “The initial search retrieved 29 studies. Upon title review, six articles were clearly unrelated and thus were primarily excluded. Ten more articles were omitted after an abstract review. The main reasons for exclusion were the absence of MS patients or an unclear patient cohort (n=3), study protocols (n=1), case reports (n=3), and review articles (n=3). The final analysis included 13 articles; in 10 of them scales are used as outcome measure while in 3 of them the studies assess the scales accuracy and psychometric properties (Table 1, Table 2). Six focused on the assessment of spasticity scales. The remaining articles involved interventions and observational studies (Figure 1) [Page 6].

33. *Material and methods: second and third paragraph - Lines 144-146 – “Three independent reviewers conducted full-text analysis in the selection process to minimize bias. A third experienced reviewer resolved disagreements.” I think there is an issue with the wording. Is the reviewer who resolved the disagreements different from the three independent reviewers? Or did you mean that from the three independent reviewers, the most experienced was the one who solved the disagreements? I believe a “fourth” experienced reviewer is the proper title for the one who resolves the disagreements. Please clarify.*

We apologize for this error. The terminology was adjusted as per your suggestion: “Three independent reviewers conducted full-text analysis in the selection process to minimize bias, the most experienced was the one who solved disagreements.” [Page 5].

34. *Material and methods: Please provide the registration information. Did the authors register the study? If that is not the case, state that the review was not registered.*

Well noted. We added the following statement as per the reviewer's suggestion: "REGISTRATION: The current review has not been registered in any prospective register databases for systematic reviews." [Page 9]

35. *Material and methods: assessment of risk of bias, lines 230-231 – Please specify what certain aspects introduced potential risk for bias.*

Thank you for pointing this out. Upon careful discussion of this section, we collectively determined that it would be best to omit it from our review. The reason being, the

articles included did not directly compare the scales, which was our aim in examining the most commonly utilized scales and their unique characteristics.

36. *Results: third paragraph, lines 185-191 – The authors mentioned, "In four studies, MAS was used as the only tool for spasticity assessment." However, throughout the paragraph, they only mentioned 2 of those 4 that only used MAS. Please reference the 2 studies missing.*

We acknowledge this comment, and we would like to clarify that we intended to highlight those studies that possess unique characteristics. Unfortunately, due to the word limitation we did not describe the characteristics of all of them.

37. *The results section is clear and straightforward. The authors describe the number of patients participating in some studies. Consider describing how many patients participated in each one of the selected studies.*

Similar to the previous comment, due to the word limit we did not mention the participants for each one of the selected studies but included them in the tables attached.

38. *References: please check the APA guidelines for citations. At least 3 references are incomplete.*

We apologize for this error. We adjusted the references following the APA guidelines for citations.

39. *Table 1: RCT abbreviation description is missing at the bottom of the table.*

Well received. We added this abbreviation at the end of Table 1. [Attached]

40. *Table 1: What do the authors mean when they put an asterisk after the author's name? I don't see it explained below. Please clarify and specify.*

The asterisk means “Corresponding author”. The equivalence is mentioned at the end of the author’s list [Page 2].

Reviewer 4

41. *The main question addressed by the authors was to investigate the usage of Spasticity Scales in MS (if there was a preferred one, what were their strengths and limitations). The discussion is rich, for example on raising that the scale selection rationale was absent from the retrieve articles. It is an original question, as I couldn’t find anything quite like it in a brief literature search. In most guidelines, the preferred scale is the MAS, but as the authors show, this choice is not hegemonic, so a literature review on the topic is welcome. The manuscript’s overall methodology is sound, but limited by a possible search strategy imprecision as discussed further on. That probably limits the final conclusion as the literature review may be incomplete. The article is overall well-written, with minor adjustments as proposed in the linked document. The conclusions were consistent with the data presented, and they address well the main question. I believe the overall goal was met, but possibly limited by the search strategy. The search terms could have included “spasticity” only. ((multiple sclerosis[Title/Abstract]) OR (multiple sclerosis[MeSH Terms])) AND ((muscle spasticity[MeSH Terms]) OR (spasticity[Title/Abstract])) AND ((assessment[Title/Abstract]) OR (scale[Title/Abstract]) OR (scales[Title/Abstract])). Doing so yielded 472 results for me (reduced to 84 by using the “Clinical Trial” filter, that is, excluding reviews), only in Pubmed. For illustration, some of these papers did indeed explore the MSSS-88 (whose absence is questioned in the discussion). At the same time, the rationale for the search strategy was sound and a coherent methodology was carried out with the retrieved papers, which can constitute a sample of the literature. Indeed, the review yielded interesting results and discussion.*

Thank you for highlighting this matter. Our search strategy was designed to limit the assessment of spasticity solely to patients with Multiple Sclerosis. We appreciate your observation and the opportunity it presents to clarify our intentions.

42. *The “Assessment of risk of bias” section needs work. There is a lot of redundant/unnecessary text, while, at the same time, the discussion of the identified biases is not well developed.*

Thank you for highlighting this topic. In fact, it was also mentioned by other reviewers. We discussed it carefully with our advisor and collectively agreed to delete this section of the manuscript. Since the articles included did not directly compare the scales, which was our aim in examining the most commonly utilized scales and their unique characteristics. Given our aim to examine the most commonly utilized scales and their unique characteristics, it is noteworthy that the included articles did not offer a direct comparison between them.

43. *This manuscript would have likely been rejected in most regular peer-reviewed journal. However, considering the didactic role of this Journal, I propose major adjustments as an academic exercise of improving the text and learning throughout the process instead of discarding it altogether (not necessarily redoing the search strategy, but addressing all the other raised issues). Perhaps the manuscript won't get to be titled a *comprehensive* review, but it was altogether a good read and a great production.*

Well received. We agreed to change the title of our manuscript to"An Overview of Clinical Scales for Assessment of Spasticity in Multiple Sclerosis" in consideration of the facts mentioned.

44. *Abstract: Ajust grammar*

We agreed with the grammar suggestions made and adjusted the abstract accordingly [Page 3-4].

45. *The introduction is mainly well-written; the proposed corrections are for the sake of conciseness. It gives the correct amount of information to contextualize the knowledge gap and research question.*

We appreciate your valuable input. The introduction has been revised in accordance with the suggested grammatical changes.

46. *Why only 1 database? What about EMBASE and CINAHL?*

Based on the purpose of this "mini-review" we focused our search only on one of the main databases. Hence, we acknowledged this in the Material and Methods section as follows: "Given the nature of this mini-review, our search was confined to the MEDLINE database (accessed through PubMed) exclusively, focusing on articles published in English, between 2003 and 2023 to ensure that our bibliography is recent and up-to-date." [Page 5].

47. *The search terms should have included "spasticity" only. ((multiple sclerosis[Title/Abstract]) OR (multiple sclerosis[MeSH Terms])) AND ((muscle spasticity[MeSH Terms]) OR (spasticity[Title/Abstract])) AND ((assessment[Title/Abstract]) OR (scale[Title/Abstract]) OR (scales[Title/Abstract])). Doing so yielded 472 results for me (reduced to 84 by using the "Clinical Trial" filter, that is, excluding reviews), only in Pubmed. Some of these papers did indeed explore the MSSS-88.*

This was mentioned in a previous response.

48. *[Pertinent studies were also identified through reference lists on related reviews and meta-analyses.] Was this done?*

Yes, that was part of the process performed during the search strategy.

49. *The study selection included all search results to be screened based on title and abstract to determine their relevance. Three Two independent reviewers conducted full-text analysis in the selection process to minimize bias. A third experienced reviewer resolved disagreements.*I assume each paper was reviewed by 2 independent blinded reviewers and a third more experienced settled**

We apologize for this error. This sentence was modified accordingly: “Three independent reviewers conducted full-text analysis in the selection process to minimize bias, the most experienced was the one who solved disagreements.” [Page 5].

50. *The numbers presented in the abstract are not in the full text [Modified Ashworth Scale and Ashworth Scale as the most frequently used (38.4% each), with approximately 30% of studies employing multiple scales for assessment].*

Thank you for noticing this. We included this statement in the results section [Page 6].

51. *Here you could highlight that this scale is the result of an exam as opposed to the subjective nature of a physician’s evaluation in the other scales.*

Although we consider this a valid recommendation, due to the word limit we decided not to include it in the manuscript.

52. *Assessment of risk of bias: this section needs work.*

This was a common recommendation from the reviewers. After a careful discussion we decided to omit it based on the purpose of the review and the fact that we are not directly performing comparisons between the articles included.

53. *Remarkably, specific well-established spasticity assessment scales, such as the Multiple Sclerosis Spasticity Scale-88 (MSSS-88), remained absent from the scales employed in the selected papers. The reasons behind the omission remains speculative (possibly an imprecise search strategy), as again, the underlying rationale for their exclusion was not elucidated within the reviewed literature.*

While we appreciate the reviewer’s feedback, we respectfully disagree. We think the search strategy was aligned with the purpose of the review [examine scales to measure spasticity only in patients with Multiple Sclerosis]. Nonetheless, we agreed to the restricted articles included as part of our limitations. For this reason, we included the following statement: “Language restrictions and the possibility of unpublished data could be considered as additional limitations.

Furthermore, the restricted number of available papers compelled us to rely on all accessible information, which precluded a meaningful comparative analysis. One pivotal factor contributing to this limitation was the inherent heterogeneity among the patient populations under review. While all subjects had MS and spasticity, the diversity in the type and severity of spasticity across the studies hindered direct comparisons." [Page 8].