Peer Review File

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Reviewer A

The authors systematically reviewed papers in order to investigate the effect of antacid therapy of lung function in IPF. Although the antacid therapy is conditionally recommended in the official 2015 ATS/ERS/JRS/ALAT guidelines, many observational studies have not find clinical effect of antacid in IPF. Also, there are a few RCT studies on the efficacy of antacid in lung functions of IPF. The present study is well analyzed and the result is consistent with present clinical situation. However, I would like to have some comments.

Comment 1: *GERD is a major complication of IPF, and the effect of antacid is quite different from patients with or without GERD. Analysis of IPF subgroup combined with GERD will be needed.*

Reply 1: We agree the importance of GERD in IPF, and the necessity to analyze this subgroup. We have conducted a subgroup analysis (qualitative analysis) on the six studies concerning IPF subgroup with GERD and made a discussion in the revised manuscript. However, we failed to conduct quantitative analysis because of limited data and identified heterogeneity across studies.

Changes in the text: Page 13, Line 273-278; Page 15, Line 322-328; Page 16, Line 329-330.

Comment 2: *The mechanism of PPI on lung function in IPF is probably different from H2RA (Ghebre and Raghu AJRCCM 2016). The authors should analyze the effect of PPI on lung function in IPF.*

Reply 2: Among included studies in our study, PPI using was apparently more than H2RA. Participants using PPI accounted for 89.58% to 100% across studies. We have conducted a subgroup analysis regarding PPI and made a discussion in the revised

manuscript.

Changes in the text: Page 12, Line 263-264; Page 13, Line 265-271; Page 16, Line 345-350; Page 17, Line 351-354.

Reviewer B

Comment 1: *An important limitation of the studies conducted so far on this area of IPF is the lack of clinical stratification regarding the presence/absence and type of GE reflux of the enrolled patients.*

This systematic review must take this into account when interpreting the results.

It has been hypothesized that GE reflux may be a risk factor for the development of IPF and that PPI and antiH2 therapy may alter the course of the disease, but this association has never been demonstrated.

There is a lack of studies with sufficient number that take into account the presence / absence of reflux, its degree of severity and type (acid / alkaline, ie gastric / biliary).

Reply 1: We agree that it is important to make clinical stratification regarding the presence of GER, its degree and type. However, to our best knowledge, relevant studies are limited. Our study is a synthetic analysis of previous studies. After a wide-range search, there are only six articles reporting IPF with GER, with different study designs and outcome variables. Therefore, we conduct qualitative analysis on the six studies instead of quantitative analysis.

Changes in the text: Page 13, Line 273-278.

Comment 2: *Therapy with the mentioned drugs may not be adequate in all patients with reflux and, on the other hand, may also be harmful in patients who do not suffer from any type of reflux. Furthermore, the proposed therapeutic interventions have never included the use of true antacid therapy, represented by drugs containing, for example, aluminum hydroxide, magnesium hydroxide (and other magnesium compounds), calcium carbonate, sodium bicarbonate.*

Reply 2: We have made a revision in the revised manuscript. The term of antacid is

replaced with anti-reflux, acid suppressive agents or anti-reflux surgery according to the context. Considering limited evidence, studies concerning the true antacids in IPF with/without GER are needed in the future.

Changes in the text: Page 1-6 and 10-17, marked in red.

Comment 3: *These factors, in association with the limitations already highlighted by the authors, do not allow to draw confident conclusions on this topic and suggest that further studies taking into account pathophysiological mechanisms of GE reflux are needed.*

Reply 3: Given limited articles, the present meta-analysis reveals a weak evidence, but consistent with previous studies. Currently, these limited studies could not be ignored because they are the main source of knowledge on this area of IPF, as well as important references for the guidelines.

Changes in the text: not applicable.

Comment 4: *In the text the authors write: Participants were diagnosed with IPF according to the ATS guideline. Please note that the referenced statement has received ATS / ERS / JRS / ALAT endorsements.*

Reply 4: We have made a revision.

Changes in the text: Page 4, Line 88; Page 9, Line 198; Page 15, Line 320-321.

Reviewer C

Comment 1: *The authors put a lot of work into this, but are dealing with very weak evidence. There were only 2 RCT with different interventions. The analytical methods they used and their approach are valid, but this does not overcome the weak data.*

The majority of studies are retrospective database studies that are prone to error because of entered data is subject to error, unless some attempt is made to validate. There is a recent opinion paper in the US about errors with using database for ILD.

Reply 1: Currently well-designed studies concerning anti-reflux therapy in IPF have

been limited. The databases for ILD have been important data sources for relevant studies. Furthermore, these studies are significant references for the guidelines. We agree the existed errors in databases for ILD, and the weak evidence induced by these errors (presented as limitation in the revised manuscript). However, the current weak evidence could not be ignored.

According to your suggestion, we find an article concerning errors with using ILD database (**Ref**), wishing it being the paper you mentioned. This article shows a discordance regarding pathologic diagnosis of ILD by pre-transplant surgical lung biopsy and the explanted pathology in a small subset of patients. We agree this kind of error, but in fact, it is hard to control this discordance in ILD databases.

Changes in the text: Page 17, Line 356-358.

Ref: Panchabhai TS, Arrossi AV, Highland KB, et al. A single-institution study of concordance of pathological diagnoses for interstitial lung diseases between pre-transplantation surgical lung biopsies and lung explants. BMC Pulm Med. 2019;19:20.

Comment 2: *I would say that antacid is the wrong term, even it is used in the ILD literature. Antacid is an agent that neutralizes gastric acid, not inhibit it like a PPI. In reality, acid suppressive agents is the correct term. Even if subjects used antacids, these are readily available without a doctors prescription and are impossible to track use.*

Reply 2: According to your suggestion, we have corrected the terms in the revised manuscript.

Changes in the text: Page 1-6 and 10-17, marked in red