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Anti-reflux therapy and mortality in patients with idiopathic pulmonary fibrosis and gastroesophageal reflux disease: a systematic review and meta-analysis

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Abstract

Gastroesophageal reflux disease (GERD) and idiopathic pulmonary fibrosis (IPF) frequently coexist, with GERD potentially exacerbating IPF progression through microaspiration and pulmonary inflammation. This systematic review and meta-analysis assessed the impact of anti-reflux therapy, including proton pump inhibitors and H2-receptor antagonists, on mortality outcomes in IPF patients with concurrent GERD. A systematic search identified six eligible studies, including 2874 patients, for quantitative synthesis. Results indicate that anti-reflux therapy may reduce IPF-related mortality, with a pooled relative risk (RR) of 0.79 [95% confidence interval (CI): 0.55-1.33], although this finding was not statistically significant. However, no significant effect was observed on overall mortality (pooled RR: 0.97, 95% CI: 0.74-1.25). Study heterogeneity was moderate (I^2=60%), reflecting variability in study designs, populations, and therapeutic regimens. The observational nature of most studies highlights the need for randomized controlled trials to better understand anti-reflux therapy's role in IPF management. While anti-reflux therapy was associated with a potential reduction in IPF-related mortality (RR: 0.79, 95% CI: 0.55-1.33), no significant effect on overall mortality was observed (RR: 0.97, 95% CI: 0.74-1.25). Future research should also evaluate the long-term safety of anti-reflux therapy, given concerns about complications such as infections and renal impairment. This analysis underscores the importance of tailored treatment approaches in IPF patients with GERD to optimize clinical outcomes.

Key words: idiopathic pulmonary fibrosis, gastroesophageal reflux disease, anti-reflux therapy, proton pump inhibitors, mortality.

Introduction

Gastroesophageal reflux disease (GERD) and idiopathic pulmonary fibrosis (IPF) are two clinically significant conditions that, while distinct in nature, demonstrate a compelling interrelationship. GERD, characterized by the retrograde flow of gastric contents into the esophagus, is increasingly recognized as a potential contributing factor to IPF progression, possibly through chronic microaspiration and related lung injury. Recent evidence suggests that up to 87% of patients with IPF have GERD, often without typical symptoms, highlighting the need for systematic evaluation [1,2]. Meanwhile, IPF is a progressive fibrotic interstitial lung disease with a median survival of 3–5 years, characterized by abnormal wound healing, recurrent alveolar injury, and pro-fibrotic cytokine release [1]. The complex and possibly bidirectional relationship between these diseases has fueled growing interest in whether GERD is merely an associated condition or an active contributor to pulmonary fibrosis [1,3].

The pathophysiology of GERD arises from a multifaceted interplay of anatomical, physiological, and environmental factors, predominantly involving dysfunction of the lower esophageal sphincter (LES), increased gastric acid secretion, and esophageal motility disorders. The LES functions as a critical barrier to prevent the reflux of gastric contents. Factors such as obesity, hiatal hernia, specific medications, and lifestyle choices, including smoking and alcohol consumption, can compromise LES integrity, leading to increased reflux episodes [3]. Conditions like gastritis or the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may further exacerbate reflux by stimulating gastric acid secretion. Additionally, impaired esophageal motility, often associated with conditions such as achalasia, scleroderma, or aging, hampers the clearance of refluxed materials, aggravating GERD symptoms [4].

The primary clinical manifestations of GERD include heartburn, regurgitation, chest pain, and dysphagia. Prolonged exposure of the esophagus to gastric acid can result in esophagitis and complications such as Barrett's esophagus, esophageal strictures, and an elevated risk of esophageal adenocarcinoma [5].

IPF, characterized by progressive lung scarring, is associated with a poor prognosis. Although etiology remains largely unknown, multiple factors are implicated in its pathogenesis. Patients with IPF commonly present with progressive dyspnea, a nonproductive cough, and diminished exercise tolerance. Pulmonary function tests often reveal a restrictive pattern, marked by reductions in forced vital capacity (FVC) and total lung capacity (TLC). High-resolution computed tomography (HRCT) is crucial for diagnosis, typically revealing features such as reticular opacities and honeycombing [3-5].

Emerging evidence indicates a higher prevalence of GERD among IPF patients compared to the general population, with studies suggesting that up to 90% of IPF patients may exhibit

GERD symptoms [5]. Several factors contribute to the increased incidence of GERD in IPF. Esophageal motility abnormalities in IPF patients may lead to impaired clearance of refluxed materials, exacerbating GERD symptoms and complicating management strategies. Furthermore, the restrictive lung disease inherent to IPF reduces lung volumes, which may increase intra-abdominal pressure and predispose individuals to reflux [6]. Additionally, a compromised cough reflex in IPF patients reduces the ability to clear aspirated material, heightening the risk of aspiration and subsequent respiratory complications [6].

Aspiration pneumonia represents a significant concern in patients with concomitant GERD and IPF. The aspiration of gastric contents can result in acute lung injury, exacerbating pre-existing pulmonary fibrosis, perpetuating chronic inflammation, and accelerating disease progression. These complications contribute to increased rates of hospitalization and a further decline in respiratory function [7,8].

The inflammatory pathways associated with GERD and IPF appear to share common mechanisms. Chronic esophageal inflammation resulting from acid exposure may provoke systemic inflammatory responses, thereby exacerbating pulmonary fibrosis. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been observed in both conditions, suggesting a mechanistic link between esophageal inflammation and pulmonary fibrosis [8-11].

To our knowledge, this is one of the few meta-analyses that quantitatively examines both IPF-related and overall mortality outcomes associated with pharmacological anti-reflux therapy in patients with coexisting IPF and GERD, thereby addressing persistent uncertainties in previous literature and providing updated evidence to inform clinical decision-making.

Materials and Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with ID number CRD42025636536.

Search strategy

A systematic search was conducted in two major databases, Medline and Cochrane, covering studies published between 1990 and 2024. Grey literature was included to enhance the comprehensiveness of the review. Additionally, the references for the studies included were manually examined to identify further relevant studies. For the PubMed search strategy, a combination of free-text terms and MeSH terms was employed. Boolean operators and specialized filters were utilized to optimize search efficiency.

The search strategy combined terms related to IPF, GERD, and mortality. The search included terms such as IPF, idiopathic pulmonary fibrosis, interstitial lung disease, gastroesophageal reflux, GERD, proton pump inhibitors (PPIs), and mortality, using Boolean operators to ensure relevant studies were identified.

Inclusion and exclusion criteria

Studies included if they involved patients diagnosed with IPF based on internationally agreed diagnostic criteria [13], evaluated therapeutic strategies for GERD, and reported relevant health outcomes, specifically overall mortality and IPF-related mortality. Eligible study designs included observational, randomized, quasi-randomized, pre-post, and historical control studies.

Studies were excluded if they were letters to the editor, editorials, comments, case reports, or case series. Studies involving non-human subjects, interventions not specifically targeting GERD, or populations with interstitial lung diseases other than IPF were excluded. Non-pharmaceutical interventions, such as surgical or lifestyle modifications, were also excluded.

Pharmaceutical treatments, including proton pump inhibitors (PPIs) and H2-receptor antagonists, were the interventions of interest. No restrictions were placed on therapy intensity, frequency, or duration. Comparator groups included placebo or no treatment.

PRISMA process

The Medline search for IPF yielded 10,678 studies, while GERD-related terms resulted in 6,550 studies. Combining these searches produced 126 studies, which were imported into reference management software. After duplicate removal, 124 studies remained. Title screening excluded 60 studies as irrelevant. The remaining 64 studies underwent full-text review, resulting in the exclusion of 58 studies due to mismatched interventions, populations, or outcomes. Ultimately, six studies met the inclusion criteria and were included in the meta-analysis [14-19]. The flowchart of the study selection process is illustrated in Figure 1.

Data extraction

Data extraction was independently performed by two reviewers (VEG and KD) using a structured extraction sheet that captured key study characteristics, including author details, publication year, location, sample size, population demographics, intervention specifics, outcome measures, results, effect sizes, and confidence intervals. Discrepancies were resolved through discussion. Extracted data were compiled into an Excel database for efficient retrieval and analysis.

Quality assessment – risk of bias

The quality of non-randomized observational studies was assessed using the Newcastle-Ottawa Scale (NOS) [20]. This tool evaluates aspects such as the representativeness of cases, comparability of controls, determination of exposures, and adjustment for confounders. Scores from the NOS provided an overall quality rating for each study, ensuring a systematic and transparent evaluation of study reliability.

PICO framework

The Population-Intervention-Comparator-Outcome (PICO) format used in this review can be summarized as follows: The study population consisted of patients diagnosed with IPF through CT or biopsy and co-diagnosed with GERD by methods such as endoscopy, esophageal pH monitoring, esophageal manometry, or barium swallow. The intervention focused on pharmaceutical treatments for GERD, including antacids and/or H2-receptor antagonists. Comparator groups consisted of placebo or no treatment. The primary outcomes were overall mortality and IPF-related mortality, measured as hazard ratios.

Statistical analysis

Statistical analysis was conducted using the Meta-Mar tool for meta-analysis. Summary measures of relative risk (RR) were calculated with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic to identify variability due to heterogeneity rather than chance. The results were interpreted considering both statistical significance and clinical relevance, providing a comprehensive understanding of the intervention's impact.

Results

The basic characteristics of the included studies are displayed in Table 1.

IPF-related mortality

The primary assessed outcome was IPF-related mortality. Three studies met the inclusion criteria and were deemed sufficiently homogeneous for synthesis. Kreuter et al. and Kreuter et al. reported a potential benefit of anti-reflux therapy compared to no therapy in reducing IPF-related mortality among patients with both IPF and GERD [14,15]. These studies yielded risk ratios (RRs) less than 1, suggesting a favorable effect; however, the confidence intervals (CIs) were wide and included 1, indicating statistical uncertainty.

Tran et al. [19], which featured a larger study population, also demonstrated a favorable outcome for anti-reflux therapy, with an RR of 0.85. Although the confidence intervals were

narrower than those in the Kreuter studies, they still included 1, precluding definitive statistical significance.

The pooled analysis of these three studies produced an overall RR of 0.79 (95% CI: 0.55–1.33, p=0.09). While the confidence interval included 1, indicating no statistically significant effect, the findings suggest a possible trend toward a beneficial impact of anti-reflux therapy on IPF-related mortality (Figure 2).

Heterogeneity among the studies was evaluated using the I^2 statistic, which was calculated to be 0%. This indicates low heterogeneity and minimal variability across the included studies.

Overall mortality

The second assessed outcome was overall mortality. Six studies were included in the quantitative analysis, as they fully met the inclusion criteria and were deemed sufficiently homogeneous for synthesis. Kreuter et al. and Kreuter et al., representing two separate studies conducted in distinct populations, did not demonstrate a significant benefit of anti-reflux therapy for overall mortality [14,18]. The reported risk ratios (RRs) were 1.04 and 2.12, respectively, indicating a potential negative effect. This finding was attributed by the authors to an increased prevalence of respiratory tract infections (RTIs) in patients receiving anti-reflux therapy, which contributed to mortality.

Conversely, Kreuter et al. [15], Liu et al. [16], and Lee et al. [17] reported more favorable outcomes, with RRs less than 1. Notably, Liu et al. demonstrated a statistically significant reduction in overall mortality, with a confidence interval (CI) of 0.09–0.97 [16]. However, Tran et al. [19], which had the largest study population, failed to show a significant benefit, reporting an RR of 1.05 (CI: 0.69–1.60).

When all six studies were combined, the overall RR was calculated as 0.97 (95% CI: 0.74–1.25, p>0.05). This result indicates no statistically significant difference in overall mortality between IPF patients with GERD receiving anti-reflux therapy and those not receiving such treatment (Figure 3).

Heterogeneity among the included studies was assessed using the I^2 statistic, which was calculated to be 60%, indicating moderate to substantial heterogeneity. This variability could be attributed to differences in study designs, intervention types (e.g., PPIs vs. H2-receptor antagonists), population characteristics (e.g., countries, age groups, IPF severity, GERD severity), and the dosage and duration of anti-reflux therapy.

Discussion

Several studies have concluded that GERD and IPF appear to coexist in many patients, some have stated that the cause of one condition can predispose to the other and some have

claimed that this association is most likely confounded rather than direct. As far as anti-reflux therapy in IPF patients and its effect in overall mortality and IPF related mortality, a small number of metanalysis have been conducted that presented conflicting results [5-9]. Overall, it was seen that anti reflux medication could possibly improve IPF related mortality but not overall mortality, fact that our metanalysis has also concluded. The overall quality of the available evidence is rather poor as mainly observational studies were included in the majority of the relevant metanalyses as was the case of ours too. The need for randomized trials could address that problem and provide a better understanding of the clinical implications of anti-reflux medications in IPF pathology.

Our analysis revealed that anti-reflux therapy was associated with a notable decrease in IPF-related mortality but not statistically important. This finding may be attributed to the complex interplay between GERD and pulmonary pathophysiology in IPF patients. GERD can exacerbate pulmonary inflammation through mechanisms such as microaspiration of gastric contents, leading to increased exacerbations and faster disease progression [21]. By effectively controlling GERD symptoms and mitigating the risk of aspiration, anti-reflux therapy may contribute to a stabilization of lung function, thereby reducing mortality directly attributable to IPF.

The mechanisms underlying the observed reduction in IPF-related mortality with ART may include several factors. First, the use of PPIs can diminish the acidity of gastric reflux, potentially lowering the irritative effects on the respiratory tract. This could reduce inflammatory responses in the lungs, thereby decreasing the frequency of acute exacerbations—a critical factor influencing mortality in IPF [11]. Furthermore, surgical interventions such as laparoscopic fundoplication may provide a more definitive solution for reflux management, enhancing quality of life and possibly prolonging survival in this vulnerable population [22].

Interestingly, while anti-reflux therapy showed a beneficial effect on IPF-related mortality, it did not significantly alter overall mortality rates [7]. This discrepancy may suggest that while GERD management is crucial for improving specific outcomes related to IPF, it does not address other comorbidities that contribute to overall mortality. Patients with IPF often have multiple concurrent health issues, including cardiovascular disease and pulmonary hypertension, which may overshadow the mortality benefits conferred by GERD treatment.

This meta-analysis encountered significant heterogeneity, as evidenced by an I^2 statistic of 60%. This variability may stem from differences in study populations, anti-reflux therapy regimens, and methodologies employed across the included studies. Additionally, the observational nature of many studies raises concerns regarding confounding variables,

including variations in disease severity and the presence of other comorbidities, which could influence mortality outcomes.

Safety profiles of anti-reflux therapy, particularly long-term PPI use, warrant careful consideration. Concerns regarding potential complications, such as Clostridium difficile infections and renal impairment undertake the need for vigilant monitoring in patients receiving prolonged therapy [23]. Clinicians should balance the benefits of GERD management with the risks associated with long-term medication use, tailored to the individual patient's clinical context.

This meta-analysis adds to the existing literature by focusing exclusively on the impact of pharmacological anti-reflux therapy—PPIs and H2-receptor antagonists—on mortality outcomes in IPF patients with coexisting GERD. In contrast to prior meta-analyses that combined surgical and medical therapies [8,9], our review isolates the effect of pharmaceutical treatment, thus reducing clinical heterogeneity and enhancing the interpretability of results. Additionally, by extending the literature search up to 2024 and applying stringent PRISMA and PICO criteria, this study incorporates the most current evidence and provides a more refined understanding of how GERD management may affect IPF-related versus overall mortality. This focused approach not only strengthens the clinical applicability of our findings but also highlights important gaps in knowledge that require targeted investigation.

Our findings are generally aligned with those of previous meta-analyses that examined the therapeutic implications of GERD in IPF. Fidler et al. and Khor et al. observed trends toward reduced IPF-related mortality with anti-reflux treatment, though without consistent statistical significance [8,9]. Similarly, Bédard Méthot et al. [2] emphasized the strong epidemiological association between GERD and IPF, but did not dissect pharmacologic treatment effects. In contrast, Tran and Suissa [19] highlighted the limitations of observational studies and advised caution when interpreting survival benefits attributed to PPIs. Compared with these prior analyses, our study uniquely quantifies treatment effects on both IPF-related and overall mortality using a robust and updated dataset, underscoring the need for future randomized controlled trials to validate these trends and guide clinical decision-making.

This meta-analysis provides valuable insights into the potential impact of anti-reflux therapy on IPF patients with concurrent GERD. A significant strength is the adherence to PRISMA guidelines, which ensured a systematic and transparent approach to study identification and selection. The inclusion of studies from major databases, along with manual searches of references, enhanced the comprehensiveness of the review. Furthermore, the use of the NOS for quality assessment provided a standardized framework to evaluate the reliability of the included studies. Additionally, the systematic analysis of IPF-related and overall mortality

outcomes offers a focused examination of a clinically significant question, contributing to the understanding of GERD management in this vulnerable population.

Despite these strengths, the meta-analysis has notable limitations, particularly the reliance on observational studies, which are susceptible to confounding and selection biases. The absence of randomized controlled trials (RCTs) limits the ability to establish causality between anti-reflux therapy and IPF-related outcomes. The included studies exhibited significant variability in population characteristics, GERD severity, and types of anti-reflux threrapy used, leading to moderate heterogeneity (I^2 = 60%) that complicates the interpretation of pooled results. Furthermore, the small sample sizes of some studies and wide confidence intervals diminished the statistical power of the findings, resulting in trends that were not statistically significant. The exclusion of non-pharmacologic interventions, such as surgical treatments, also limits the scope of the conclusions.

The findings of this meta-analysis have important clinical implications for the management of patients with IPF and coexisting GERD. Although the reduction in IPF-related mortality was not statistically significant, the observed trend suggests that anti-reflux therapy may offer a potential benefit in slowing disease progression by mitigating microaspiration-related injury. This supports the rationale for a more proactive approach to diagnosing and managing GERD in IPF patients. Clinicians should consider the inclusion of anti-reflux pharmacotherapy, particularly in individuals with documented GERD symptoms or objective evidence of reflux, as part of a comprehensive disease management plan. Moreover, given the potential risks associated with prolonged PPI use, individualized risk-benefit assessments are warranted. Integration of gastroenterological consultation into IPF care pathways may also enhance multidisciplinary management and optimize long-term outcomes.

Future research should prioritize well-designed RCTs to address the limitations of observational studies and establish a causal relationship between anti-reflux therapy and mortality outcomes in IPF patients. Larger and more diverse study populations are needed to enhance statistical power and generalizability, and subgroup analyses could elucidate the effects of specific anti-reflux therapy modalities or disease severities. Additionally, future studies should investigate the long-term safety profiles of anti-reflux therapy, given the potential risks associated with prolonged use of PPIs. Expanding the scope to include non-pharmacologic interventions, such as laparoscopic fundoplication, could provide a more comprehensive understanding of GERD management in IPF patients. These efforts are critical to optimizing therapeutic strategies and improving outcomes for this high-risk population.

Conclusions

In conclusion, the systematic review and meta-analysis suggest that anti-reflux therapy may be associated with a reduction in IPF-related mortality in patients with concurrent GERD, although the results were not statistically significant. However, no substantial impact on overall mortality was observed. The findings underscore the importance of integrated therapeutic approaches for managing GERD in IPF patients, potentially mitigating disease progression and associated respiratory complications. Future research, particularly randomized controlled trials, is essential to confirm these observations and establish definitive clinical guidelines.

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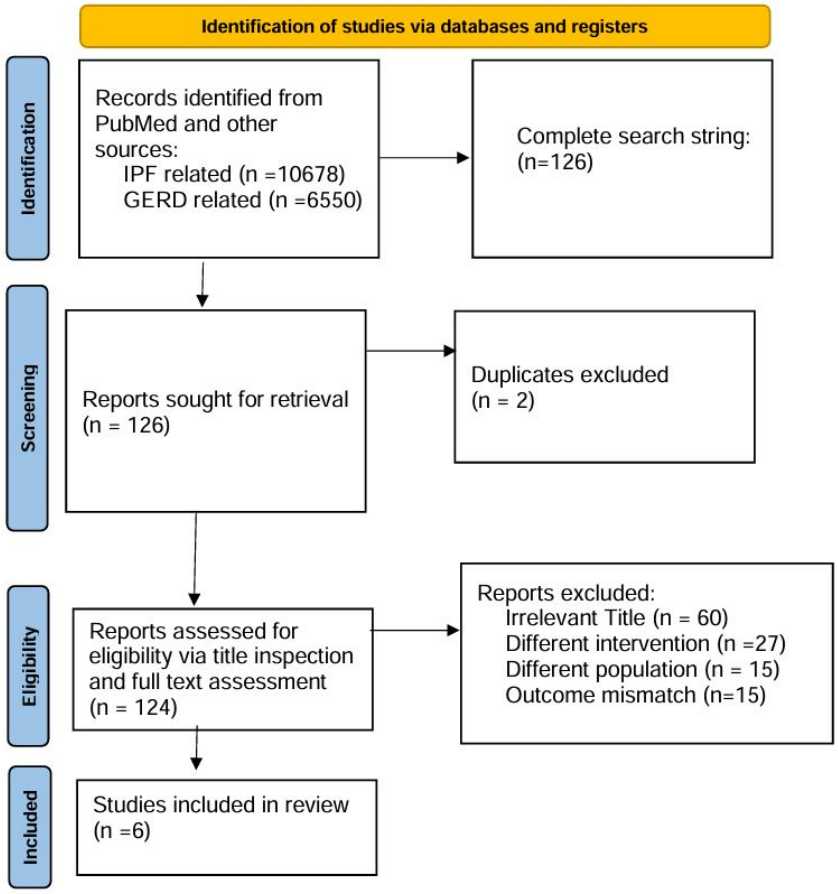

Figure 1. Flowchart of the study selection process. GERD, gastroesophageal reflux disease; IPF, idiopathic pulmonary fibrosis.

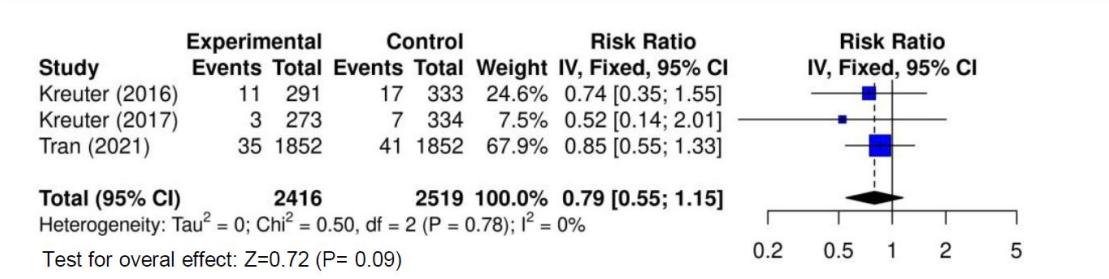

Figure 2. Forest Plot for IPF-related mortality.

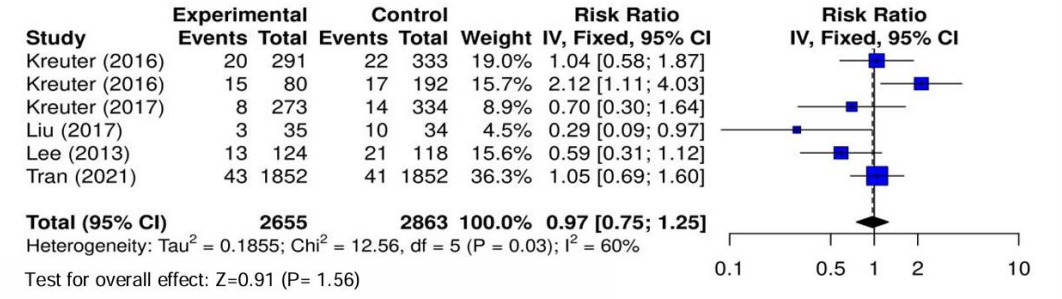

Figure 3. Forest Plot for overall mortality.

Table 1. Basic characteristics of the included studies.

Study	Type	Country	Intervention	Population	Comparator	Outcome	RR	Ottawa rating
Tran *et al*. [19]	Retrospective observational	UK	PPIs	1852	1852	Overall mortality + IPF related	1.07-1.10	8
Kreuter *et al*. [14]	Retrospective observational	Germany	PPIs / H2A	291	333	Overall mortality + IPF related	1.04-0.74	8
Kreuter *et al*. [15]	Retrospective observational	Germany	PPIs / H2A	273	350	Overall mortality + IPF related	0.70-0.52	8
Lee JS *et al*. [17]	Retrospective observational	China	PPIs / H2A	124	118	Overall mortality	0.59	6
Kreuter *et al*. [18]	Retrospective observational	Germany	PPIs	76	193	Overall mortality	2.12	8
Liu *et al*. [16]	Retrospective observational	China	PPIs / H2A	34	35	Overall mortality	0.29	6

H2A, histamine-2 receptor antagonists; IPF, idiopathic pulmonary fibrosis; NOS, Newcastle-Ottawa Scale; PPI, proton pump inhibitors; RR, relative risk.