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REVIEW ARTICLE

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Clinical significance of pulmonary hypertension in interstitial lung disease: A consensus statement from the Pulmonary Vascular Research Institute's innovative drug development initiative—Group 3 pulmonary hypertension

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Abstract
Pulmonary hypertension (PH) has been linked to worse outcomes in chronic lung diseases. The presence of PH in the setting of underlying Interstitial Lung Disease (ILD) is strongly associated with decreased exercise and functional capacity, an increased risk of hospitalizations and death. Examining the scope of this issue and its impact on patients is the first step in trying to define a roadmap to facilitate and encourage future research in this area. The aim of our working group is to strengthen the communities understanding of PH due to lung diseases and to improve the care and quality of life of affected patients. This introductory statement provides a broad overview and lays the foundation for further in-depth papers on specific topics pertaining to PH-ILD.

KEYWORDS
epidemiology, interstitial lung disease, prognosis, pulmonary hypertension, symptom assessment and management

INTRODUCTION

Pulmonary hypertension (PH) complicates the course of many patients with chronic lung disease (CLD-PH). The worldwide prevalence of CLD, with chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILD) as the prototypical diseases, is in the tens of millions.[1] Given this, it is likely that the number of CLD-PH patients significantly outnumbers Group 1 pulmonary arterial hypertension (PAH) patients. However, much of the research, literature, and pharmaceutical resources have been directed toward PAH. The Pulmonary Vascular Research Institute's Innovative Drug Development Initiative (PVRI IDDI) has initiated a number of workstreams to address various aspects of PH, with one such group devoted to PH due to lung diseases. This endeavor is a comprehensive collaborative effort constituted by academicians from across the globe, with pharmaceutical and regulatory representation. The aim of our working group is to strengthen the communities understanding of PH due to lung diseases and to improve the care and daily living of those patients. This paper will serve as the introduction to the deliberations of our group, with further manuscripts to follow which will delve deeper into specific areas.

PH caused by CLD-PH and/or hypoxia is classified under Group 3 PH.[2] The etiology of CLD-PH is complex and multifactorial, with differences in the pathogenic mechanisms between the diverse forms of CLD such as COPD and ILD.[3] The focus of this manuscript will be primarily on PH due to underlying ILD (PH-ILD).

Interstitial lung disease is a broad umbrella term encompassing a wide range of conditions that have in common their diffuse involvement of the interstitium of the lung.[4] Diagnostic work-up is usually pre-empted by the presence of interstitial abnormalities on conventional chest radiographs or high-resolution computed tomographic (HRCT) scans.

Once these disparate ILDs develop PH, their survivals are remarkedly similar. This lends credence to the concept that once PH supervenes, it is this that drives outcomes rather than the nature of the underlying lung disease (see also Table 3). The presence of PH in the setting of underlying ILD is strongly associated with decreased functional capacity, greater supplemental oxygen requirements, increased risk of hospitalizations, impaired health-related quality of life (HrQoL), and higher mortality.[3,5] Examining the scope of this issue and its impact on patients is the first step in trying to suggest solutions, and where no solutions exist, defining a roadmap to facilitate and encourage future research to address these unmet needs.

DEFINITIONS

Similarly to PAH, PH in the setting of ILD is diagnosed hemodynamically by right heart catheterization (RHC) derived parameters.

At the Sixth World Symposium on Pulmonary Hypertension, the definitions discussed by the task forces on "Hemodynamic definitions and clinical classification"[6]

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TABLE 1 Comparison between hemodynamic definitions of PH versus PH in CLD[6,7]

Hemodynamic definitions according to Simonneau et al.[6]	PH in CLD according to Nathan et al.[7]
Precapillary PH	**CLD without PH**
mPAP > 20 mmHg	mPAP < 21 mmHg or
PAWP ≤ 15 mmHg	mPAP 21–24 mmHg
PVR ≥ 3 WU	With PVR < 3 WU
Isolated postcapillary PH	**CLD with PH**
mPAP > 20 mmHg	mPAP 21–24 mmHg
PAWP > 15 mmHg	With PVR ≥ 3 WU
PVR < 3 WU	or mPAP ≥ 25 mmHg
Combined pre- and postcapillary PH	**CLD with severe PH**
mPAP > 20 mmHg	mPAP ≥ 35 mmHg
PAWP > 15 mmHg	or mPAP ≥ 25 mmHg
PVR ≥ 3 WU	With CI < 2.0/min/m^2

Abbreviations: CI, cardiac index; CLD, chronic lung disease; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

and "PH due to chronic lung disease"[7] were a little discordant (Table 1).

The discrepancy between these two definitions arises from the lack of clarity about the need for a pulmonary vascular resistance (PVR) ≥ 3 WU in those patients with an mPAP ≥ 25 mmHg as defined by the CLD-PH task force, which we believe should be a necessary prerequisite for any definition of precapillary PH. The rationale for the choice of mPAP ≥ 35 mmHg as a cut-off for severe PH follows previously presented evidence.[8] There have been other refinements of this definition. In 2018 the Cologne consensus conference defined severe PH due to lung disease based on having two of the following criteria PAP > 35 mmHg; PAP ≥ 25 mmHg and cardiac index (CI) < 2.0 L/min/m^2; PVR > 6 WU.[9] Most recently, another grading of severity of PH-ILD using a PVR cut-off> 5 WU was proposed by Olssen et al. based on the COMPERA registry data in 2021.[10,11] A PVR cut-off level of 8 WU had even a better *p* value and provided the best discrimination in survival.[10]

These changing definitions underscore the important concept that pulmonary vasculopathy in the context of ILD is a continuum, rather than distinct categories. It should be borne in mind that most distinct categorizations are imperfect, especially with hemodynamic cutpoints which represent just one "snapshot" in time. Figure 1 provides a depiction of the link between the radiographic appearance of ILD with histologic fibrosis and associated vascular changes, and the continuum of right ventricular decompensation as demonstrated on echocardiography.

EPIDEMIOLOGY/PREVALENCE

The ILDs represent a very large group of more than 200 different entities, many of which are rare or "orphan"diseases. The idiopathic interstitial pneumonias (IIPs) are a subset of ILD of unknown etiology characterized by variable amounts of inflammation and fibrosis of the interstitial compartment. There are eight histologic subtypes of IIP, with idiopathic pulmonary fibrosis (IPF) being the most common.[12]

The reported prevalence of PH seems to vary among the different ILD forms. However, this is probably not only dependent on the type of disease, but also on the characteristics of the cohort studied, including their disease severity and methods used to make a diagnosis of PH (Table 2). In addition, most of these data were reported before the change in definition and are based on the older definition of a mPAP ≥ 25 mmHg. Most of the data on the prevalence and impact of PH complicating ILD have been derived from the IPF literature. The variable global prevalence of IPF is estimated to be in the range from 1.3 to 43 per 100,000 persons.[13–16] In the earlier stages of the disease, precapillary PH has been described in 14% of IPF patients[17] but as IPF advances, the incidence of PH increases markedly up to 32%–50%, and in more than 80% of those with end-stage IPF (Table 2).[18–20]

It is not fully known how the updated definition for PH will affect the prevalence of PH-ILD. In one study of 8991 IPF patients listed for lung transplantation through the United Network for Organ Sharing, PH was more prevalent under the new definition (73.6%) compared to the former definition (47.6%) with the precapillary phenotype being present in 36.8% of the IPF patients.[32]

There are limited data on the role of ethnicity in the predilection for PH in patients with ILD. However, in one study, African American patients were reported to have a significantly higher prevalence of PH in the context of lung disease.[31] ILDs that are more prevalent in underdeveloped countries have not been studied for complicating PH. For example, post-tuberculosis pulmonary fibrosis is an underrepresented entity in the literature with a dearth of information on complicating PH. This is an area that is "overripe" for future research as we strive within the PVRI to impact global health disparities pertaining to PH.

There have been several studies that have shown a lack of correlation between the extent of lung damage as determined by the forced vital capacity,[31] or by computed tomographic measured fibrosis score,[33] and the presence or severity of PH. This attests to other factors aside from the extent of the physiologic or morphologic lung involvement as contributing to the genesis of PH. This

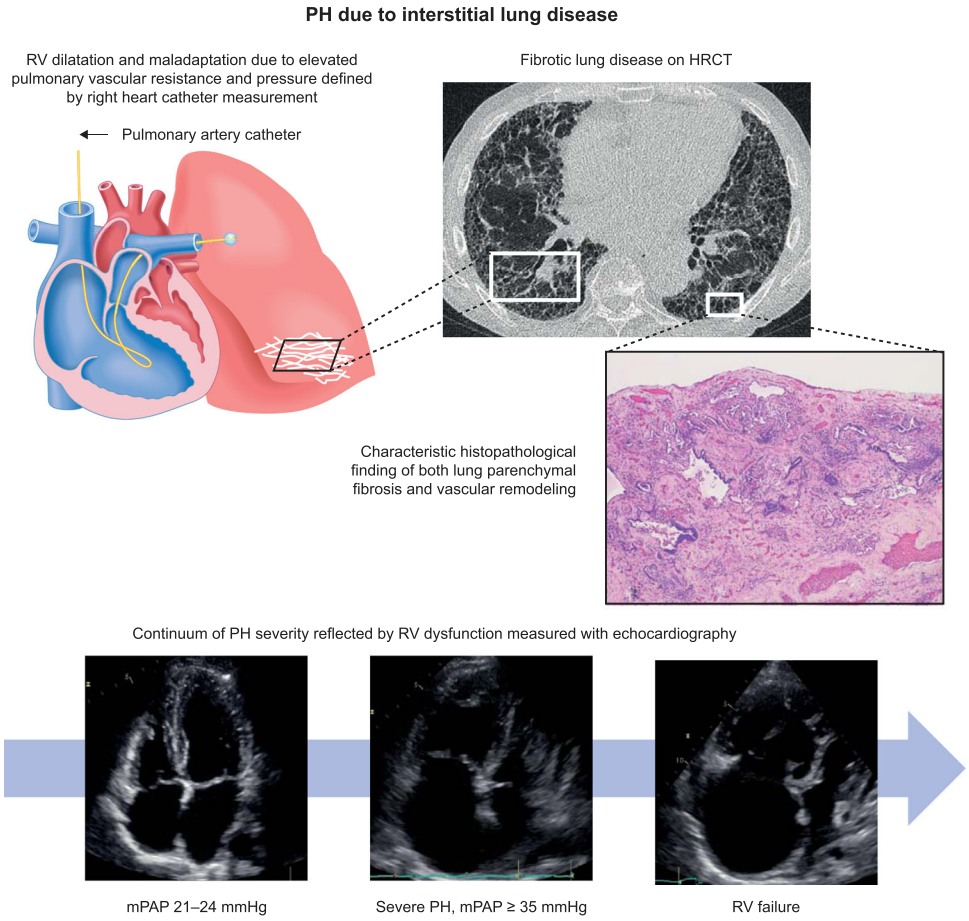

FIGURE 1 Continuum of pulmonary vasculopathy in interstitial lung disease in the context of histologic abnormalities and serial echocardiographic changes.

will be the subject of a subsequent paper from our working group. The one pulmonary function parameter that does appear to correlate with the presence of PH is a low single breath diffusing capacity for carbon monoxide (DLco) with a DLCO < 30% being associated with an increased risk of concomitant PH.[34] The occurrence of PH in patients with well-maintained lung function underscores the importance of awareness and early detection of this complication since PH has both prognostic and management implications for the patient.[23]

SYMPTOMS AND THE IMPORTANCE OF EARLY CLINICAL DIAGNOSIS

Patients with PH-ILD typically suffer from breathlessness which may be accompanied by cough, the latter being mostly due to the fibrotic component of their disease. Over time, there is progression such that they may develop overt signs of PH. ILD patients typically already suffer from breathlessness, however, there might be a subtle or imperceptible change in the quality of breathlessness once PH develops.

PH-ILD results in progressive shortness of breath which significantly impacts the patient's quality of life. In the early stages of the disease, dyspnoea is often triggered by physical activity (PA) and may lead to premature interruption of exercise or activities of daily living. Patients may progress to experience WHO functional Class 4 symptoms with dyspnoea at rest or with minimal exertion, even despite supplemental oxygen. Aside from gas exchange abnormalities, there are mechanical reasons that contribute to the sensation of dyspnoea; specifically, reduced lung compliance, increased minute ventilatory requirements, and increased work of breathing may all be contributory factors.

Unfortunately, the clinical diagnosis can be challenging to make, as there is a significant overlap of symptoms between fibrotic lung disease and PH as depicted in Figure 2.

Clinical examination alone lacks the sensitivity to predict PH-ILD accurately. Typical signs of PH such as a parasternal heave and a loud P2 heart sound are important clues; however, other signs of right heart

TABLE 2 Prevalence of PH in different chronic lung diseases

Chronic lung disease	Prevalence of PH	Study design	References
Idiopathic pulmonary fibrosis	14%	Analysis of 488 subjects with IPF enrolled in a placebo-controlled study who underwent right heart catheterization.	Raghu et al.[17]
	39% at initial evaluation 86% at time of transplant	44 consecutive patients at a single center with right heart catheterization undergoing evaluation for lung transplant.	Nathan et al.[19]
	46%	Retrospective review of 2525 patients with IPF listed for lung transplant in the United States from January 1995 to June 2004.	Shorr et al.[22]
	41%	Retrospective review of 118 patients with IPF over an 8-year interval.	Nathan et al.[23]
	48%	Cross-sectional study in 239 patients at one Indian center over 1 year	Tyagi et al.[24]
Nonspecific interstitial pneumonia	31%	Retrospective review of 35 patients with NSIP diagnosed between 2002 and 2016	King et al.[25]
Combined pulmonary fibrosis and emphysema	30%–50%	Retrospective study of 40 patients with CPFE	Cottin et al.[26]
CHP	20%	Prospective database from tertiary referral center for patients with ILD including 211 patients with CHP	Waelscher et al.[27]
	44%	Prospective evaluation of 50 consecutive patients with CHP undergoing right heart catheterization	Oliveira et al.[28]
	52%	Cross-sectional study in 239 patients at one Indian center over one year	Tyagi et al.[24]
ILD	21%	Retrospective analysis of 163 consecutive patients, including 85 with CTD-ILD	Handa et al.[29]
	3%	Prospective screening for PH using echocardiography in an unselected cohort of 147 patients with mixed connective tissue disease.	Gunnarsson et al.[30]
	64%	Presence of PH was assessed in 70 patients with advanced interstitial pneumonia undergoing right heart catheterization, including 14 patients with CTD-ILD.	Todd et al.[31]
IIPs	29%	Presence of PH was assessed in 70 patients with advanced interstitial pneumonia undergoing right heart catheterization, including 56 patients with IIP.	Todd et al.[31]

Abbreviations: CHP, chronic hypersensitivity pneumonitis; CPFE, combined pulmonary fibrosis and emphysema; CTD, connective tissue disease; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; PH pulmonary hypertension.

failure including jugular venous distension, hepatomegaly, and peripheral edema tend to occur later and are not usually associated with mild or moderate PH.[34,35] PH should be suspected in ILD patients when shortness of breath worsens in the setting of preserved lung function or appears to be out of proportion to the severity of the patient's underlying ILD.

ILD patients only develop symptoms and signs of right heart failure if they develop significant associated PH. This tends to occur at a later stage of the disease when patients already have a poor prognosis; in fact, it is not unusual for patients to succumb before the development of overt right heart failure.[35,36] Syncope can occur as a consequence of PH especially during exercise, due to reduced tissue oxygen delivery with variable contributions from an inadequate cardiac output response and arterial hypoxemia. In ILD, the occurrence of syncope may trigger the suspicion of PH.[37] However, syncope can also be induced by paroxysms of coughing, which ILD patients are predisposed to.[38]

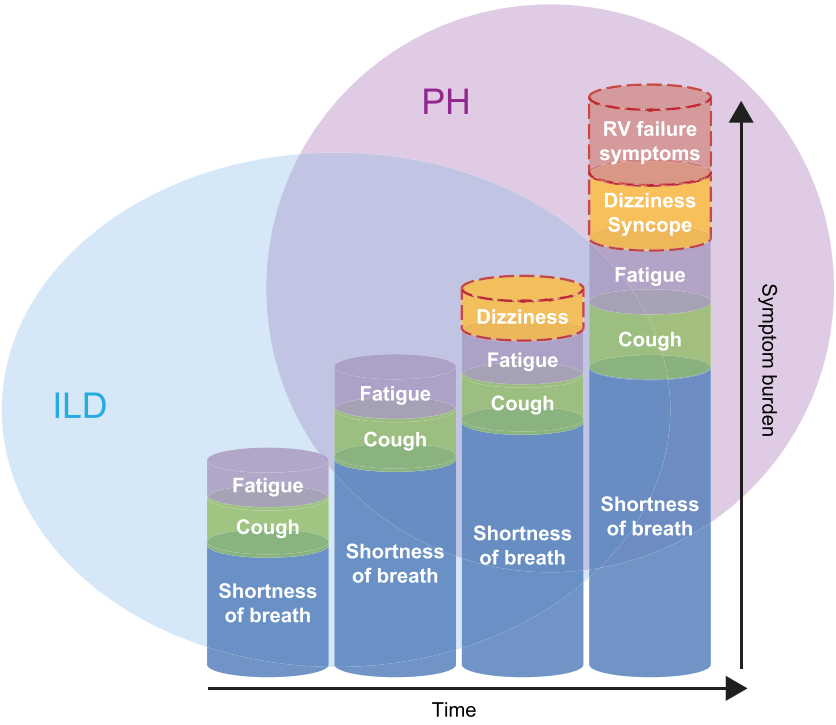

FIGURE 2 Concept depiction of the overlapping symptom burden of ILD and complicating PH. The *x* axis depicts the progressive nature of the symptoms over time, while the *y* axis depicts the magnitude of the global symptom burden imposed by the ILD and PH. The dashed symptoms are less common and do not occur in all patients. ILD, interstitial lung disease; PH, pulmonary hypertension.

There are important noninvasive and readily available parameters from the routine testing of patients with ILD (pulmonary function tests, 6MWD, high resolution computed tomography of the chest) that can provide clues to the presence of interceding PH in ILD patients. This will be covered in detail in a forthcoming manuscript from our group.

IMPACT AND MANAGEMENT OPTIONS

IPF, one of the most common forms of ILD, historically had a median survival range of 2.5–5 years.[39–42] The advent of antifibrotic therapy appears to be associated with improved survival; nonetheless, it remains clear that when PH develops, the risk of death is greatly increased.[43] Numerous studies have documented that PH due to ILD is an independent risk factor for morbidity and mortality with an associated median survival as low as 0.7 years (Table 3).[44] In fact, the development of PH-ILD is of such consequence that it is a criterion for listing for lung transplant according to the Consensus Document of the International Society for Heart and Lung Transplantation published in 2021.[45] Nathan et al.[19] reported that the prevalence of PH rapidly increases from 39% to 86% between the initial evaluation for lung transplant and the time of transplant.

The first tenant of addressing PH-ILD is to treat the underlying lung disease and any associated comorbidities that might be contributory. The underlying ILD should be optimally treated according to current guidelines; for example, with pirfenidone or nintedanib in the case of IPF,[55] or nintedanib in patients with other forms of fibrotic ILD such as scleroderma-ILD.[56,57] Long-term oxygen therapy is used in the treatment of hypoxemic patients, although its role in ameliorating PH progression in interstitial lung diseases has not been clearly delineated.[55] Active infections/exacerbations should be treated before formal PH evaluation where possible. Thromboembolic disease should be sought if clinically suspected and treated if present. Venous thromboembolic events can be observed in approximately one-fourth of patients with CTD-ILD or IIP.[58] A sleep study should be considered as patients with ILD commonly exhibit abnormal sleep architecture and increased sleep fragmentation on polysomnography.[59]

Currently approved and available PAH therapies—which are mostly systemically applied pulmonary vasodilators—are not recommended for patients with PH-ILD based on established PH as well IPF guidelines.[55,60] There is theoretic concern that they may impair gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction, although it has rarely been seen in either clinical trials or everyday practice.[61–63] Until recently, there has been a lack of data supporting their efficacy, as well as other data having demonstrated a negative benefit-/risk profile.[3] Indeed, some studies were not only negative but also demonstrated harm. Endothelin receptor antagonists have been studied in

TABLE 3 Effect of PH in ILD

References	Study design and patient population	PH threshold predefined or investigated	Key findings
Nadrous et al.[46]	136 patients with IPF undergoing transthoracic echo within 3 months of initial evaluation	Echo: Stratified three groups: <35 mmHg (14 patients), 36–50 mmHg (47 patients), and >50 mmHg (27 patients).	• Median survival of 0.7 years for patients with estimated sPAP > 50 mmHg compared to >4 years for those ≤50 mmHg.
Lettieri et al.[47]	Retrospective analysis of 79 consecutive patients with IPF	RHC: mPAP > 25 mmHg at rest	• Linear correlation between increased mPAP and risk of mortality. • Presence of PH associated with significantly diminished 6MWD and SpO_2 nadir. • 1-year mortality for patients with PH 28.0% versus 5.5% for patients without PH.
Hamada et al.[43]	Prospective analysis of 78 consecutive IPF patients	RHC: mPAP ≥ 17 mmHg	• 5-year survival: 62.2% without PH, whereas only 16.7% with PH.
Song et al.[48]	Retrospective review of 131 patients with IPF seen at a tertiary referral center	Echo: sPAP ≥ 40 mmHg	• 1-year mortality of 61.2% for patients with sPAP ≥ 40 mmHg compared to 19.9% for patients with sPAP < 40 mmHg.
Boutou et al.[49]	Retrospective analysis of 81 consecutive patients with IPF	Echo: Mildmoderate PH: sPAP > 35–49 mmHg Severe PH: sPAP ≥ 50 mmHg	• Decreased maximum work rate, anaerobic threshold, and peak O_2 consumption in severe PH.
Kimura et al.[50]	Retrospective analysis of 101 consecutive IPF	RHC: mPAP > 20 mmHg	• Increased mPAP was an independent predictor of death, even after controlling for lung disease severity; patients with an mPAP of ≤20 mmHg had a median survival of 37.5 months vs. 20.8 months for mPAP > 20 mmHg.
Oliveira et al.[51]	Observational study of 47 patients with CHP	RHC: PVR ≥ 3.3 WU	• Patients with an increased PVR had significantly poorer survival at 1, 2, and 3 years, even after adjusting for age, sex, and time from diagnosis.
Alhamad et al.[52]	Retrospective analysis of ILD and PH in a registry of 340 patients; 96 patients had PH and another 56 patients had severe PH	RHC: mPAP 21–24 mmHg with PVR ≥ 3 WU, or mPAP 25–34 mmHg; severe PH defined as mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg with low CI < 2.0 L/min/m^2[7]	• 28% of ILD patients had PH and 16% fulfilled severe PH definition; PVR ≥ 4.5 WU, sPAP, CI, and declined FVC were identified as independent predictors of outcomes.
Chen et al.[21]	Retrospective analysis of 608 ILD patients, 132 with progressive pulmonary fibrosis-ILD	Echo: sPAP > 36.5 mmHg	• Patients with the threshold of sPAP > 36.5 mmHg had significant poorer outcome.
Corte et al.[53]	Retrospective analysis of 66 consecutive patients with diffuse lung disease (DLD)	RHC: PVR > 6.23 WU	• In severe DLD, early mortality is strongly linked to increased PVR (>6.23 WU) but not to other RHC or noninvasive variables.
Gruenig et al.[54] Olsson et al.[10]	• 2015: COMPERA data from 165 PH-ILD patients analyzed as enrolled within 6	RHC: mPAP ≥25 mmHg at inclusion	• Despite targeted therapy patients with PH-ILD had a significant worse survival than patients with iPAH.

(Continues)

TABLE 3 (Continued)

References	Study design and patient population	PH threshold predefined or investigated	Key findings
	months of newly diagnosed PH • 2021: 449 PH-ILD patients analyzed		Survival rate at 1, 2, and 3 years: 73.3%, 51.2%, and 34.1%, respectively.[54] • PVR > 5 WU was associated with significantly worse survival.[10]

Abbreviations: CHP, chronic hypersensitivity pneumonitis; CI, Cardiac Index; CTD, connective tissue disease; DLD, diffuse lung disease; Echo echocardiography; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; mPAP, mean pulmonary arterial pressure; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with ILD; PVR, pulmonary vascular resistance; RHC, right heart catheterization; sPAP, systolic pulmonary arterial pressure; WU, Wood Units.

ILD or PH-ILD and have not been shown to be effective, while ambrisentan was demonstrated to be potentially harmful.[20,64,65] Phosphodiesterase inhibitors, specifically sildenafil, have been studied more extensively, and while efficacy remains equivocal, these at least have been shown to be safe and well tolerated.[66–68]

Despite these results, studies in this area are still strongly encouraged given the biological plausibility of targeting PH, the high unmet medical need, and the poor prognosis of these patients.[69]

There is a rationale for pulmonary selective treatment approaches using inhaled vasodilators rather than systemic agents, which may have the advantage of limiting side effects and reducing the likelihood of worsening ventilation/perfusion (V/Q) mismatching. Based on the pioneer work by Olschewski et al., inhaled iloprost was developed for Group 1 PAH, and approved worldwide.[70–72] Although there were initial promising reports of using inhaled prostacyclin and iloprost in severe PH-ILD,[73] it took another two decades to demonstrate the efficacy of an inhaled prostanoid for this condition. The recent positive phase 3 INCREASE trial of inhaled treprostinil in PH-ILD, which led to subsequent marketing approval in the United States, will hopefully provide a firm basis and rejuvenate further research of targeted pulmonary vascular therapies for Group 3 PH. The treatment of PH in patients with ILD will be covered in greater detail in our groups forthcoming paper on management and novel treatment approaches in PH-ILD.

WHAT IS KNOWN, WHAT IS UNKNOWN/AREAS FOR FUTURE RESEARCH

Preclinical research

From a preclinical point of view, identification of driving mechanisms for both the ILD and the PH and how they interrelate, require further exploration. More studies into factors that have the most substantial impact on the pulmonary vasculature and subsequently on RV function in PH-ILD are still warranted. In addition to how the progression of the primary ILD "might drive" the development of PH, the converse might also hold true with endothelial dysfunction of the pulmonary vasculature driving remodeling and further fibrosis.[74,75]

In addition to their primary mode of action, vasodilators have shown additional beneficial effects on the endothelium, inflammation, and proliferation in animal studies.[76–79] However, the clinical relevance of these findings has yet to be demonstrated in clinical outcome studies.

Future studies of pathogenesis should also concentrate on environmental, ethnic, and geographic factors. The relationship of genetic and molecular markers pertaining to specific diagnostic groups within the wide umbrella of ILD, as well as specific imaging patterns, are of particular interest to establish definite endophenotypes.

Clinical research

PH has a strong association with patient symptomatology and outcomes and is, therefore, a prime target for future research and therapeutic intervention. Further studies and guidance are needed into how best to identify interceding PH, as it remains mostly unrecognized in many of these patients. The development of specific algorithms to enhance screening and early diagnosis might enable earlier recognition, not only by experts at specialized ILD and PH centers, but also by general pulmonologists. The earlier recognition of PH-ILD might be further compromised through the delayed referral to ILD specialist clinics.[80] Since many ILD centers are separate and distinct from PH centers, there might be a lack of recognition of PH among ILD experts, while similarly, there might be an underappreciation for the optimal management of any ILD in patients with

purported PAH being managed at PH programs. The overall aim from a patient perspective is to optimize their care and enable a seamless integration of their PH and ILD management.

While the earlier identification of PH-ILD is a laudable goal, there are looming questions of how to intervene when it is found. Optimizing management extends beyond just providing important prognostic information, but also includes identification of the phenotypes that might best benefit from therapy and those that might not, and to avoid deleterious effects from specific therapeutic interventions. This remains an important topic to investigate and will be discussed in a future paper by this group addressing phenotypes in PH-ILD.

While it is well established that any PH in the context of ILD is associated with a worse prognosis, other factors impacting patient outcomes have not been fully elucidated in this population. Are there patient phenotypes who are at greater risk of having an accelerated course to their PH? What is the role of the pathogenic mechanism of the underlying primary ILD, and how does the progression of this impact the development of PH?

Risk assessment scores for the prediction of PH in ILD, as well as to predict outcomes after the development of PH are lacking. Initial attempts have extrapolated from PAH to PH-ILD using a truncated version of the European Society of Cardiology/European Respiratory Society (ESC/ERS) PH risk stratification scheme.[81] However, independent studies of PH-ILD are clearly needed to adequately account not only for the PH, but also the ILD and how these interrelate.

Recent encouraging studies with inhaled prostanoids have opened the door and hopefully will encourage further randomized controlled therapeutic trials in PH-ILD.[82] However, the defining criteria of patients who might best benefit from therapy remains to be further elucidated. Are there any patient phenotypes, pharmacologic agents, or modes of their delivery where alterations of V/Q-matching might be more than a theoretical concern? Is there a need to balance the extent of the underlying lung disease with the severity of the PH or is this only of theoretic concern? Are there patients without hemodynamically defined PH who could benefit from therapy directed at the pulmonary vasculature? Expectations should be managed with regard to what might be accomplished by targeting the pulmonary vasculature with vasodilators. Specifically, a modest benefit at best can be hoped for since these agents do not target the lung fibrosis itself, although, interestingly, there was a significant difference observed regarding placebo-corrected forced vital capacity improvements in both the INSTAGE study (nintedanib + sildenafil in IPF) as well as the INCREASE study (inhaled treprostinil in PH-ILD).[83,84]

Early studies describing the phenotype of "cor pulmonale" in COPD[85] raise similar questions in PH-ILD.[86,87] However, overt right heart failure as the cause of death is much less likely in ILD as the terminal aspects of the disease are driven more by respiratory failure. IPF disease progression or acute exacerbations were reported as the cause of death in 55% of decedents versus 13.8% for cardiovascular reasons from the British Thoracic Society IPF Registry.[88] However, such reports need to be interpreted in the context that the exact clinical differentiation between causes of death is very difficult to tease out and indeed might be multifactorial. This should be borne in mind for clinical trials with mortality as the endpoint and reinforces why all-cause mortality is generally recommended.

The impact of changes in the right ventricle (RV) is important to explore in future studies since this might help identify patients most likely to benefit from therapy. A focus on RV function is perhaps a lesson to be drawn from other forms of PH, where this has been shown to be an important determinant of outcomes and mortality. This raises the question as to whether RV dysfunction is the unifying factor that best identifies the phenotype to target among the various ILD types.[89,90] In one paper, RV dysfunction characterized by a right ventricular fractional area change of below 28% measured by echocardiography was associated with an increased risk of heart failure hospitalization or death.[91] In addition, a subgroup analysis of the STEP-IPF study of IPF patients with echocardiographic evidence of RV dysfunction demonstrated a favorable 99-m placebo corrected treatment effect in the 6-min walk distance with sildenafil.[92]

Determining phenotypes and endophenotypes may be achieved using machine learning and artificial intelligence. These approaches may incorporate the study of genetics, epigenetics, proteomics, and metabolomics; the use of imaging repositories to detect unifying morphologic patterns in ILD, and cluster analyses for evidence of clinical phenotypes, especially with regard to treatment response, such as has been applied in PAH.[93] What is known of distinct phenotypes and knowledge gaps, as well as the prerequisites to define new phenotypes, will be addressed in our groups forthcoming paper on pathogenesis and phenotypes.

Finally, there is an ongoing need for biomarkers or composites thereof that can discriminate between the extent of pulmonary vascular versus parenchymal aberrations. This search for biomarkers combined with advanced imaging, such as functional respiratory imaging, sequential computed tomography scans, hyperpolarized magnetic resonance imaging, or artificial intelligence techniques are areas ripe for further research.

Clinical trial design and endpoints

The few successes and many failures in PH-ILD clinical trials have afforded a few lessons, but perhaps pose more questions to be addressed to enable future trial designs that are primed for success. Two critical components are the most appropriate patient phenotypes and the implementation of clinically relevant endpoints. Provision should be made for the early identification of excess risk through diligent Data Safety and Monitoring Boards. Enrolment criteria should be pragmatic and not too exclusive as to render studies too difficult to recruit, but balancing this with enrichment of the study population. The trial duration should be sufficiently long to enable effective up-titration of the drug while allowing adequate follow-up time to discriminate a treatment effect.[94]

There is a need for endpoints that reflect patient's outcomes as accurately as possible; specifically, these should focus on how patients feel or function or survive. An endpoint of death from PH-ILD is obviously the most relevant and may be considered the most robust endpoint in this deadly disease. However, it may be impractical in the context of a typical clinical trial to serve as a standalone primary endpoint. In this regard, a composite of clinical deterioration, to include mortality, may be more feasible and pragmatic. It should also be borne in mind that treatment of PH-ILD may result in the improvement of the clinical condition and symptoms. Therefore, an alternate approach is an endpoint incorporating both clinical improvement and clinical deterioration, thereby providing both ends of the outcome spectrum in a competing risk analysis of time to clinical change.[95]

While death should always be included as the extreme of clinical deterioration, the other components of both clinical deterioration and improvement should meaningfully reflect how patients feel or function, while ideally also serving as surrogates for "harder" outcomes such as death or hospitalization.

In recent years, public and regulatory health policy has encouraged drug developers to consider the patient's perspective as a critical driver in the development of new therapies and treatments. With this change in perspective, regulatory agencies have supported public meetings to discuss and hear directly from those patients impacted by various diseases. Such discussions have reported that daily PA is most meaningful to those living within the spectrum of this disease (FDA patient-focused drug development Meeting September 26, 2014) and correlates to everyday management of their illness. These patients also reported that the most significant symptoms were coughing, shortness of breath, and fatigue/malaise and that the onset of these symptoms are triggered most often during PA (see Figure 2). The limitation and progressive decline in PA levels were reported to impact all aspects of the patient's emotional, social, and daily aspects of life—from struggling to perform basic household tasks (walking, climbing stairs, showering, cleaning) to sustaining a career and having to give up hobbies they previously enjoyed. An improvement in PA levels measured by 6-min walking distance or digital activity monitoring reflects how patients' function. Given the relatively small population of patients affected by this rare but potentially deadly disease, a patient-centric benefit-risk assessment would support the use of therapies that can impact PA.

Patient-reported outcomes (PROs) reflect how patients feel and are strongly recommended for inclusion in PH-ILD clinical trials. While there are numerous well-validated PROs for ILD or PAH, which ones should be employed and their performance characteristics in PH-ILD remain unknown. Whether a specific PH-ILD PRO needs to be developed is another area for future research. Since breathlessness and fatigue are the most prominent symptom in both PH and ILD, PROs that capture and are weighted to these might be most appropriate for clinical trials in ILD-PH. However, a worthy goal within the framework of any such future clinical trials should be to validate whichever PRO is instituted. A more detailed manuscript pertaining to clinical trial design in PH-ILD will be forthcoming from our group.

SUMMARY AND RECOMMENDATIONS

There is a growing appreciation for the prevalence and impact of pulmonary vascular aberrations in ILD. The most recent iteration of the hemodynamic definition of PH-ILD from the 2018 World PH symposium provides a framework for hemodynamic categorization within the continuum of these derangements. More insight is needed into the factors driving this vasculopathy and how this intersects with the interstitial process.

Future research is strongly encouraged to include studies focused on the early identification of PH, risk assessment, driving pathophysiologic and molecular factors, as well as deep phenotyping of PH-ILD subgroups. The patient perspective should be a ubiquitous theme in any future treatment trials. It is hoped that future insights will foster the development of novel clinical trial design and endpoints, which hopefully will lead to further innovative therapeutic options that are sorely needed and eagerly anticipated.

AUTHOR CONTRIBUTIONS

Sylvia M. Nikkho, Manuel J. Richter, Eric Shen, and Steven D. Nathan were involved in the conception and design of the study, conducted the searches and data extraction as well as wrote the first draft of the manuscript. All authors analyzed and interpreted the data, revised the manuscript critically for important intellectual content, approved the final manuscript, and agreed to be accountable for its overall content.

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CONFLICTS OF INTEREST

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ETHICS STATEMENT

There are no ethical concerns since this is a review based on the available literature and consensus expert opinion.

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