Author’s response to reviews

Title: Gastroesophageal reflux and antacid therapy in IPF: Analysis from the Australia IPF Registry

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Author’s response to reviews:

Reviewer 1:
The authors assessed the use of antiacid therapy, GORD diagnosis and GORD symptoms, and the relationship of such features with prognosis in a large sample of IPF patients from Australia. Although this study has not significant novelty, there are some relevant results, including the sample size and the evaluation of the frequency scale for symptoms of GORD (FSSG).

The following issues need to be addressed by the authors:

1) It would be important to reinforce in the conclusions of the abstract that robust studies to confirm these statements are still missing.

Thankyou for your suggestion. The first sentence of the conclusion has been changed to reflect this:

“While further, robust randomised controlled trials are still needed, this study adds weight to the gathering evidence that antacid therapy may not be beneficial in IPF patients and that reflux directed therapy should be considered on an individual basis.”

2) Is there any information about the rate of functional decline of those (14%) who have not completed the questionnaire? If such information is available, the authors may consider to include it in the manuscript.

Thankyou for your comment. There was no difference in the progression free survival (death, fall in FVC and/or DLco) between patients included or excluded from the analysis (HR 1.28 95% CI 0.93, 1.62, p=0.149).

3) The authors should include as a limitation that the diagnosis of GORD was based on self-reported answer of patients and it could have underestimate or overestimate the prevalence, with impact on the results. Did the authors try to establish how the diagnosis of GORD was confirmed? If such information is available, the authors should include it in the manuscript.

Thankyou for your comment. We agree that the self-reported nature of GORD diagnosis is a limitation. As this is registry that only collects pre-defined investigations that are performed as part of the patients routine clinical care, we were not able to establish how the diagnosis of GORD was confirmed. We have amended the manuscript to reflect this limitation:

“Due to the retrospective nature of this study, there are several limitations. Firstly, the diagnosis of GORD was self-reported and may under or overestimate prevalence. For this reason, we looked at many GORD related variables to assess the impact of GORD and GORD treatment.”
4) It would be important to briefly reinforce in the first paragraph of the introduction the limitations of pHmetry mainly to detect non-acid reflux.

We agree with the authors commend that non-acid reflux cannot be detected by pHmetry and may be clinically meaningful as discussed in the discussion. We have therefore amended the introduction to read:

“Additionally, ambulatory pH monitoring cannot detect the presence of non-acid reflux, which may have important clinical implications, further limiting the utility of this test.”

5) Is the rate of annual decline in DLCO% available? The authors could consider to include such information and the impact of the use of antiacid therapy, GORD diagnosis and GORD symptoms on this parameter.

While we debated using the rate of annual decline in DLco% in this study, given the higher variability in DLco results, we decided to use FVC as this is the most commonly used lung function variable with robust data with regards to reproducibility, especially in patients with severe lung disease. We do however, also acknowledge that the presence of emphysema may impact the interpretation of this result however given the relatively large numbers in the study we presume the impact overall to be negligible.

6) Did the authors consider that there was a significant discrepancy between %FVC and %DLCO? How many patients had associated emphysema or pulmonary hypertension? Were these variables assessed in the survival analysis?

While we do collect information on the diagnosis of COPD and pulmonary hypertension, this data is self reported and has not been shown to predict survival in our cohort (data previously published)1. Additionally, the FVC and DLco of the Australian IPF Registry is comparable to other registries and clinical trial cohorts and we do not believe that there is a significant discrepancy between FVC and DLco % predicted1.

7) It is not completely clear why the authors decided to use FSSG in the current study based on the fact that it has a modest accuracy. What the use of FSSG adds to the evaluation of GORD?

We have clarified in the manuscript our reason for using the FSSG in IPF at the end of the introduction:

“If clinically meaningful, this questionnaire may be a simple way to predict prognosis and treatment in IPF without resorting to invasive testing.”
8) The authors should include in the discussion section the difficulties in determining the diagnosis of GORD and which complementary tools are used to confirm it. Which method they propose as a potential gold standard? Impedance-pHmetry?

We do not believe that there is a gold standard for determining the diagnosis of GORD, especially given the subjective nature of its definition. If any gold standard is to be found in IPF specifically, we believe that this test should be able to predict outcomes in IPF and that treatment based on this diagnosis should also alter outcomes. Further studies on this are urgently needed.

Reviewer 2:

The manuscript by Jo et al deals with an important and currently widely discussed topic in IPF - the use of anti-acid drugs (AAT), which are recommended in the current guideline for the treatment of IPF. While this manuscript adds important evidence, especially real world evidence, to this question, there are some limitations which should be addressed:

- the use of AAT is widespread, but the diagnosis of GERD less frequent in their cohort. What were reasons for the use of AAT in those patients w/o GERD and what would be results if the colleagues would concentrate only on AAT& GERD (group 1) vs. No-GERD & no-AAT (group 4). Would outcomes be similar as reported here?

As the registry only collects data and decisions regarding treatment are made by the participants physician, it is not clear what the reasons for use of AAT in patients without GORD may be.

Overall, there are:

215 participants on AAT & have a self reported GORD diagnosis

174 participants on no AAT & have no GORD diagnosis

There was no difference in survival between the 2 groups (HR 1.00, 95%CI 0.89, 1.11; p=0.935)

- may the self reported incidence of GERD be biased as pts. may perhaps not report to suffer from symptoms of GER under AAT and thus GERD is underreported ? please discuss this as a limitation in your discussion section

Thankyou for your comment, which was also mentioned by reviewer 1. We agree that the self-reported nature of GORD diagnosis is a limitation. As this is registry that only collects pre-defined investigations that are performed as part of the patients routine clinical care, we were not
able to establish how the diagnosis of GORD was confirmed. We have amended the manuscript to reflect this limitation:

“Due to the retrospective nature of this study, there are several limitations. Firstly, the diagnosis of GORD was self-reported and may under or overestimate prevalence. For this reason, we looked at many GORD related variables to assess the impact of GORD and GORD treatment.”

- I would recommend to change this sentence in the introduction "While IPF is limited to the lungs, comorbidities are common in this population and many studies have shown that gastroesophageal reflux (GOR) is highly prevalent4-7, and may contribute to pathogenesis" to "While IPF is limited to the lungs, comorbidities are common in this population and many studies have shown that gastroesophageal reflux (GOR) is highly prevalent4-7, may contribute to pathogenesis and is reported to be associated with a better survival" as this reflects where the idea of PPI came from and was reported in 2 independent retrospective analyses: Lee et al. AJRCCM 2011; Kreuter et al, PlosOne 2016.

Thankyou for your comment. We have amended the sentence as suggested. It now reads:

“While IPF is limited to the lungs, comorbidities are common in this population and many studies have shown that gastroesophageal reflux (GOR) is highly prevalent2-5, may contribute to pathogenesis and is reported to be associated with a better survival6, 7.”

- do authors have data on respiratory hospitalisations / acute exacerbations ? if so, to reflect the data by Costabel et al in the NIntedanib cohort, it would be interesting to see whether the data from the Australian registry would mirror these data or not

While the registry has endeavoured to collect data on respiratory hospitalisations and acute exacerbations, the reporting currently is dependent on the physician reporting these results to the registry. On provisional analysis, this is inconsistently performed and we are looking at ways to collaborate physician reporting with hospital admissions etc. At the present time however, this data is not readily available.

- data might be biased by different disease severities in the groups reported. Authors should please provide baseline characteristics of the groups in a table.

We agree that different disease severities may bias results. In table 1 we include the differences in the groups divided by treatment with antacid therapy- as this is the major outcome assessed in our study. There was no significant difference in the lung function impairment or deficit assessed by the CPI between the two groups (details shown below). We thought that the addition of these
Extra tables would cause more confusion rather than clarity and thus these were not included in the original manuscript.

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