Author's response to reviews

Title: The relationship of systemic inflammation to hospitalization in adult patients with cystic fibrosis

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Version: 4 Date: 9 September 2011

Author's response to reviews: see over
Many thanks for asking us to revise and re-submit our manuscript for possible publication in BMC Pulmonary. In a point-by-point format, we have addressed all the concerns raised by the reviewers. We hope that our response meets your approval.

Reviewer 1

Major comment 1: The study would be much cleaner if the primary emphasis was on correlating the markers with FEV at the time of their collection.

RESPONSE: As requested by the reviewer, we have emphasized the relationship between the blood biomarkers and FEV1, which was collected at the time of venipuncture.

Major comment 2a: The term “risk factor for hospitalization” is used throughout the manuscript. This term can only be used in a prospective study correlating markers with subsequent risk of hospitalization. Correlating a marker with hospitalization in the prior 5 years in no way implies that it is a risk factor for hospitalization.

RESPONSE: As requested by the reviewer, we have removed the phrase “risk factor for hospitalization” and in lieu we have indicated “history of hospitalization”.

Major comment 2b: Hospitalization in the prior 5 years should be treated as a covariate (eg in table 1) but not an outcome. Table 1 should show differences in the inflammatory markers by each patient characteristic (eg age group, gender, hospitalized in last 5 years) and removing columns for hosp/non hosp, and table 2 should be removed as well as Figure 1.

RESPONSE: As requested by the reviewer, we have removed hospitalization data in Table 1 and 2 and figure 1. In lieu, we have provided data based on low or high FEV1.

Major comment 2c: The discussion is currently written that the data suggest that these markers are good candidates for health outcome/risk factors for disease progression. Although potentially true, the study results are unable to support these conclusions.

RESPONSE: We agree and have removed our previous assertion that the blood proteins are good candidate biomarkers for hospitalization.

Minor comment 1: Multivariate analysis should be “multivariable”

RESPONSE: “multivariate” has been changed to “multivariable”.

Minor comment 2: Methods – definition of “chronically colonized” does not seem appropriate with just one positive culture for Pa needed to meet the definition

RESPONSE: We have replaced “chronically colonized” with “infected”.

Minor comment 3: The term risk factor should be removed throughout unless the study is redone to look at hospitalizations after assessment of the inflammatory markers.
RESPONSE: We have removed “risk factor for hospitalization” whenever it was used

Minor comment 4: There should be a multivariable model exploring which set of markers is associated with FEV, as they are highly correlated

RESPONSE: The data from the multivariable model are presented in Table 2.

Minor comment 5: Results refer to a false positive result – this is not informative and fails to address the complexity of the data

RESPONSE: We have deleted the phrase “false positive” from the manuscript

Reviewer 2
Comment 1: The question posed by the authors is well defined.

RESPONSE: We thank the reviewer for his kind words.

Comment 2: Introduction. The last sentence says "by products of Gram-negative pathogens". Actually it is only one by-product. Please change accordingly.

RESPONSE: Wording has been changed to reflect discussion of a single by-product.

Comment 3(methods)a: What were the dates of sampling the patients? In other words, when did the study begin and end?

RESPONSE: Added the study period to the Study Population and Blood Collection section.

Comment 3b: The manuscript reads as if all patients had nasal potential difference studies. This would be a bit unusual. Please confirm this.

RESPONSE: Measurement of nasal potential difference was not done for this study and the line has been removed.

Comment 3c: "such as” is used a lot in the description of biomarker assays. It would be better to say exactly what was measured and leave out the "such as" phrase. "Such as” implies that more tests were done.

RESPONSE: Wording has been changed to remove instances of “such as” and clarify the text.

Comment 3d: The coefficients of variation are reported to two decimal places. Would one place be sufficient? It is distracting to the reader to see extra decimal places.

RESPONSE: Coefficients of variation have been updated to display a single decimal place.
Comment 3e: Statistical analysis. How were results below the limit of detection handled?

RESPONSE: For those samples that fell below the limit of detection, we assigned the lowest value that can be detected by the assay. We have added this statement in the Statistical analysis section of the manuscript.

Comment 3(d): The spread of ages in table 1 would be better reported as ranges rather than standard deviations. The authors give the age range appropriately in the text.

RESPONSE: Spread of ages has been changed to display as ranges within Table 1.

Comment 3b: The presentation of the biomarker results is given to two decimal places. Again, are the authors confident of this level of precision?

RESPONSE: The decimal places on biomarker results have been reduced to two decimal places as suggested by the reviewer.

Comment 3c: We should be told the percent of samples below the limit of detection for each biomarker. This could be a figure or a table.

RESPONSE: The percent of samples below the limit of detection has been added to the text of the Biomarker Assays section under Methods.

Comment 3d: I understand that the reviewers do not have controls without CF but it would be helpful if they included the manufacturer’s reference ranges or reported reference ranges.

RESPONSE: The manufacturers’ reported ranges for healthy volunteers (or dynamic ranges when not available) has been added to the text of the Biomarker Assays section under Methods.

Comment 3e: Most important is that the lung function impairment associations are adjusted for BMI, FEV1 and Pseudomonas status but the way the results read the hospitalization results only take into account BMI, FEV1 and not Pseudomonas. Pseudomonas should be included in the hospitalization analysis.

RESPONSE: We have analyzed the data including pseudomonal status in the hospitalization analysis and have included the new data in Table 3.

Comment 3f: Please give the c statistics generated by adding IL-6, IL-1beta or LPS mentioned on the bottom of page 8.

RESPONSE: We have provided these data in Table 3 and have included in the text.

Comment 8: The title is appropriate. The abstract should reflect the analysis controlling for Pseudomonas for both hospitalization and lung function impairment as mentioned above.

RESPONSE: We have provided these data in the abstract.
Comment 10: Remove extraneous digits on p-value.

RESPONSE: Extra digits have been removed for P-values.