Author’s response to reviews

Title: Comparison of disease progression subgroups in idiopathic pulmonary fibrosis

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Version: 2 Date: 18 Feb 2019

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PULM-D-18-00525R1

Comparison of disease progression subgroups in idiopathic pulmonary fibrosis

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BMC Pulmonary Medicine

Reviewer reports:

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

Comment 1. Please correct reference 1 as full reference eg page numbers are not given.

Response 1. Reference 1 has now been corrected with the issue, volume and page numbers. Please see the revision marked with red font in reference 1 in page 16.

Comment 2. Line 30 The word Index is missing from Composite physiological INDEX (CPI)

Response 2. The word “Index” has now been added into the text, please see page 3 line 14.
Comment 3. Page 6 line 1 the authors use the term probable UIP for 22.1% of HRCT cases however this is not a feature of the 2011 IPF guidelines for HRCT classification. Probable UIP HRCT classification is a feature of the 2018 IPF classification. Please clarify which HRCT classification you have used in this study

Response 3. We apologize for this error. The guidelines according to the 2011 IPF statement have been used in the study. The terms “possible” and “probable” have unfortunately been mixed and the term “probable” was accidentally used in the HRCT classification when the original intention was to use the term “possible”. The term “possible” has now been corrected into the text, please see page 6 line 3. The use of 2011 IPF guidelines has also been pointed out in the Background section, please see page 3 line 22.

Comment 4. In the discussion there needs to be a paragraph discussing the limitations of this study eg retrospective, small numbers of patients over a 10 year period, limitations of ICD classification, limitations of documentation of comorbidities ie was asthma diagnosis confirmed.

Response 4. A new paragraph discussing the limitations of the study has now been included into the Discussion section (please see page 12, lines 7 – 17). We would like to emphasize that clinical information of the patients was gathered in a very detailed manner using a specially designed form. At baseline, the subjects were collected from Kuopio University Hospital (KUH) pulmonology clinic in-patient and out-patient medical records using ICD-10 codes, but subsequently the data of each patient was carefully re-evaluated and re-classified. In addition, the patients with other types of interstitial lung diseases except IPF were excluded. Thus, the inclusion of the subjects of the present study was not based exclusively on ICD-10 coding but rather on a careful re-evaluation of all available data. Comorbidities including hypertension, coronary artery disease, heart failure, diabetes, asthma, COPD, obstructive sleep apnea, GER, depression, TIA, cerebral infarction and lung cancer, were collected from medical records of KUH, representing a tertiary health care organization, being therefore trustworthy data. In addition, the information of medications prescribed for the patients was collected. Moreover, comorbidities collected from death certificates were collated.

Comment 5. please discuss the differences in comorbidities between slow and rapid decliners in the discussion and why you think these may be

Response 5. Differences in comorbidities have now been discussed, please see Discussion page 11 lines 8 – 16.

Silvia Terraneo, MD (Reviewer 2):

Comment 1. The most important concern about this work is how you communicated the aim of the study. At the end of background section you reported the aim of the study. I suggest to better clarify it. It is too long and difficult to follow. . Furthermore it results different from the aim you
reported in the abstract. The sentence "The aims of this study were to re-evaluate a retrospective cohort of patients with IPF from Kuopio University Hospital (KUH), a tertiary hospital in eastern Finland, using the international guidelines and to study retrospectively the clinical factors and comorbidities that could distinguish between patients categorized into subgroups according to their observed lifespan i.e. different courses of disease" is really too long and need a simplification to be more concise and informative about your aims. Is it a aim of your study to re-evaluate the IPF case?? You wrote about the assessing of "functionality" of scores. Could you better explain it? In the abstract is reported the applicability of the score… could you please explain?

The results section need to be re organized consequently.

Response 1. Thank you very much for this comment. We have revised the manuscript according to the Reviewers suggestions to clarify the aims of the study. Some sentences have been re-written in an attempt to make them easier to understand. The words “functionality” and “applicability” have been removed from the text. The aims of the study have now been clarified by shortening and simplifying the sentences, please see the Abstract section page 2, lines 4 – 7 and the Background section from page 3, line 23 to page 4, line 4.

The Results section has been re-organized and the headings “Comorbidities”, “Cut-off values in separating rapidly progressing disease” and “Hazard analyses” have been removed. Headings have been modified to better respond to the aims. The headings in the revised manuscript are as follows “Course of disease” “GAP and CPI” and “Clinical factors in mortality prediction”.

Felix Chua (Reviewer 3):

Comment 1. The authors used the 2011 ATS/ERS/JRS/ALAT guideline to categorise the HRCT pattern of disease. Confusingly, they have used the diagnostic radiological term 'probable UIP' which was only proposed in the 2017 Fleishner white paper and the latest 2018 ATS/ERS/JRS/ALAT guideline. Can the authors please clarify? 'Probable UIP' was indeed applied in 2011 but only as a histopathological description, not on CT.

Response 1. The Reviewer is quite correct about this and we indeed apologize for this mistake. The terms “possible” and “probable” have been inadvertently mixed and the term “probable” was accidentally used in HRCT classification when the original intention was to use the term “possible”. Please see also the Response 3 to Reviewer 1.

Comment 2. Out of 131 patients with HRCT for evaluation, 81 were felt to satisfy criteria for 'definite UIP' - this seems high in light of other grouped analyses reporting a rate between 30 - 40% (e.g. 35% in the INPULSIS study). Can the authors please comment on this sizeable disparity?

Response 2. 81 patients out of 131 comprised 61 % of the patients of our study, which was a similar proportion to that in the study of Romei et al. (Radiol Med 120:930 – 940, 2015) in
which 44 out of 70 patients (62.8 %) were classified into the definite UIP group. The study protocols of Romei’s study and our’s were similar since both of them were retrospective cohorts; this may explain at least partly the higher percentage of definite UIP patterns in HRCT. Both of these studies included real-life IPF-patients and it is likely that some IPF-cases with possible or not UIP in HRCT may have been excluded due to missing histopathology or inadequate clinical follow-up information.

Instead, the INPULSIS study was a prospective randomized controlled clinical trial with strict inclusion criteria. For example, the patients in the INPULSIS study should have lung functions of FVC % ≥50 % and DLco % 30 – 79 %. The INPULSIS study also included patients with a possible UIP pattern i.e. without honeycombing in HRCT without a surgical lung biopsy (Richeldi et al NEJM 2014). Moreover, in the INPULSIS study, the eligibility criteria were based on chest HRCT if a surgical lung biopsy was not available i.e. the criteria were different than those of the year 2011 IPF consensus statement (please see Table S1, Richeldi et al NEJM 2014).

Comment 3. Assuming that the rate of ‘definite UIP’ is truly 61% as they authors contend, then it would be helpful to have a comment on the lack of influence of honeycombing on the rate of disease progression since roughly a third of cases met criteria for each of the three subgroups, i.e. rapid, moderate and slow progression respectively, despite the presence of definite UIP in nearly two-thirds of the whole cohort. As an extension, it would also be informative to know how many cases of definite UIP were present in each of these three subgroups. This is a point of particular interest since other reports have suggested that honeycombed and non-honeycombed UIP progress at a comparable rate.

Response 3. The numbers of “definite UIP” patterns in HRCT have been presented in Table 2 in the original manuscript. The proportion of definite UIP patterns did not differ statistically significant between the disease progression subgroups. This has now been pointed out in the Results section (please see page 7, lines 1 – 3) and also included in the Discussion (please see page 10, lines 17 – 22).

Comment 4. Of the 21 cases with a non-UIP pattern on CT, 12 underwent surgical biopsy and in all 12 cases, histological UIP was revealed. Can the authors please clarify if these 12 cases met the ancillary CT criteria to achieve an overall diagnosis of UIP, i.e. did their CT also show subpleurally based fibrosis with traction bronchiectasis in multiple lobes, and thus qualify for inclusion in the current study? Or did their CTs show changes of an alternative diagnosis (e.g. fibrotic HP) where a biopsy finding of UIP may also have been conceivable? If their CTs showed a truly non-UIP pattern (even though the histology was consistent with UIP), a discussion of discordance would be helpful.

Response 4. The study material included the patients treated in KUH between the years 2002 and 2012. Thus, most of the patients were originally diagnosed and treated according to the IPF statement of the year 2000 which affected the clinical practices. A total of 223 patients with pulmonary fibrosis (PF) treated in KUH between 1st January 2002 and 31st December 2012
were collected from the medical records of the hospital by using ICD-10 codes J84.X. Clinical, radiological and histological information of each patient was collected from medical records and also death certificates were obtained. All the patients with known causes of PF were excluded. Radiological data from the first and last HRCT investigations of the patients were evaluated by an experienced radiologist according to the 2011 diagnostic guidelines and categorized as UIP, possible UIP, non-classifiable fibrosis and not UIP. The diagnoses of the lung biopsy samples were reviewed and uncertain cases were re-analyzed if the samples were obtainable. When radiological and/or histological criteria of IPF were fulfilled, the patient was included into the study. If the diagnostic criteria were not fulfilled, the patient was evaluated in the multidisciplinary discussion (MDD) with pulmonologists and pathologist with all clinical data including also information from death certificates and the radiological statement from the radiologist. When the MDD agreed about the diagnosis of IPF, the patient was included into the study. Thus a total of 132 patients fulfilled the IPF diagnosis after thorough investigations and were included into this study i.e. all fibroses with known etiologies and with radiological changes suggestive of other ILDs were excluded.

As to reviewer’s specific questions regarding the biopsied cases. The CTs of the biopsied cases showed features typical for IPF i.e. subpleural and basal fibrosis and reticulation. The cases with CT features or findings suggestive for other types of ILDs like fibrotic HP were excluded. The histopathological diagnosis of UIP was obtained from video-assisted thoracic surgery (VATS) in 9 cases, of these, histopathology was also confirmed in 4 cases in autopsy samples. In three cases, the histopathological samples were obtained only from autopsy. The mean age of the patients was 64 years.

Comment 5. From the previous point, I assume there were 9 cases who had a CT pattern of non-UIP and who did not undergo lung biopsy. If so, how did the authors justify including these 9 cases in a study of UIP?

Response 5. The original manuscript included a detailed clarification of the patients included into this study (page 6, lines 7 – 12): “The nine cases categorized as not UIP in HRCT, included cases with severe physical disabilities and comorbidities, which affected their possibilities for undergoing certain diagnostic procedures. In these nine cases, that have all deceased, HRCT was categorized as not UIP due to the distribution of honeycombing (n=5), concomitant interference of heart failure (n=3) or predominant emphysema (n=1). However, after re-examining the information of the course of disease and causes of death, these cases were categorized as IPF after careful consideration by the MDD.”

Comment 6. Regarding the three subgroups with a different rate of disease progression - data in table 2 - it may be helpful to briefly discuss the possibility that a higher mean DLco is the reason why there are more GAP I patients in the slow group and more GAP II patients in the moderate group. It cannot after all be an FVC effect since this parameter is no different between the moderate and slow progressors.
Response 6. Thank you for this comment. This point has now been taken into account and added in the discussion, please see Discussion section page 9, line 21 to page 10, line 1.

Comment 7. Whilst DLco is acknowledged and shown to be an important determinant of both the rate of disease progression and survival, there is no discussion of pulmonary hypertension as a possible contributor to impaired gas transfer. Can the authors offer any information on the presence of PH in the three subgroups?

Response 7. Due to the time-point of the study (the years 2002 to 2012) and the retrospective study design, the data concerning pulmonary hypertension (PH) was not confidently available since the accurate diagnosis of PH requires right heart catheterization. PH was reported in the follow-up data of two patients included into the study, who both belonged to the rapid disease progression subgroup, but the difference between disease progression subgroups was not statistically significant. There were 115 deaths in this patient cohort and in none of the death certificates was there any mention of PH as the cause of death.

Adele Valentini (Reviewer 4):

No Comments