Author's response to reviews

Title: Re-evaluation of diagnostic parameters is crucial for obtaining accurate data on idiopathic pulmonary fibrosis

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Title: Preliminary Results from the Finnish IPF Registry


Dear Editor,

We are pleased that the reviewers of our work agree that the manuscript will be a valuable contribution to the literature in this area and we are grateful to the reviewers for their constructive criticism and suggestions to improve our work. We feel that the quality of the manuscript has been significantly improved as a result.

Please find attached the revised version of the manuscript with changes highlighted in red and a point-by-point response to the reviewers’ comments (below). We agree with the editor and both reviewers that data on histopathological re-evaluation should be added to the manuscript and as suggested, we have collected histopathological biopsies from five university hospitals and re-evaluated them centrally. In addition, we have added details about the collected data and specific causes of death. We also changed the title of our manuscript to better fit the scope of our work. We hope that in its current form, the manuscript could be acceptable for publication in your journal.

Yours sincerely,

Jaana Kaunisto
Marjukka Myllärniemi
Eija-Riitta Salomaa
Here below, please find our point-by-point responses to the referees comments

Reviewer 1

**Major points:** The aim of this report was to report on incidence and prevalence of IPF in Finland, then the inclusion only of tertiary care centers might have led of the exclusion of several patients outside of these centers.

Moreover, the rate of patients who consented to this analysis (or had died already) was heterogeneous and also led to the exclusion of IPF patients. Therefore it is almost impossible to calculate prevalence and incidence of IPF in Finland from these data.

We agree with the reviewer, that the patient material can differ significantly in tertiary care centers and secondary hospitals. We are currently extending our study to secondary hospitals and surprisingly the patient material after re-evaluation is strikingly similar in terms of patient demographics (FVC at diagnosis, patient numbers per center, etc). The health care system in Finland differs markedly from many other countries, so that patients are referred to hospitals according to their living address. According to our national guidelines IPF patients are always referred to hospitals for initial evaluation. Therefore, for example, if you happen to live in the Helsinki University Hospital district, you will be referred to the university hospital. This, from our perspective limits the disease identification-related bias to a minimum, but we are aware that this still exists. We have discussed this in the "study limitations" of our discussion (page 11 lines 249-253). We have also added an explanatory sentence to "Methods" page 3 lines 45-47.

What comes to the second part of this comment – we could not agree more. Initially, we wanted to have our study based on informed consent, and we are aware that this is a major limitation in our study, as the most advanced cases and rapid progressors are probably lost from the cohort. However, we have previously shown (Kaunisto et al 2013), that the published epidemiological data on IPF varies according to the method used, so that any method used is going to yield in mere estimations of true epidemiology. At least in our data we can estimate that we have at least this number of patients that will possibly be in the scope of therapy (whereas the rapid progressors or highly advanced disease stages might not). This limitation has now also been taken into account in the discussion (page 12, lines 253-260).

-the information provided by the authors is limited. It would be very interesting to compare the treatment habits, risk factors etc in Finland to those in Germany. For the later, an interesting paper has been recently published. I would propose the authors to increase the amount of information in their report and to compare the data to the German registry.

Here, we agree and have now included comparisons to similar studies and on the mentioned study to our work (p. 25, Table 5.). As our clinical data has been collected from patient journals, we have very limited data on risk factors (other than smoking or occupation). Overall, we think that this cohort is too small to yield any good estimates of risk/environmental factors, but future studies (maybe also comparative studies on a bigger cohort) are being pursued. We are keen on the possibility of international collaboration and comparisons of these parameters in different geographical location.
-was a statistican included in the evaluation of the data?

Our research group included an experienced researcher (MK) that helped in statistical analysis and did most of the calculations. This information has now been added to the manuscript Methods part page 6 line 108.

**what about missing data?** Missing data was not computed as we had very little missing data (i.e. spirometry was available 107/111 patients and smoking history for 109/111 patients). This data has now been clarified in the manuscript methods part p. 4, lines 63-65.

**how profound is the dataset?** We have now added Table 1 (page 21) in which we show the parameters collected to the registry.

-did the authors re-evaluate histology ? why was histology not concisely reported in the manuscript?

Thank you for this valid question. We have added results on histopathological re-evaluation of the surgical lung biopsies performed by two experienced pathologists. p. 5 lines 89-95 and, p 7 lines 143-153 and Table 3, p. 23.

**Minor essential revision:**


Quote 4 has now been changed as suggested.

-the value of reporting the FVC and DLCO measures in the 5 different cities is questionable. Why is this important to the authors ? is the regional distribution linked to any risk factor ?

In this small cohort the FVC and DLCO according to 5 cities is not that important and as suggested, we have now omitted this data.

-an important point the authors raise is the minor value of ICD-10 for IPF. There was a nice commentary a couple of weeks ago in the ERJ which should be quoted and discussed

Here we agree and added the suggested reference and discussed it (page 9 lines 190-196)

**Reviewer 2**

**Major concerns:**

1. The authors talk about “early or relatively early stage” of IPF just because the FVC-DLCO mean values. However, 14 patients died before the end of 2012, 76% of cases showed honeycombing on HRCT and typical UIP in 87%, and, finally, the time from the onset of symptoms to the date of diagnosis was 1.9 years. The patients were classified in mild-moderate stage, but it is argued if most patients were diagnosed in an “early” stage. This
term is incorrect for this cohort, the authors can refer mild-moderate stage but not “early”. The last sentence of Conclusions should be changed by “mild-moderate stage”.

We agree with the reviewer, that here, the term “early” is an overestimation and have revised the manuscript accordingly throughout the manuscript. Also, we have added a comparison to similar, previously studies to the discussion (p. 11 lines 239-245 and Table 5, p. 25), where it can be shown, that at least according to DLCO, our cohort represents milder disease forms than the ones published by Danish and German colleagues, that is not completely explainable by different reference value equations. Here, more studies are warranted.

2. If 87% of cases presented a typical UIP radiological pattern, how only 76% showed honeycombing?

Actually, as shown in Table 3. 87 patients (70.1%) had typical radiological UIP pattern. Please re-check Table 3. p. 23.

3. 70-80% were not really IPF, the authors should present more in detail how these cases were diagnosed as another ILD. What was the cause of the overdiagnosis of IPF in this cohort? (radiological and clinical mistakes in non-expert physicians).

In a vast majority of cases misdiagnosis was due to coding of either RA-ILD or some other non-idiopathic ILD to an idiopathic form of the disease. In a limited number of cases no pulmonary diagnosis had ever been made, suggesting a typing error related to the diagnosis code. The limitations of ICD-10 have now been discussed on page 9. lines 190-196.

4. Patient data was re-evaluated by pulmonary physicians and radiologists in order to estimate the prevalence of IPF, what about the pathologists for the 27 cases with lung biopsy? The role of the pathologist is crucial in some IPF diagnoses and it seems that the authors did not include any pathologist in the ILD multidisciplinary team for the evaluation, why? If they did it, they should include it in more detail in the Results. Only in discussion the authors mention the possible role of pathologists.

This is a valid question. We have now added the results of the re-evaluation of the surgical lung biopsies performed by two experienced pathologists, p. 5 lines 89-95 and, p. 7 lines 143-153 and Table 3, p. 23. Due to re-evaluation of biopsies, one patient dropped out of the cohort that had inconsistent findings in the biopsy presenting morphology of chronic hypersensitivity pneumonitis.

5. Another limitation of the estimated IPF prevalence, not only in this cohort but also in other Registries based on ILD codes, is that some ILD cases could be misdiagnosed and, therefore, not codified. It should be included in discussion.

Thank you for this important viewpoint. This has now taken into account in “discussion”, p 9, lines 190-196 and page 11, lines 249-253.

6. If there is no data about IPF treatments in this cohort why the authors include the last sentences in Discussion about Nintedanib or Pirfenidone? The authors should include data about IPF treatment in the cohort or to delete at least the last sentence (to avoid unrelated speculations).
We agree that data on given therapies should be available if they are discussed. However, our patient cohort was collected before any specific drugs entered market. The point in this part of the discussion was, according to our results, over 50% of patients are not yet eligible for drug therapy reimbursement due to “too good” lung function, as pirfenidone in our country is only reimbursed in the FVC range of 50-80%. Therefore we feel, that this important finding should be discussed. We have, however, deleted speculations about the early diagnostics and tried thus to clarify this point in the “discussion”. We hope that in the future, we can also include data on the effect of modern therapies to IPF progression.

7. Smoking history was different among different centres. There is no data about the possible relationship of this difference with the outcome (relationship with FVC-DLCO values? Reported deaths?)

Thank you for this important point. At this stage, we feel that this initial cohort is not big enough and the time elapsed not long enough to be able to evaluate differences in smoking and mortality yet. This will certainly be a scope for future studies in larger cohort of patients with more reliable follow-up times.

8. 14 patients died during 2012, could you include more clinical details about these cases?

We have now added the causes of death and specific details on this group of patients of these patients from our national death registry. This data is presented in p.8 lines 164-174.

Minor concerns;

- 10 from 18 cases with possible UIP radiological pattern were still included without lung biopsy, could you explain better why? (because follow-up? Family history?...).

We included 10 patients in whom the radiological pattern was possible UIP and who were not biopsied. Some of these patients had been diagnosed before the modern guidelines and some of them were so old or surgery was otherwise contraindicated. The diagnoses of these patients were confirmed later on follow-up in multidisciplinary evaluation (typical disease progression, lack of response to corticosteroids, appearance of UIP-pattern in HRCT). We hope that the addition of data to Table 3 (p.23) now makes this more clear.

- The sentence of Discussion about study limitations; “Only a small percentage of patients were excluded after the re-evaluation of the diagnostic HRCTs, which in part proves the high quality of the public care health system”. It would be more correct if it points; “…the high quality of the radiological evaluation of the public health care system…”, since previously a high % of cases were discharged as not IPF and this sentence refers specifically to the HRCTs evaluation.

This is changed as suggested (p. 12, lines 264-265), thank you for the comment.