**Author’s response to reviews**

**Title:** Comparison of disease progression subgroups in idiopathic pulmonary fibrosis

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**POINT-BY-POINT RESPONSE TO REVIEWER COMMENTS**

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Comparison of disease progression subgroups in idiopathic pulmonary fibrosis
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BMC Pulmonary Medicine

Reviewer comments:

Nazia Chaudhuri, MB ChB BSc PhD (Reviewer 1):

Comment 1: Thanks for addressing the reviewers comments:

I have just some minor additional corrections please and then i am happy to accept

Abstract paragraph one needs re-writing:

Consider changing to:
"The aims of this study were to retrospectively re-evaluate a cohort of patients with IPF according to the 2011 international IPF guidelines to 1. Characterise the patients according to different courses of disease progression and 2. Evaluate whether CPI, GAP or other clinical factors could predict mortality."

Response 1: We would like to thank the Reviewer for the suggestion to clarify the paragraph in the Abstract. The paragraph has now been revised as suggested: “The aims of this study were to retrospectively re-evaluate a cohort of patients with IPF according to the 2011 international IPF guidelines and 1) to characterize the subgroups of patients when classified according to their observed survival times and 2) to evaluate whether Composite Physiologic Index (CPI), Gender-Age-Physiology (GAP) Index or clinical variables could predict mortality.” Please see Abstract on page 2, lines 4 – 7.

Comment 2: Page 3 Line 22 : Change to :"using the 2011 international IPF guidelines"

Response 2: The word “IPF” has now been added to the sentence as the Reviewer suggested, please see page 3, line 21.

Comment 3: Page 4 Line 2: :as well as the” should be "as well as other"

Response 3: The word “other” has now been added into the sentence instead of the prefix “the”. Please see page 4, line 1.

Comment 4: Page 6 Line 3: As per Felix Chua comment I think it would be helpful to note that the re-evaluation of HRCT to Definite UIP was based on analysis of both first and second HRCTs - and how far apart was the second scan from the first? –

Response 4: Thank you for noticing this relevant point of view. The mean time between the first and last HRCT scans was 38 months. A paragraph including this data has now been added in Results section of the second revised version of the manuscript, please see page 5, lines 22 – 23.

Comment 5: Page 6 Line 5: in HRCT should be "on" HRCT

Response 5: The prefix has now been corrected from “in” to “on”, please see page 6, lines 4 – 7.

Comment 6: Page 6 Line 6: 47 patients evaluated in MDD - please explain and breakdown which patients were discussed in MDD and how you decided which to discuss

Response 6: After re-analyses of HRCT and an evaluation of histological reports as well as clinical data and death certificates, the patients with definite UIP pattern on HRCT and the patients with possible UIP pattern on HRCT confirmed by histological evaluation were included into the study without MDD, while the rest of cases were handled in the MDD. Thus forty-seven
(35.6 %) patients with possible UIP or not UIP on HRCT were evaluated in the MDD to confirm their IPF diagnosis. This information has been now added into the second revised version of the manuscript (please see page 6, lines 11 – 13).

Comment 7: Page 7 Line 7: There were 12 cases characterised as not UIP on HRCT…Do you mean 9 of the 12 patients characterised as not UIP could not have a biopsy due to …

Response 7: The Reviewer has noticed an important point in the text, which needs clarification. The sentence has now been revised in the text as follows: ”Nine out of the twenty-one patients categorized as not UIP on HRCT were cases with severe physical disabilities and comorbidities, which affected their possibilities for undergoing certain diagnostic procedures to histologically confirm their diagnosis.” Please see page 6, lines 5 – 7.

Silvia Terraneo, MD (Reviewer 2): Dear authors

thank you, the paper is now more concise and clear.

Felix Chua (Reviewer 3):

Comment 1: There remains some confusion and a lack of clarity about how some of the patients are classified which I believe should be fundamentally addressed. In my original review, I stated: 'Of the 21 cases with a non-UIP pattern on CT, 12 underwent surgical biopsy and in all 12 cases, histological UIP was revealed.' The authors have responded: 'The CTs of the biopsied cases showed features typical for IPF i.e. subpleural and basal fibrosis and reticulation.' The issue is this - if the CTs showed features typical for IPF, then these cases cannot be kept within the group of 21 described as 'non-UIP'. This assertion materially skews the final interpretation of results.

Response 1: The Reviewer is quite right about this matter i.e. the response to his comment in the previous point-by-point response was insufficient, for which we sincerely apologize. In brief, in twelve cases classified as radiological “not UIP” in HRCT’s, showed basal fibrosis and reticulation, but honeycombing was absent i.e. these cases could not be classified as a definite UIP pattern. In addition, suboptimal HRCT image quality (N=3), wide emphysema (N=1), heart failure due pulmonary hypertension (N=1) and infection/exacerbation (N=1) interfered with the interpretation of the changes in HRCT of six patients. Furthermore, an atypical distribution of the changes in HRCT was the reason for the “not UIP” classification of the additional three cases. In one case, the histopathological diagnosis revealed UIP, but HRCT showed wide reticulation and constrictive fibrotic areas i.e. non-specified fibrosis. In one case, the histology revealed UIP when in the HRCT images, ground glass and reticulation with possible subpleural sparing were evident.