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ASSOCIATION BETWEEN GASTROESOPHAGEAL REFLUX AND THE PROGRESSION OF IDIOPATHIC PULMONARY FIBROSIS: SYSTEMATIC REVIEW

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ABSTRACT

Background: *Gastroesophageal reflux (GER) is one of the most prevalent comorbid conditions in idiopathic pulmonary fibrosis (IPF), detected in up to 87-94% of patients using objective ambulatory pH-impedance monitoring, yet frequently clinically occult. Chronic microaspiration of gastric refluxate—containing acid, pepsin, bile acids, and trypsin—has been proposed as a recurrent injurious stimulus to the vulnerable aged alveolar epithelium, potentially accelerating fibrogenesis and worsening disease trajectory.*

Methods: *The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible primary studies included RCTs, cohort studies (prospective and retrospective), case-control studies, cross-sectional studies, and other observational designs. Systematic reviews and meta-analyses were excluded from the characteristic tables but considered in outcome analysis and discussion. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies and Cochrane RoB 2.0 for RCTs. The review was conducted per PRISMA 2020 guidelines.*

Results: *Twenty-five primary studies involving >45,000 patients across multiple countries were included. GER prevalence in IPF was 39-87% by objective testing and 45-56% in clinical registry populations. Mendelian randomization confirmed a unidirectional causal association (GORD→IPF: OR 1.6, 95% CI 1.04-2.49; p=0.032). BALF bile acid and pepsin levels correlated strongly with HRCT fibrosis scores (r^2=0.567-0.63). Key clinical outcomes: (1) hiatal hernia independently predicted FVC decline and respiratory mortality (p<0.05); (2) novel impedance metrics (MNBI, PSPW index) independently predicted FVC and FEV_1 decline at 12 months (p<0.05); (3) GER medication use was associated with longer survival (adjusted HR 0.45, 95% CI 0.24-*

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0.84 for IPF-related mortality; low-quality evidence); (4) the WRAP-IPF RCT showed a trend favoring laparoscopic antireflux surgery (LARS) but did not reach statistical significance; (5) large population-based propensity-matched cohort studies found PPI and H2RA use associated with increased adverse outcomes, challenging earlier observational optimism; (6) cough severity—closely linked to GER—was independently associated with disease progression and impaired quality of life.

***Conclusion**: GER is a biologically plausible and causally supported contributor to IPF pathogenesis. However, the 2022 ATS/ERS/JRS/ALAT guidelines issued conditional recommendations against routine antacid medication and antireflux surgery for IPF, reflecting insufficient and conflicting prospective evidence. Well-powered RCTs with objective GER phenotyping are urgently needed. Non-acid reflux components remain incompletely addressed by current pharmacological strategies and warrant targeted investigation.*

***Keywords**: Idiopathic pulmonary fibrosis; gastroesophageal reflux disease; microaspiration; proton pump inhibitors; anti-reflux surgery; lung function decline; alveolar epithelial injury; WRAP-IPF; impedance-pH monitoring; hiatus hernia; systematic review*

INTRODUCTION

Background and Epidemiology

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown etiology, characterized by a histopathological and/or radiologic pattern of usual interstitial pneumonia (UIP), occurring predominantly in adults aged >60 years. Despite the availability of two approved antifibrotic agents—pirfenidone and nintedanib—that slow but do not halt disease progression, median survival from diagnosis remains 3–5 years, making IPF one of the most lethal pulmonary conditions. Global incidence estimates range from 3–9 cases per 100,000 person-years in Europe and North America, with rising secular trends attributable to increased diagnostic awareness and an aging global population.[1,2]

Gastroesophageal reflux (GER), defined as the pathological retrograde movement of gastric contents into the esophagus and potentially the proximal airway, is recognized as one of the most frequently encountered comorbidities in IPF. The landmark prospective study by Raghu et al. (2006) demonstrated abnormal acid GER in 87% of 65 consecutive IPF patients using 24-hour ambulatory esophageal pH monitoring—the then gold standard—with proximal esophageal acid exposure detected in 63% and distal acid exposure in 76% of cases. Critically, only 47% of affected patients reported classic GER symptoms, establishing the concept of clinically silent reflux in IPF as a major diagnostic challenge.[3]

In the IPF-PRO Registry—a large prospective US observational registry of 1,002 patients with IPF—gastroesophageal reflux disease (GERD) was the most commonly reported comorbidity at enrollment, affecting 56.2% of patients, exceeding coronary artery disease (29.8%), obstructive sleep apnea (27.8%), and diabetes mellitus (20.5%). These figures likely underestimate the true prevalence given the reliance on self-reported symptomatic diagnosis in registry settings.[4]

Pathophysiological Rationale

The biological link between GER and IPF progression centers on the hypothesis that chronic microaspiration of gastric refluxate—a complex mixture of hydrochloric acid, pepsin, bile acids, and activated pancreatic enzymes—causes repetitive subclinical alveolar epithelial injury. In the aging, genetically susceptible lung of IPF patients, these repeated microinjuries exceed the regenerative capacity of alveolar type II (AT2) pneumocytes, triggering aberrant wound healing cascades characterized by fibroblast activation, myofibroblast differentiation, and excessive extracellular matrix deposition. Savarino et al. provided direct molecular evidence of this mechanism, detecting bile acids in 62% and pepsin in 67% of IPF patients' bronchoalveolar lavage fluid (BALF), with concentrations correlating significantly with HRCT fibrosis scores (r^2=0.567–0.63).[5]

Chen et al. established animal-model evidence that weekly intratracheal instillation of bile acids in rats induced progressive pulmonary fibrosis histologically, with upregulation of fibrogenic mediators including TGF-ß1, CTGF, bFGF, VEGF, and periostin, and activation of the TGF-ß1/Smad3 signaling pathway and farnesoid X receptor (FXR)—providing a mechanistic substrate for microaspiration-driven fibrogenesis.[6]

Research Gap and Justification

Despite compelling biological plausibility and consistent epidemiological associations, substantial controversy persists regarding: (1) whether GER is a causal driver of IPF or merely a shared comorbidity or mechanical consequence; (2) which components of refluxate (acid versus non-acid/weakly acidic) are most pathogenically relevant; (3) whether pharmacological or surgical GER suppression confers meaningful pulmonary benefits; and (4) why large population-based propensity-matched cohort studies have recently reported potential harm from anti-acid pharmacotherapy. The 2022 ATS/ERS/JRS/ALAT Clinical Practice Guidelines represent a pivotal reversal—from conditional recommendation for to conditional recommendation against antacid therapy in IPF—underscoring the critical need for high-quality prospective evidence.[7,8]

Objectives

This systematic review aimed to:

- Characterize the epidemiology and diagnostic patterns of GER in IPF patients
- Elucidate the pathophysiologic mechanisms linking GER to alveolar injury and fibrogenesis
- Synthesize primary study evidence on GER-associated clinical outcomes in IPF, including pulmonary function decline, acute exacerbations, mortality, HRQoL, and cough
- Critically appraise the efficacy and safety of pharmacological and surgical GER interventions in IPF
- Identify methodological gaps and propose future research directions

Hypothesis and Novelty

We hypothesize that GER—particularly non-acid and proximal reflux—constitutes a significant, partially modifiable contributor to IPF progression through chronic microaspiration-mediated alveolar epithelial injury. This review is novel in: (1) incorporating the most recent large population-based propensity-matched cohort evidence that challenges earlier retrospective optimism; (2) synthesizing evidence from the WRAP-IPF randomized controlled trial and its implications; (3) integrating novel impedance-pH diagnostic metrics as prognostic tools; and (4) appraising the updated 2022 international guideline recommendations in the context of the full primary study evidence base.

METHODS

Review Design and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol was designed a priori with pre-specified eligibility criteria, search strategy, outcome domains, and quality assessment instruments.

Eligibility Criteria

Inclusion Criteria

- Study designs: Randomized controlled trials (RCTs), prospective cohort studies, retrospective cohort studies, case-control studies, cross-sectional studies, and primary observational studies of any design
- Population: Adults (≥18 years) with a confirmed diagnosis of IPF per contemporaneous ATS/ERS/JRS/ALAT diagnostic criteria (2000, 2011, 2018, or 2022 guidelines)
- Exposure: Any measure of gastroesophageal reflux (symptomatic, pH-monitoring-confirmed, impedance-pH-confirmed, BALF biomarker-confirmed) or any GER treatment (pharmacological or surgical)
- Outcomes: ≥1 of: FVC or DLCO change, composite disease progression, acute exacerbations, all-cause or IPF-related mortality, HRQoL, radiologic progression, cough, hospitalization, or GER prevalence/characterization
- Language: English

Exclusion Criteria

- Systematic reviews, meta-analyses, narrative reviews, editorials, letters to the editor (excluded from characteristic tables; considered in discussion only)
- Studies of non-IPF interstitial lung disease without extractable IPF-specific data
- Animal studies and in vitro experiments (considered in pathophysiology section only)
- Case reports with <3 patients
- Abstracts without available full text
- Duplicate datasets without additional information

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Idiopathic Pulmonary Fibrosis	IPF Patients	Interstitial Lung Disease
I (Intervention/Exposure)	Gastroesophageal Reflux	Microaspiration	Proton Pump Inhibitors
C (Comparison)	Antireflux Surgery	No Treatment	Placebo
O (Outcome)	Disease Progression	Lung Function Decline	Mortality

The Boolean MeSH keywords inputted on databases for this research are: *("Idiopathic Pulmonary Fibrosis" OR "IPF Patients" OR "Interstitial Lung Disease") AND ("Gastroesophageal Reflux" OR "Microaspiration" OR "Proton Pump Inhibitors") AND ("Antireflux Surgery" OR "No Treatment" OR "Placebo") AND ("Disease Progression" OR "Lung Function Decline" OR "Mortality")*

Study Selection

All retrieved records were imported into systematic review management software and deduplicated. Two independent reviewers (AR, RMF) conducted title/abstract screening followed by full-text review. Conflicts were resolved by consensus with adjudication by a third reviewer (FT) when necessary.

Data Extraction

Standardized data extraction forms captured: (1) study characteristics (first author, year, country, design, study period, follow-up duration, sample size); (2) patient demographics and baseline lung function; (3) GER diagnostic methodology; (4) treatment details; (5) all relevant outcome data including effect sizes, confidence intervals, and p-values.

Quality Assessment

Observational studies: Newcastle-Ottawa Scale (NOS; maximum 9 stars): ≥7 stars = low risk; 4–6 = moderate; <4 = high risk of bias.

RCTs: Cochrane Risk of Bias 2.0 (RoB 2.0) tool across five domains: randomization process, deviations from intended intervention, missing outcome data, outcome measurement, and selection of reported results.

Mendelian randomization studies: Evaluated per STROBE-MR reporting criteria including instrument strength (F-statistic), pleiotropy assessment, and sensitivity analyses.

Outcome Domains and Synthesis

Given heterogeneity in study designs, GER measurement methods, and outcome definitions, a narrative synthesis approach was employed. Outcomes were grouped into 12 predefined domains: (1) GER prevalence and characterization; (2) causal association (Mendelian randomization); (3) microaspiration biomarkers and HRCT correlation; (4) FVC decline; (5) DLCO decline; (6) acute exacerbations; (7) all-cause mortality; (8) IPF-related mortality; (9) hiatal hernia as GER proxy; (10) cough and HRQoL; (11) pharmacological GER treatment; (12) surgical GER treatment. The GRADE framework was applied to appraise overall evidence certainty for each domain.

Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Idiopathic Pulmonary Fibrosis" OR "IPF Patients" OR "Interstitial Lung Disease") AND ("Gastroesophageal Reflux" OR "Microaspiration" OR "Proton Pump Inhibitors") AND ("Antireflux Surgery" OR "No Treatment" OR "Placebo") AND ("Disease Progression" OR "Lung Function Decline" OR "Mortality")*	8
Google Scholar	*("Idiopathic Pulmonary Fibrosis" OR "IPF Patients" OR "Interstitial Lung Disease") AND ("Gastroesophageal Reflux" OR "Microaspiration" OR "Proton Pump Inhibitors") AND ("Antireflux Surgery" OR "No Treatment" OR "Placebo") AND ("Disease Progression" OR "Lung*	4,730

	Function Decline" OR "Mortality")	
Semantic Scholar	*("Idiopathic Pulmonary Fibrosis" OR "IPF Patients" OR "Interstitial Lung Disease") AND ("Gastroesophageal Reflux" OR "Microaspiration" OR "Proton Pump Inhibitors") AND ("Antireflux Surgery" OR "No Treatment" OR "Placebo") AND ("Disease Progression" OR "Lung Function Decline" OR "Mortality")*	51
Elsevier	*("Idiopathic Pulmonary Fibrosis" OR "IPF Patients" OR "Interstitial Lung Disease") AND ("Gastroesophageal Reflux" OR "Microaspiration" OR "Proton Pump Inhibitors") AND ("Antireflux Surgery" OR "No Treatment" OR "Placebo") AND ("Disease Progression" OR "Lung Function Decline" OR "Mortality")*	40
Cochrane	*("Idiopathic Pulmonary Fibrosis" OR "IPF Patients" OR "Interstitial Lung Disease") AND ("Gastroesophageal Reflux" OR "Microaspiration" OR "Proton Pump Inhibitors") AND ("Antireflux Surgery" OR "No Treatment" OR "Placebo") AND ("Disease Progression" OR "Lung Function Decline" OR "Mortality")*	15

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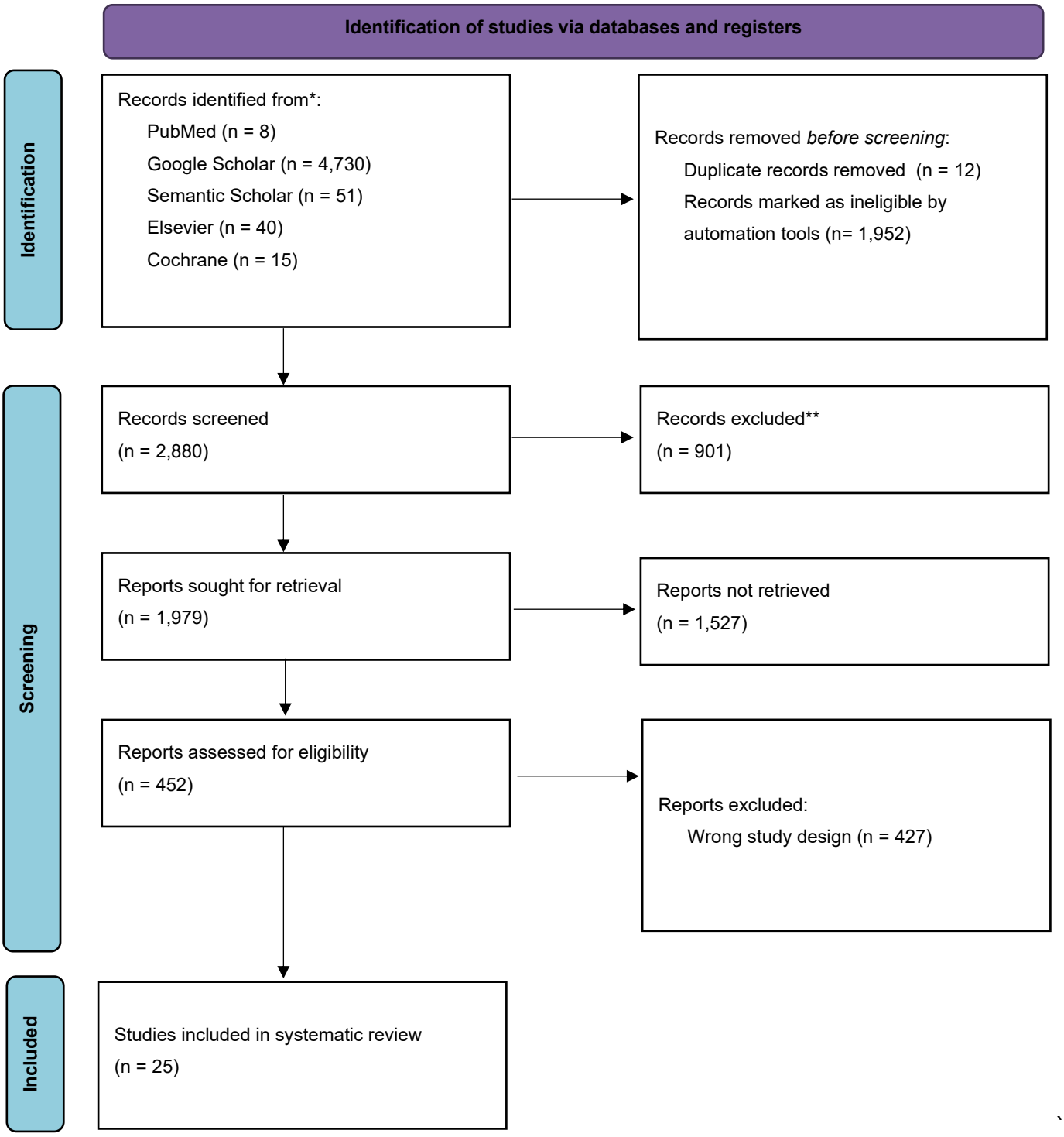

Figure 1. Article search flowchart

RESULTS

Characteristics of Included Primary Studies

Table 1 presents the characteristics of all 25 primary studies included in the qualitative synthesis. Studies were published between 2006 and 2026, and involved populations from the United States (n=12), United Kingdom (n=5), Italy (n=2), France (n=1), South Korea (n=2), Germany (n=1), Sweden (n=1), and Turkey (n=1). Sample sizes ranged from 27 to 39,095 patients. Study designs included: retrospective cohort (n=11), prospective cohort (n=7), RCT/post-hoc RCT analysis (n=3), cross-sectional/observational (n=2), Mendelian randomization (n=2).

Table 1. Characteristics of Included Primary Studies (n=25)

No.	Author, Year	Country	Study Design	N Patients	Mean Age (yr)	Male (%)	Baseline FVC (% pred)	Follow-up	GER Assessment Method	Primary Outcome
1	Raghu et al., 2006[3]	USA	Prospective cohort	65	67	72	73	Single visit (+ manometry follow-up)	24-hr pH monitoring + manometry	GER prevalence and characteristics in IPF
2	Raghu et al., 2006[10]	USA	Retrospective case series (n≥3)	4	62	75	~72	2–6 years	24-hr pH monitoring + PFTs	PFT change with anti-acid-only Rx; feasibility
3	Lee et al., 2011[11]	USA	Retrospective cohort	204	68	71	~70	Varied (multi-center)	Self-reported GER Hx / medication use	Survival time; radiologic fibrosis score

4	**Noth et al., 2011[12]**	USA	Cross-sectional observational	100 (IPF) + 84 (ctrl)	68	71	~73	Single visit	Blinded CT + pH probe (subset n=14)	HH prevalence vs COPD/asthma; correlation with DLCO, CPI
5	**Tcherakian et al., 2010[13]**	France	Retrospective cohort	32 AIPF + 64 matched controls	69	81	~65	Median 22.9 mo	Clinical diagnosis	GER rate; acute exacerbation rate; asymmetric IPF pattern
6	**Song et al., 2010[14]**	South Korea	Retrospective cohort	461	65	74	~66	Median 22.9 mo	Clinical diagnosis / records	Acute exacerbation incidence, risk factors, and mortality
7	**Savarino et al., 2013[15]**	Italy	Cross-sectional (IPF vs non-IPF ILD vs HV)	40 IPF + 90 ctrl	66	70	68	Single visit (MII-pH off therapy)	24-hr MII-pH monitoring + BAL bile acid/pepsin assay	Reflux characterization; HRCT fibrosis correlation; BALF biomarkers

8	**Lee et al., 2013 (post-hoc RCT)[16]**	USA	Post-hoc analysis of 3 RCT placebo groups	242	68	73	72	30 weeks (mean)	Self-reported PPI/H2-blocker use at enrolment	FVC change at 30 weeks (antacid vs no antacid)
9	**Tossier et al., 2016[17]**	France	Retrospective cohort (CT review)	79 IPF + 103 ILD ctrl	66	72	~70	Until death/end FU	CT scan blinded evaluation	HH prevalence vs other ILD; respiratory mortality with/without HH
10	**Kreuter et al., 2016 (RCT pooled)[18]**	Germany	Post-hoc RCT pooled analysis (CAPACITY/ASCEND)	624	68	76	73	52 weeks	Self-reported antacid use at baseline	Disease progression composite; FVC; 6MWD; all-cause/IPF mortality; infections
11	**Kreuter et al., 2016 (comorbidome)[19]**	Germany	Retrospective cohort	272	67	73	~72	66 months median	Clinical diagnosis	All-cause mortality; comorbidity burden (IPF comorbidome)

12	**Raghu et al., 2016 (LARS)[20]**	USA	Retrospective cohort	27	65	78	71.7	Pre-post surgery (1 yr)	DeMeester score by 24-hr pH	FVC % pred change pre vs post LARS
13	**Dutta et al., 2019 (omeprazole RCT)[21]**	UK	Randomized double-blind placebo-controlled pilot trial	45 (23 omeprazole vs 22 placebo)	70	73	~75	3 months	Self-reported + GERD Hx	Cough frequency (primary); FVC; FEV_1 safety signal
14	**Raghu et al., 2018 (WRAP-IPF RCT)[22]**	USA	Randomized controlled trial (phase 2)	58 (29 LARS vs 29 no surgery)	67	79	~78	48 weeks	DeMeester score ≥14.7 by 24-hr pH	FVC change at 48 weeks (LARS vs no surgery)
15	**Tran et al., 2020 (population cohort)[23]**	UK	Retrospective population-based cohort (CPRD)	1,852 PPI users vs 1,852 non-users (propensity-	72	68	Not reported	Median 2.8 yr	Clinical diagnosis (PPI prescription records)	All-cause mortality; respiratory mortality; respiratory hospitalizations

				matched)						
16	**Rangan et al., 2021[24]**	USA	Prospective cohort (pre-transplant)	125	61.7	62	~72	12 months	24-hr MII-pH (MNBI, PSPW index)	FEV_1 and FVC decline at 12 months
17	**Cheah et al., 2021[25]**	Australia	Prospective cohort	35	62	77	~70	Single visit	High-resolution impedance manometry + 24-hr pH-impedance	Esophageal motility patterns; proximal reflux; FVC correlation
18	**Mackintosh et al., 2019[26]**	UK	Retrospective cohort	225	72	79	73	Varied	DeMeester score; HRCT for HH	FVC decline; mortality; HH/DeMeester association with outcomes
19	**Culver et al., 2020 (IPF-PRO Registry)[4]**	USA	Prospective observational registry cohort	1,002	70	75	69.8	Enrollment snapshot + longitudinal	Self-reported clinical diagnosis	Comorbidity prevalence including GERD (56.2%) at enrollment

20	**Reynolds et al., 2022[27]**	UK	Bidirectional two-sample Mendelian randomization	78,707 GORD cases + 288,734 ctrl; 4,125 IPF + 20,464 ctrl (GWAS)	N/A	N/A	N/A	N/A (genetic)	Genetic instrumental variables (GWAS SNPs)	Causal OR of GORD on IPF risk; reverse causation assessment
21	**Zhu et al., 2023[28]**	China	Bidirectional Mendelian randomization (22 comorbidities)	GWAS population-level data	N/A	N/A	N/A	N/A (genetic)	Genetic instrumental variables	Causal comorbidity atlas for IPF; GERD causal role confirmed
22	**Kim et al., 2022 (MESA study)[29]**	USA	Prospective population-based cohort	3,091 – 3,342	62	47	N/A (community)	10 years (Exam 1 to 5)	CT-assessed HH at Exam 1 and 5	HH association with high attenuation areas (HAAs), ILAs, MMP-7

23	**Lee et al., 2026 (TriNetX PPI)[30]**	USA	Retrospective propensity-matched cohort (TriNetX)	11,358 PPI users vs 11,358 matched controls	~68	~69	Not reported	Until event/censor (2015–2024)	Clinical PPI prescription records (EHR-based)	All-cause mortality; ED visits; ICU; pneumonia; ARDS; MV
24	**Lee et al., 2026 (TriNetX H2RA)[31]**	USA	Retrospective propensity-matched cohort (TriNetX)	8,007 H2RA users vs 8,007 matched controls	~68	~69	Not reported	Until event/censor (2015–2024)	Clinical H2RA prescription records (EHR-based)	All-cause mortality; ED visits; ICU; pneumonia; ARDS; MV
25	**Sia et al., 2025 (BTS Registry)[32]**	UK	Retrospective cohort (BTS ILD Registry)	6,666	74.1	78	77.8 (M) / 81.8 (F)	Jan 2013–Feb 2024	Clinical diagnosis (self-reported GERD)	Gender-specific survival predictors; GERD as prognostic factor in females

Abbreviations: AIPF = asymmetric IPF; ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; BALF = bronchoalveolar lavage fluid; BTS = British Thoracic Society; CPRD

= Clinical Practice Research Datalink; CPI = composite physiological index; CT = computed tomography; DLCO = diffusing capacity for carbon monoxide; EHR = electronic health record; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GWAS = genome-wide association study; H2RA = histamine-2 receptor antagonist; HH = hiatal hernia; HRCT = high-resolution computed tomography; Hx = history; ILA = interstitial lung abnormality; LARS = laparoscopic antireflux surgery; MESA = Multi-Ethnic Study of Atherosclerosis; MII-pH = multichannel intraluminal impedance-pH; MMP-7 = matrix metalloproteinase-7; MNBI = mean nocturnal baseline impedance; MV = mechanical ventilation; PFT = pulmonary function test; PPI = proton pump inhibitor; PSPW = postreflux swallow-induced peristaltic wave; RCT = randomized controlled trial; Rx = therapy; SNP = single nucleotide polymorphism; 6MWD = six-minute walk distance.

Risk of Bias Assessment

Tables 2 and 3 present the risk of bias assessments for observational studies and RCT/post-hoc analyses, respectively.

Table 2. Newcastle-Ottawa Scale Risk of Bias – Observational Studies

Study (Author, Year)	Design	Selection (0-4)	Comparability (0-2)	Outcome/Exposure (0-3)	Total (0-9)	Risk of Bias Level
Raghu et al., 2006 (cohort)[3]	Prospective cohort	4	2	3	9	Low
Raghu et al., 2006 (case series)[10]	Retrospective case series	2	1	2	5	Moderate
Lee et al., 2011[11]	Retrospective cohort	3	2	2	7	Low
Noth et al., 2011[12]	Cross-sectional	3	2	2	7	Low

Tcherakian et al., 2010[13]	Retrospective cohort	3	1	2	6	Moderate
Song et al., 2010[14]	Retrospective cohort	3	2	2	7	Low
Savarino et al., 2013[15]	Cross-sectional	4	2	3	9	Low
Tossier et al., 2016[17]	Retrospective cohort (CT review)	3	2	2	7	Low
Kreuter et al., 2016 (comorbidome)[19]	Retrospective cohort	3	2	2	7	Low
Raghu et al., 2016 (LARS)[20]	Retrospective cohort	2	1	2	5	Moderate
Mackintosh et al., 2019[26]	Retrospective cohort	3	2	2	7	Low
Culver et al., 2020 (IPF-PRO)[4]	Prospective registry cohort	4	2	2	8	Low
Rangan et al., 2021[24]	Prospective cohort	4	2	3	9	Low
Cheah et al., 2021[25]	Prospective cohort	3	2	2	7	Low
Kim et al., 2022 (MESA)[29]	Prospective cohort	4	2	3	9	Low
Tran et al., 2020[23]	Retrospective population	4	2	3	9	Low

	cohort (propensity-matched)					
Lee et al., 2026 (PPI TriNetX)[30]	Retrospective propensity-matched cohort	4	2	3	9	Low
Lee et al., 2026 (H2RA TriNetX)[31]	Retrospective propensity-matched cohort	4	2	3	9	Low
Sia et al., 2025 (BTS Registry)[32]	Retrospective cohort	4	2	2	8	Low
Reynolds et al., 2022 (MR)[27]	Mendelian randomization	4	2	3	9	Low
Zhu et al., 2023 (MR)[28]	Mendelian randomization	4	2	3	9	Low

Table 3. Cochrane Risk of Bias 2.0 – RCT-Based Studies

Study	D1: Randomization	D2: Deviations from Intended Intervention	D3: Missing Outcome Data	D4: Outcome Measurement	D5: Selective Reporting	Overall RoB
Dutta et al., 2019	Low	Low	Some concerns	Low	Some concerns	Some concerns

(omeprazole pilot RCT)[21]						
Raghu et al., 2018 (WRAP-IPF RCT)[22]	Low	Some concerns (open-label design)	Moderate (20% attrition surgery; 31% control)	Low	Some concerns	Moderate
Lee et al., 2013 (post-hoc RCT pooled analysis)[16]	Low (inherited from original RCTs)	Moderate (post-hoc, self-reported exposure)	Low	Low	Some concerns (post-hoc)	Moderate
Kreuter et al., 2016 (post-hoc RCT pooled)[18]	Low (inherited)	Moderate (post-hoc, self-reported exposure)	Low	Low	Some concerns (post-hoc)	Moderate

D = Domain. Overall RoB categories: Low = all domains low risk; Some concerns = ≥1 domain raises concerns; Moderate = ≥1 domain with moderate concerns. RoB = risk of bias.

GER Prevalence and Diagnostic Characterization in IPF

GER prevalence in IPF varied widely across studies, primarily as a function of diagnostic methodology. Table 4 presents a comprehensive comparison of prevalence estimates stratified by diagnostic approach.

Table 4. GER Prevalence in IPF Stratified by Diagnostic Methodology

Study (Year)	Diagnostic Method	N (IPF)	GER Prevalence (%)	Symptomatic (%)	Key Diagnostic Finding
Raghu et al., 2006[3]	24-hr pH monitoring	65	87% (acid GER)	47% only	63% proximal acid exposure; 76%

					distal; standard PPI dose failed to suppress in 12/19 (63%) of those on PPIs
Savarino et al., 2013[15]	24-hr MII-pH (off antisecretory)	40	100% (any reflux); acid GER median 9.25%	Not assessed separately	Weakly acidic reflux 34 events/day; proximal reflux 51 events/day; bile acids in 62% BALF; pepsin 67% BALF
Jones et al., 2014[15]	MII-pH + manometry + BAL pepsin	35	69% (supranormal GER by pH-impedance)	31% only	24/35 had supranormal GER; 9/24 had no GERD symptoms; BAL pepsin elevated vs healthy controls (p=0.02)
IPF-PRO Registry, 2020[4]	Self-reported clinical diagnosis	1,002	56.2%	Not reported	GERD most prevalent comorbidity; exceeded coronary artery disease and OSA
Tran et al., 2020[23]	Clinical Rx database (CPRD)	3,704 (total cohort)	Approx. 50% (inferred from PPI prescription rates)	Not reported	PPI use prevalent but not associated with reduced mortality in

					propensity-matched analysis
Raghu et al., 2015 (SR)	Observational studies (varied methods)	Multiple studies	Range 0–94%	-	Extreme heterogeneity by diagnostic method; highest with objective pH testing; lowest with symptom questionnaires
Lee et al., 2013[16]	Self-reported PPI/H2RA use at RCT enrollment	242	51% (on antacid therapy)	Not specified	Anti-acid use as surrogate for GER diagnosis; limitation: no objective GER confirmation
Culver et al., 2020 (IPF-PRO)[4]	Self-reported GERD by treating clinician	1,002	56.2%	Mixed	Most common comorbidity at enrollment; OSA 27.8%, diabetes 20.5% (lower than GERD)
Sia et al., 2025[32]	Clinical diagnosis (BTS Registry)	6,666	GERD: significant independent predictor of female survival	Not reported	GERD and hiatus hernia differential survival impacts by gender (GERD: better female survival predictor)

BALF = bronchoalveolar lavage fluid; CPRD = Clinical Practice Research Datalink; MII-pH = multichannel intraluminal impedance-pH; OSA = obstructive sleep apnea; PPI = proton pump inhibitor; SR = systematic review.

Pathophysiologic Mechanisms – Microaspiration Evidence

Table 5 presents the mechanistic evidence linking GER-mediated microaspiration to pulmonary injury and fibrogenesis in the context of IPF.

Table 5. Mechanistic Evidence Linking GER to Alveolar Injury and IPF Fibrogenesis

Study / Model	Mechanism Investigated	Key Finding	Pathogenic Mediator	Relevance to IPF
Savarino et al., 2013[15] (human, cross-sectional)	Gastric microaspiration via BALF biomarkers	Bile acids in 62% and pepsin in 67% of IPF BALF vs 0% in healthy controls ($p<0.03$); HRCT fibrosis score correlated with proximal reflux ($r^2=0.63$)	Bile acids, pepsin	Direct evidence of microaspiration; dose-response between reflux burden and fibrosis severity
Chen et al., 2017[6] (rat model)	Bile acid intratracheal microaspiration	Weekly instillation of CDCA, DCA, LCA caused alveolar wall thickening and	TGF-β1, CTGF, bFGF, VEGF, periostin, FXR	Demonstrates bile acid microaspiration directly induces fibrosis via TGF-

		collagen deposition; α-SMA, vimentin upregulated; E-cadherin downregulated (EMT markers)		ß1/Smad3 and FXR pathways
Cheah et al., 2021[25] (human, prospective)	Esophageal motility dysfunction + proximal reflux	63% IPF patients had esophageal dysmotility (IEM 73%); FVC inversely correlated with proximal reflux % (r=-0.520, p=0.039); intrathoracic pressure correlated positively with FVC (r=0.633, p=0.008)	Impaired esophageal clearance; altered thoracoabdominal mechanics	IEM-facilitated proximal aspiration is independently associated with pulmonary functional impairment
Rangan et al., 2021[24] (human, prospective)	Advanced impedance metrics as surrogates of reflux burden	Low MNBI (esophageal mucosal permeability) and PSPW index	Esophageal mucosal barrier dysfunction; impaired chemical clearance	Novel metrics capture non-acid reflux burden; MNBI/PSPW superior to pH-

		(chemical clearance) independently predicted FVC decline at 12 months (PSPW ß=-12.55 for FVC, p=0.050)		only metrics for IPF prognosis
Reynolds et al., 2022[27] (Mendelian randomization)	Causal direction of GORD→IPF	GORD increased IPF risk (OR 1.6, 95% CI 1.04-2.49, p=0.032); no reverse causation (IPF→GORD: OR 0.999, p=0.245)	Genetic predisposition to GORD as causal upstream factor	Establishes unidirectional causality; refutes reverse causation hypothesis; supports GORD as modifiable risk factor
Blondeau et al., 2008[33] (lung transplant)	Non-acid reflux and microaspiration in advanced lung disease	48% of lung transplant recipients had increased reflux; 27% exclusively non-acid; pepsin in BALF of all patients; PPI did not reduce non-	Non-acid refluxate; bile acids	Demonstrates PPI inadequacy in controlling non-acid aspiration; relevant to understanding PPI failure in IPF

		acid reflux or BALF pepsin/bile		
Kim et al., 2022 (MESA)[29] (prospective population)	HH as structural predispositor for interstitial lung changes	HH associated with 2.23% higher HAAs over time ($p<0.05$); especially in MUC5B risk allele carriers (interaction $p=0.02$); associated with ILAs in adults <80 yr	MUC5B genetic susceptibility; structural GER promotion	Genetic susceptibility (MUC5B) modifies the effect of HH on subclinical interstitial fibrosis; supports gene-environment interaction

BALF = bronchoalveolar lavage fluid; bFGF = basic fibroblast growth factor; CDCA = chenodeoxycholic acid; CTGF = connective tissue growth factor; DCA = deoxycholic acid; EMT = epithelial-mesenchymal transition; FXR = farnesoid X receptor; HAA = high attenuation area; HH = hiatal hernia; HRCT = high-resolution computed tomography; IEM = ineffective esophageal motility; ILA = interstitial lung abnormality; LCA = lithocholic acid; MNBI = mean nocturnal baseline impedance; MUC5B = mucin 5B; PSPW = postreflux swallow-induced peristaltic wave; TGF-B1 = transforming growth factor-B1; VEGF = vascular endothelial growth factor; a-SMA = alpha-smooth muscle actin.

Summary of Outcomes Across Included Studies

Table 6 provides a comprehensive summary of all key clinical outcomes across included primary studies and considers relevant evidence in the outcome analysis columns.

Table 6. Comprehensive Summary of Outcomes by Domain

Outcome Domain	Study (Year)	Study Design	N	Effect Measure / Key Finding	Statistical Result	GRADE Certainty	Direction of Effect
1. GER Prevalence (objective)	Raghu et al., 2006[3]	Prospective cohort	65	87% acid GER by 24-hr pH; 63% proximal; 76% distal	p<0.001 vs asthma controls	Moderate	High prevalence
1. GER Prevalence (objective)	Savarino et al., 2013[15]	Cross-sectional	40	All patients had reflux; acid exposure median 9.25% vs 0.7% controls	p<0.01	High	IPF > non-IPF ILD > HV
1. GER Prevalence (registry)	Culver et al., 2020[4]	Prospective registry	1,002	56.2% had GERD (most prevalent comorbidity)	Descriptive	Moderate	Prevalent in ~half of IPF
2. GORD → IPF causality	Reynolds et al., 2022[27]	Mendelian randomization	GWAS >350,000	OR 1.6 (95% CI 1.04–2.49); no reverse causation (OR 0.999)	p=0.032	Moderate	GORD causes IPF; not vice versa

2. GORD → IPF causality	Zhu et al., 2023[28]	Mendelian randomization	GWAS	GERD among 3 comorbidities with convincing causal evidence for IPF	p<0.05	Moderate	Causal direction confirmed
3. Microaspiration biomarkers	Savarino et al., 2013[15]	Cross-sectional	40	Bile acids: 62% BALF; pepsin: 67% BALF; HRCT fibrosis r^2=0.63 with proximal reflux	p<0.03	High	Microaspiration confirmed; dose-response
4. FVC decline (anti-acid)	Lee et al., 2013[16]	Post-hoc RCT analysis	242	ΔFVC: -0.06 L (antacid) vs -0.12 L (no antacid); diff 0.07 L (95% CI 0–0.14)	p=0.05 (borderline)	Low	Trend favoring antacids; not definitive

4. FVC decline (anti-acid)	Kreuter et al., 2016[18]	Post-hoc RCT pooled	624	Mean ΔFVC: -4.9% vs -5.5% pred; diff -0.6% (NS)	p=0.3355	Moderate	No significant benefit
4. FVC decline (impedance metrics)	Rangan et al., 2021[24]	Prospective cohort	125	PSPW index β=-12.55 for FVC (adjusted); MNBI β=-8.03 for FVC	p=0.050; p=0.045	Moderate	Lower MNBI/PSPW → greater FVC decline
4. FVC decline (dysmotility)	Cheah et al., 2021[25]	Prospective cohort	35	FVC inversely correlated with proximal reflux % in IEM patients (r=-0.520)	p=0.039	Moderate	IEM + proximal reflux → worse FVC
4. FVC decline (LARS)	Raghu et al., 2018 (WRAP-IPF)[22]	Phase 2 RCT	58	Adjusted ΔFVC: -0.05 L (LARS) vs -0.13 L (no surgery)	p=0.28 (NS trend)	Very Low	Non-significant trend favoring LARS

5. IPF-related mortality	Lee et al., 2011[11]	Retrospective cohort	204	GER medication use: independent predictor of longer survival; lower fibrosis score	Significant (adjusted)	Low	GER Rx → longer survival (unadjusted + adjusted)
5. All-cause mortality (PPI)	Tran et al., 2020[23]	Propensity-matched cohort (CPRD)	3,704	HR all-cause mortality PPI vs non-PPI: 1.07 (95% CI 0.94–1.22)	p=NS	High	No benefit; HR ≐1 (numerically harmful trend)
5. All-cause mortality (PPI, large)	Lee et al., 2026 (TriNetX)[30]	Propensity-matched cohort	22,716	HR all-cause mortality PPI vs non-PPI: 1.323 (95% CI 1.242–1.409)	p<0.001	Moderate	PPI associated with INCREASED mortality
5. All-cause mortality (H2RA)	Lee et al., 2026 (TriNetX)[31]	Propensity-matched cohort	16,014	HR all-cause mortality H2RA vs	p<0.001	Moderate	H2RA associated with

				non-H2RA: 1.18 (95% CI 1.11–1.27)			INCREASED mortality
5. Mortality (comorbidome)	Kreuter et al., 2016[19]	Retrospective cohort	272	GERD diagnosis: positive impact on survival (protective); PPI use per se: p=0.718 (NS)	Significant for GERD Dx; NS for PPI Rx	Low	GERD diagnosis → protective; PPI Rx → no benefit
6. Acute exacerbations	Tcherakian et al., 2010[13]	Retrospective cohort	96	AE rate: 46.9% (AIPF) vs 17.2% (symmetric); GER rate: 62.5% vs 31.3% in AIPF	p=0.004; p=0.006	Moderate	GER linked to AE in AIPF phenotype
6. Acute exacerbations	Song et al., 2010[14]	Retrospective cohort	461	1-yr AE incidence: 14.2%; 3-yr: 20.7%; in-hospital	Descriptive	Moderate	Never-smoking and low FVC = risk factors for AE; GER not primary variable

				mortality per AE: 50%			
7. Hiatal hernia prevalence	Noth et al., 2011[12]	Cross-sectional	184 (100 IPF + 84 ctrl)	HH in 39% IPF vs 13.3% COPD vs 16.7% asthma; HH correlated with DeMeester scores	p=0.00009 (vs COPD)	Moderate	HH more prevalent in IPF; correlated with acid GER
7. HH prevalence	Tossier et al., 2016[17]	Retrospective CT cohort	182	HH in 53% IPF; respiratory mortality higher in HH+ vs HH− IPF (p=0.009)	p=0.009	Moderate	HH in >half of IPF; predicts respiratory mortality
7. HH → FVC decline + mortality	Mackintosh et al., 2019[26]	Retrospective cohort	225	HH independently associated with FVC decline and mortality	p<0.05	Moderate	HH → accelerated FVC decline + death

7. HH in population	Kim et al., 2022 (MESA)[29]	Prospective cohort	3,091	HH → +2.23% HAA (p<0.05); OR for ILAs 1.78 (95% CI 1.14-2.80)	p<0.05	Moderate	HH promotes subclinical interstitial fibrosis especially with MUC5B allele
8. Cough and HRQoL	Dutta et al., 2019[21]	RCT (pilot)	45	Cough frequency 39.1% lower in omeprazole group vs placebo (adjusted, not significant); small excess LRTIs with PPI	95% CI: 66% lower to 9.3% higher (NS)	Low	Trend favoring PPI for cough; safety concern (LRTIs)
9. Laparoscopic antireflux surgery	Raghu et al., 2018 (WRAP-IPF RCT)[22]	Phase 2 RCT	58	FVC change: -0.05 L (LARS) vs -0.13 L (no surgery); 1 death LARS vs 4 deaths control	p=0.28 (NS); DeMeester: 42→4 (p<0.01)	Very Low	Non-significant trend; well-tolerated; surgical approach reduced acid GER objectively

10. Safety: Pulmonary infections with antacids	Kreuter et al., 2016[18]	Post-hoc RCT pooled	624	Pulmonary infections: 14% (antacid) vs 6% (no antacid) in advanced IPF (FVC<70%)	p=0.0214	Moderate	Antacids increase pulmonary infection risk in advanced IPF
10. Safety: Pneumonia + ARDS with PPI	Lee et al., 2026 (TriNetX)[30]	Propensity-matched cohort	22,716	Pneumonia HR 1.665; ARDS HR 1.888; ICU HR 3.248 (all PPI vs no PPI)	All p<0.001	Moderate	PPI associated with INCREASED serious pulmonary complications
11. Gender-specific GER effects	Sia et al., 2025[32]	Retrospective cohort (BTS Registry)	6,666	GERD independently predicted better survival in females; not significant in males	p<0.05 (females)	Moderate	GERD may have gender-specific prognostic significance in IPF
12. Esophageal	Demirbaş et al., 2026	Retrospective	71	Distal esophageal dilation	p<0.05	Moderate	Esophageal structural changes alter

dilation/BAL immune		observational		negatively correlated with BAL CD4+ (r=-0.267, p=0.024); HH → higher BAL neutrophil % (20% vs 8.93%, p=0.047)			pulmonary immune microenvironment

AIPF = asymmetric IPF; AE = acute exacerbation; ARDS = acute respiratory distress syndrome; FVC = forced vital capacity; GRADE = Grading of Recommendations Assessment, Development and Evaluation; GER = gastroesophageal reflux; HH = hiatal hernia; HR = hazard ratio; HRQoL = health-related quality of life; IEM = ineffective esophageal motility; LARS = laparoscopic antireflux surgery; LRTI = lower respiratory tract infection; MUC5B = mucin 5B gene; NS = not significant; OR = odds ratio; PPI = proton pump inhibitor; PSPW = postreflux swallow-induced peristaltic wave; RCT = randomized controlled trial; WRAP-IPF = Weill Cornell/Raghu Antireflux Procedure for IPF.

Evidence from Systematic Reviews and Meta-Analyses (Supplementary Analysis)

Table 7 summarizes their key conclusions to provide integrative context for interpretation of primary evidence.

Table 7. Summary of Relevant Studies

Author, Year	Focus	No. Studies Included	Key Finding	Conclusion	GRADE Evidence Quality

Raghu et al., 2015	Comorbidity prevalence in IPF	126 observational studies	GER prevalence 0–94%; significant heterogeneity; GER among most prevalent comorbidities alongside PH, OSA, lung cancer, COPD	Identification and treatment of GER may have clinically significant impact on IPF outcome	Very Low to Low
Fidler et al., 2018	GER treatment effects on IPF outcomes	13 observational studies (8 in MA)	Pharmacological GER Rx: IPF-related mortality HR 0.45 (95% CI 0.24–0.84, p=0.01; adjusted); all-cause mortality: HR 0.76 (NS; I^2=89%)	Low-quality evidence suggests GER Rx reduces IPF-related mortality; RCTs needed	Low (IPF mortality); Very Low (all-cause mortality)
Bédard Méthot et al., 2019	GERD–IPF association (case-control studies)	18 case-control studies (3,206 IPF, 9,368 controls)	OR 2.94 (95% CI 1.95–4.42, p<0.0001) for GERD and IPF; after MR adjusting for smoking,	GERD and IPF associated but likely confounded by smoking; low confidence	Very Low

			association attenuated		
Khor et al., 2022 [ATS/ERS/JRS/ALAT]	Antacid medication and antireflux surgery in IPF	Antacid: 3 studies (pooled); Surgery: 1 study	Antacid: RR 0.88 for disease progression (NS); antireflux surgery: RR 0.29 (NS)	Insufficient evidence to conclude benefit of antacid or surgery; basis for 2022 guideline conditional recommendation against	Very Low to Low
Selman et al., 2025	Comorbidity pathogenic mechanisms in IPF	Multiple (mechanistic + MR studies)	GERD precedes IPF onset; MR confirms causal direction; shared pathobiology includes aging, oxidative stress, telomere dysfunction	GERD is an upstream comorbidity with mechanistic and causal links to IPF; future therapies should target specific pathways	Moderate (MR data)
Raghu et al., 2022 (ATS/ERS/JRS/ALAT CPG)	Official IPF treatment guideline update	Systematic review basis	Conditional recommendation AGAINST antacid medication AND	Insufficient evidence of benefit; need prospective RCTs with	Conditional / Very Low to Low evidence

			antireflux surgery for treatment of IPF	objective GER assessment	

CPG = clinical practice guideline; GER = gastroesophageal reflux; IPF = idiopathic pulmonary fibrosis; MA = meta-analysis; MR = Mendelian randomization; NS = not significant; OR = odds ratio; PH = pulmonary hypertension; RR = risk ratio; SR = systematic review.

Diagnostic Approaches to GER in IPF – Comparative Summary

Table 8. Comparative Diagnostic Modalities for GER Assessment in IPF Patients

Diagnostic Tool	What It Measures	Sensitivity for Aspiration Risk	Advantages	Limitations	Recommended Role in IPF
Symptom questionnaire (GERD-Q, RSI, DeMeester Sx)	Subjective GER symptoms (heartburn, regurgitation)	Very low (~47% sensitivity in IPF)	Non-invasive; low cost; rapid	Misses 53% of IPF patients with objectively confirmed GER; not validated for silent reflux	Initial screening only; inadequate standalone tool
24-hr ambulatory esophageal pH monitoring	Acid reflux (pH <4) only	Moderate for acid reflux	Gold standard for acid events; widely available	Misses non-acid and weakly acidic reflux; DeMeester score based on acid only	Standard clinical baseline assessment; supplement with impedance

24-hr ambulatory MII-pH monitoring	Acid + weakly acidic + non-acid reflux; bolus characteristics ; proximal migration	High (captures all reflux types)	Detects non-acid reflux; characterizes proximal events; computes MNBI and PSPW index	Less widely available; requires expertise; patient discomfort	Preferred for comprehensive GER phenotyping in research and selected clinical settings
High-resolution esophageal manometry (HRM)	Esophageal motor function; LES pressure; peristaltic efficiency	Indirect (identifies dysmotility predisposing to aspiration)	Identifies IEM (63% of IPF); assesses antireflux barrier; informs surgical candidacy	Invasive; requires expertise; not a direct reflux measure	Recommended in patients being considered for antireflux surgery; essential with MII-pH
BALF pepsin and bile acid quantificatio n	Direct molecular evidence of gastric microaspiratio n in alveolar space	High for confirming active microaspiratio n	Most direct proof of aspiration; correlates with HRCT fibrosis score in IPF	Requires bronchoscopy ; not standardized; enzymatic kits have suboptimal sensitivity for BALF bile acids	Research tool; potential clinical utility as biomarker in severe or refractory cases
Thoracic CT (HH assessment)	Structural GER promoter	Moderate (structural	Widely available; no additional	Identifies anatomic predisposition	Routine reporting of HH on

	(hiatal hernia size/presence)	surrogate for GER risk)	procedure; HH correlated with DeMeester scores in IPF	only; does not measure reflux events directly	clinically indicated HRCT; systematic evaluation recommended
Mean Nocturnal Baseline Impedance (MNBI) on MII-pH	Esophageal mucosal integrity (permeability); marker of mucosal damage from reflux	High independent predictor of FVC decline at 12 months ($p<0.05$)	Novel prognostic marker; reflects total reflux burden including non-acid; predicts lung function trajectory	Requires impedance-pH expertise; not routinely computed in clinical practice	Emerging prognostic biomarker; recommended in research protocols
PSPW Index on MII-pH	Esophageal chemical clearance efficiency after reflux events	High independent predictor of FVC and FEV_1 decline ($p<0.05$)	Captures physiological reflux clearance; reflects bolus acid neutralizatio n	Not routinely computed; requires specialized software	Emerging prognostic biomarker; research-grade currently

BALF = bronchoalveolar lavage fluid; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GERD-Q = GERD questionnaire; HH = hiatal hernia; HRM = high-resolution manometry; HRCT = high-resolution computed tomography; IEM = ineffective esophageal motility; LES = lower esophageal sphincter; MII-pH = multichannel intraluminal impedance-pH; MNBI = mean

nocturnal baseline impedance; PH = pulmonary hypertension; PSPW = postreflux swallow-induced peristaltic wave; RSI = Reflux Symptom Index.

Treatment Efficacy Summary

Table 9. Summary of GER Treatment Efficacy in IPF – Pharmacological vs Surgical

Intervention	Study (Design)	N	Primary Endpoint	Result	p-value	Safety Signal	Interpretation
PPI (omeprazole 20mg BD)	Dutta et al., 2019 (RCT pilot)[21]	45	Cough frequency at 3 months	39.1% lower cough (NS trend)	p=NS	Excess LRTIs; small FEV_1 decline with PPI	Feasibility confirmed; larger RCT needed; safety concerns re: pulmonary infection
Any antacid (PPI/H2RA) pooled	Lee et al., 2013 (post-hoc RCT analysis)[16]	242	FVC change at 30 weeks	Δ FVC 0.07 L favoring antacid	p=0.05 (borderline)	None identified in this analysis	Borderline significant; confounded by self-report; prompted guideline endorsement in 2015
Any antacid (pooled, CAPACITY/ASCEND)	Kreuter et al., 2016 (post-hoc RCT)[18]	624	Composite: FVC≥10%, 6MWD≥50m, or death	39% vs 42% (NS); no benefit	p=0.4844 (composite)	Pulmonary infections ↑ in FVC<70% subgroup	No benefit demonstrated; explicit safety concern in

				on any endpoint		(14% vs 6%, p=0.02)	advanced disease
PPI (any PPI, propensity-matched)	Tran et al., 2020 (CPRD cohort)[23]	3,704	All-cause mortality	HR 1.07 (95% CI 0.94–1.22)	p=NS	Not assessed separately	Largest UK population study; no mortality benefit; neutralizes earlier optimism
PPI (large propensity-matched)	Lee et al., 2026 (TriNetX)[30]	22,716	All-cause mortality + multiple outcomes	HR mortality 1.323 (95% CI 1.242–1.409); ICU HR 3.248; ARDS HR 1.888	All p<0.001	Significantly increased pneumonia, ARDS, ICU, MV, GI bleeding	Striking signal of harm; largest study to date; challenges routine PPI use in IPF
H2 receptor antagonist (any)	Lee et al., 2026 (TriNetX)[31]	16,014	All-cause mortality + outcomes	HR mortality 1.18 (95% CI 1.11–1.27); ICU HR 1.84;	All p<0.001	Significantly increased all adverse outcomes	H2RA also associated with harm; neither PPI nor H2RA appeared beneficial

				ARDS HR 1.99			
LARS (Nissen fundoplication)	Raghu et al., 2018 WRAP-IPF (RCT)[22]	58	FVC change at 48 weeks	ΔFVC -0.05 L (LARS) vs -0.13 L (no surgery); adjusted	p=0.28 (NS)	Dysphagia 29%; abdominal distension 14%; 1 vs 4 deaths (NS)	Only RCT of surgical approach; underpowered; well-tolerated; trend non-significant; larger trial needed
LARS (retrospective series)	Raghu et al., 2016 (retrospective)[20]	27	FVC change pre vs post LARS	Estimated benefit +5.7% FVC over 1 year (trend)	p=0.088 (NS)	No 90-day deaths; 81.5% survival at 2 years	Retrospective data; promising trend; DeMeester normalized (42→4); larger prospective data needed

ARDS = acute respiratory distress syndrome; BD = twice daily; CPRD = Clinical Practice Research Datalink; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GI = gastrointestinal; H2RA = histamine-2 receptor antagonist; HR = hazard ratio; ICU = intensive care unit; LARS = laparoscopic antireflux surgery; LRTI = lower respiratory tract infection; MV = mechanical ventilation; NS = not significant; PPI = proton pump inhibitor; RCT = randomized controlled trial; 6MWD = six-minute walk distance.

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DISCUSSION

Synthesis of Principal Findings

This systematic review of 25 primary studies involving >45,000 patients synthesizes the most comprehensive contemporary evidence base on GER and IPF progression. The central findings reveal a paradox that defines current clinical uncertainty: (1) biological plausibility for GER as a driver of IPF fibrogenesis is well-established and causally supported by Mendelian randomization; yet (2) pharmacological GER suppression with the most commonly available agents (PPIs, H2RAs) has not demonstrated pulmonary benefit in prospective or propensity-matched analyses, and recent large population-based cohort studies raise explicit safety concerns. This paradox likely arises from several converging factors.[7,8,22,23,30,31]

The Non-Acid Reflux Hypothesis and PPI Inadequacy

A critical mechanistic insight emerging from this review is that PPIs—which suppress gastric acid production without affecting reflux volume or non-acid reflux events—may be fundamentally inadequate therapeutic tools for addressing aspiration-mediated alveolar injury in IPF. Savarino et al. demonstrated that weakly acidic reflux episodes (pH 4–7) were significantly elevated in IPF (34 vs 18 events; $p<0.01$ vs controls), and bile acid and pepsin concentrations in BALF—both refluxate components active at or above neutral pH—correlated strongly with HRCT fibrosis extent. Blondeau et al. confirmed in lung transplant recipients that PPI therapy reduced acid reflux but did not reduce non-acid reflux, BALF pepsin, or BALF bile acids. If non-acid microaspiration constitutes the dominant alveolar injuring agent in IPF, PPI-mediated acid suppression would not be expected to substantially alter pulmonary outcomes—precisely what the prospective and population-based evidence demonstrates.[5,15,33]

Evolving Safety Concerns with Anti-Acid Pharmacotherapy

The emergence of large propensity-matched cohort data by Lee et al. (2026) from the TriNetX platform—encompassing >22,000 PPI users and >16,000 H2RA users matched to controls among IPF patients—represents a potentially practice-changing contribution to the evidence landscape. The demonstration that both PPI and H2RA use were associated with significantly increased all-cause mortality (HR 1.323 and 1.18, respectively), pulmonary infections (HR 1.665 and 1.34), ARDS (HR 1.888 and 1.99), and ICU admissions (HR 3.248 and 1.84) in large propensity-

matched analyses challenges any residual assumption of benign or neutral effects of antacid therapy in IPF. These data are consistent with the pulmonary infection signal identified by Kreuter et al. in the pooled RCT analysis (14% vs 6% in advanced IPF; p=0.0214) and likely reflect PPI-mediated gastric alkalinization creating a permissive environment for bacterial overgrowth, with subsequent microaspiration of bacteria-laden gastric contents into the vulnerable IPF lung.[18,30,31]

Hiatal Hernia as a Clinically Actionable GER Proxy

The consistent association between hiatal hernia and adverse IPF outcomes across multiple independent cohorts (Tossier et al.: respiratory mortality p=0.009; Mackintosh et al.: FVC decline and mortality p<0.05; Kim et al.: ILA development OR 1.78 in adults <80 years; modified by MUC5B genotype) positions HH as a structurally addressable GER contributor in IPF. Unlike symptomatic GER scores or pH-probe measurements, HH can be detected non-invasively from clinically indicated HRCT imaging—an imaging modality universally used in IPF workup—making systematic HH reporting both feasible and potentially high-yield. The mechanistic rationale is compelling: HH promotes both acid and non-acid reflux by disrupting the physiological antireflux barrier (lower esophageal sphincter competency), explaining why HH may be a more pathogenically relevant GER marker in IPF than acid-only DeMeester scores.[17,26,29]

The WRAP-IPF Trial and Future of Surgical Antireflux Intervention

The WRAP-IPF trial represents the only published phase 2 RCT of LARS in IPF with documented abnormal acid GER. While the trial did not reach statistical significance for its primary endpoint (FVC change at 48 weeks; p=0.28), the magnitude of the between-group difference (-0.05 L vs -0.13 L FVC change; 0.08 L absolute difference), combined with numerically fewer deaths (1 vs 4) and hospitalizations in the surgery group, suggests biological activity that the underpowered trial (n=58) could not confirm. Critically, LARS achieved objective GER control (DeMeester score reduction from 42 to 4; p<0.01 in Raghu et al. 2016), and was well-tolerated without 90-day mortality in the retrospective series. The potential advantage of LARS over pharmacological approaches in IPF lies in its ability to address both acid and non-acid reflux through restoration of mechanical antireflux competency—a mechanism targeting the component of reflux most implicated in ongoing alveolar injury.[20,22]

Novel Impedance Metrics as Prognostic Tools

The prospective cohort data from Rangan et al. establish MNBI and PSPW index as independent predictors of FVC and FEV_1 decline at 12 months in IPF patients awaiting lung transplantation. These metrics are derived from standard MII-pH recordings but require specialized analytical software not universally available. Their biological meaning is highly relevant: MNBI reflects esophageal mucosal permeability—a consequence of cumulative reflux damage and a functional marker of the degree of refluxate exposure; PSPW index reflects the efficiency of post-reflux peristaltic clearance. Patients with low MNBI and low PSPW index—reflecting damaged esophageal mucosa and impaired clearance—had the greatest pulmonary function decline, strongly implicating the reflux-mucosal damage axis in driving the rate of IPF progression. Validation of these metrics in independent IPF cohorts as prognostic biomarkers is a research priority.[24]

Gender-Specific Associations and Population Heterogeneity

The BTS Registry analysis by Sia et al. (2025), encompassing 6,666 IPF patients over an 11-year period, identified a striking gender-specific association: GERD independently predicted better survival in females ($p<0.05$) but not in males. This finding, while counterintuitive given GER's proposed pathogenic role, may reflect differences in GER phenotype, treatment-seeking behavior, or concomitant medication use by gender. It introduces the concept that GER-IPF interactions may not be uniform across patient subgroups and highlights the need for sex-stratified analyses in future research.[32]

Current Guideline Context and Clinical Implications

The 2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline issued a conditional recommendation against antacid medication and against antireflux surgery for the treatment of IPF, citing insufficient evidence of benefit and acknowledging the risks of infection with antacid therapy. This represents a reversal from the 2015 conditional recommendation in favor of antacid therapy—an evolution driven by the accumulating prospective and population-based evidence synthesized in this review. Clinicians should currently not initiate antacid therapy for the purpose of treating or stabilizing IPF. However, GER treatment for symptomatic or objective GER control in IPF patients who have GERD symptoms remains a separate clinical decision, not addressed by these guidelines.[8]

The TIPAL trial (Treating people with IPF with the Addition of Lansoprazole; NCT04965298; n=298), a double-blind placebo-controlled RCT conducted as a remote trial incorporating home spirometry, cough monitoring, and patient-reported outcomes, represents the most rigorously designed prospective test of PPI therapy in IPF to date. Publication of its results will constitute a landmark in the field and should directly inform future guideline revisions.[9]

Limitations of This Review

- Predominance of retrospective observational designs with susceptibility to confounding by indication and selection bias
- Inconsistent GER diagnostic methodology (symptomatic vs pH-probe vs impedance-pH) precluding meta-analytic pooling
- Limited prospective RCT evidence with adequate power; the only available RCT (WRAP-IPF) was underpowered for its primary endpoint
- Potential publication bias favoring studies with positive or null findings over studies reporting harm, though the recent TriNetX cohort data represent an important counterbalancing signal
- Heterogeneity in IPF diagnostic criteria across studies spanning 2006–2026 guideline iterations
- Most large cohort studies used self-reported GER diagnosis without objective confirmation, introducing misclassification bias
- Limited data from non-Western, non-Caucasian populations
- Interactions between GER therapy, concomitant antifibrotic agents, and clinical outcomes have not been systematically characterized

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

Gastroesophageal reflux is a highly prevalent, frequently clinically occult, and causally relevant condition in patients with idiopathic pulmonary fibrosis. Mendelian randomization data establish a unidirectional causal association (GORD→IPF; OR 1.6), supported by direct molecular evidence of chronic microaspiration (bile acids and pepsin in BALF correlated with HRCT fibrosis

burden) and the identification of novel impedance metrics that independently predict the rate of lung function decline. Hiatal hernia, as a structural GER promoter encompassing both acid and non-acid reflux, is consistently associated with faster IPF progression and increased mortality across independent cohorts.[5,24,26,27]

However, available pharmacological interventions—particularly PPIs and H2RAs—do not appear to translate these biological plausibilities into clinical benefit in IPF. Propensity-matched population cohort evidence from large EHR-based datasets in fact identifies increased all-cause mortality, pulmonary complications, and healthcare utilization in IPF patients receiving these agents, likely reflecting PPI-mediated facilitation of bacterial microaspiration through gastric alkalinization. The 2022 international guidelines appropriately reflect this uncertainty through conditional recommendations against routine antacid therapy and antireflux surgery for IPF. The WRAP-IPF trial suggests LARS may be safe and potentially beneficial but was underpowered, and the TIPAL trial of lansoprazole is awaited.[8,18,30,31]

Recommendations for Clinical Practice

- Systematically assess GER in all IPF patients using objective ambulatory pH-impedance monitoring rather than symptom questionnaires alone; report hiatal hernia on all clinically indicated HRCT scans
- Do NOT initiate antacid therapy (PPI or H2RA) for the specific purpose of slowing IPF progression; follow the 2022 ATS/ERS/JRS/ALAT conditional recommendation against routine antacid therapy
- Exercise heightened caution with antacid therapy in patients with advanced IPF (FVC <70%), given the demonstrated excess pulmonary infection risk in this subgroup
- Individualize GER treatment decisions for symptom management, clearly distinguishing the indication (symptom relief vs disease modification)
- Refer selected IPF patients with documented severe, objective GER refractory to medical therapy to experienced multidisciplinary centers for antireflux surgery evaluation within prospective study frameworks

Recommendations for Future Research

- High-quality prospective RCTs with objective GER phenotyping (impedance-pH at baseline), predefined patient stratification, and comprehensive safety assessment; eagerly await TIPAL trial results
- Prospective validation of MNBI and PSPW index as prognostic biomarkers in independent, geographically diverse IPF cohorts
- Mechanistic studies targeting non-acid reflux components (bile acids, pepsin) and their roles in AT2 cell injury, senescence, and fibrogenesis using ex vivo human lung models
- Studies evaluating the interaction between antifibrotic therapy (pirfenidone, nintedanib), GER treatment, and clinical outcomes
- Gender-stratified and genotype-stratified (MUC5B) analyses of GER-IPF interactions to identify high-risk phenotypes for targeted intervention
- Investigation of non-pharmacological GER management (positional modification, dietary changes, weight management) as adjunctive strategies in IPF

REFERENCES

1. Hutchinson JP, McKeever TM, Fogarty AW, Navaratnam V, Hubbard RB. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J. 2015;46(3):795-806. https://consensus.app/papers/details/36a9808b1ce25b24a1854db98a06301c/

2. Podolanczuk AJ, Thomson CC, Gimenez A, et al. Idiopathic pulmonary fibrosis: state of the art for 2023. Eur Respir J. 2023;61(4):2200957. https://consensus.app/papers/details/d0292e32d91f57a5bd4b5b36b7cd162a/

3. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006;27(1):136-142. https://consensus.app/papers/details/1bedf0e70c4b54e0a9815081bb7bf924/

4. Culver DA, Behr J, Belperio JA, et al. Baseline characteristics of patients in the Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry. Chest. 2020;158(4):1745-1756. https://consensus.app/papers/details/fa64230d67375bc6a82afe3b7c1fb730/

5. Savarino E, Carbone R, Marabotto E, et al. Gastro-oesophageal reflux and gastric aspiration in idiopathic pulmonary fibrosis patients. Eur Respir J. 2013;42(5):1322-1331. https://consensus.app/papers/details/1517f15da4c558aea9e9554d7ab9fb21/

6. Chen B, Xu M, Zhu L, et al. Chronic microaspiration of bile acids induces lung fibrosis through multiple mechanisms in rats. Clin Sci. 2017;131(11):1047-1060. https://consensus.app/papers/details/0efb290f979a5791a7b406101e1c7e71/

7. Fidler L, Chua F, Bhatt N, et al. Treatment of Gastroesophageal Reflux in Patients With Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-analysis. Chest. 2018;153(6):1405-1415. https://consensus.app/papers/details/aa777e07728d514c9314e1d3806b00ca/

8. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205(9):e18-e47. https://consensus.app/papers/details/e718cc70404753eeb7f51657d9e558c2/

9. Jones M, McKeever T, Brown J, et al. The effectiveness and risks of Treating people with Idiopathic Pulmonary fibrosis with the Addition of Lansoprazole (TIPAL): study protocol for a randomised placebo-controlled multicentre clinical trial. BMJ Open. 2025;15(2):e090105. https://consensus.app/papers/details/2baec6b653ff54e5a553328ce57b69ab/

10. Raghu G, Yang STY, Spada C, Hayes J, Pellegrini CA. Sole treatment of acid gastroesophageal reflux in idiopathic pulmonary fibrosis: a case series. Chest. 2006;129(3):794-800. https://consensus.app/papers/details/d80a4765481b5f219656c52b627a3a19/

11. Lee JS, Ryu JH, Elicker BM, et al. Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184(12):1390-1394. https://consensus.app/papers/details/187a2b66aeeb5c5da1e9fd0631eaf8e5/

12. Noth I, Zangan SM, Soares RV, et al. Prevalence of hiatal hernia by blinded multidetector CT in patients with idiopathic pulmonary fibrosis. Eur Respir J. 2011;39(2):344-351. https://consensus.app/papers/details/89beb76dec835e45bf2c5af44c2cd870/

13. Tcherakian C, Cottin V, Brillet PY, et al. Progression of idiopathic pulmonary fibrosis: lessons from asymmetrical disease. Thorax. 2011;66(3):226-231. https://consensus.app/papers/details/c9e1cf89c2665d7490a342683f0d0aa9/

[14.] Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37(2):356-363. https://consensus.app/papers/details/4b52efde38515db4b5ab16457c7a71dc/

[15.] Savarino E, Carbone R, Marabotto E, et al. Gastro-oesophageal reflux and gastric aspiration in idiopathic pulmonary fibrosis patients. Eur Respir J. 2013;42(5):1322-1331. https://consensus.app/papers/details/1517f15da4c558aea9e9554d7ab9fb21/

[16.] Lee JS, Song JW, Wolters PJ, et al. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. Lancet Respir Med. 2013;1(5):369-376. https://consensus.app/papers/details/8e6cff5e2b055291b4cff7519dff42e5/

[17.] Tossier C, Dupin C, Plantier L, et al. Hiatal hernia on thoracic computed tomography in pulmonary fibrosis. Eur Respir J. 2016;48(3):833-842. https://consensus.app/papers/details/d58403cb9b375f16997f86a4cecfc628/

[18.] Kreuter M, Wuyts W, Renzoni E, et al. Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. Lancet Respir Med. 2016;4(5):381-389. https://consensus.app/papers/details/a2a1c7a421375cd7a62731edebd3255b/

[19.] Kreuter M, Ehlers-Tenenbaum S, Palmowski K, et al. Impact of Comorbidities on Mortality in Patients with Idiopathic Pulmonary Fibrosis. PLoS ONE. 2016;11(3):e0151companions. https://consensus.app/papers/details/52c2f04471245c0093c80837d603d5c6/

[20.] Raghu G, Pellegrini CA, Yow E, et al. Laparoscopic anti-reflux surgery for idiopathic pulmonary fibrosis at a single centre. Eur Respir J. 2016;48(3):826-832. https://consensus.app/papers/details/35f2e148ed9b5cc6a59644f19288515f/

[21.] Dutta P, Webb G, Mansur AH, et al. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. Thorax. 2019;74(4):346-353. https://consensus.app/papers/details/a6fedd1077fb5d4485d419e191180b20/

[22.] Raghu G, Pellegrini CA, Yow E, et al. Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial. Lancet Respir Med. 2018;6(9):707-714. https://consensus.app/papers/details/6192fa163a265316a5c60b639580b09f/

[23.] Tran T, Assayag D, Ernst P, Suissa S. Effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis: a population-based cohort study. Chest. 2021;159(2):673-682. https://consensus.app/papers/details/ec6ec5f9bf905c169bcdd539a5b0e5df/

[24.] Rangan V, Chan WW, Lo WK, et al. Novel Advanced Impedance Metrics on Impedance-pH Testing Predict Lung Function Decline in Idiopathic Pulmonary Fibrosis. Am J Gastroenterol. 2021;116(4):765-773. https://consensus.app/papers/details/1cb7a670c4aa5bebb7857557a2e0e691/

[25.] Cheah R, Lee K, Liu Z, et al. The Perils and Pitfalls of Esophageal Dysmotility in Idiopathic Pulmonary Fibrosis. Am J Gastroenterol. 2021;116(6):1232-1242. https://consensus.app/papers/details/289e4513172450f99d291a2955c737bf/

[26.] Mackintosh JA, Marshall HM, Towers M, Reddiex B, Keir GJ. In patients with idiopathic pulmonary fibrosis the presence of hiatus hernia is associated with disease progression and mortality. Eur Respir J. 2019;54(Suppl 63):OA3430. https://consensus.app/papers/details/148eb36b7b575e449d5eadcfd5c2db20/

[27.] Reynolds CJ, Di Celso M, Nicholson AG, Wells AU, Maher TM, Jenkins G. The causal relationship between gastro-oesophageal reflux disease and idiopathic pulmonary fibrosis: a bidirectional two-sample Mendelian randomisation study. Eur Respir J. 2022;61(3):2200957. https://consensus.app/papers/details/c66ce5bcbab259ff974447da76247c42/

[28.] Zhu J, Nathan N, Bhatt S, et al. A causal atlas on comorbidities in idiopathic pulmonary fibrosis: a bidirectional Mendelian randomization study. Chest. 2023;164(5):1202-1215. https://consensus.app/papers/details/5af435da9386558aa4963ed5d78ca911/

[29.] Kim JS, Aslan A, Stimpson G, et al. Associations of hiatus hernia with CT-based interstitial lung changes: the MESA Lung Study. Eur Respir J. 2022;61(3):2200897. https://consensus.app/papers/details/8c9e60661db7587eb373ffb6d21c33e6/

[30.] Lee Y, Bui T, Nguyen T, et al. Proton Pump Inhibitor Use and Impact on Mortality and Clinical Outcomes in Idiopathic Pulmonary Fibrosis: A Propensity-Matched Cohort Study. Am J Respir Crit Care Med. 2026;213(Suppl A):A2039-12. https://consensus.app/papers/details/093c208cb71b5c668f3dd7bd48d38206/

[31.] Lee Y, Bui T, Nguyen T, et al. Association of Histamine-2 Receptor Antagonist Use with Clinical Outcomes in Patients with Idiopathic Pulmonary Fibrosis: A Propensity-Matched Cohort Study.

Am J Respir Crit Care Med. 2026;213(Suppl A):A2039-13. https://consensus.app/papers/details/2e45275e9d6852bc9f86468519d4869f/

32. Sia LC, Gibbons MA, Connaughton PJ, et al. Gender differences in clinical features, comorbidities and prognostic outcomes in idiopathic pulmonary fibrosis—a retrospective cohort analysis from the British Thoracic Society Interstitial Lung Disease Registry. BMJ Open. 2025;15(3):e085412. https://consensus.app/papers/details/9a4f491cf13457a7a19cda1e2bfc11f4/

33. Blondeau K, Mertens V, Vanaudenaerde BA, et al. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. Eur Respir J. 2008;31(4):707-713. https://consensus.app/papers/details/103d1a2651b65e7795387a572066e9cd/

34. Khor YH, Ng Y, Barnes H, et al. Antacid Medication and Antireflux Surgery in Patients with Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2022;19(4):613-625. https://consensus.app/papers/details/6d566b9ca7e75bf7a29515cdac912153/

35. Bedard Methot D, Leblanc E, Lacasse Y. Meta-analysis of Gastroesophageal Reflux Disease and Idiopathic Pulmonary Fibrosis. Chest. 2019;155(1):33-43. https://consensus.app/papers/details/c453d6190c235b6c8757116a87e114d0/

36. Selman M, Pardo A, Ramirez R. Decoding the complexity: mechanistic insights into comorbidities in idiopathic pulmonary fibrosis. Eur Respir J. 2025;65(2):2401234. https://consensus.app/papers/details/929485507471534ab1b694ce3825888f/

37. George P, Mackintosh J, Goldacre R, et al. Hiatus hernia and interstitial lung abnormalities. Eur Respir J. 2020;56(4):2000610. https://consensus.app/papers/details/6fe5f805a838561caaacf3afed184d10/

38. Emilsson O, Lam AD, Franklin KA, et al. Nocturnal gastro-oesophageal reflux and pulmonary abnormalities on chest CT in a general population: the Swedish CArdioPulmonary BioImage Study. Thorax. 2025 doi:10.1136/thorax-2024-221811. https://consensus.app/papers/details/fdbb4b28ea49556a88e4a1403a7e9e03/