Author response to reviewer comments v.1

Reply to Reviewers:

Reviewer 1:

1. I have several comments that need to be addressed before it can be accepted for publication. Minor:

1) In the introduction change test to testing.

2) change crucial to defining

3) Change to: …. in severe asthma, airway obstruction may become permanent and less responsive to treatment.

7) (p>0.05) designations are redundant, please delete.

Answer: Thank you for that suggestions. We have corrected all of the selected points.

2. Minor: 4) clarify if the patients were recruited by pulmonologist in an Allergy clinic? Not by allergists? Combined program??

A. Thank you for this comment. The description in the text was not clear. At our hospital there is an alergological outpatient clinic employing allergists and pulmonologists. All of the patients were examined and qualified by doctors with at least double or triple specializations: internist, pulmonologist, allergologist.

3. Minor: 5) Please expand on the GINA criteria used for diagnosis

A. The basic diagnostic principia including symptoms, variable airflow limitation and lung function testing according to GINA guidelines were added.

4. Minor: 6) Please under patient population define the timeframe of "stable" well controlled condition, and in regards to exacerbations.

A. All patients were examined in a stable, well-controlled condition according to ACT (score of 20-25) and at least 4 weeks after their last exacerbation.

5. Major: 1) The subsection titled "Available imaging techniques" is beyond the scope of the objective of the manuscript. This should be significantly reduced and incorporated in the introduction or discussion.

A. Thank you for this comment. We have rewritten and corrected this paragraph, and moved to introduction section.

6. Major: 2) Under patient population, please define severe refractory asthma.

A. The refractory asthma referred to patients with irreversible airflow limitation despite step 5 treatment.

7. Major 3) Under limitations, please add that only 1 observer was utilized. Although intra observer evaluations are important. For radiographic measurements is important to have inter observer evaluations.

A. Thank you. We have corrected as you recommend.

8. Major 4) Is there any other information regarding exacerbations or other relevant clinical outcomes? Albuterol use? Biologicals?

Major 6) Do we have information regarding inhaled steroids?? And other therapies??

A. Thank you for that important questions. All subjects were treated according to the GINA guidelines. All patients were on inhaled corticosteroids, other controllers and SABA as needed. The most-severe patients with diagnosed refractory asthma were on biologicals. Due to numerous therapies we did not analyze potential correlations in this study. Your remark is an inspiration for further studies on relationship between treatment and image findings.

9. Major 5) Were analyses made between the different severities of asthma?

A. We have made such analysis. The differences between asthma severity subgroups are the objective of another study. The results were presented at ESTI – Fleinschner Annual Meeting this May in Paris and could not be published before. The manuscript is in preparation.

10. Major 7) In the introduction, the authors describe the "progression" of remodelling from the early stages of severity in asthma to the fixed airflow limitation in severe asthma, yet there are no comparisons between the subgroups of asthmatics?

A. Thank you for this comment. The process of remodeling is still not fully understood just as the relationship between remodeling and asthma severity. We decided to abandon this section.

11. Major 8) The conclusion is misleading, this study did not "confirm" airway remodeling in patients with asthma, this is a pathologic diagnosis. The study showed increased airway thickness in patients with asthma compared to healthy volunteers.

Major 9) In the conclusion, please expand on how the results are useful in the management of asthma.

A. Thank you, for that valuable insights. We have corrected this paragraph.

B. The results bring the base for further studies to improve asthma management.

Reviewer 2:

1. The idea and the way it was crafted into this draft are very good but there are a lot of unnecessary data included in this analysis. Please argument why you chose FEF75 and FEF50 as lung function parameters and why you compared it with all ranges of bronchi sizes

A. Thank you for this valuable comment. We agree, that mentioned parameters are of limited clinical relevance, and we decided to correct this section and abandon concerning relationship between these parameters and bronchial tree parameters.

2. please discuss why you did not choose PEF

A. Thank you, for this valuable question. We have analyzed that parameter, but there was no correlation between PEF and LA nor ID.

3. p values in tables 3,4 are for means or for medians?

A. Thank you for your notice, p values in that tables are for medians. To compare two groups, we used the Mann-Whitney test and presented the results as a median and IQR. Putting means and SD to that tables could be confusing. We decided to remove that parameters.

4. fig 6 does not represent a correlation (overall or individually) please correct

A. Thank you. We agree that this figure does not fully represent correlations. We decided to remove this figure.

5. please discuss why your findings are important for clinical practice

A. Thank you for your remark. The revealment of relationship between airway thickness and airflow limitation can be potentially helpful for further studies to improve asthma management and prognosis.