Peer Review File

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Reviewer A

Highlighting specific biomarkers such as EDN, MBP-1 and EPO and their association with eosinophilic esophagitis provides valuable insights that could guide future research and clinical practice. The selection of studies ranging in size and scope and the analysis of different biomarkers demonstrate a robust approach to data synthesis.
However, there are some areas that can be improved:
1. The manuscript could benefit from clearer structuring and simplification of complex sentences to improve readability and comprehension
Thank you very much. The manuscript went through re-structuring and complex sentences or paragraphs have been made hopefully easier to read.
2. While you have selected a number of studies, a more varied representation in terms of geography, demographics and types of studies could provide a more comprehensive overview. Please consider highlighting the importance of non-invasive diagnostic tools in the pediatric population in the introduction (see PMID: 37870118)
Thank you very much for your suggestion. Yes, indeed. We added the geographical area, the demographics, and the type of investigation of the retrieved and discussed studies.
3. A more detailed discussion of the limitations of the current studies, including your own methodology, would strengthen the scientific rigor of the manuscript.
Yes, thank you very much. We changed to in-depth review and added a paragraph with regard to the limitations observed in perusing the literature and in writing our manuscript.
4. Practical implications: Addressing how these findings might directly impact clinical practice and what this means for future research would add strength to the conclusions.
Yes, the reference provided was very useful and we tried to emphasize some implications of this study, which may be useful for future studies targeting potential biomarkers for eosinophilic esophagitis.

Reviewer B

Odetola and others have written a review article on biomarkers in EoE. Unfortunately, I do not think it contains anything new, and adds nothing to the current state of knowledge, which is why I choose to reject it.
Thank you for your comments. We restructure the manuscript and we consider that

advocating for the eosinophilic ratio considering granulated and degranulated eosinophils may be useful for future studies targeting the potential biomarkers for diagnosis and monitoring of eosinophilic esophagitis.

Line 26, should complications be mentioned here? They are very rare
We considered to restrict the study to what we have observed and reduced substantially the introduction. The fibrosis of the lamina propria was mentioned in the discussion.

Line 27, It is not the diagnosis that is challenging because of relapsing, but the disease?
Thank you very much for this point. Yes, we agree, but some authors have expressed discordant opinions in the literature. Thus, we did not emphasize particularly this aspect.

Line 31, the aim is to study biomarkers released by eosinophils. But you also look at others? I don't understand that.
Yes, thank you. We clarified the aims in both the abstract and in the manuscript.

Line 45, is it this ratio that is the aim? Or main conclusion?
As above, we tried to make the manuscript more easy to follow clarifying our aims.

Line 63, are there more studies describing this?
We revised again the literature retrieved and identified 10 studies that match our criteria.

Figure 1 seems unnecessary.
Thank you for your suggestion. Since we are strongly advocate of the peak eosinophilic count considering both granulated and degranulated eosinophils, we consider that figure 1 may help a non-pathologist to better understand what we can observe in reading an esophageal biopsy.

Line 98, This paragraph should be rewritten. There are many studies on symptoms and their variation across age groups. Why describe just this two and what they showed.
Yes, we restructured the manuscript and added some references on clinical symptoms without going into details.

Line 107.Consider here that in the pediatric population, string test, cytosponge, trans-nasal endoscopy are invasive and difficult to do without anesthesia. May need to be rewritten
Yes, indeed. We emphasize that some procedures considered minimal invasive in adults, they are invasive in children.

Line 120. What biomarkers?
We clarified this point in the restructuring of the table 1 and in the manuscript.

Line 137. There are many different treatment studies, why do you choose one and why this one?
We tried to identify the few studies that may be useful in the discussion, but obviously, we agree that there are multiple treatment studies in the literature.

Line 174, delete (SO)
Thank you, we deleted it.

Line 178. delete (CMS)
Thank you, we deleted it.

Line 182. I would not mention who did what here.
Yes, the cleaned version should not contain details on the single authors.

It is a long introduction and much is better suited to the discussion section. Mentioning individual study after study is not good. It is better if you evaluate how good the study was, and take into account the number of individuals in it, etc.
Yes, thank you. The manuscript was restructured and much of the introduction was deleted and/or placed in the discussion section.

Comments on table 1.
Including a study with 14 individuals and no controls is questionable. Yes, I agree, we put a section on limitations.
The number of individuals mentioned in Schoepfer's study is wrong, it is 200 and not 2000. Yes, thank you the table as revised in detail.
Was this really the conclusion in the study on 15(S)-HETE? We extended the conclusions of this study.
Should not all studies mentioned in this table be included in the reference list?
Yes, thank you. All references cited in the table 1 are also in the reference list.

Figure 4 is a nice one.
Thank you for your comments.

line 287, How and who? Describe this result in more detail.
We tried to be more specific in the revised version of the manuscript.

line 294, wrong numbers of included patients
We reviewed all published papers in detail and hope to have all data correct. Thank you.

line 304, In what way were these the most useful biomarkers? How was the sensitivity? Adjusted for asthma, allergy, etc. why is 15(S)-HETE not included in the discussion?
We did not go in detail with this study, but we used it to emphasize the heterogeneity of the studies targeting the potential biomarkers for eosinophilic esophagitis. We still think that a more standardized and structured approach will benefit a good evaluation of the studies.

line 315, What then were the clinically useful areas?
We tried to emphasize the importance of more homogeneity in approaching the evaluation of potential biomarkers for eosinophilic esophagitis.

Reviewer C

I was hoping to clarify a few points:
1. In the eligibility criteria section, the study mentioned that "Articles were included based on diagnostic criteria used in the study by A5" - I was wondering which study this might be referring to? It was also mentioned in the results section that studies with treatment interventions were excluded - could the study authors explain why these were excluded despite not being part of the exclusion criteria?
Thank you for your suggestion. We reviewed all studies that matched our criteria and tried to include all studies, but we have identified such high heterogeneity that has limited a statistical evaluation. A session on limitations was also included. With regard to the single studies, some studies have been exhibiting some discordance between data and we opted to not include them.
2. In the study selection section, you mentioned that "The first author (SO) reviewed all abstracts independently and included only articles that met all inclusion criteria" - is there a reason why this screening was performed by a single author and not two independent authors?
Two independent authors performed the evaluation for the revision, as suggested.
3. Would the study authors be able to provide a checklist for study quality for all the studies, and also the actual results for the studies especially the overall effect sizes and confidence intervals for biomarkers that were studied in more than one study? This may be an issue with the review homepage but I am only able to see the table/figures without any actual statistical results which I would expect in a systematic review/meta-analysis (based on keyword search) - at this stage, the report reads more like a narrative review

of the current literature.

Yes, we agree that a systematic review should indicate such data, but the heterogeneity of the studies and the lack of some data have been an obstacle to correctly perform the PRISMA-based systematic review as you suggested. Thus, we changed the title to in-depth review, despite considering the PRISMA flowchart and checklist useful start points for this review.

I hope my comments are useful for the study authors - I believe the study findings are useful to add to the literature and emerging evidence for alternative biomarkers for eosinophilic oesophagitis, but would like to see more statistical analysis of the studies included or justification for not having a quantitative analysis of the included studies. This could potentially be addressed by the authors in a limitations section justifying the methodology/data analysis plan.

We added a specific section on limitations. We hope that in the future more homogeneity and a more standardized approach in targeting potential biomarkers may be addressed.