

Manuscript ID: 79919

Manuscript title: Role of FeNO in pediatric eosinophilic esophagitis and relationship with gastric and duodenal eosinophils

Dear Editors and Reviewers,

We appreciate the opportunity to improve our submission given the insightful comments by your reviewers. Please see below our point-by-point rebuttal/revision of the concerns raised by the reviewers. Thank you for your continued consideration and support of our manuscript.

Reviewer Comments (italicized) and responses (highlighted):

Reviewer #1 *Scientific Quality: Grade C (Good) Language Quality: Grade A (Priority publishing) Conclusion: Major revision Specific Comments to Authors:*

- 1. This paper presents a study designed to evaluate the utility of FeNO as a non-invasive biomarker of esophageal eosinophilic inflammation for monitoring disease activity. This is an interesting cross-sectional study. This paper has merit; however, the description of the study subjects was superficial. We don't have the clinical and endoscopic characteristics in detail. This question profoundly compromises the evaluation and conclusion of the study*

Thank you. Noted, agreed and amended. The clinical, endoscopic and histology characteristics of the subjects are now included in Table III. The study data was collected before EREFS and EOEHS was validated. We have adapted as close as possible to these scores by retroactively collecting this additional data.

Reviewer #2: *Scientific Quality: Grade B (Very good) Language Quality: Grade B (Minor language polishing) Conclusion: Minor revision Specific Comments to Authors:*

- 1. Title. The title should emphasize the "diagnostic role"*

Noted, agreed and amended accordingly

2. *Results. Two paragraphs of the discussion cannot be found at results section: 1. “. Since patients with EoE have a high incidence of atopic diseases, a subgroup analysis was performed to control for atopy, which still produced similar correlation results between FeNO and presence of EoE. These findings have not been noted in the previous studies and may attribute to an adequately powered study. “relevant results must be presented and the mentioned analysis must be added into the methods section.*

We have amended it to include a supplemental table to document details of the relevant logistic regression analysis. We described it in Methods, subsection ‘Atopy’: “The presence of atopy was also controlled for and analyzed in a multivariate logistic regression model to discern its effects on FeNO in EoE patients.” Subsequently, we described the results under ‘FeNO & EoE’ subsection of ‘Results’: “On multivariate analysis adjusting for presence of atopy, similar relation between FENO and EoE was noted with p value of 0.003.”.

3. *“American Thoracic Society clinical practice guidelines for asthma suggest that a reduction of at least 20% in FeNO for values > 50 ppb (or > 10 ppb for values lower than 50 ppb) be used as the cutoff point to indicate a significant response to anti-inflammatory therapy [17]. Our data suggest that a similar cutoff could be established for FeNO levels in patients with EoE for use in surveillance, particularly in those with high levels. Following an individual patient’s FENO levels over time could allow for monitoring of esophageal inflammation in this subgroup. “The authors did not mention any therapy follow-up. This paragraph must be changed or the relevant results must be presented.*

Thank you, we have clarified, amended and expanded on the discussion section with reference to the results on this point

4. *Discussion. The normal values of the FeNO levels in healthy children should be given and discussed*

Noted, agreed and amended in discussion

5. *Units. long form of iNO must be given*

We apologize for this oversight and error. We have amended the manuscript to reflect the corrected abbreviation NO with long form provided.

Reviewer #3: Scientific Quality: Grade C (Good) Language Quality: Grade B (Minor language polishing) Conclusion: Major revision Specific Comments to Authors:

1. *RESULTS: "On multivariate analysis adjusting for presence of atopy, similar relation between FENO and EoE was noted with p value of 0.003."---The author should provide detailed data including statistical analysis.*

Noted, agreed and amended. We have now included a supplemental table to document details of the relevant logistic regression analysis. It has been described in methods and result section.

2. *Discussion should be more developed. The manuscript is lack of deep discussion for the current results. The described limitations within the reflection of the results could be worked out more deeply within this part.*

Noted and expanded on discussion including limitations.

3. *TABLE II. Patient demographics---The authors should provide the clinical and laboratory characteristics of the subjects.*

Noted and amended. Included Table III for clinical, endoscopic and histology characteristics of the subjects

Please let us know if you have any additional feedback. Thank you for your time.

Sincerely,

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