

Review

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# Diagnosis and minimally invasive treatment of gastroesophageal reflux disease in patients with advanced lung disease

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## Abstract

Biomechanical damage to the respiratory epithelium by acidic refluxate and endopeptidases (such as activated pepsin) are thought to be key mechanisms by which gastroesophageal reflux disease (GERD) contributes to the development and worsening of chronic respiratory disorders. These chronic disorders include chronic cough, asthma, suppurative lung diseases, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis (IPF). In such patients, acid suppression therapy to treat GERD and associated respiratory symptoms has produced controversial results, as these treatments decrease the acidity of the refluxate but do not prevent gastroesophageal reflux and aspiration itself. Consequently, mechanical control of GERD through laparoscopic and endoscopic procedures is a plausible option to halt the progression of such chronic respiratory disorders. This article provides an overview of GERD diagnosis and therapeutic alternatives (i.e., pharmacological therapy, antireflux surgery, and other minimally invasive procedures) in the context of advanced pulmonary disease, particularly IPF.

**Keywords:** Antireflux surgery, fundoplication, gastroesophageal reflux, GERD, lung diseases, respiratory diseases, pulmonary fibrosis, respiratory aspiration



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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as the retrograde flow of gastric juices into the esophagus through the esophagogastric junction (EGJ)<sup>[1]</sup>, and this condition affects ~ 25% of the general population (regional variations range from 2.5%-51.2%)<sup>[2]</sup>. GERD presents with a wide range of clinical manifestations, including typical symptoms such as heartburn and regurgitation, as well as esophageal complications like erosive esophagitis, strictures, and Barrett's esophagus. Additionally, it can lead to extra-esophageal complications, including laryngopharyngeal reflux, dental erosions, and macroaspiration, as well as recurrent silent microaspiration. The latter may contribute to the progression of respiratory diseases such as idiopathic pulmonary fibrosis (IPF)<sup>[1,3,4]</sup>.

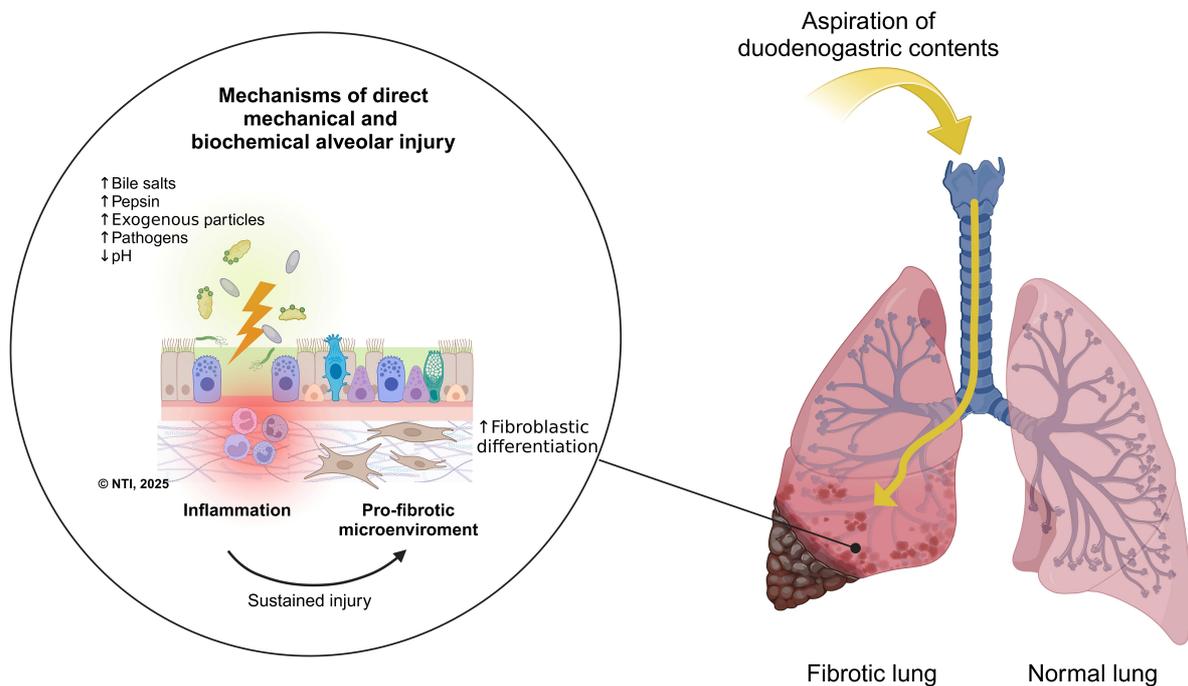
The pathophysiological mechanisms of GERD that may contribute to the development of chronic pulmonary disease are cyclical and progressive. Patients with GERD may aspirate refluxate into the upper airway due to impaired protective mechanisms, including dysfunction of the lower and upper esophageal sphincters, as well as the presence of esophageal motility disorders. Recurrent aspiration of duodenogastric contents, particularly in low volumes (i.e., silent aspiration), can lead to disruption of the respiratory epithelial barrier<sup>[5-7]</sup>. This is facilitated by direct mechanical and biochemical injury due to the presence of food particles, low pH aspirate, proteolytic enzymes like activated pepsin, and erosive substances such as bile acids and salts. Repeated exposure over time leads to a fibrotic remodeling of the lung parenchyma [Figure 1]<sup>[5-7]</sup>.

The resulting profibrotic status is associated with decreased pulmonary compliance, reduced lung volumes, and a change in the diffusion capacity at the alveolar level. The restrictive nature of the fibrotic process increases both the negative inspiratory thoracic pressure with breathing and the thoracoabdominal pressure gradient<sup>[6,7]</sup>. These biomechanical changes exacerbate esophageal motility disorders and impair the competency of the EGJ and upper esophageal sphincter<sup>[7,8]</sup>. Consequently, the frequency of reflux episodes increases, further amplifying the risk of recurrent microaspiration. This cycle perpetuates the worsening of pulmonary function and the progression of the underlying respiratory condition<sup>[5-7]</sup>.

Although GERD is highly prevalent in the general population, the prevalence of lung-related complications can be difficult to estimate<sup>[9]</sup>. Recent studies have shown that GERD as a risk factor for IPF may have been historically underestimated<sup>[10,11]</sup>. Baqir *et al.*<sup>[10]</sup> conducted a population-based case-control study (113 IPF patients and 226 matched controls) and reported that the odds of having GERD were 1.78 times higher in patients with IPF than in controls. (odds ratio [OR]: 1.78; 95% confidence interval [CI]: 1.09-2.91,  $P = 0.02$ ). Similarly, Bédard *et al.*<sup>[11]</sup> performed a meta-analysis of 18 case-control studies (3,206 IPF patients and 9,368 controls), demonstrating a significant association between GERD and IPF (OR: 2.94 [95%CI: 1.95-4.42],  $P < 0.01$ ). These findings highlight the critical importance of early diagnosis and treatment of GERD - whether through pharmacological or surgical interventions - in patients with an established diagnosis of IPF, with the goal of halting or delaying the progressive nature of this condition. The aim of this article is to provide an overview of the evaluation and management of GERD in the context of advanced pulmonary disease, with a particular focus on IPF and minimally invasive procedures.

## ESOPHAGEAL FUNCTIONAL TESTING: WHEN AND WHY?

In the setting of chronic pulmonary diseases such as IPF, the clinical presentation of concomitant GERD is often silent or asymptomatic<sup>[5]</sup>. Several studies have shown that symptoms typically associated with GERD, such as heartburn, regurgitation, or dysphagia, are uncommon in patients with pulmonary fibrosis<sup>[5,9,12]</sup>. In fact, the prevalence of typical symptoms ranges from 25% to 65% in these patients. Furthermore, symptoms alone have a poor sensitivity and specificity for indicating pathological reflux (65% and 71%, respectively)



**Figure 1.** Mechanisms of chronic lung damage facilitated by GERD. Created in BioRender. Latorre, A. (2025) <https://BioRender.com/t31v415> GERD: gastroesophageal reflux disease.

compared to 24-h pH-monitoring studies<sup>[5,13,14]</sup>. Consequently, it is important to use esophageal functional tests (esophageal pH-monitoring [i.e., 24-h catheter-based or prolonged wireless capsule-based testing], high-resolution manometry [HRM], barium esophagram, or esophagogastroduodenoscopy [EGD]) to confirm the presence or absence of GERD, as well as to guide surgical decision making and tailor antireflux procedures. It could be argued that pH testing, regardless of the platform used, is appropriate for all patients with a diagnosis of pulmonary fibrosis as such a high proportion of these patients will have objective evidence of GERD.

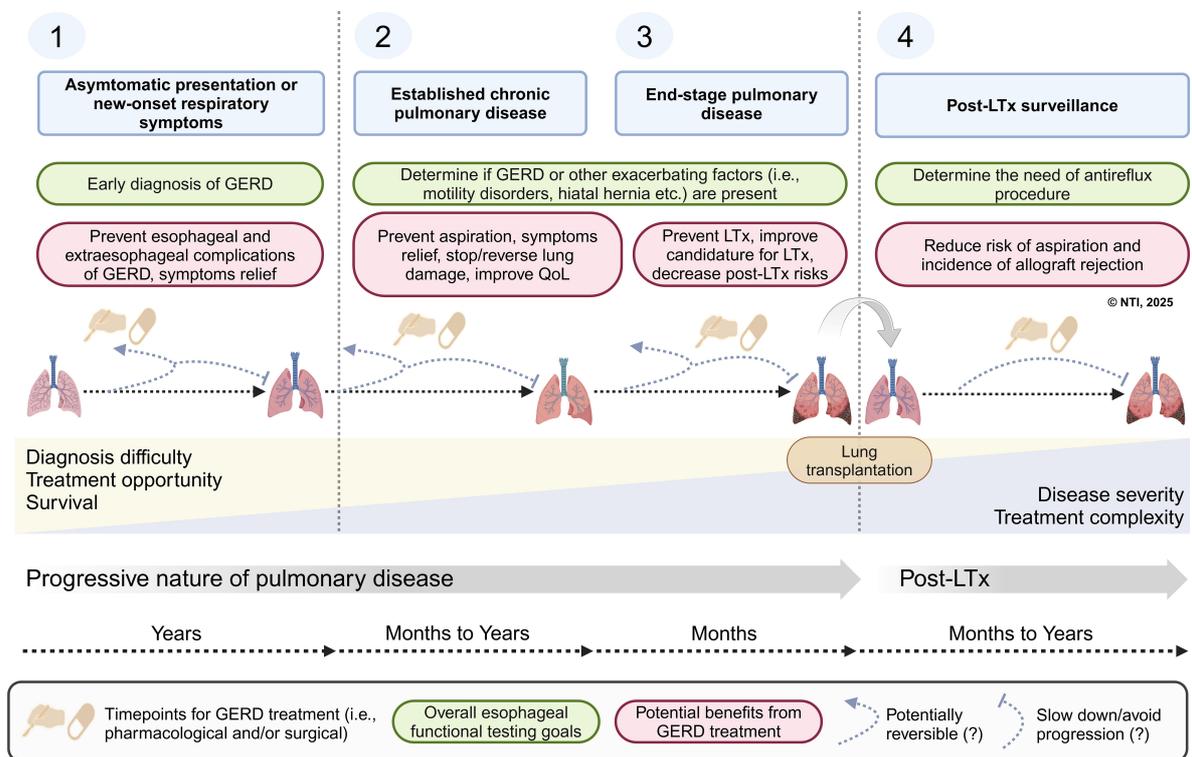
Importantly, the timing and objectives of esophageal functional testing are closely tied to the progressive nature (i.e., stage) of the underlying pulmonary condition. Esophageal functional testing may be performed in four distinct clinical scenarios: *i*) patients with new-onset respiratory symptoms; *ii*) patients with established chronic lung diseases; *iii*) patients with end-stage lung disease who are candidates for lung transplantation (LTx); and *iv*) lung transplant recipients [Figure 2].

### New-onset respiratory symptoms

The primary goal at this stage is to determine early if GERD may be an underlying cause of respiratory symptoms or a potential contributor to the development of a new lung disease, such as IPF<sup>[15,16]</sup>. Hence, the use of pH-monitoring along with impedance testing can provide reliable information to the clinician and may prompt consideration of early treatment alternatives for GERD to not only alleviate cardinal symptoms but also to prevent or monitor esophageal complications (e.g., erosive esophagitis, Barrett's esophagus)<sup>[17]</sup>.

### Established chronic lung diseases

In patients with a diagnosis of GERD-related chronic lung diseases (e.g., chronic cough, asthma, IPF) who have not undergone prior GERD evaluation, a complete esophageal functional workup (e.g., pH-monitoring, HRM, barium esophagram, and EGD) has multiple goals beyond confirming a diagnosis of



**Figure 2.** Role of esophageal functional testing and antireflux therapy along the natural history of chronic pulmonary diseases. Created in BioRender. Latorre, A. (2025) <https://BioRender.com/p04u114> GERD: gastroesophageal reflux disease; LTx: lung transplantation; QoL: quality of life.

GERD. These include ruling out micro- or silent aspiration, identifying motility disorders, and identifying other exacerbating factors such as a hiatal hernia that may be amenable to treatment. Of note, several studies over the last two decades have hypothesized that early detection and prompt treatment of these conditions may not only improve the patient's clinical condition and satisfaction, but may also delay the progression of the underlying respiratory disease<sup>[17-20]</sup>.

### Before lung transplantation

It is well documented that LTx candidates have a higher prevalence (i.e., 32-68%) of GERD than the general population, and furthermore, GERD is associated with worse lung allograft outcomes after transplantation (i.e., overall survival and incidence of graft rejection)<sup>[21-25]</sup>. Therefore, conducting esophageal functional testing in patients with end-stage lung disease who are LTx candidates is being gradually adopted as standard practice in lung transplant centers across the United States<sup>[26]</sup>. At this stage, the primary goal is to determine the candidate's suitability for LTx, as well as to establish a multidisciplinary plan for the management of GERD and associated motility disorders both before and after transplantation<sup>[17]</sup>.

### After lung transplantation

Studying and monitoring esophageal function after LTx is important for guiding surgical decision making, such as determining the need for antireflux procedures<sup>[17]</sup>. These measures aim to reduce the incidence or slow the progression of chronic lung allograft dysfunction (CLAD), which may result from recurrent silent aspiration<sup>[6,7,27-31]</sup>. Additional complementary tests at this stage, such as gastric emptying studies, can help identify patients presenting with delayed gastric emptying, which is also a common but treatable condition after LTx (prevalence up to 57%)<sup>[32]</sup>.

Of note, in the lung transplant setting, the underlying respiratory condition (i.e., restrictive *vs.* obstructive) differentially affects esophageal function<sup>[6]</sup>. Prior studies suggest that, before LTx, patients with restrictive disease typically show greater distal acid exposure and higher thoracoabdominal pressure gradients than those with obstructive disease<sup>[7]</sup>. On the other hand, after LTx, esophageal motility often improves regardless of the initial condition, reducing acid exposure. Importantly, severe motility disorders like aperistalsis are associated with worse outcomes and higher GERD prevalence, but recovery of peristalsis after LTx (reported in up to 65.5% of cases) can restore survival rates comparable to those of recipients with preserved motility before LTx<sup>[6,7,33]</sup>. These findings underscore the importance of evaluating esophageal function both before and after transplantation to guide candidate selection and post-LTx care.

## GERD TREATMENT IN ADVANCED PULMONARY DISEASE

### Pharmacological treatment

Acid suppression therapy (e.g., proton pump inhibitors [PPIs], histamine H<sub>2</sub>-receptor antagonist [H<sub>2</sub>RAs], and potassium-competitive acid blockers, as well as nitrates and calcium channel blockers) in conjunction with lifestyle interventions (e.g., weight loss, anti-refluxogenic diet) are usually considered the cornerstone of GERD treatment<sup>[34]</sup>. PPIs (e.g., omeprazole, lansoprazole, pantoprazole, esomeprazole, dexlansoprazole) are the most commonly prescribed pharmacological agents, as they effectively reduce acid secretion and the pH of gastric contents (due to irreversible binding to the gastric H<sup>+</sup>/K<sup>+</sup> ATPase proton pump) while alleviating typical GERD symptoms in most cases<sup>[34-37]</sup>. PPI therapy has success rates that range from 56% to 76% for symptom relief and from 80% to 85% for esophageal mucosal healing<sup>[38]</sup>. However, some patients, particularly those presenting with severe esophagitis or extraesophageal symptoms, may require higher acid control, which can often be achieved by increasing to twice-daily PPI therapy<sup>[38,39]</sup>.

Potential mechanisms by which PPIs may improve respiratory symptoms and pulmonary function extend beyond increasing the pH of refluxate<sup>[40]</sup>. Some preclinical studies have shown that PPIs are anti-inflammatory as they downregulate the expression of proinflammatory chemokines (i.e., TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8), suppress neutrophil migration, and reduce apoptosis of pneumocytes; together, these findings support the potential role of PPIs as an antifibrotic adjuvant pharmacological group<sup>[40,41]</sup>. Nevertheless, to date, only a limited number of clinical studies have specifically explored the benefits of PPI therapy in IPF, with conflicting results<sup>[5,42]</sup>.

The 2006 case series by Raghu *et al.*<sup>[43]</sup> was perhaps the opening for this discussion. The authors reported the case of 4 newly diagnosed IPF patients with increased acid exposure, 3 treated with PPIs and conservative measures, and 1 with PPIs and fundoplication. Pulmonary function was monitored for 2 to 6 years, showing stabilization of predicted forced vital capacity (FVC) and carbon monoxide diffusion capacity (DL<sub>CO</sub>) during periods of adequate adherence, while slight declines in pulmonary function were observed during non-compliance periods<sup>[43]</sup>.

More recently, Khor *et al.*<sup>[42]</sup> conducted a well-designed meta-analysis that provided a comprehensive overview of the current evidence. The analysis included 15 studies - 9 observational studies, 4 post-hoc analyses of randomized clinical trials, 1 randomized clinical trial, and 1 case series. Among these, 11 studies assessed the use of PPIs and/or H<sub>2</sub>RAs, whereas 4 focused only on PPIs<sup>[42]</sup>. The authors found that antacid use in patients with IPF had no statistically significant impact on disease progression, defined as a  $\geq 10\%$  decline in FVC, a reduced 6-min walking distance, or death (2 studies, risk ratio [RR]: 0.88 [95% CI: 0.76-1.03]). Similarly, no significant effects were observed on 1-year mortality (3 studies, RR: 1.27 [95% CI: 0.64-2.55],  $P = 0.68$ ) or fewer exacerbations (2 studies, RR: 0.96 [95% CI: 0.27-3.36]) or hospitalizations within 30 weeks to 1 year (RR: 0.91 [95% CI: 0.56-1.46],  $P = 0.69$ ). However, serious adverse events, particularly

pulmonary infections, were more frequent among patients receiving antacid therapy over the midterm (i.e., 1-year follow-up)<sup>[42,44-46]</sup>.

The use of H2RAs (e.g., cimetidine, ranitidine, famotidine, roxatidine) in patients who cannot tolerate PPIs is widely accepted, despite their relatively lower pharmacological potency, tachyphylaxis, and overall efficacy (i.e., PPIs vs. H2RAs: 68% vs. 45%; RR: 0.66 [95%CI: 0.60-0.73],  $P < 0.01$ )<sup>[47]</sup>. However, H2RAs may offer an advantage of fewer long-term adverse effects than PPIs<sup>[48]</sup>. The primary role of H2RAs in advanced lung disease may lie as an adjunct therapy to reduce nocturnal acid breakthrough and related symptoms<sup>[38,39,48,49]</sup>. A retrospective observational study by Rackoff *et al.*<sup>[39]</sup> demonstrated that adding H2RAs (i.e., ranitidine 300 mg or famotidine 40 mg) to PPI-based therapy for 56 GERD patients - including 17 with predominantly atypical symptoms, such as chronic cough - alleviated nocturnal symptoms in ~ 74% of cases. Nonetheless, there is controversy regarding the potential to develop a tolerance to H2RAs with chronic use<sup>[39,49,50]</sup>.

Other complementary options include alginate-based therapies, which create a physical barrier to prevent reflux, and prokinetic agents (i.e., metoclopramide), which aim to improve esophageal peristalsis, increase lower esophageal sphincter pressure, and accelerate gastric emptying<sup>[50-52]</sup>. A meta-analysis by Leiman *et al.*<sup>[53]</sup> including 14 randomized controlled trials found that alginate therapies significantly increased the odds of resolving patient-reported GERD symptoms compared to placebo or antacids (OR: 4.42 [95%CI: 2.45-7.97],  $P < 0.01$ ). Similarly, a meta-analysis by Xi *et al.*<sup>[54]</sup> on the combination of PPIs with prokinetics showed that although adding prokinetics did not improve endoscopic findings (RR: 0.996 [95%CI: 0.929-1.068],  $P = 0.92$ ), it marginally improved symptom relief compared to PPI monotherapy (RR: 1.185 [95%CI: 1.042-1.348],  $P = 0.01$ ). Notably, although prokinetics are less frequently used due to limited efficacy and potential adverse effects (e.g., nausea, vomiting, extrapyramidal symptoms)<sup>[55]</sup>, they may be particularly relevant for patients with IPF, as antifibrotic treatments like pirfenidone have been associated with delayed gastric emptying in preclinical studies<sup>[56,57]</sup>.

The strategy of increasing gastric pH by reducing gastric acid production to relieve symptoms and prevent complications is beneficial for patients presenting with typical GERD symptoms (e.g., heartburn, regurgitation) and esophageal complications (e.g., erosive esophagitis)<sup>[34]</sup>. However, in the context of GERD-related respiratory disorders, acid suppression therapy (particularly PPIs) may be appropriate only for patients with a low risk of aspiration (e.g., individuals without evidence of aspiration on fluoroscopic swallow studies, with preserved esophageal motility, predominantly mild upright acid exposure, and no history of nocturnal choking), as it may improve GERD-related symptoms but not pulmonary function. Indeed, the most recent international clinical practice guidelines for IPF management (2022)<sup>[58]</sup> concluded that available evidence was predominantly indirect and low quality. Thus, a conditional recommendation was issued against the routine use of antacid therapy (i.e., PPIs and/or H2RAs) solely for pulmonary function improvement in patients with IPF. However, for patients with confirmed GERD, the guidelines suggest that antacid therapy remains appropriate for managing GERD-related symptoms<sup>[58]</sup>.

In our opinion, the quagmire around pharmacological treatments may stem from the inability of current options to fully prevent the backward flow of refluxate through the EGJ or reduce the risk of recurrent aspiration. Consequently, additional therapeutic measures, including mechanical reflux control, may be necessary for effective GERD treatment in patients with advanced pulmonary disease.

## Surgical treatment

Classically, the term laparoscopic antireflux surgery (LARS) has been used by the medical community to refer to fundoplication (i.e., total or partial) with or without hiatal hernia repair. However, over the last few decades, other minimally invasive techniques involving surgical and/or endoscopic approaches and technologies have emerged as part of the therapeutic arsenal for GERD. Therefore, a broader term such as *antireflux procedures* may be more appropriate to refer to the entire spectrum of procedures (i.e., fundoplication, magnetic sphincter augmentation (MSA), transoral incisionless fundoplication [TIF], radiofrequency ablation [RFA], antireflux mucosectomy [ARMS], electric stimulation therapy (i.e., EndoStim), and Roux-en-Y gastric bypass [RYGB]). [Table 1](#) summarizes the available minimally invasive surgical and endoscopic treatment options for GERD.

Briefly, LARS (i.e., conventional laparoscopic or robotic-assisted laparoscopic) is still considered the gold standard for surgical treatment of GERD due to its efficacy in preventing pathological acid exposure and resolving associated symptoms, with a success rate of 90% within 5 years and 75% to 80.4% at 20 years<sup>[59,60]</sup>. Therefore, as expected, most emerging evidence regarding antireflux procedures in patients with advanced pulmonary conditions, as well as LTx candidates and recipients, are focused on LARS (i.e., particularly Nissen fundoplication)<sup>[5,42]</sup>.

The rationale for performing LARS in patients with respiratory disease and GERD may have originated from a seminal study summarizing early experiences in post-LTx GERD treatment by the Duke University group. In 2004, Cantu *et al.*<sup>[27]</sup> reported the results of a retrospective analysis involving 457 LTx recipients, of whom 127 were diagnosed with post-LTx GERD. Among these, 76 patients ultimately underwent post-LTx fundoplication, including 14 who underwent early fundoplication (i.e., within 90 days after transplant), achieving a 100% survival rate at both 1 and 3 years. In contrast, patients with reflux who did not receive surgical intervention had survival rates of 92% and 76% at 1 and 3 years, respectively ( $P < 0.02$ ). Furthermore, those who underwent early fundoplication had better CLAD-free survival compared to those who did not undergo fundoplication (1 year: 100% vs. 96%; 3 years: 100% vs. 60%,  $P < 0.01$ ). This opened an exciting avenue to understand non-alloimmune-mediated lung allograft injury mechanisms and to explore the role of LARS in preventing such complications, a concept that was later extended to the pre-LTx setting.

In 2006, Linden *et al.*<sup>[61]</sup> published the first “large” single-center experience on the use of LARS in patients with end-stage respiratory diseases on the LTx waitlist. This study investigated the role of fundoplication among 19 such patients, including 14 with IPF, 3 with chronic obstructive pulmonary disease, 1 with cystic fibrosis, and 1 with Kartagener syndrome. Among these patients, 15 underwent laparoscopic Nissen fundoplication, 3 underwent laparoscopic Collis-Nissen fundoplication, and 1 underwent laparoscopic Toupet fundoplication. The authors compared changes in oxygen requirements, 6-min walk distance, predicted FVC, forced expiratory volume in 1 s (FEV<sub>1</sub>), and DL<sub>CO</sub> before and after LTx. They found that waitlisted IPF patients who underwent fundoplication had stable oxygen requirements, whereas those who did not undergo fundoplication experienced a statistically significant worsening of oxygen requirements. Hence, the authors suggested that LARS may stabilize or slow the progression of lung disease, help prevent aspiration in the peritransplant period, and provide early protection against the detrimental effects of reflux on the transplanted lung.

Since then, additional studies evaluating LARS in patients with IPF have been published, including 2 retrospective observational studies and 1 randomized controlled trial<sup>[14,20,62]</sup>. Notably, all of these studies were included in a well-conducted meta-analysis by Khor *et al.*<sup>[42]</sup> and considered during the development of the latest international clinical practice guidelines for IPF management<sup>[58]</sup>. Their findings, in terms of efficacy

**Table 1. Minimally invasive surgical and endoscopic treatment options for gastroesophageal reflux disease**

Surgical procedures	Endoscopic procedures
Laparoscopic fundoplication	Transoral incisionless fundoplication*
Total fundoplication (i.e., Nissen)	Radiofrequency ablation (e.g., Stretta)
Partial fundoplication (e.g., Dor, Toupet)	Antireflux mucosectomy
Magnetic sphincter augmentation (i.e., LINX)	
Electrical stimulation therapy (i.e., EndoStim)	
Roux-en-Y gastric bypass**	

\*Hybrid if concomitant laparoscopic crural repair is performed simultaneously (i.e., c-TIF). \*\*A viable option in patients with obesity or as a salvage procedure when other alternatives (e.g., fundoplication) failed. TIF: transoral incisionless fundoplication.

(e.g., disease progression, pulmonary function, mortality, and respiratory disease-related exacerbations and hospitalizations) and safety (e.g., perioperative morbidity), are discussed later in this manuscript. Table 2 summarizes the study design and relevant findings from studies assessing the role of LARS in patients with IPF.

In regards to the newly adopted antireflux procedures, varying degrees of effectiveness for managing GERD in the general population have been reported [62-66]. Although MSA and radiofrequency ablation therapy have not been studied as pre-LTx interventions for GERD, they are the only non-LARS GERD procedures explored in the post-LTx setting [67,68]. Data on other hybrid or endoscopic minimally invasive procedures, such as TIF with or without crural repair (c-TIF), ARMS, or electrical stimulation therapy, are lacking in patients with advanced pulmonary diseases.

Halpern *et al.* [67] reported a single-center retrospective study comparing the safety of MSA in 17 LTx recipients with GERD to a matched control group who underwent laparoscopic fundoplication. The authors found no significant differences between groups in pulmonary function changes (FEV<sub>1</sub>), 1-year overall survival ( $P = 0.38$ ), allograft rejection-free survival ( $P = 0.34$ ), or reoperation-free survival ( $P = 0.33$ ). However, MSA was associated with a higher incidence of early postoperative complications within the first year (70.6% vs. 47.1%,  $P = 0.02$ ), most of which were considered minor (i.e., new-onset dysphagia, vomiting, or return of GERD symptoms). An additional technical consideration regarding the use of MSA among patients with advanced lung disease is the potential restriction for undergoing magnetic resonance imaging on a > 1.5T device [69].

Similarly, Kolbeinsson *et al.* [68] reported the use of RFA (i.e., Stretta, Mederi Therapeutics, Inc.) in 11 LTx recipients with GERD, with a median follow-up time of 11 months after LTx. Pulmonary function was monitored until death, the need for surgical intervention (i.e., LARS), or the end of the study period. No procedure-related complications were reported. Post-RFA evaluation was completed in 10 of 11 patients; 7 showed a decrease in DeMeester score compared to baseline, and 8 exhibited reflux on a barium esophagram 3 months after RFA. Before RFA, the median predicted FEV<sub>1</sub> was 84% (range: 41%-97%), decreasing to 71% (range: 23%-108%) at a median of 1-year post-RFA. Notably, at the last follow-up or prior to subsequent LARS, 4 patients had developed CLAD, and 1 had died from CLAD, which the authors attributed to poor medical compliance. At a median of 11 months after RFA, 7 of the 11 patients underwent Toupet fundoplication due to persistent reflux. Overall, these results raise several concerns about the efficacy of RFA for GERD treatment after LTx. Indeed, the authors recommended against its use; moreover, the use of this procedure has decreased over time, and it is not available worldwide [68].

**Table 2. Summary of studies reporting the use of antireflux surgery (i.e., fundoplication) for treatment of gastroesophageal reflux disease among patients with idiopathic pulmonary fibrosis**

Author (year)	Design	Intervention group	Comparison group	Summary of results
Raghu <i>et al.</i> (2006) <sup>[43]</sup>	Case series	3 Patients with IPF and GERD receiving PPI therapy + conservative measures and 1 patient PPI + Nissen fundoplication	N/A	The patient who underwent LARS presented an initial pulmonary function improvement within 2 years (predicted FVC: from 74% to 101%); nevertheless, it slowly decreased (last f/u at 6 years, predicted FVC: 73%)
Linden <i>et al.</i> (2006) <sup>[6]</sup>	Retrospective cohort study	From 145 LTx candidates, 14 patients with IPF underwent laparoscopic fundoplication (i.e., multiple types) for GERD treatment	31 patients with IPF without GERD	Follow-up intervals ranged from 1-65 months in the control group and 1-23 months in the LARS group. LARS patients showed a reduction in median O <sub>2</sub> requirement (3 to 2.5 L/min), while controls had an increase (2 to 3 L/min) ( $P = 0.002$ ). FVC, FEV <sub>1</sub> , and DL <sub>CO</sub> remained similar regardless of the intervention. In addition, LARS patients showed a trend toward stable 6-min walk distances (1832 to 1241.5 ft), whereas controls exhibited a decline (1324.5 to 989 ft)
Lee <i>et al.</i> (2011) <sup>[14]</sup>	Retrospective cohort study	204 patients with IPF. 11 of these patients underwent laparoscopic Nissen fundoplication for GERD treatment	Remaining 193 IPF patients with or without PPI therapy	Median survival time estimates based on the presence or absence of a history of Nissen fundoplication were higher for those with a history of Nissen fundoplication than those without (2,252 vs. 1,019 days, HR: 0.29, [95%CI: 0.09-0.92], $P = 0.04$ ); however, in an adjusted analysis, LARS was not related to longer survival (HR: 0.74 [95%CI: 0.21-2.59], $P = 0.64$ )
Raghu <i>et al.</i> (2016) <sup>[62]</sup>	Retrospective longitudinal study	27 patients with IPF and GERD who underwent laparoscopic fundoplication	N/A	The authors estimated a benefit of LARS in predicted FVC over 1 year of 5.7% (95%CI: -0.9 to 12.2%, $P = 0.088$ ) along with successful control of GERD (mean DeMeester scores decreased from 42 to 4, $P < 0.01$ )
Raghu <i>et al.</i> (2018) <sup>[20]</sup>	Phase 2, multicenter, randomized controlled trial	29 patients with IPF and GERD underwent 360° floppy Nissen fundoplication	29 patients with IPF and GERD treated with conservative measures and antacid therapy (PPI and H2RAs)	An intention-to-treat analysis, adjusted for baseline antifibrotic use, indicated a slight trend toward FVC stabilization over 48 weeks in LARS patients (-0.05 L [95%CI: -0.15 to 0.05]) compared to those receiving pharmacological therapy (-0.13 L [95%CI: -0.23 to -0.02], $P = 0.28$ ). Likewise, while acute exacerbations, respiratory-related hospitalizations, and mortality were less frequent in the surgery group, these differences did not reach statistical significance

DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s; GERD: gastroesophageal reflux disease; H2RAs: histamine-2 receptor antagonists; IPF: idiopathic pulmonary fibrosis; LARS: antireflux surgery; LTx: lung transplant; PPI: proton pump inhibitor; N/A: not applicable

Lastly, while RYGB is widely used for obesity and as a salvage therapy for GERD, its role in managing GERD in patients with advanced pulmonary disease remains unclear. However, in 2019, Ardila-Gatas *et al.*<sup>[70]</sup> reported the outcomes of 25 patients with obesity and end-stage interstitial lung disease who underwent bariatric surgery, including 17 RYGB cases. One year after surgery, pulmonary function significantly improved (median FVC: 62% to 74%,  $P = 0.003$ ; DL<sub>CO</sub>: 53% to 66%,  $P = 0.003$ ). Among 7 potential LTx candidates, 6 became eligible after weight loss, and 1 successfully underwent LTx 88 months later. Notably, there were no mortalities at 1 year among the 17 RYGB cases, though 4 patients experienced 30-day complications, and 1 required reoperation. Therefore, it could be argued that RYGB, if performed as an antireflux procedure, may have a similar safety profile in this medically complex population and may provide some degree of improvement in pulmonary function.

## EFFICACY OF LARS IN ADVANCED PULMONARY DISEASE

Since LARS efficacy is well established for controlling distal esophageal exposure, our review focuses on its efficacy regarding pulmonary function and respiratory symptoms<sup>[59,60]</sup>. The retrospective cohort study by Linden *et al.*<sup>[61]</sup> reported that patients who underwent laparoscopic Nissen fundoplication ( $n = 14$ )

had a slight but statistically significant reduction in median oxygen requirements compared to those who did not undergo fundoplication ( $n = 31$ ) (3 to 2.5 L/min vs. 2 to 3 L/min,  $P = 0.002$ ). Moreover, predicted FVC (57.5% to 54% vs. 56.5% to 63%,  $P = 0.881$ ), FEV<sub>1</sub> (62% to 56% vs. 59.5% to 62%,  $P = 0.973$ ), and DL<sub>CO</sub> (36% to 35% vs. 30.5% to 26.5%,  $P = 0.973$ ) remained stable regardless of the intervention during an overall median follow-up of 6.8 to 12.7 months. Additionally, patients who underwent LARS showed a trend toward maintaining stable 6-min walk distances, whereas controls exhibited a decline in distance (1,832 to 1,241.5 ft vs. 1,324.5 to 989 ft,  $P = 0.664$ ) at a median follow-up of 7.1 months.

Lee *et al.*<sup>[14]</sup> reported the results of a retrospective study including 204 patients with interstitial lung disease from two high-volume centers. Of these, 11 patients received a Nissen fundoplication for the treatment of GERD. The primary outcome was mortality, and the authors reported that LARS was a predictor of greater survival (HR: 0.29, [95%CI: 0.09-0.92],  $P = 0.04$ ); nevertheless, in an adjusted analysis, LARS was no longer a significant predictor of longer survival times (HR: 0.74, [95%CI: 0.21-2.59],  $P = 0.64$ ).

Furthermore, Raghu *et al.*<sup>[62]</sup> initially reported the results of a single-center, retrospective longitudinal study that included 27 patients with IPF who underwent LARS, and the primary endpoint was the change in predicted FVC over 1 year. The authors observed a trend toward benefit, with a mean increase in predicted FVC of 5.7% (95%CI: -0.9 to 12.2%,  $P = 0.088$ ). Two years later, Raghu *et al.*<sup>[20]</sup> reported the results of the WRAP-IPF trial, a multicenter, randomized controlled trial. A total of 58 patients with IPF were assigned to either LARS ( $n = 29$ , floppy Nissen) or medical therapy ( $n = 29$ , PPI and H<sub>2</sub>RAs) and followed for 48 weeks. The adjusted rate of change in FVC over 48 weeks was -0.05 L (95% CI -0.15 to 0.05) in the surgery group and -0.13 L (95%CI: -0.23 to -0.02) in the medical therapy group ( $P = 0.28$ ). Acute exacerbations of respiratory disease (3% vs. 16%,  $P = 0.19$ ), respiratory-related hospitalizations (7% vs. 21%,  $P = 0.25$ ), and death (3% vs. 18%,  $P = 0.13$ ) occurred less frequently in the surgery group, though these differences were not statistically significant. Despite some concerns regarding the randomization process (e.g., the inclusion of only patients with late-stage IPF and baseline demographic imbalances between the groups), unpowered analysis (i.e., likely due to small sample size), and the selection of reported results (i.e., from multiple eligible outcome measures), the WRAP-IPF trial provides some optimism regarding the protective role of LARS in patients with advanced pulmonary disease.

In summary, although available evidence shows trends indicating a slight benefit from LARS in patients with IPF, the overall experience is limited to Nissen fundoplication, the reported confidence in these effects is low, and the risk of bias is substantial<sup>[14,20,58,61,62]</sup>. This ultimately aligns with the recommendation made in the 2022 international IPF clinical practice guidelines<sup>[58]</sup>, which conditionally advise against referring patients with IPF for LARS solely for improving pulmonary function and related outcomes.

## SAFETY OF LARS IN ADVANCED PULMONARY DISEASE

There is concern that a general anesthetic and a surgical procedure could result in an exacerbation of pulmonary disease (e.g., an IPF exacerbation), which could potentially require intubation and lead to death. In the study conducted by Linden *et al.*<sup>[61]</sup>, 19 patients with advanced pulmonary disease underwent antireflux surgery: 15 underwent laparoscopic Nissen fundoplication, 3 underwent Collis-Nissen fundoplication, and 1 underwent Toupet fundoplication. The mean hospital stay was 3.5 days (range: 2-6). One patient required conversion to an open approach due to gastric perforation. Postoperative complications occurred in 5 patients (26.3%), including 3 cases of wound infection, 1 case of transient gastric dilation, and 1 case of nausea.

The initial study by Raghu *et al.*<sup>[62]</sup>, which included 27 IPF patients who underwent Nissen fundoplication, reported a mean hospital stay of 2 days (range: 1-6 days) with no intraoperative complications. However, within 30 days, 2 patients (7.4%) developed new-onset dysphagia requiring dilation, 1 patient (3.7%) experienced nausea, and 1 patient (3.7%) had urinary retention. Additionally, 2 patients (7.4%) required reoperation during the follow-up period. Similarly, in the WRAP-IPF trial, no major intraoperative complications were reported among patients undergoing Nissen fundoplication; nevertheless, 2 (6.8%) of 29 patients experienced postoperative complications, including dehydration and respiratory failure due to metabolic acidosis<sup>[20]</sup>. Thus, it appears that major pulmonary exacerbations after antireflux surgery may be an exaggerated phenomenon; however, out of an abundance of caution, lung transplant candidacy should be ascertained prior to surgery when there is a potential for lung transplant in case the patient needs to be urgently listed.

Together, the incipient evidence indicates that LARS remains a feasible and safe option in patients with advanced pulmonary disease<sup>[20,42,61,62]</sup>. When performed by experienced multidisciplinary teams, the procedure demonstrates acceptable risk levels and postoperative morbidity rates comparable to those observed in GERD patients from the general population<sup>[71]</sup>. In our opinion, the primary concerns regarding the safety of LARS in highly comorbid patients are anesthesia-related risks and potential pulmonary complications (e.g., pneumothorax, worsened hypoxia). However, these perioperative risks can be further reduced through a comprehensive, multidisciplinary preoperative assessment that includes postoperative pulmonary complication risk quantification and targeted preoperative optimization strategies<sup>[72]</sup>.

## CONCLUSIONS

Growing evidence supports plausible pathophysiological mechanisms linking GERD and respiratory diseases, although determining the strength and nature of this association remains challenging due to the multifactorial nature of both conditions. Notably, the growing understanding of how reflux contributes to the progression of chronic pulmonary diseases, such as IPF, has led to an ongoing discussion on how to improve patient management strategies. Routine acid suppression therapy alone does not seem to provide additional benefits for pulmonary function or respiratory symptoms in IPF patients without typical GERD symptoms. On the other hand, LARS effectively controls reflux and has an acceptable safety profile, even in patients with end-stage lung disease; nevertheless, its role in stabilizing pulmonary function is polemic, and current evidence does not support its routine use. In the meantime, LARS may be best reserved for carefully selected patients, particularly those with typical GERD symptoms and those at high risk of aspiration. Additionally, RYGB appears to be a safe option for obesity management in patients with advanced pulmonary disease, offering some degree of pulmonary function stabilization; hence, its use as a salvage therapy for GERD in obese patients may be reasonable. Other minimally invasive antireflux procedures, such as MSA or c-TIF, warrant further investigation in patients with advanced pulmonary disease, as their use remains very limited in this population.

## DECLARATIONS

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