Effect of anti-reflux therapy on pulmonary function in idiopathic pulmonary fibrosis: a systematic review and meta-analysis

Mei Yang[1#]^, Jiajia Dong[1#], Jing An[1#], Lin Liu[2], Lei Chen[1]^

[1]Department of Respiratory and Critical Care Medicine, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China; [2]Department of Respiratory and Critical Care Medicine, 363 Hospital, Chengdu, China

Contributions: (I) Conception and design: L Chen, L Liu; (II) Administrative support: L Liu; (III) Provision of study materials or patients: M Yang, J Dong, J An; (IV) Collection and assembly of data: M Yang, J An, J Dong; (V) Data analysis and interpretation: M Yang, L Chen, L Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Lei Chen. Department of Respiratory and Critical Care Medicine, West China Hospital, West China School of Medicine, Sichuan University, Chengdu 610041, China. Email: lchens@126.com; Lin Liu. Department of Respiratory and Critical Care Medicine, 363 Hospital, Chengdu 610041, China. Email: lliniu@126.com.

Background: Current guideline conditionally recommends regular use of anti-reflux medication in idiopathic pulmonary fibrosis (IPF). However, the effect of anti-reflux therapy in this group remains controversial. We systematically reviewed literatures to evaluate whether anti-reflux therapy could ameliorate pulmonary function in IPF.

Methods: We performed electronic search in PubMed, Embase and CENTRAL (Cochrane Central Register of Controlled Trials) to identify original articles published in English language. We included randomized controlled trials (RCTs) and observational studies regarding anti-reflux therapy on pulmonary function in IPF. Qualitative and quantitative analyses were conducted. In quantitative analysis, the inverse-variance method with fixed-effect model was used to analyze pooled data.

Results: Fifteen studies (2 RCTs and 13 observational studies) including 3,891 patients with IPF were included. Pooled analysis suggested that anti-reflux therapy did not improve forced vital capacity (FVC)% predicted [mean difference (MD) =0.88, 95% confidence interval (CI): –0.22 to 1.98, P=0.12, I^2 =0%, 8 studies, n=3,076], diffusing capacity of the lung for carbon monoxide (DLCO) % predicted (MD =0.75, 95% CI: –0.13 to 1.62, P=0.10, I^2 =0%, 8 studies, n=3,073), and FVC decline (MD =0.02, 95% CI: –0.01 to 0.04, P=0.29, I^2 =17%, 5 studies, n=1,586) in IPF.

Discussion: Anti-reflux therapy may not ameliorate pulmonary function in IPF. However, adequately powered studies are warranted to validate the present findings.

Keywords: Anti-reflux therapy; idiopathic pulmonary fibrosis; pulmonary function

^ ORCID: Mei Yang, 0000-0002-9349-9183; Lei Chen, 0000-0003-3476-0035.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic lung disease, characterized by unknown cause, progressive worsening of dyspnea and lung function, as well as high mortality (1-4). The pathogenetic mechanisms of IPF has been generally regarded as repetitive micro-injuries and aberrant repair of alveolar epithelium, which are induced by multiple genetic and environmental risk factors (4,5). Therapeutic approaches for IPF have changed from inflammation suppression to antifibrotic treatment and comorbidity management in recent years (5,6). However, no treatment has been demonstrated to significantly decrease mortality (7). It was reported that median survival time of IPF was 2–5 years after diagnosis, with significant variation across countries (3,8,9). Several features including level of dyspnea, extent of fibrosis, pulmonary function and comorbidities were indicated to correlate with survival in IPF (1). Among which, deterioration of pulmonary function, comprising ventilating and diffusing capacity, is clearly an important predictor for disease progression and prognosis (1). Currently there are only two drugs, nintedanib and pirfenidone, being proved to improve lung function (7,10). With limited options, novel treatment strategy is the need of the hour.

Gastroesophageal reflux (GER) and GER disease (GERD) have been regarded as a common comorbidity of IPF, with a prevalence of 0 to 94% across different cohorts (2,11-13). The GER and consequent micro-aspiration of gastric juice, acidic and nonacidic mixtures, could play momentous roles in pathogenesis and progression of IPF (13-15). It was reported that alveolar and bronchial epithelial cells were exquisitely sensitive to acid-mediated and nonacid-mediated triggers, which could increase cell membrane permeability, further induce airway inflammation and lung remodeling in animal models (16-18). Treatment for GER, mainly comprising acid suppressive agents and laparoscopic anti-reflux surgery (LARS), has been considered could improve clinical outcomes in patients with IPF (11,19,20). Currently, researches on anti-reflux therapy in IPF mainly focus on cough frequency, lung function and survival, and the majority is non-randomized controlled trials (RCTs) (21-25). Therefore, effect of anti-reflux therapy has been controversial, especially after the 2015 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) guideline conditionally recommended a regular acid suppressive therapy in IPF (19). There are only two relevant meta-analyses being found after a wide-range search, which are mainly focused on mortality, indicating anti-reflux therapy may be ineffective when avoiding immortal time bias (24,25). However, pooled analysis on pulmonary function is still lacking.

Several observational studies suggested that anti-reflux therapy did not mitigate deterioration of forced vital capacity (FVC)% predicted and diffusing capacity of the lung for carbon monoxide (DLCO)% predicted in IPF (26-28). One RCT further observed worse FVC in the omeprazole group (23). While another two reports observed that anti-reflux therapy alleviated decline in ventilating capacity (29,30). Therefore, to provide the latest and comprehensive evidence, we systematically reviewed the current available literature and conducted this study to evaluate effect of anti-reflux therapy on pulmonary function, including ventilating and diffusing capacity, in IPF patients. We also explored association between anti-reflux therapy and exercise capacity, measured with six-minute walking distance (6MWD).

We present the following article in accordance with the PRISMA reporting checklist (31) (available at https://dx.doi.org/10.21037/jtd-21-771).

Methods

Literature search and selection criteria

PubMed (1965 to September 2020), Embase (1974 to September 2020) and CENTRAL (1996 to September 2020) were searched for records related to anti-reflux therapy for IPF by two reviewers (M Yang and J Dong). The search strategy is shown in *Table 1*. The final search was conducted on September 15, 2020. English-language restriction was applied. The titles and abstracts were identified for all search results. The reference lists of eligible studies and relevant review articles were also hand-searched to find additional reports. Studies meeting the following criteria were selected: (I) population: adult patients diagnosed with IPF according to guideline criteria (1,32); (II) intervention: anti-reflux therapy (pharmacologic or non-pharmacologic); (III) comparison: placebo or no anti-reflux therapy; (IV) outcome: pulmonary function (ventilating and diffusing capacity) and 6MWD; (V) study design: RCTs, observational and pre-post studies. If the title of an article or its abstract suggested any possibility that it might be relevant, both investigators reviewed its contents and assessed for a final decision about inclusion.

Table 1 Search strategy

Search term
1. (Gastroesophageal reflux treatment) OR (anti-reflux surgery) OR (antacid therapy) OR (proton pump inhibitor) OR (H2-receptor antagonist)
2. (Idiopathic pulmonary fibrosis) OR (pulmonary fibrosis) OR (Idiopathic pulmonary disease) OR (parenchymal lung disease)
3. (Pulmonary function) OR (lung function) OR FVC OR DLCO OR 6MWD
1 AND 2 AND 3

FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; 6MWD, six-minute walking distance.

Discrepancies in study inclusion were discussed amongst all authors until consensus was achieved.

Data extraction

Data extraction was performed by two reviewers (M Yang and J An) independently. The following information was extracted from each eligible study: publication year, first author, country, study design and duration, number of participants, baseline characteristics of participants, interventions, outcomes concerning lung function and 6MWD. We attempted to contact study authors in the case of missing data, as well as to clarify study outcomes to allow for meta-analysis where appropriate.

Outcomes

The primary outcomes were FVC% predicted and DLCO% predicted reported after any treatment duration. Secondary outcomes included change in FVC and 6MWD reported after any treatment duration.

Risk of bias and quality assessment

The Cochrane risk of bias tool was adopted to assess the risk of bias for RCT. Details concerning random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases were fully assessed in RCT. The judgments were expressed as "low risk", "high risk", or "unclear risk" of bias. For observational studies, the Newcastle-Ottawa Scale was used (33), and a total score ≤5 indicated a high risk of bias (34). The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group system was applied to assess overall quality of evidence for each outcome (35). We considered within-study risk of bias, directness of evidence, heterogeneity, precision of effect

estimates and risk of publication bias in evaluating quality of evidence. We also investigated the influence of a single study on the overall pooled estimate by omitting one study in each turn for all studies.

Statistical analysis

Data were analyzed for RCTs and observational studies. Post-hoc analysis of RCTs was considered equivalent to observational study. According to data format (continuous), pooled measures were expressed as mean difference (MD) with 95% confidence interval (CI). Statistical heterogeneity was tested with the I^2 statistic, a quantitative measure for inconsistency across studies. I^2 statistic >50% indicates significant heterogeneity (36). According to I^2 statistic value, the inverse-variance method with fixed-effect model was used to calculate pooled MDs and 95% CIs. P value <0.05 was considered statistically significant, except where otherwise specified. All statistical analyses were performed using review manager (RevMan) (computer program), version 5.4, the Cochrane collaboration, 2020.

Results

Study selection

A total of 1,692 records were identified from the initial search. One hundred and sixty records were excluded for duplication. In total, 1,511 were removed for other reasons based on the titles and abstracts (reviews, unrelated abstracts, animal studies or other irrelevant studies). Six were removed for uncorrelated outcomes (survival rate or cough frequency) after full-text article assessment. Finally, 15 studies were included in qualitative analysis (23,26-30,37-45) and nine were included in quantitative analysis (23,26-29,37-39,45). All the 15 studies reported at least one primary or secondary outcome. The selection process was shown in *Figure 1*. The Cohen k statistic
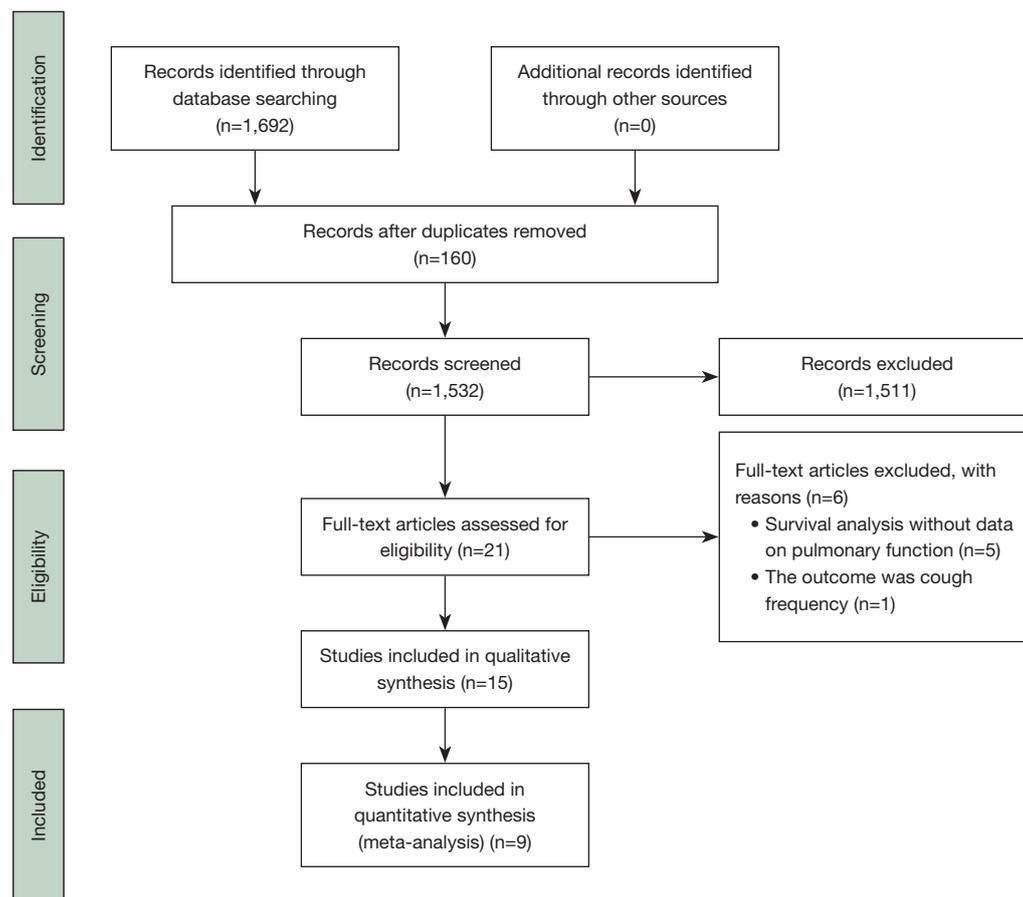
Figure 1 Flowchart of study selection.

for agreement on study inclusion was more than 0.9.

Study characteristics and quality assessment

Main characteristics and risk of bias assessment were presented in *Tables 2,3* and Tables S1,S2. All studies were published between 2011–2019 and in English. The sample size ranged from 4 to 638. Two studies were RCTs (23,45) and others were observational studies (26-30,37-44). Six were multicenter studies enrolling patients from Americas, Europe, Asia and Oceania (29,37-40,45). Eight were single-center studies (23,26-28,30,41,42,44) and the majority was conducted in the United States (26,28,30,41,42,44). Participants were diagnosed with IPF according to the ATS/ERS/JRS/ALAT criteria (1), with the mean age ranging from 65 to 72 years. Therapeutic intervention in four studies was LARS (42-45) while acid suppressive agents [proton pump inhibitor (PPI) and H2-receptor antagonist (H2RA)] were

applied in the other 11 studies (23,26-30,37-41). Compared with control groups, GER was more frequent in treatment groups. Across these studies, prevalence of GER in treatment groups were 51.7–89%, while in control groups was 5.8–60% (27-29,38-41). Based on the Newcastle-Ottawa Scale rating, 10 observational studies were rated as a total score of >5 (26-30,37-39,42,44) and two studies as a score of ≤5 (40,41), indicating a high risk of bias (Table S2). One study published in abstract form was not assessed because of full details not available (43).

Among the 15 studies, nine were included in quantitative analysis (23,26-29,37-39,45). They all have independent control groups, without a high risk of bias (score of >5). Particularly, the study by Ulrich Costabel comprised two parts. In one part (Costabel 1), all participants were taking nintedanib while patients in the other part (Costabel 2) were not taking (37). Data on the two parts were analyzed separately.

Table 2 Risk of bias assessment of the randomized controlled trial

Study	Random sequence generation?	Allocation concealment?	Blinding of participants, personnel, and outcome assessors?	Incomplete outcome data?	Selective reporting?	Other bias?	Overall risk of bias
Dutta 2019 (23)	Yes	Yes	Yes	No	No	No	Low
Raghu 2018 (45)	Yes	Yes	No	No	No	No	Low

Risk of bias was assessed using the Cochrane risk of bias tool.

Primary outcomes

Twelve studies reported FVC% predicted and DLCO% predicted during treatment (23,26-30,37-42), including 11 observational studies (26-30,37-42) and one RCT (23).

Among which, 10 (including the RCT) revealed no significant difference concerning FVC% predicted and DLCO% predicted between treatment groups and control groups (23,26-29,37-39,41,42). In the RCT, compared with placebo group, FVC was significantly lower, while KCO (the transfer factor for carbon monoxide, TLCO, corrected for accessible alveolar volume) was apparently increased in omeprazole group (23). For the other two studies, one case series on four IPF patients taking PPIs showed stability of FVC% predicted and DLCO% predicted during 2–6 years of follow-up (30). The study conducted by Helen E. Jo also indicated significant improvement of FVC% predicted and DLCO% predicted in treatment group (40). However, in this study, a significant difference on mean age of participants between groups was observed (71.6 vs. 69.7 respectively, P=0.008), which weakened reliability of the results.

In quantitative analysis, pooled data on eight studies (23,26-29,37-39) showed anti-reflux therapy did not ameliorate FVC% predicted (MD =0.88, 95% CI: –0.22 to 1.98, P=0.12, I^2 =0%, 8 studies, n=3,076) and DLCO% predicted (MD =0.75, 95% CI: –0.13 to 1.62, P=0.10, I^2 =0%, 8 studies, n=3,073). Further exclusion of any single study did not materially alter the overall combined MDs. As presented in *Figures 2,3*.

Secondary outcomes

Eight studies (23,29,37-39,43-45) reported change in FVC during treatment. Four studies suggested no significant improvement in FVC in treatment groups (23,37-39). Similar results were also found in patients simultaneously taking pirfenidone or nintedanib and subgroups stratified by baseline 70% predicted FVC (37-39). Inversely, four reports demonstrated non-significant decline in FVC after treatment,

with at least 7-month follow-up (29,43-45). Among which three applied a self-controlled design. Five studies were further included in meta-analyses (23,29,38,39,45). As shown in *Table 4*, pooled data indicated anti-reflux therapy did not significantly alleviate FVC decline [MD =0.02, 95% CI: –0.01 to 0.04, P=0.29, I^2=17%, 5 studies (23,29,38,39,45), n=1,586]. Further exclusion of any single study did not materially alter the overall combined MD.

Six studies reported 6MWD during treatment, including two RCTs (23,29,38,39,42,45), which unanimously suggested no apparent difference on 6MWD between groups. As presented in *Table 4*, quantitative analysis on four studies demonstrated anti-reflux therapy did not promote improvement of 6MWD in IPF [MD =–7.70, 95% CI: –17.61 to 2.20, P=0.13, I^2 =0%, 4 studies (23,29,38,39), n=1,527]. Further exclusion of any single study did not materially alter the overall combined MDs.

Subgroup analysis

LARS was reported in four studies (42-45). three reports with self-controlled design indicated non-significant decline in FVC or FVC% predicted for at least 7 months after LARS (42-44) whereas another RCT showed no improvement in FVC compared with no surgery group (45). In 11 acid suppressive agents associated reports, PPI using was apparently more than H2RA (23,26-30,37-41). Participants using PPI accounted for 89.58% to 100% across studies. Ten studies revealed no statistical significance on FVC% predicted and DLCO % predicted (23,26-29,37-41), including two studies with 100% patients taking PPI (23,26). As shown in *Figures 2,3*, quantitative analysis showed favorable effect of PPI on DLCO% predicted (MD =4.90, 95% CI: 0.86 to 8.94, P=0.02, I^2 =0%, 2 studies, n=251), while not significant in FVC% predicted (MD =1.50, 95% CI: –3.01 to 6.00, P=0.52, I^2 =59%, 2 studies, n=254). Quantitative analysis concerning LARS or H2RA was not conducted because the extracted data was limited.

Table 3 Characteristics of included studies

Author, year	Setting	Setting	Study design	No. patients [experimental/ control]	Age, years (experimental/ control)	Gender (F/M)	Intervention	Newcastle-Ottawa Scale rating
Dutta, 2019 (RCT) (23)	Single center (United Kingdom)	Single center (United Kingdom)	RCT	45 [23/22]	71±7/71±7	10/35	PPI (Omeprazole)	NA
Ghebremariam, 2015, (26)	Single center (United States)	Single center (United States)	Retrospective cohort	215 [130/85]	66 [55–73]/ 67 [61–76]	80/135	PPI	8
Jo, 2019, (40)	Multicenter (Australia)	Multicenter (Australia)	Retrospective cohort	587 [384/203]	72±8/70±9	181/406	PPI and/ or H2RA	5
Kreuter, 2016, (38)	Multicenter (19 countries¶)	Multicenter (19 countries¶)	Retrospective cohort	624 [291/333]	67±7/67±8	159/465	PPI and/ or H2RA	8
Kreuter, 2017, (39)	Multicenter (19 countries¶)	Multicenter (19 countries¶)	Retrospective cohort	623 [273/350]	68±8/67±7	160/463	PPI and/ or H2RA	8
Lee, 2011, (28)	Single center (United States)	Single center (United States)	Retrospective cohort	203 [96/107]	69±10/70±8	62/141	PPI and/or H2RA, Nissen fundoplication	7
Lee, 2013, (29)	Multicenter (United States)	Multicenter (United States)	Retrospective cohort	242 [124/118]	68±8/67±9	52/190	PPI and/ or H2RA	7
Linden, 2006, (42)	Single center (United States)	Single center (United States)	Retrospective cohort	45 [14/31]	NR	NR	Nissen fundoplication	6
Liu, 2017, (27)	Single center (China)	Single center (China)	Retrospective cohort	69 [34/35]	67±7/70±5	23/46	PPI or H2RA	7
Noth, 2012, (41)	Single center (United States)	Single center (United States)	Retrospective cohort	74 [35/39]	68/65	NR	PPI and/ or H2RA	4
Raghu, 2006, (30) (case report)	Single center (United States)	Single center (United States)	Retrospective self-controlled	4 [NA]	65±5	4/0	PPI and/ or fundoplication	6
Raghu, 2013, (43) (abstract)	NR	NR	Retrospective, self-controlled	14 [NA]	63	NR	Nissen fundoplication	NR
Raghu, 2016, (44)	Single center (United States)	Single center (United States)	Retrospective self-controlled	27 [NA]	65 [51–77]&	12/15	LARS	6
Raghu, 2018, (45) (RCT)	Multicenter (United States)	Multicenter (United States)	RCT	58 [29/29]	71±6/69±7	11/47	LARS	NA
Costabel 1*, 2018, (37)	Multicenter (24 countries§)	Multicenter (24 countries§)	Retrospective cohort	638 [244/394]	67±8/66±8	131/507	PPI or H2RA	7
Costabel 2#, 2018, (37)	Multicenter (24 countries§)	Multicenter (24 countries§)	Retrospective cohort	423 [162/261]	68±7/66±8	89/334	PPI or H2RA	7

Data are presented as n, median (interquartile range) or mean ± SD unless otherwise stated. ¶, Australia, Belgium, Brazil, Canada, Croatia, France, Germany, Ireland, Israel, Italy, Mexico, New Zealand, Peru, Poland, Singapore, Spain, Switzerland, United Kingdom, United States; §, 24 countries in Americas, Europe, Asia and Australia; &, median (range); *, all patients in Costabel 1 receiving nintedanib; #, all patients in Costabel 2 not taking nintedanib. RCT, randomized controlled trial; PPI, proton pump inhibitor; NA, not applicable; H2RA, H2-receptor antagonist; NR, not reported; LARS, laparoscopic anti-reflux surgery.
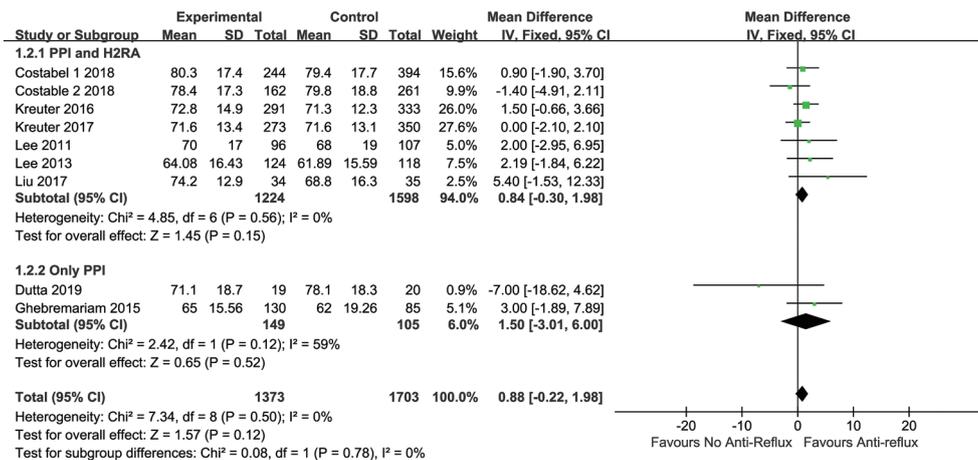
Figure 2 Effect of anti-reflux therapy on FVC% predicted in IPF. CI, confidence interval; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.
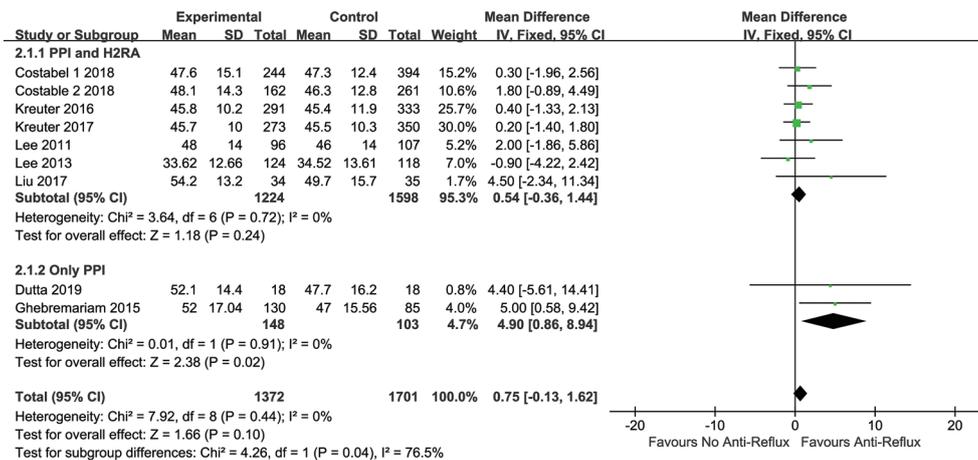

Figure 3 Effect of anti-reflux therapy on DLCO% predicted in IPF. CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.

Six studies investigated IPF subgroup with GER, but with different study designs (30,41-45). Detailed characteristics were summarized in *Table 5*. Four self-controlled studies unanimously showed potentially improved FVC% predicted (30,42-44). However, in the other two studies with better designs, similar result was not indicated (41,45). Quantitative analysis was not performed because of identified heterogeneity across studies. Additionally, three studies enrolling patients taking nintedanib or pirfenidone at the same time. They demonstrated the addition of anti-reflux therapy could not further improve pulmonary function (37-39).

Grading the quality of evidence

As shown in *Table 6* and the supplementary material (Appendix 1), the quality of evidence for outcomes on FVC% predicted, DLCO% predicted and change in FVC was judged as low due to serious risk of bias, which was upgraded because all plausible confounding would reduce demonstrated effect. The quality of evidence for outcome on 6MWD was judged as very low due to serious risk of bias and serious imprecision, which was upgraded because all plausible confounding would reduce demonstrated effect.

Table 4 Effect of anti-reflux therapy on change in FVC and 6MWD

Outcome	MD and 95% CI for each study	Pooled MD and 95% CI	Forest plot
Change in FVC (L)	−0.12 (−0.56, 0.32) (23)	0.02 (−0.01, 0.04)	
	0.00 (−0.05, 0.05) (38)		
	0.01 (−0.03, 0.05) (39)		
	0.12 (0.00, 0.24) (29)		
	0.08 (−0.06, 0.22) (45)		
6MWD	5.20 (−71.55, 81.95) (23)	−7.70 (−17.61, 2.20)	
	−7.90 (−22.77, 6.97) (38)		
	−12.50 (−27.19, 2.19) (39)		
	16.44 (−17.52, 50.40) (29)		

FVC, forced vital capacity; 6MWD, six-minute walking distance; MD, mean difference; CI, confidence interval; SD, standard deviation.

Table 5 Studies on IPF subgroup with GER

Study	Experiment group	Control group	Assessment of GER	Therapeutic intervention	Follow-up	Results
Linden 2006, (42)	GERD (post-LARS)	GERD (pre-LARS)	Symptoms, endoscopy and ambulatory pH monitoring	LARS	15 months	No significant decline in FVC% predicted and DLCO% predicted
Noth 2012, (41)	GER	No GER	Symptoms and ambulatory pH monitoring	PPI or H2RA	NA	FVC% predicted and DLCO% predicted were higher in GER group but not significant
Raghu 2006, (30) (case report)	GER (end-point)	GER (baseline)	Symptoms and 24-hour esophageal pH study	PPI	24–72 months	FVC% predicted and DLCO% predicted were stable compared to baseline
Raghu 2013 (43) (abstract)	GER (post-LARS)	GER (pre-LARS)	24-hour esophageal pH study	LARS	7 months	Mean FVC increased by 0.08 L (3.5% predicted)
Raghu 2016, (44)	GER (post-LARS)	GER (pre-LARS)	24-hour esophageal pH study	LARS	2 years	No significant change in FVC and FVC% predicted over 185 days
Raghu 2018, (45) (RCT)	GER (surgery)	GER (no surgery)	24-hour esophageal pH study	LARS	52 weeks	No significant difference on FVC decline over 48 weeks between groups

IPF, idiopathic pulmonary fibrosis; GER, gastroesophageal reflux; GERD, GER disease; LARS, laparoscopic anti-reflux surgery; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; PPI, proton pump inhibitor; H2RA, H2-receptor antagonist; NA, not available; RCT, randomized controlled trial.

Discussion

This study systematically summarized and evaluated effect of anti-reflux therapy, comprising acid suppressive agents and LARS, on pulmonary function in patients with IPF. The main findings suggested anti-reflux therapy did not ameliorate pulmonary function and 6MWD. However, as the majority of included studies was observational and retrospective, our confidence in the results was low.

The progressive interstitial fibrosis in IPF induces continuous impairment of lung function. Amelioration of lung function has been closely associated with better quality

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Table 6 Overall quality of evidence for each outcome

Outcome	Certainty of the evidence GRADE
FVC% predicted	⊕⊕ Low
DLCO% predicted	⊕⊕ Low
Change in FVC	⊕⊕ Low
6MWD	⊕ Very low

Quality of evidence for each outcome was assessed using the GRADE criteria. GRADE, the Grades of Recommendation, Assessment, Development and Evaluation; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; 6MWD, six-minute walking distance.

of live and prognosis. The hypothesis of anti-reflux therapy for IPF is mainly based on its effect of reducing aspiration or micro-aspiration (2,14,16). Besides, emerging data indicate extending effects of PPIs concerning suppression of airways inflammation and regulation of immune, further indicating the possibility to be applied in IPF (46). However, these hypotheses seem not to be supported by clinical investigations, which have revealed inconsistent findings during the past few decades (2). The meta-analysis by Lee Fidler summarized data from three retrospective studies and showed acid suppressive agents did not slow annual decline in FVC (24). After this meta-analysis, several relevant reports were published (23,37,40,45), including RCTs (23,45). Based on current clinical data, we conducted this study to firstly provide a comprehensive overview with regard to effect of anti-reflux therapy on lung function in IPF. After a wide-range literature search, we found that therapeutic interventions across studies mainly comprised PPIs, H2RA and LARS. To sum up, qualitative and quantitative analyses preliminarily suggested anti-reflux therapy could not mitigate deterioration of pulmonary function and 6MWD in patients with IPF, also may not impact the treatment effect of nintedanib or pirfenidone (37-39). There were only two articles reporting significantly improved FVC% predicted and DLCO% predicted after anti-reflux therapy (30,40). However, one was a case report only enrolling four patients (30) and in the other one, there existed poor comparability on mean age of participants between groups, as mentioned above (40). It is worth noting that, results in the present study could not challenge the recommendation of the ATS/ERS/JRS/ALAT guideline because most included studies were non-RCTs (19).

Although GER is highly prevalent in patients with IPF, it remains undetermined whether anti-reflux therapy is exclusively effective for IPF with GER. Currently, the majority of studies on this subgroup are focused on LARS and with self-controlled design (42-44), which tends to show that LARS may mitigated FVC decline. However, considering limitation in study design, small sample size, and discrepancy induced by different interventions (acid suppressive agents *vs.* surgery), it should be careful to interpret these findings. By contrast, subgroup analysis of our study suggested studies with better design showed non-significant effect of anti-reflux therapy. Therefore, future advanced research is warranted.

Additionally, two intriguing findings regarding therapeutic interventions were detected. Firstly, effect of acid suppressive agents and LARS could be different. As described above, investigations on LARS showed mitigated FVC decline for at least seven months (42-44), which was not duplicated in studies on acid suppressive agents (23,37-39). LARS has been reported to provide effective control of GER in more than 90% of cases, suggesting more effective than acid suppressive agents (47). Besides, durable long-term effect and improved quality of life are also observed in patients undergoing LARS (48,49). However, in the RCT by Ganesh Raghu (45), difference regarding adjusted rate of change in FVC over 48 weeks was non-significant between surgery and no surgery groups. This might indicate previously observed benefit of LARS was induced by low-quality study design. Meanwhile, nearly all patients receive treatment of acid suppressive agents before undergoing LARS (43,45). This could induce false-positive findings concerning LARS.

Secondly, difference between PPIs and H2RA should also be noted, and PPIs could be more valuable. Molecular and cell biological studies found that PPIs favorably regulated the oxidant–antioxidant system and suppressed key inflammatory molecules in tracheal epithelial cells, which were not reproduced in H2RA (50-52). Clinical study by Joyce S. Lee demonstrated alleviated FVC decline among patients taking PPIs or H2RA, and similar result was also observed when excluding H2RA (29). Stable fluctuation of pulmonary function during at least two years was also indicated in patients taking PPIs only (30). Our subgroup analysis presented significant benefit of PPI for improving DLCO% predicted. Similar result was not underlined in studies enrolling patients taking H2RA.

Several potential limitations should be noted when interpreting the present results.

First, the majority of included studies are observational database studies, which are highly subject to selection bias,

database related error (53) and confounding by indication. Second, although no apparent heterogeneity was observed for all outcomes, population characteristics and lung function varied across studies. We failed to conduct detailed subgroup analyses with respect to potential confounding factors, such as GER, therapeutic measure (acid suppressive agents or LARS) and study design (RCT or non-RCT), but an influence analysis was performed to add robustness. Third, not all studies provided detailed information of anti-reflux medication including type, dose and duration, which undermined reliability of the present results.

Conclusions

In conclusion, this systematic review and meta-analysis preliminarily indicates that anti-reflux therapy may not ameliorate pulmonary function deterioration in IPF. Our confidence in the results is limited because of lacking RCTs. Although current guideline recommends application of acid suppressive agent therapy in IPF, high-quality RCT on specific subgroup suitable for anti-reflux therapy is warranted.

Acknowledgments

Footnote

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Quality assessment for included studies

This study included two randomized controlled trials (RCTs) and 13 observational studies. We used the Cochrane risk of bias tool to assess the quality of RCTs, and for observational studies, the Newcastle-Ottawa Scale was adopted (Tables S1,S2).

Grading the quality of evidence

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria was applied to assess quality of evidence for each outcome.

The quality of evidence for outcomes on forced vital capacity (FVC)% predicted, diffusing capacity of the lung for carbon monoxide (DLCO)% predicted and change in FVC was judged as low due to serious risk of bias, which was upgraded because all plausible confounding would reduce demonstrated effect. The quality of evidence for outcome on six-minute walking distance (6MWD) was judged as very low due to serious risk of bias and serious imprecision, which was upgraded because all plausible confounding would reduce demonstrated effect.

How results can be interpreted given the quality of the included studies?

Taken together, the majority of included studies was observational studies with relatively higher risk of bias than RCTs, although we excluded several observational studies with high risk of bias (assessed a score of ≤5 using the Newcastle-Ottawa Scale) in the meta-analysis. We applied the GRADE criteria to evaluate quality of each evidence, which revealed low quality of the primary results. Therefore, our confidence in the evidence was limited and these findings should be interpreted with caution. However, given limited synthetic analysis on anti-reflux therapy for idiopathic pulmonary fibrosis (IPF) currently, this study could provide a preliminarily systematic review with regard to anti-reflux therapy on pulmonary function in IPF. Additionally, several suggestions for future research were also proposed.

Table S1 Quality assessment for RCTs

Study	Random sequence generation? (selection bias)	Allocation concealment? (selection bias)	Blinding of participants, personnel, and outcome assessors? (performance and detection bias)	Incomplete outcome data? (attrition bias)	Selective reporting? (reporting bias)	Other bias?	Overall risk of bias
Dutta 2019, (23)	Yes	Yes	Yes	No	No	No	Low
Raghu 2018*, (45)	Yes	Yes	No	No	No	No	Low

Risk of bias was assessed using the Cochrane risk of bias tool. *, this RCT was unblinded for participants, personnel, and outcome assessors because the intervention in this RCT was surgery, which was difficult to reach blinding of participants. Meanwhile, the primary outcome, change in FVC, was measured in accordance with ATS/ERS standards. Therefore, the assessed overall risk of bias for this study was also low. RCT, randomized controlled trial; ATS, American Thoracic Society; ERS, European Respiratory Society.

Table S2 Quality assessment for observational studies

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Costabel 2018, (37)	*	*	–	–	**	*	*	*	7
Ghebremariam 2015, (26)	*	*	*	–	**	*	*	*	8
Jo 2019, (40)	*	*	–	*	–	*	*	–	5
Kreuter 2016, (38)	*	*	*	–	**	*	*	*	8
Kreuter 2017, (39)	*	*	*	–	**	*	*	*	8
Lee 2011, (28)	*	*	*	–	*	*	*	*	7
Lee 2013, (29)	*	*	*	–	**	*	*	–	7
Linden 2006, (42)	–	*	*	–	**	*	*	–	6
Liu 2017, (27)	*	*	–	–	**	*	*	*	7
Noth 2012, (41)	*	*	–	–	–	*	–	*	4
Raghu 2006, (30)	–	–	*	–	**	*	*	*	6
Raghu 2013[#], (43)	–	–	–	–	–	–	–	–	–
Raghu 2016, (44)	–	–	*	–	**	*	*	*	6

Risk of bias was assessed using the Newcastle-Ottawa Scale. A higher overall score corresponds to a lower risk of bias; a score of ≤5 (out of 9) indicates a high risk of bias. [#], this study was not assessed because it was published in abstract form without reporting detailed information.