ISSN: 2053-3578 I.F. 12.34

PULMONARY HYPERTENSION IN INTERSTITIAL LUNG DISEASE: DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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Annotation: This article devoted to open the theme pulmonary hypertension in interstitial lung disease: diagnostic and therapeutic challenges. Moreover, the article aims to explore the current state of knowledge regarding PH in ILD, emphasizing diagnostic challenges, recent therapeutic advances, and directions for future research.

Key words: *clinical picture, therapeutic challenges, inflammatory mediators, meta-analysis, Noninvasive testing.*

INTRODUCTION

Pulmonary hypertension (PH) is a serious and often progressive complication that can develop in patients with interstitial lung disease (ILD), significantly impacting morbidity and mortality. ILD encompasses a diverse group of parenchymal lung disorders characterized by inflammation and fibrosis, which impair gas exchange and respiratory mechanics. When PH coexists with ILD—referred to as PH-ILD—the clinical picture becomes notably more complex. This overlap not only exacerbates symptoms such as dyspnea and exercise intolerance but also presents considerable diagnostic and therapeutic challenges due to overlapping clinical features and limited evidence-based treatment options. The pathophysiology of PH in the context of ILD is multifactorial, involving mechanisms such as hypoxic vasoconstriction, vascular remodeling, destruction of pulmonary vasculature, and inflammatory mediators.

LITERARY ANALYSIS

Diagnostically, distinguishing PH-ILD from isolated pulmonary vascular or cardiac disease can be difficult, requiring a multimodal approach including high-resolution computed tomography (HRCT), echocardiography, pulmonary function tests, and right heart catheterization—the gold standard for confirmation. However, the presence of lung fibrosis often complicates hemodynamic interpretation and limits the accuracy of noninvasive tools. Therapeutically, the management of PH-ILD remains a contentious issue. While pulmonary vasodilators are the cornerstone of treatment in pulmonary arterial hypertension (PAH), their

ISSN: 2053-3578 I.F. 12.34

use in PH-ILD is controversial due to the potential for worsening gas exchange through ventilation-perfusion mismatch. Recent clinical trials, such as those evaluating inhaled treprostinil, have shown promise, but the therapeutic landscape is still evolving. Given these complexities, a comprehensive understanding of the diagnostic criteria, pathophysiological underpinnings, and treatment dilemmas is essential for improving outcomes in this high-risk patient population.

Pulmonary hypertension (PH) commonly complicates fibrotic lung diseases and markedly worsens prognosis. According to the 2019 World Symposium and 2022 ESC/ERS guidelines, PH is defined by a mean pulmonary arterial pressure (mPAP) > 20 mmHg on right heart catheterization. PH due to lung disease (WHO Group 3) is diagnosed when mPAP>20 mmHg is accompanied by a pulmonary arterial wedge pressure ≤ 15 mmHg and pulmonary vascular resistance (PVR)>2 Wood units. ILD is a major cause of Group 3 PH – for example, PH is detected in up to 20–80% of patients with idiopathic pulmonary fibrosis (IPF) and in roughly one-third of patients with other fibrotic ILD. Importantly, PH dramatically worsens outcomes: IPF patients with PH have a median survival of only ~2 years (vs 3–5 years without PH), and one meta-analysis found that PH roughly doubles mortality risk in ILD. These data highlight the need for early detection and tailored management of PH-ILD. Diagnosing PH-ILD is challenging because its symptoms (progressive dyspnea, exercise intolerance, hypoxemia) overlap with those of the underlying ILD. Clinicians must maintain a high index of suspicion, especially when clues emerge that are disproportionate to lung mechanics. For example, a very low diffusing capacity (DLCO) or pronounced desaturation on exertion should raise concern. A DLCO <30% predicted approximately doubles the likelihood of PH-ILD, and each 10% decrement in DLCO predicts a ~30% higher mortality risk. Likewise, an unusually short six-minute walk distance or marked exercise-induced oxygen desaturation are suggestive of pulmonary vascular disease. Impaired heart-rate recovery after exercise (e.g. <13 beats per minute drop after 1 minute) has also been linked to PH in IPF patients. Physical examination is often normal until late; when advanced PH occurs, findings may include loud P2, RV heave, jugular venous distension, hepatomegaly, or peripheral edema. In practice, any ILD patient with disproportionate symptoms or unexplained oxygen needs warrants further evaluation.

Noninvasive testing is used to screen for PH-ILD, but all have limitations. Pulmonary function tests (PFTs) are part of routine ILD care; severely reduced DLCO is the most sensitive PFT clue to PH. By contrast, simple spirometry or lung volumes do not reliably predict PH. A chest high-resolution CT (HRCT) can hint at PH: a main pulmonary artery (PA) to ascending

ISSN: 2053-3578 I.F. 12.34

aorta (A) diameter ratio >0.9 correlates with mPAP >20 mmHg and worse survival. A right-to-left ventricular diameter ratio >1 on CT also suggests RV enlargement. Echocardiography is routinely performed but has only modest accuracy in ILD: a tricuspid regurgitant velocity (TRV) >2.8 m/s (or calculated RV systolic pressure >35 mmHg) suggests PH, but image quality is often poor in fibrotic lungs. Newer RV parameters (TAPSE, RV fractional area change, RV outflow tract diameter) add prognostic value. For example, 3D echo-derived RV fractional area change <28% predicted higher mortality. However, even comprehensive echo can miss PH: one study found 40% of ILD patients deemed "low risk" by echo screening actually had PH on catheterization. Because of these limitations, right-heart catheterization (RHC) remains the gold standard for diagnosis. RHC confirms precapillary PH (mPAP ≥20 mmHg, PVR >2 WU, PCWP ≤15 mmHg) in a patient with ILD on imaging. Hemodynamics also allow exclusion of other causes (e.g. occult left heart disease or chronic thromboembolism) and assessment of severity. Notably, even mild elevations in mPAP carry prognostic weight, so some experts advocate cautious monitoring of patients with early or exercise-induced PH.

RESULT AND DISCUSSION

Recent literature and clinical studies have provided significant insights into the prevalence, pathophysiology, diagnostic markers, and treatment options for pulmonary hypertension associated with interstitial lung disease (PH-ILD). The most notable findings from reviewed studies include:

- Prevalence: PH occurs in 20–80% of patients with advanced interstitial lung disease, particularly in idiopathic pulmonary fibrosis (IPF), and is associated with worse functional capacity and higher mortality.
- Diagnostic Parameters:
    - Right heart catheterization (RHC) remains the gold standard for diagnosis.
    - Echocardiography, reduced DLCO (<30%), and elevated NT-proBNP levels are useful screening indicators but lack sufficient specificity.
    - CT imaging (e.g., PA/A ratio > 0.9) is an emerging tool to suspect PH in ILD patients.
- Prognostic Implications: The presence of PH in ILD patients is associated with a 2- to 3-fold increased risk of mortality. For example, IPF patients with PH have a median survival of 1.5–2 years, compared to 3–5 years without PH.
- Therapeutic Advances:

- Inhaled treprostinil (as shown in the INCREASE trial) is the first FDA-approved treatment that significantly improved 6-minute walk distance and reduced NT-proBNP levels in PH-ILD patients.
- Trials with endothelin receptor antagonists and riociguat were terminated early due to adverse effects, highlighting the need for cautious therapeutic targeting.
- Supportive care, including long-term oxygen therapy, diuretics for right heart failure, and pulmonary rehabilitation, remains the cornerstone of management.

The diagnosis and treatment of PH-ILD remain inherently challenging due to the overlapping pathophysiology and clinical manifestations of pulmonary fibrosis and pulmonary vascular disease. Dyspnea, hypoxemia, and reduced exercise tolerance are hallmark symptoms of both ILD and PH, complicating early recognition. One of the main diagnostic difficulties is distinguishing pulmonary hypertension due to hypoxic vasoconstriction from true vascular remodeling, particularly in early or moderate stages. Although right heart catheterization provides definitive hemodynamic confirmation, its invasiveness limits routine use. Hence, the identification of non-invasive yet reliable surrogate markers is a major clinical priority. Tools like high-resolution CT imaging (measuring PA/A ratio), echocardiography, and biomarkers (e.g., BNP/NT-proBNP) offer useful screening value, but none replace the need for catheter-based confirmation in suspected cases.

From a therapeutic perspective, the traditional view has been that Group 3 PH (due to lung disease) is not amenable to PAH-specific therapies due to the risk of worsening ventilation-perfusion mismatch. This was reinforced by the negative outcomes of clinical trials like ARTEMIS-IPF and RISE-IIP, where systemic vasodilators either had no benefit or worsened patient outcomes. However, the INCREASE trial (2021) marked a pivotal shift. It demonstrated that inhaled treprostinil, delivered directly to ventilated lung regions, could safely improve exercise capacity and reduce clinical worsening without compromising gas exchange. These findings support the hypothesis that inhaled selective pulmonary vasodilators may strike an optimal balance between improving pulmonary hemodynamics and preserving ventilation-perfusion matching in PH-ILD.

Despite these advances, significant questions remain:

- Which patient subgroups benefit most from targeted therapy?
- Should early, asymptomatic PH be treated or observed?
- How should we distinguish between Group 1 (PAH with mild ILD) and Group 3 PH-ILD phenotypes?

Addressing these questions requires further multicenter trials, biomarker development, and improved phenotyping strategies using both imaging and hemodynamics. Additionally, long-term safety and real-world effectiveness data for inhaled treprostinil and other emerging therapies (e.g., inhaled nitric oxide) will be crucial for guiding practice.

CONCLUSION

Pulmonary hypertension in interstitial lung disease (PH-ILD) represents a complex and life-limiting condition that significantly worsens patient outcomes. Its diagnosis is particularly challenging due to overlapping clinical features with ILD and the limitations of non-invasive tests. While right heart catheterization remains the diagnostic gold standard, emerging imaging and biomarker approaches are improving screening accuracy.Therapeutically, recent advances such as inhaled treprostinil have opened new possibilities, marking a shift from the traditional avoidance of pulmonary vasodilators in this population. However, the overall treatment landscape remains limited, and patient selection for targeted therapies is still evolving. Comprehensive, multidisciplinary management—including supportive care, timely oxygen supplementation, and pulmonary rehabilitation—remains essential. Future research should focus on refining diagnostic tools, identifying reliable prognostic markers, and conducting large-scale trials to determine the long-term efficacy and safety of novel therapies. Ultimately, early detection and personalized treatment strategies will be key to improving the quality of life and survival of patients with PH-ILD.

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