Chapter

Gastroesophageal Reflux and Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) and Gastroesophageal reflux disease (GERD) commonly co-exist. Pathophysiological mechanisms causing IPF are still not well understood, and GERD has been implicated in both as a probable causative and disease-promoting entity. Although not conclusively proven, this relationship has been the subject of several studies, including therapeutic interventions aimed at treating GERD and its resultant effect on IPF and related outcomes. Our review aims to present the current concepts and understanding of these two disease processes, which are multifaceted. Their complex interaction includes epidemiology, pathophysiology, diagnosis, treatment, review of research studies conducted to date, and future directions for research.

Keywords: idiopathic pulmonary fibrosis (IPF), gastro-esophageal reflux disease (GERD), microaspiration, proton pump inhibitor, risk factors

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is the most common type of Idiopathic Interstitial Pneumonia. It is more prevalent in men, and its incidence increases with age, especially beyond the fifth decade [1]. Its incidence is estimated to be 3–9 cases per 100,000 per year in the western hemisphere [2]. As per a systematic review, the prevalence is estimated to be 0.5–27.9/100,000 [3]. Although newer therapies such as

Pirfenidone and Nintedanib are available to slow the progression of the disease, the mortality and prognosis remain dismal, comparable to that of certain malignancies [4]. A key consideration has been the lack of optimal understanding of the pathophysiological mechanisms underlying the disease process, as interventions can then be targeted to modify the disease process and achieve better outcomes for the patients [4]. In a genetically susceptible individual, many risk factors have been proposed [1]. One such factor that has been closely associated with IPF is Gastroesophageal reflux disease (GERD) [1]. Their association has been hypothesized, studied, and targeted therapeutically. However, its role as a causative and aggravating factor has not yet been crystallized. Our chapter aims to review the association of GERD with IPF, its alleged role in causing or promoting lung injury, the effect of GERD therapy on IPF, recommendations from clinical guidelines, and the direction for future research.

1.1 Gastroesophageal reflux disease (GERD) and its relevance to IPF

GERD is a disease caused by reflux of stomach contents into the esophagus and beyond, causing troublesome symptoms and complications [5]. It causes esophageal and stomach symptoms characterized by chest pain, nausea, bloating, heartburn, and regurgitation. It can also cause extraesophageal symptoms such as throat pain, burning, lump in the throat, the sensation of needing to clear the throat, hoarseness of voice, cough, wheezing, bronchospasm, etc. [5, 6]. Importantly not all reflux events are symptomatic as there could be non-acid reflux [5–7].

Prevalence of GERD is very common in the western world, with North American estimates being 18.1–27.8% [8]. Europe, similarly, has a prevalence of up to 25% [8]. In a United Kingdom general practice database, IPF was much more likely to be associated with a diagnosis of GERD (65%) or use of anti-reflux therapy (71%) when compared to controls [4, 7, 9]. The prevalence of erosive esophagitis and hiatal hernia, both of which are associated with increased reflux, is also much higher in pulmonary fibrosis patients when compared to the general population [8, 10]. Hence there is a strong epidemiological association between these two disease entities.

GERD occurs commonly as a result of increased frequency of transient lower esophageal sphincter relaxations (TLESRs), which are defined as brief moments of lower esophageal sphincter tone inhibition that are independent of a swallow [11]. Other pathophysiological mechanisms implicated in the causation of GERD are reduced lower esophageal sphincter (LES) pressure, reduced upper esophageal sphincter pressure, reduced esophageal motility, Hiatal hernias, which distorts the gastroesophageal junctional anatomy, impairment of esophageal clearance, and sluggish gastric emptying [4, 5, 7]. A combination of these factors leads to the reflux establishing contact with mucosa in the upper gastrointestinal tract, pharynx, tracheobronchial tree, and lungs, causing extra esophageal symptoms as previously described [4, 5, 7].

Evaluation of GERD can be made by direct visual examination by esophagogastroduodenoscopy (EGD). The chief advantage is that the mucosa can be visualized directly and is helpful in the diagnosis of possible complications of GERD, including Barret's esophagitis, esophagitis, gastritis, gastric and esophageal stricture, and malignancy. However, pH monitoring better evaluates reflux, wherein a pH measuring probe is placed in the esophagus [5]. The primary measurement is the amount of time spent with a pH less than 4.0 [5]. However, it has its inherent limitations, as non-acid reflux cannot be measured and can remain totally asymptomatic. This limitation has been overcome by the placement of channels that measure impedance. Liquid reflux has low impedance and high conductance, while gaseous reflux, such as belching, has high impedance with low conductance [12]. Combined 24-hr multichannel intraluminal impedance-pH monitoring (MII-pH) are available to determine the amount of refluxate, its proximal extent, and/or the presence of

both acid and weakly acidic reflux [7, 13]. The chief metric when using MII-pH is the "Total number of refluxes" (Pathological when more than 80 and normal if less than 40 in a 24-hour period) and esophageal "Acid exposure time (AET)" as the percentage of time with pH less than 4.0 in the distal esophagus [14]. The use of MII-pH in GERD associated with extra esophageal disease, particularly in IPF, is rather novel and promising to help illuminate the pathophysiological mechanisms between the two diseases [15]. It is noteworthy that IPF belongs to a group of diseases that are only possibly or likely associated with GERD, and its role is only speculated [7]. The use and application of MII-pH for the study of extraesophageal diseases and symptoms has not been as productive as for typical GERD [7].

1.2 The pathophysiological relationship and co-existence between GERD and IPF

The relationship between IPF and GERD is quite intriguing. The epidemiological association suggests that there appear to be plausible biological and mechanical factors underlying this pathophysiology.

It is suggested that GERD is associated with decreased upper and lower esophageal sphincter tone (hypotensive esophagogastric junction) with or without increased frequency of transient lower esophageal sphincter relaxations (TLESRs), leading to increased refluxate with an associated micro-aspiration of the gastric contents into the trachea and lungs [16–18]. Contrary to this proposed theory, it has been proposed that lung fibrosis causes decreased lung compliance along with lower lung elasticity, resulting in increased negative intrathoracic pressure during inspiration that is transmitted to the mediastinal structures, including the esophagus and its sphincters [17]. This causes increased transient lower esophageal sphincter relaxations (TLESRs) with lower and upper esophageal sphincters [17]. There is also a pressure gradient across the diaphragm in respiratory diseases like IPF, which may promote these favorable refluxate mechanisms, especially during coughing, increased respiratory excursions during exacerbations, and may potentially be further aggravated by hypoxia/hypercapnia, medications like antacids, glucocorticoids, and obstructive sleep apnea/hypopnea syndromes [19]. Hiatal hernia alters the physical and physiologic function of the lower esophageal sphincter, thereby promoting reflux [20–22]. Furthermore, it has been proposed that esophageal dysmotility may contribute to reflux [23, 24]. Ultimately, the result of these phenomena is that the gastric refluxate, which contains both acidic and non-acidic contents, leads to delayed esophageal clearance and micro-aspiration in the tracheobronchial tree injure the pulmonary parenchyma consisting of both alveolar and interstitial components [4, 7, 19]. The healing of this injury eventually occurs by fibrosis, and the pulmonary remodeling that ensues culminates in a distorted fibrotic architecture [4, 7].

Many studies have been performed to provide evidence and study the relationship between GERD and IPF. Most of these studies have limitations and often conclude with contradictory results. Therefore, evidence has shown a co-existence and/or association between IPF and GERD. However, causality has yet to be determined [4, 7, 25].

Gao et al. conducted a study involving 69 IPF patients, 62 healthy volunteers, and 88 IPF negative GERD patients. The prevalence of GERD was high in patients with IPF, and in relation to their comparator group showed the variable presence of esophageal dysmotility and decreased lower and upper esophageal sphincter pressure. IPF patients also had increased reflux events proximally and impaired bolus transit time [16]. Raghu et al. studied 65 patients with IPF who were subjected to 24-h pH monitoring and esophageal manometry with a comparison group of 133 asthmatic patients and symptoms of GERD. The prevalence of abnormal

gastroesophageal reflux in IPF patients was high at 87%, with 76% and 63% demonstrating abnormal distal and proximal esophageal acid exposures, respectively; a finding higher than within the comparison group [18]. The study also showed that the presence of GERD was not always symptomatic, and there was no correlation with IPF severity [18]. This was further confirmed in a study involving 28 patients with histologically confirmed IPF using hypopharyngeal multichannel intraluminal impedance (HMII) [26]. HMII used a specialized impedance catheter to directly measure laryngopharyngeal reflux (LPR) and full column reflux (reflux 2 cm distal to the upper esophageal sphincter). The study included 16 males and 12 females with a mean age of 60.4 years (range, 41–78) and a BMI of 28.4 (range, 21.1–38.1), respectively. Abnormal proximal exposure was present in 54% (15/28) of patients. This latter group was more likely to have a defective lower esophageal sphincter (LES) compared with those without (93% vs. 75%). Fourteen patients (56%) had abnormal esophageal motility, including aperistaltic esophagus (n = 9), suggesting that this may be common in this patient population [26].GERD was noted to be highly prevalent at more than 70% in patients with IPF; abnormal proximal reflux events such as LPR and full column reflux were also quite common despite a frequently negative DeMeester score (It is a composite of six different parameters which measures acid exposure giving a pH score used to diagnose GERD), suggesting that nonacid reflux (25% of patients) is prevalent in this patient population [26]. A high rate of esophageal mucosal injury and a longer acid clearance time was also noted [26].67–76% of the systematic review demonstrated abnormal esophageal acid exposure off PPI treatment [27].

In another study conducted by Savarino et al. [28], 40 IPF patients were studied alongside 40 non-IPF ILD patients and 50 healthy volunteers, who served as controls. Patients were off reflux therapy and underwent a High-resolution Lung CT scan (HRCT) and pH-impedance monitoring. Patients with IPF had significantly increased esophageal acid exposure, the number of acidic, weakly acidic, and proximal reflux events relative to the comparison groups. Pulmonary fibrosis HRCT scores correlated well with reflux episodes in both the distal and proximal esophagus. Patients with IPF had more bile acids and pepsin ($p < 0.03$) in bronchoalveolar lavage fluid (62% and 67%, respectively) and saliva (61% and 68%, respectively) relative to the comparison groups [28]. Gavini et al. conducted an elegant study involving 45 pre-transplants patients with IPF who had received pulmonary function tests within the last 3 months. Patients were off reflux therapy and had no reflux surgery. They measured GER on multichannel intraluminal impedance and pH study (MII-pH). Six pH/acid reflux parameters with corresponding MII/bolus reflux measures were prespecified. Multivariate analyses were applied using forward stepwise logistic regression. Severe pulmonary dysfunction was defined using diffusion capacity for carbon monoxide (DLCO) ≤40%. Abnormal total reflux episodes and prolonged bolus clearance time (OR = 1.21 p = 0.05), but not the refluxate pH values, were significantly associated with pulmonary dysfunction severity on univariate and multivariate analyses [29]. Overall, it appears that esophageal dysmotility, the total number of acidic, weakly acidic, and non-acidic refluxes with prolonged bolus clearance time, appear to impact the underlying lung pathology.

Animal and human studies have shown that the presence of gastric contents (pepsin, bile acids, gastric acid) via microaspiration in bronchoalveolar lavage (BAL) fluid can cause tissue damage and inflammatory infiltrate [28, 30–35]. Histologically presence of thickened alveolar walls, collagen deposition in the interstitium, epithelial-mesenchymal transition, and presence of various fibrogenic factors has been found [28, 34, 35]. The latter consists of TGF-beta, NFκB, Farnesoid X receptor, and others. TGF-beta can be induced by gastric contents, leading to fibroblast proliferation and fibroproliferative changes [4, 7].

1.3 The role of proton pump inhibitor (PPI)/histamine-2 receptor blockers (H2RA) and anti-reflux surgery in IPF

There has been a long-standing interest in the use of anti-secretory therapy/anti-reflux surgery in IPF patients, given that GERD has been thought of as having a relationship with IPF [4, 7]. While it is not unreasonable to give anti-secretory therapy to patients with symptomatic GERD patients, it has certainly been hard to objectively justify the use in all patients with IPF, some of whom may not have any reflux or reflux with non-acidic gastric contents [36]. This has indeed been a recommendation from international guidelines, albeit it was a week level of recommendation [37]. As per literature, PPIs are the most frequently used medications, and further discussion will relate henceforth to PPI.

PPIs are known for increasing the pH of gastric acid; a mechanism thought to prevent microaspiration of acidic contents into the lung and hence potentially protect against acid-induced pneumonitis [37]. In vitro studies show that PPIs like Esomeprazole have pleiotropic effects, can inhibit expression of pro-inflammatory molecules like vascular cell adhesion molecule-1, inducible nitric oxide synthase, tumor necrosis factor-alpha (TNF-α), and interleukins (IL-1β and IL-6), and exhibit antioxidant and anti-fibrotic properties by downregulation of profibrotic proteins including receptors for transforming growth factor β (TGFβ), fibronectin and matrix metalloproteinases (MMPs) [38, 39]. They may also inhibit apoptosis of pneumocytes expressing Surfactant (SP-C) [38, 39]. Retrospective studies have also demonstrated that PPIs may prolong transplant-free survival of IPF patients [38, 39].

However, PPIs are not without risks. They have been shown to alter the microbiome of the respiratory tract and increase the risk of pneumonia [17]. Furthermore, they increase the risk of micronutrient deficiencies like Vitamin B12, cause dementia, *Clostridium difficile* infection, decrease bone density and increase the risk of fractures. They may increase the risk of chronic kidney disease progressing to end-stage renal disease [40]. However, it is to be noted that most of the evidence for this comes from observational data and meta-analyses, which have their own inherent limitations [40].

Anti-reflux surgery is an important therapeutic option in patients with GERD. Nissen fundoplication and Laparoscopic anti-reflux surgery (LARS) are the two most performed surgeries, both of which are generally safe in IPF [4, 14]. Lee JS et al. reported a retrospective cohort of 204 IPF patients consisting of individuals with symptoms of GERD (34%), a history of GERD (45%), reported use of GERD medications (47%), and Nissen fundoplication (5%). After the multivariate adjustment, the use of GERD medication was associated with a lower radiologic fibrotic score. It was also an independent predictor of longer survival time in patients with IPF [41]. Lee JS et al. also reported the combined results of 3 prospectively collected randomized controlled trial data, including 242 patients only from the placebo arm. Although the data came from RCTs, this was not an RCT. Of the total 242 patients, 124 patients were taking PPI/H2RA, and 118 patients were not taking any antisecretory therapy. In IPF, a slower decline in Forced vital capacity (FVC) has shown a correlation with improved survival time in IPF [42]. The study showed that there was a slower decline in FVC in the PPI/H2RA group, which was statistically significant. Also, there were fewer acute exacerbations in the PPI/H2RA group, and this result did not contribute to the slower decline in FVC. However, there was no change in mortality, presumably due to the follow-up period not being sufficient. This study result generated an interesting hypothesis that the use of PPI/H2RA could slow disease progression [43].

Furthermore, Fidler et al. conducted a systematic review and meta-analysis, studying the effect of pharmacological therapy of GERD in IPF patients, which showed a significant improvement in IPF related survival (adjusted risk: HR 0.45) but no effect on all-cause mortality. There was a change in progression-free

survival, FVC, acute exacerbation, and other Pulmonary function test parameters. In patients with FVC less than 70% of predicted, there was an increase in pulmonary infection, which was significant as this is a known side effect of PPI affecting patients with more advanced disease [44]. It follows from this discussion that the studies once again have small numbers, mostly observational, and hence have limitations providing poor or limited quality of evidence [44].

In a randomized controlled trial, Raghu et al. analyzed data from 27 patients who underwent Laparoscopic anti-reflux surgery (LARS) and 20 patients who did not undergo surgery with FVC measurement at 48 weeks as the endpoint in an intention to treat analysis. All patients had abnormal acid GER with a confirmed DeMeester score of ≥14·7; measured by 24-h pH monitoring and preserved forced vital capacity (FVC) of more than 50%. Patients were allowed to use Nintedanib and Pirfenidone. Patients in the surgery group had a slower decline in FVC, which was not statistically significant at 48 weeks in the non-surgery group (p = 0·28)}. Acute exacerbation of IPF, hospitalization for respiratory etiology, and mortality were also less in the surgical group, however not to statistical significance [45].

2. Discussion

GERD has been known to be co-existent with many Pulmonary disorders such as Systemic Sclerosis, Chronic obstructive pulmonary disease (COPD), Bronchial Asthma, IPF, Bronchiectasis, Aspiration Pneumonia, Lung transplant complications such as Bronchiolitis obliterans (BOS), etc. [6]. These plethora's of lung conditions being associated with GERD are likely due to the shared common genetic embryological and developmental origin of the two organ systems from the foregut [6, 60]. In addition, they share the intrathoracic cavity and also have the same vagal innervation [6, 60]. As such, two predominant theories are in vogue, the "Refluxate theory" and the "Reflux theory," which attempt to explain the disease mechanisms with their common origin and development as background. The "Refluxate theory," as previously described, implicates acid reflux from the GI tract and its micro-aspiration into the Respiratory tree, causing physicochemical damage to the latter culminating in fibrosis [6]. The "Reflex theory" pertains to the reflex increase in bronchoconstriction and airway resistance in response to the presence of acid in the esophagus and respiratory tree [6]. Furthermore, as discussed previously, the presence of pulmonary fibrosis may aggravate the gastroesophageal reflux due to decreased compliance, elasticity, and need for increased negative intrathoracic pressure generated during inspiration, causing increased gradient across thoracic and abdominal compartments [6]. Hence there is possibly a bidirectional relationship between the two organ systems, as depicted in **Figure 1.** A Summary of the studies that evaluated the role of antireflux therapy and surgery in the management of IPF is available in **Table 1**.

Studies designed to test the relationships between the two diseases entities have several limitations. They are mostly retrospective, have small sample sizes, with poorly defined inclusion and exclusion criteria, resulting in many confounders. While these limitations can be addressed partially by conducting prospective studies, randomized controlled data with a large sample size will remain elusive due to the prolonged time required for a disease process like IPF takes to evolve and manifest [25]. Besides, diseases like IPF are not clearly recognizable early, and GERD with non-acid reflux or poorly acidic reflux may not manifest with classic symptoms [6, 25], hence denying the opportunity for early recognition and follow up. Hence, our reliance on smaller case-controlled studies with a few well-conducted meta-analyses has only revealed an association between GERD and IPF, far from the nine causality criteria propounded by "Hill" [61, 62]. Although not ruling out causality, a weak association between the two

diseases still needs to be viewed with an abundance of caution as the effects of residual confounding generate sufficient bias to prevent a robust causal inference from these types of studies [62]. Although such challenges will limit future studies, investigating

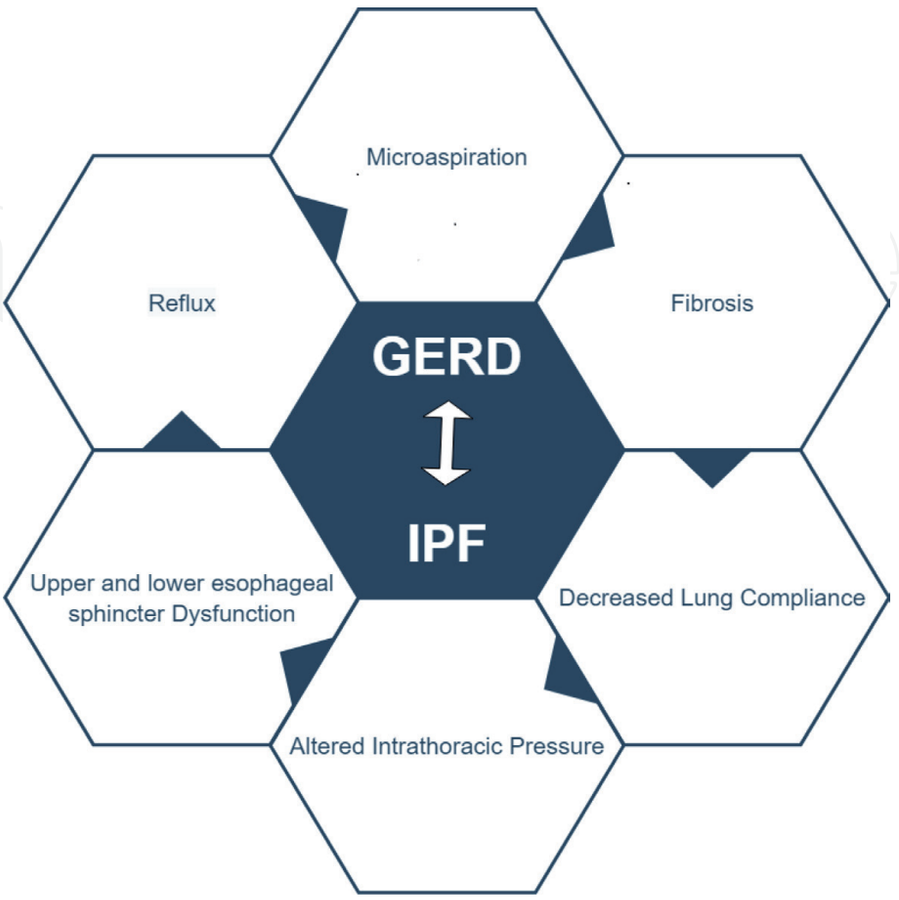

Figure 1.
The bidirectional relationship between IPF and GERD.

Authors	Year	Study type	Anti-reflux therapy type	Population size	Outcomes
Cantu et al. [46]	2004	Retrospective cohort study	Fundoplication	457	• Fourteen patients with early fundoplication had better survival when compared to those with reflux and no intervention. • As compared to patients with reflux who did not have early fundoplication, those who had early fundoplication had less incidence of BOS at 1 and 3 years.
Raghu et al. [18]	2006	Case series	PPIs	4	• In all four patients, PFTs stabilized or improved, and their status was maintained with proper PPI therapy. • At the latest follow-up, all of the patients were still alive, and none of them had an acute exacerbation of IPF or required therapy for respiratory difficulties during this time.

Authors	Year	Study type	Anti-reflux therapy type	Population size	Outcomes
Linden et al. [47]	2006	Retrospective cohort study	Fundoplication	45	• During the average 15-month follow-up, there were no perioperative complications or a reduction in lung function. • Patients with idiopathic pulmonary fibrosis treated with fundoplication had better oxygen levels, but the oxygen requirements of control patients with idiopathic pulmonary fibrosis who did not have the surgery increased significantly
Lee et al. [41]	2011	Retrospective cohort study	PPIs–H_2RAs	204	• The usage of anti-reflux medications was found to be an independent predictor of a prolonged life expectancy. • Using antacids for gastric reflux was linked to a reduced radiologic fibrosis score.
Fisichella et al. [48]	2011	Prospective study	LARS	39	• GERD patients with lung transplants had higher pepsin in their BALF than lung transplant patients who had LARS.
Noth et al. [10]	2012	Retrospective cohort study	PPIs–H_2RAs	74	• Compared to matched controls, IPF patients with hiatal hernia who used antacid medicines had substantially higher DLCO and better composite physiologic index scores.
Raghu et al. [49]	2016	Retrospective cohort study	LARS	27	• FVC measurements taken before and after LARS revealed no significant change over1 year but there was a trend towards stabilization of FVC
Lee et al. [43]	2013	Post hoc analysis of RCTs	PPIs–H_2RAs	242	• FVC loss is lower at 30 and 52 weeks with fewer acute exacerbations.
Ghebremariam et al. [38]	2015	A retrospective analysis from 2 databases	PPIs	215	• Patients with IPF who used PPIs lived longer than those who did not (median survival of 3.4 vs. 2 years).
Raghu et al. [37]	2015	Post hoc analysis of RCTs	PPIs–H_2RAs	1061	• The use of anti-acid medications at the start of the study had no effect on the therapeutic effect of Nintedanib on slowing FVC decrease in IPF patients.

Authors	Year	Study type	Anti-reflux therapy type	Population size	Outcomes
Kreuter et al. [50]	2016	*Post hoc* analysis of RCTs	PPIs–H2RAs	624	• Antacid therapy was not associated with disease progression, all-cause mortality, IPF-related mortality, absolute FVC decrease of 10% or more, mean observed change in FVC and FVC percent of predicted, hospital admission rate, 6 Minute walk distance(MWD) stratified by baseline FVC, and adverse events at 52 weeks.
Lee et al. [51]	2016	Retrospective cohort study	PPIs	786	• PPI usage for more than 4 months was linked with a lower IPF-related mortality rate than PPI use for less than 4 months.
Kreuter et al. [52]	2016	Retrospective cohort study	PPIs	272	• PPI use at the start was not linked to a longer median survival time.
Elkstrom et al. [53]	2016	Prospective population-based study	PPIs–H_2RAs	462	• The use of antacids was not linked to mortality.
Kulkarni et al. [54]	2016	Retrospective cohort study	PPIs–H2RAs	284	• Antireflux treatment was not linked to an increased risk of mortality or lung transplantation.
Raghu et al. [55]	2016	Retrospective cohort study	LARS	27	• There were no fatalities in the first 90 days after surgery, and 81.5 percent of the individuals were still alive two years later. • Over the course of a year, there were no statistically significant variations in FVC decreased rates pre- and post-LARS.
Kreuter et al. [56]	2017	Post hoc analysis of RCTs	PPIs–H_2Ras	632	• There were no significant differences in disease progression, all-cause mortality, IPF-related mortality, all-cause hospitalization rate, or mean change in % FVC at 52 weeks between the two groups (with or without antacid therapy).
Restivo et al. [57]	2017	Population-based study	PPIs–H_2RAs	6797	• PPI usage was linked to fewer high attenuation regions in CT scans of a large group of asymptomatic community-dwelling middle-aged and older people, suggesting a possible benefit in ILD.

Authors	Year	Study type	Anti-reflux therapy type	Population size	Outcomes
Raghu et al. [45]	2018	A prospective randomized controlled study	LARS	58	• LARS was linked to a reduced rate of FVC decrease, a longer duration until FVC decline or death, and fewer clinical events and fatalities.
Costabel et al. [58]	2018	*Post hoc* analysis of RCTs	PPIs–H_2RAs	406	• In both antisecretory therapy treated and nontreated individuals, the yearly decline rate of FVC was identical in both Nintedanib/placebo-treated patients. • Antisecretory medicine did not influence the therapeutic effect of Nintedanib and was not related to a better course of illness
Helen et al. [59]	2019	A retrospective analysis from 1 database	PPIs–H_2RAs	587	• There were no differences in survival or illness progression in patients on antacid therapy

Abbreviations: BOS: bronchitis obliterans syndrome; PPIs: proton pump inhibitors; PFT: pulmonary function tests; H_2RAs: H2 receptor antagonists; LARS: laparoscopic anti-reflux surgery; GERD: gastroesophageal reflux disease; IPF: idiopathic pulmonary fibrosis; DLCO: diffusion lung capacity for carbon monoxide; BALF: bronchoalveolar lavage fluid; RCTs: randomized controlled trials; FVC: forced vital capacity; ILD: interstitial lung disease; CI: confidence interval; HR: hazard ratio.

Table 1.
Summary of the studies that evaluated the role of antireflux therapy and surgery in the management of IPF.

therapeutic interventions like LARS and PPIs along with disease-modifying therapies like Nintedanib and Pirfenidone may improve outcomes for our IPF patients [25].

The large database-based clinical studies with robust timestamping of initiation of each disease entity will be helpful in establishing a temporal relationship. A machine learning model development is the need of the hour to answer this clinical question.

3. Conclusion

The co-existence of IPF and GERD is very common. There is likely a bidirectional pathophysiological relationship between the two disease entities. Although there is no causality established, current guidelines do recommend therapy with PPI in all patients with IPF. There remain many important challenges to the study of these coexisting conditions, and it may not be possible to obtain robust data establishing causality. Nevertheless, an attempt can be made to further conduct well-designed interventional studies to benefit patients in need.

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Conflict of interest

The authors declare no conflict of interest.

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