

Comments to the Author

The manuscript describes a meta-analysis of available scientific literature on miRNAs linked to asthma and their potential as diagnostic biomarkers. The authors reported on the inconsistencies found throughout the literature and reanalysed a subset of data available from previously published studies in order to assess a set of statistical measures pertaining to the diagnostic value of several miRNAs, culminating on a recommended panel of five miRNAs for potential asthma diagnosis. The reported work will be of considerable interest to those working on the potential usage of miRNAs as biomarkers not only in asthma, but in the wider immunology field.

1. The manuscript requires proofreading and minor sentence revisions to improve the quality of English. For example, sentences in the Results section such as “We found that there were four kinds of miRNAs” and “greatly supported they may be good diagnosis biomarker candidates” need to be restructured. Additionally, the mixed use of “FEV1” and “FEV<sub>1</sub>” in the introduction, and typos such as “quantiative” on Figure 1, and “hot differently” in the Results, should be corrected. The usage of the word “like” should also be greatly reduced. These types of errors occur throughout the manuscript.

2. Material and Methods, Section 2.2: please fully describe which “other accepted criteria” (line 48), “other acceptable methods” (line 49), and “other cohorts design” (line 56) were used.

3. Figure 1: Judging by the position of the penultimate box in the figure, it is not clear if the studies used for qualitative are part of the “Eligibility” or “Included” steps.

4. Table 1: Please explain why studies that display a diagnosis criterion of “NA” were included in the qualitative analysis. Additionally, there’s a hidden value after miR-155 in the “Differentially expressed miRNAs’ column on the second page of Table 1 (line 19, Tang X. 2018), this is easily corrected by increasing the row height.

5. Table 2: To make it clearer, I would suggest replacing “ meta-analysis” with “quantitative analysis”.

6. Results, Section 3.2:

- Line 36: Missing reference at “and et al.”.

- Lines 37 and 38: please explain the intended meaning of the sentence “any change from the above samples could be explained by the disease itself other than statistical difference”.

- Line 8, Page 9: miR-21 is listed as being present in Figure 2a, however, this figure shows miR-21 family. The text should be corrected to reflect it refers to miR-21 family.

- Line 11, Page 9: maybe a typo on "PBMCs than controls", since the comparison to controls doesn't fit in the list.

#### 7. Figure 2

- Make it clearer that Figure 2a displays both miRNA families and individual miRNAs. The current text omits the fact that some of the bars are miRNA families.

- Line 60: please remove what seems to be the title for Figure 3 at the end of the title for Figure 2.

8. Figure 3: I would recommend adding the miRNA names to their respective publications in Figure 3.

#### 9. Figure 4:

- Please include in the figure key what each number in the "observed data" circles represent.

- The sentence "The red dot standards" could be replaced with "The red diamond represents". Also consider rephrasing the remaining of this sentence on Line 26.

10. Results, Section 3.3, Line 30: please explain the usage of pre-test probabilities in this context.

#### 11. Results, Section 3.4:

- Lines 11 and 12: This sentence about heterogeneity is a little confusing and needs to be rewritten to improve clarity.

- Lines 17 and 18: This sentence about heterogeneity is a little confusing and needs to be rewritten to improve clarity.

- Line 21: Here it is mentioned that a regression analysis was applied. Please include details of the model and statistical analysis in the methods section. Additionally, it is not clear what the authors mean by "age and sample on heterogeneity respectively", please clarify.

12. Figure 6: I would recommend adding the miRNA names to their respective publications in Figure 6.

#### 13. Discussion:

- Lines 42 to 45: This paragraph is a little confusing and should be rewritten for clarity.

- Lines 52 to 54: A hypothesis should be contained to a pre-determined set of variables; therefore, it is unclear why this paragraph ends with “and so on”. Please explain the reasoning or amend it.

- Line 55: Consider replacing “meta-analysis” with “quantitative analysis”, in order to make this sentence clearer.

- Lines 56 to 59: The sentence “other related miRNAs of good biomarker candidate features” is too vague. What would be considered good biomarker features? Furthermore, consider rewriting this paragraph as it doesn’t clearly explain the limitations in the present study.

- Lines 3 to 5, Page 13: Consider rewriting these sentences as they don’t clearly explain the limitations in the present study.

14. Supplemental Figure 1: In the title, replace “Quality assessment of five quantitative studies” with “Quality assessment of five studies selected for quantitative analysis”.

15. References: Some of the references are missing a title or journal, others are formatted differently from the rest, and two seem to have been joined in the same line. Please review all references and formatting.