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Research Progress on Interstitial Lung Disease Complicated with Gastroesophageal Reflux Disease

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Abstract. Interstitial lung disease (ILD) and gastroesophageal reflux disease (GERD) are highly comorbid and closely related in pathophysiology. Epidemiological data show that the prevalence of GERD in patients with ILD is significantly higher than that in the general population. ILD can induce reflux disease through abnormal respiratory mechanics, dysfunction of the diaphragm and esophagus, and increased abdominal pressure caused by cough. Microaspiration resulting from reflux can irritate lung tissue, aggravate pulmonary inflammation and fibrosis progression, and affect patients' clinical symptoms, quality of life, and prognosis after lung transplantation. Clinically, a multi-level treatment strategy has been established for comorbid conditions. Non-pharmacological interventions can reduce reflux triggers. The use of acid-suppressive drugs requires distinguishing indications for prophylactic medication according to disease types. Surgery and traditional Chinese medicine can be selected appropriately based on the disease condition. Standardized treatment of GERD can reduce lung tissue injury, delay the progression of ILD, and improve the overall prognosis of patients. Clinically, relevant guidelines should be followed, and diagnosis and treatment strategies should be formulated according to individual conditions to improve the comprehensive intervention effect of comorbidities.

Keywords: Interstitial lung disease; Gastroesophageal reflux disease; Comorbidity; Reflux.

1. Background

Interstitial lung disease (ILD) is a group of diffuse pulmonary diseases characterized by involvement of the alveoli, pulmonary interstitium, microvessels, and distal airways. Over the past decade, the global incidence of ILD has been on the rise, reaching 207.2 per 100,000 population in 2019, an increase of 51% compared with ten years ago. The etiology of ILD is complex, including idiopathic pulmonary fibrosis (IPF), connective tissue disease-related ILD, hypersensitivity pneumonitis, drug- or environment-induced ILD, and other subtypes. Among them, the prevalence of IPF is 7–1,650 per 100,000 population, and the incidence is 2.3–331 per 100,000 population per year, making it the most representative subtype with the worst prognosis. The common pathological features of ILD are interstitial inflammation, fibroblast proliferation, extracellular matrix deposition, and lung structural remodeling. Clinically, it is manifested as progressive exertional dyspnea, persistent dry cough, and some patients have clubbing of the fingers and basal crackles in both lungs. Pulmonary function shows restrictive ventilatory disorder and decreased diffusion capacity, which seriously affects patients' quality of life. In particular, IPF has an insidious onset and rapid progression, with a median survival of only 2–3 years, and is a critical and difficult disease in clinical practice [2].

Gastroesophageal reflux disease (GERD) is a common digestive system disease caused by abnormal lower esophageal sphincter function, decreased esophageal clearance, delayed gastric emptying, and other factors, leading to the reflux of gastric and duodenal contents into the esophagus, resulting in symptoms or mucosal injury. Epidemiological data from North America show that the prevalence of GERD is 18.1%–27.8% [3]. Its typical symptoms include acid regurgitation, heartburn, and substernal pain, and it can also manifest as asymptomatic occult reflux. Long-term uncontrolled GERD can induce complications such as esophagitis, Barrett's esophagus, and esophageal stricture. Reflux contents inhaled into the lower respiratory tract through the throat are an important cause of various respiratory diseases [3].

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Based on the high incidence and clinical importance of these two diseases, further studies have found that ILD and GERD have a high clinical comorbidity. The prevalence of GERD in patients with ILD is significantly higher than that in the general population, and there are subtype differences. The comorbidity is most significant in idiopathic pulmonary fibrosis (IPF), and the severity of reflux is much higher than that in other ILD subtypes [4]. The prevalence of GERD symptoms in IPF patients is 52.6%–65.6%, and GERD can independently aggravate respiratory symptoms and reduce quality of life in patients.

A number of epidemiological and genetic studies have confirmed that there may be a causal relationship between GERD and ILD. Population-based case-control studies have shown that the risk of GERD in IPF patients 5 years before onset is 1.78 times that of the general population, suggesting that GERD may play an important role in the early stage of pulmonary fibrosis. Meta-analysis further confirmed that GERD can significantly increase the risk of ILD (OR=1.28, 95% CI: 1.05–1.57), and the association is stronger after multivariate adjustment (OR=4.96) [8]. This suggests that clinical attention should be paid to the early identification and standardized intervention of ILD complicated with GERD.

2. Pathophysiological Mechanisms of High GERD Prevalence in ILD Patients

The high prevalence of GERD in ILD patients is related to multiple factors such as abnormal respiratory mechanics, diaphragmatic dysfunction, esophageal motility defects, cough-related increased abdominal pressure, connective tissue disease involvement, and demographic and lifestyle factors. These factors interact with each other, jointly destroy the anti-reflux barrier, and induce reflux.

2.1. Abnormal Respiratory Mechanics and Crural Diaphragm Dysfunction

Abnormal respiratory mechanics and crural diaphragm dysfunction may be important factors by which ILD affects GERD. ILD is characterized by restrictive ventilatory dysfunction. Decreased lung compliance leads to abnormally increased intrathoracic negative pressure during inspiration, which directly pulls the esophagogastric junction (EGJ) and destroys the anti-reflux barrier formed by the lower esophageal sphincter and the crural diaphragm. A controlled study by Joshua et al. using high-resolution esophageal manometry showed that ILD patients have specific crural diaphragm dysfunction. The transdiaphragmatic pressure increases significantly during inspiration, while the EGJ anti-reflux pressure decreases significantly. 53.8% of patients have uncoupling of EGJ pressure and transdiaphragmatic pressure. Meanwhile, the incidence of sliding hiatal hernia is as high as 34.6%, which is significantly higher than that in healthy controls. These anatomical and mechanical abnormalities are the core mechanisms for the high prevalence of GERD in ILD patients. These abnormalities collectively lead to impaired anti-reflux barrier function and ultimately increase the risk of GERD.

2.2. Esophageal Motility Disorder

Esophageal motility abnormality is a key pathophysiological basis for ILD complicated with GERD. ILD can induce esophageal peristaltic dysfunction, which is more prominent in IPF patients. Studies have shown that the incidence of ineffective esophageal motility (IEM) in IPF patients is 31%, significantly higher than 16% in non-IPF ILD patients. Ineffective esophageal motility directly leads to decreased esophageal clearance, prolongs acid exposure time, and increases the risk of proximal reflux and microaspiration. The median acid exposure time in IPF patients is 4.8%, significantly higher than 1.5% in non-IPF ILD patients, with more proximal reflux events. The degree of lung function decline is negatively correlated with the degree of proximal reflux, suggesting that esophageal motility defects are key factors aggravating reflux burden. Connective tissue disease-related ILD (such as systemic sclerosis) is more likely to be accompanied by decreased esophageal peristalsis and swallowing dysfunction, further increasing the risk of GERD [11]. In summary, esophageal motility defects are important causes of weakened anti-reflux barrier function and increased reflux risk in ILD patients.

2.3. Increased Abdominal Pressure Caused by Chronic Cough and Abnormal Swallowing-Respiration Coordination

ILD patients often have persistent, irritating dry cough. Frequent cough leads to a sharp increase in intra-abdominal pressure, which directly impacts the lower esophageal sphincter and induces reflux attacks [11]. At the same time, ILD patients have abnormal swallowing-respiration coordination, delayed swallowing reflex, and decreased airway protection ability, which significantly increases the risk of microaspiration and acute exacerbation of reflux contents. Studies have shown that the risk of acute exacerbation of ILD in patients with swallowing abnormalities increases by 4.86 times [11]. These multiple factors interact, ultimately leading to impaired anti-reflux defense mechanisms in ILD patients and a significantly increased risk of GERD.

2.4. Other Factors

Advanced age, high BMI, and smoking are independent risk factors for ILD complicated with GERD. Among them, smoking amount is positively correlated with GERD risk (OR=1.015). Obesity increases intra-abdominal pressure and further weakens anti-reflux barrier function [11].

3. Effects of GERD on the Progression and Prognosis of ILD

GERD participates in the onset, progression, symptom aggravation, and poor prognosis of ILD through multiple pathways such as microaspiration, inflammation activation, and upregulation of pro-fibrotic pathways. It is an important controllable risk factor affecting the clinical outcome of ILD [12].

3.1. Chronic Microaspiration-Mediated Lung Injury

Microaspiration of reflux contents (gastric acid, pepsin, bile salts, food particles) into the lower respiratory tract is the core pathophysiological mechanism by which GERD aggravates ILD. The level of pepsin in bronchoalveolar lavage fluid (BALF) is significantly elevated in ILD patients. A study including 52 ILD patients and 79 lung cancer controls showed that the pepsin concentration in BALF of the ILD group was 15.6±8.9 ng/ml, significantly higher than 10.58±5.4 ng/ml in the control group ($P<0.001$), directly confirming frequent microaspiration in ILD patients [12]. Microaspiration can activate alveolar epithelial cell injury, inflammatory cell infiltration, and release of pro-fibrotic factors (TGF-β, IL-6, TNF-α), induce fibroblast proliferation and extracellular matrix deposition, and promote the progression of pulmonary fibrosis [12]. Even asymptomatic GERD with persistent microaspiration can cause occult lung injury and promote the progression of ILD from early inflammation to irreversible fibrosis [12].

3.2. GERD Aggravates Clinical Symptoms and Reduces Quality of Life in ILD

GERD can significantly aggravate the core symptoms of ILD and reduce patients' quality of life. In patients with fibrotic ILD, GERD can independently reduce the Chronic Respiratory Questionnaire (CRQ) fatigue score and aggravate respiratory symptoms such as dyspnea and cough [6]. The severity of cough in ILD patients is closely related to GERD. Patients with GERD have more severe and frequent cough, and severe cough further increases abdominal pressure and aggravates reflux, forming a "reflux-cough-reflux" vicious cycle.

3.3. Effects of GERD on Prognosis After Lung Transplantation in ILD

GERD is an important complication after lung transplantation in ILD patients and a key factor affecting graft function and long-term survival. The median survival of ILD patients after lung transplantation is significantly lower than that of other lung disease transplant populations. GERD can induce primary graft dysfunction, chronic lung allograft dysfunction (CLAD), recurrent pulmonary infection, and airway lesions, further reducing survival after transplantation. Therefore, preoperative evaluation and postoperative anti-reflux management are of great clinical significance[15].

4. Standardized Treatment Strategy for ILD Complicated with GERD

GERD is a common comorbidity in ILD. Reflux contents invade the airway, cause occult microaspiration, continuously induce pulmonary inflammation, and accelerate the progression of fibrosis, which is an important risk factor for disease deterioration. Standardized anti-reflux treatment can block the vicious cycle of reflux, aspiration, and lung injury, and is of key significance for relieving symptoms, delaying ILD progression, and improving prognosis. At present, clinically, for patients with ILD complicated with GERD, anti-reflux intervention is the core, combined with management of the primary disease, adopting a stepped and individualized comprehensive plan including lifestyle adjustment, acid-suppressive drugs, surgery, and traditional Chinese medicine conditioning, so as to achieve the treatment goals of controlling reflux, reducing lung injury, and delaying disease progression.

4.1. Non-Pharmacological Treatment

Non-pharmacological treatment is the basic intervention measure for all patients with ILD complicated with GERD. It has the advantages of safety, non-invasiveness, and long-term maintenance. Its core purpose is to reduce reflux events and reduce aspiration risk through behavioral and mechanical interventions. It is suitable for all patients, especially those with mild to moderate reflux and drug intolerance [16].

4.1.1. Lifestyle Intervention.

Lifestyle adjustment is the primary link in reflux control. The main contents include: fasting 2–3 hours before bedtime, elevating the head of the bed by 15–30°, adopting left lateral decubitus position, quitting smoking and limiting alcohol, controlling body weight, avoiding overeating and high-fat diet, reducing gastric content reflux through gravity effect and behavioral management [16]. Studies have shown that 87%–94% of IPF patients have abnormal esophageal acid exposure. Standardized lifestyle intervention can significantly reduce reflux frequency and improve acid regurgitation, heartburn, and nocturnal cough [16]. Although this method cannot reverse pulmonary fibrosis, it can effectively reduce respiratory tract irritation and reduce the risk of acute exacerbation, which is an indispensable part of comorbidity management.

4.1.2. Physical Adjuvant Intervention.

Chest band is a new physical intervention method used in ILD complicated with GERD in recent years. It moderately restricts thoracic expansion, reduces intrathoracic negative pressure during inspiration, reduces traction on the esophagogastric junction, and thus reduces reflux driving force. Clinical studies have confirmed that wearing a chest band can significantly improve patients' reflux symptoms. The total FSSG score decreased from 4 to 2 (P=0.018), and the acid reflux symptom score decreased from 2 to 0 (P=0.027). The improvement of quality of life score is significantly correlated with reflux relief, providing a safe supplementary option for patients with poor drug response.

4.2. Pharmacological Treatment

Pharmacological treatment is the core control method for ILD complicated with GERD. It mainly controls symptoms by inhibiting gastric acid, improving esophageal barrier function, promoting gastric emptying, and reducing irritation of reflux contents. Clinically, acid suppressants are the mainstay, and single or combined regimens are selected according to the condition.

4.2.1. Acid-Suppressive Therapy.

The official clinical practice guideline for adults with IPF and progressive pulmonary fibrosis released by ATS/ERS/JRS/ALAT in 2022 clearly states that acid-suppressive therapy is an important adjuvant for ILD complicated with GERD. The guideline conditionally recommends proton pump inhibitors (PPIs) for patients with IPF and progressive fibrotic ILD (PFILD) with confirmed GERD, with low to moderate evidence level. Its core benefit is to reduce acidic reflux contents and occult microaspiration, relieve intractable cough, reduce airway inflammation, delay lung function decline,

and reduce the risk of acute exacerbation. However, it cannot reverse the fibrosis process and cannot replace anti-fibrotic drugs such as nintedanib and pirfenidone.

Acid-suppressive therapy for ILD should be individualized. Prophylactic medication is not required for patients without evidence of reflux to avoid risks such as intestinal flora disturbance, vitamin deficiency, and osteoporosis caused by long-term medication. However, in systemic sclerosis-related ILD (SScILD), acid-suppressive therapy is not only effective but also has clear value for prophylactic medication. Studies have shown that the prevalence of GERD in SScILD patients is as high as 96%. Single PPI can reduce the risk of death (HR=0.5, P=0.031), and the combined regimen of PPI and H2 receptor antagonist has more significant benefits (HR=0.3, P=0.0009). A large German SSc cohort (n=1,931) further confirmed that PPI increased the 5-year overall survival rate from 70.9% to 91.4% and the progression-free survival rate from 45.9% to 66.8% (both P<0.0001). Given the extremely high incidence of reflux and clear benefits of acid suppression in SScILD, clinical prophylactic acid-suppressive therapy can be actively carried out for high-risk populations according to individual conditions, exerting lung protection by reducing microaspiration, and significantly improving long-term prognosis.

4.2.2. Antioxidant and Comorbidity Pathway Regulation Therapy.

GERD and ILD share pathological pathways such as oxidative stress and inflammation activation. Antioxidants can intervene in both pathways simultaneously and become an important adjuvant therapy. N-acetylcysteine, quercetin, etc., can scavenge oxygen free radicals, reduce lung injury caused by reflux, and inhibit TGF-β-mediated fibrosis signals, especially suitable for patients with frequent reflux and rapid decline in lung function [21]. Such drugs do not directly inhibit gastric acid, but can reduce subsequent lung injury caused by reflux, achieving the dual goals of "controlling reflux and protecting lungs".

4.3. Surgical Anti-Reflux Treatment

Anti-reflux surgery is mainly used for patients with poor drug response, severe reflux, confirmed microaspiration, and hiatal hernia. It reconstructs the anti-reflux barrier mechanically to achieve long-term control, and is an important intensive intervention for ILD complicated with refractory GERD.

4.3.1. Laparoscopic Anti-Reflux Surgery.

In addition to drug therapy, anti-reflux surgery represented by laparoscopic fundoplication can effectively repair the valve function of the esophagogastric junction, control both acidic and non-acidic reflux, and fundamentally reduce the occurrence of microaspiration. Studies have shown that 74% of patients have complete relief of reflux symptoms after surgery, with high safety and low short-term complication rates, most of which resolve spontaneously. Clinical data further confirmed that anti-reflux surgery can stabilize or even improve lung function in ILD patients. A study including 35 patients showed that forced vital capacity (FVC), percentage of predicted FVC, and forced expiratory volume in one second (FEV1) were significantly improved after surgery, suggesting that surgery can effectively delay the decline of lung function. However, the 2022 international guideline clearly states that anti-reflux surgery is not recommended as a routine method to improve respiratory prognosis in ILD, and its value lies more in relieving reflux symptoms and improving quality of life. Therefore, whether to choose drug or surgical treatment for ILD patients with GERD requires comprehensive evaluation by the attending physician based on the severity of reflux, lung function status, drug efficacy, and individual tolerance, and an individualized plan should be formulated.

4.4. Traditional Chinese Medicine Treatment

Traditional Chinese medicine has unique adjuvant value in the comprehensive intervention of ILD complicated with GERD. Relying on the advantages of holistic regulation and multi-target intervention, it has high safety and can be used as an important supplementary means in integrated traditional Chinese and Western medicine treatment. Clinical traditional Chinese medicine treatment follows the core principle of regulating both lung and stomach, selects classic prescriptions and

Chinese herbal medicines according to syndrome differentiation based on patients' clinical symptoms, effectively improves patients' discomfort symptoms, reduces lung tissue injury, delays disease progression, and plays an active role in the long-term management of comorbidities [24].

4.4.1. Clearing Heat, Resolving Phlegm and Removing Stagnation.

For the common clinical symptoms of ILD complicated with GERD such as acid regurgitation, chest tightness, cough and asthma, shortness of breath, classic prescriptions such as Xiaoxianxiong Decoction and Daxianxiong Pill are often modified clinically. Such prescriptions can effectively relieve patients' reflux and respiratory discomfort symptoms and improve the overall clinical state. Modern pharmacological studies have confirmed that such prescriptions can effectively inhibit the body's inflammatory response, reduce the expression of related inflammatory factors, reduce inflammatory infiltration and injury of lung tissue, and inhibit the deposition of fibrosis-related matrix in the lung, thereby delaying the progression of pulmonary fibrosis, providing auxiliary support for the repair of lung injury [24].

4.4.2. Pungent Dispersion and Bitter Downbearing for Regulation.

Pungent dispersion and bitter downbearing method is a commonly used treatment for ILD complicated with GERD. Clinically, Banxia Xiexin Decoction and Xiaoxianxiong Decoction are used as the basic prescriptions for syndrome differentiation and modification. Such prescriptions can effectively regulate gastrointestinal function, reduce abnormal gastric acid secretion, enhance esophageal peristaltic function, improve esophageal clearance, reduce persistent injury of airway and lung tissue caused by reflux and microaspiration, indirectly protect lung function by improving gastric reflux, achieve the therapeutic effect of treating both lung and stomach, and significantly relieve patients' reflux and lung discomfort symptoms [25].

4.4.3. Tonifying Qi and Consolidating the Root for Regulating Qi.

In view of the characteristics of deficiency in origin and excess in superficiality in patients with ILD complicated with GERD, the treatment idea of tonifying qi and regulating qi is often adopted clinically, with Chinese herbal medicines such as Pseudostellaria heterophylla, Astragalus membranaceus, Inula japonica, and Salvia miltiorrhiza. Such drugs can effectively improve patients' typical symptoms such as shortness of breath, chronic cough, acid regurgitation, and general fatigue, and at the same time stabilize the state of lung lesions and inhibit the continuous progression of the disease. Compared with single symptomatic treatment, this method can take into account regulating the overall state of the body and controlling local lesions, and has good clinical application value in improving quality of life and delaying the course of ILD [26].

5. Summary and Prospect

There is a clear bidirectional relationship between ILD and GERD, forming a vicious cycle. On the one hand, pulmonary fibrosis and elevated intrathoracic negative pressure in ILD, together with diaphragmatic dysfunction, directly induce GERD. On the other hand, microaspiration of GERD reflux contents injures alveolar epithelium, activates inflammation and fibrosis pathways, and accelerates ILD progression. This bidirectional association is most prominent in IPF patients, with GERD prevalence as high as 42%–87%, mostly asymptomatic occult reflux, which is easily missed and leads to continuous progression of lung injury [12]. Standardized treatment of GERD can reduce microaspiration of acidic substances, reduce inflammatory stimulation of the lung, and inhibit the development of pulmonary fibrosis. At the same time, it can relieve discomfort such as cough and asthma, block the cycle of mutual aggravation of symptoms, and slow down the decline of lung function. Active management of reflux can also reduce the risk of acute exacerbation of the disease and the probability of complications after lung transplantation, effectively protecting lung tissue and improving the overall prognosis of ILD.

According to international clinical guidelines, routine prophylactic acid-suppressive therapy is not recommended for ordinary ILD patients without reflux-related symptoms and objective examination

evidence, to avoid adverse reactions of long-term medication. However, the incidence of reflux in systemic sclerosis-related ILD is extremely high, and prophylactic use of acid-suppressive drugs can effectively reduce the risk of death and improve long-term survival. Such high-risk populations can be considered for preventive anti-acid intervention as appropriate. Clinically, the timing of medication should be comprehensively judged based on examination results and disease subtypes.

With reference to authoritative guidelines, a multi-step individualized comorbidity treatment plan has been established. Lifestyle adjustment and physical intervention are used as basic means to control reflux triggers daily; acid-suppressive and antioxidant drugs are the core to simultaneously improve reflux symptoms and lung injury; surgical repair of anti-reflux structure can be evaluated when drug efficacy is limited; traditional Chinese medicine can also be used as an adjuvant to stabilize the condition. The treatment model takes into account both diseases, which can simultaneously control the condition and delay disease progression.

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