DOI: 10.1002/pul2.70005

REVIEW ARTICLE

Pulmonary Circulation Open Access | PVRi | WILEY

Screening and diagnosis of pulmonary hypertension associated with chronic lung disease (PH-CLD): A consensus statement from the pulmonary vascular research institute's innovative drug development initiative—group 3 pulmonary hypertension

P. Vitulo MD[1] | L. Piccari[2] | S. J. Wort[3] | O. A. Shlobin[4] | G. Kovacs[5] | C. D. Vizza[6] | P. M. Hassoun[7] | H. Olschewski[8] | R. E. Girgis[9] | S. M. Nikkho[10] | S. D. Nathan[4]

[1]Department of Pulmonary Medicine, IRCCS Mediterranean Institute for Transplantation and Advanced Specialized, Therapies, Palermo, Sicilia, Italy

[2]Department of Pulmonary Medicine, Hospital del Mar, Pulmonary Hypertension Unit, Barcelona, Catalunya, Spain

[3]National Pulmonary Hypertension Service at the Royal Brompton Hospital, London, UK and National Heart and Lung Institute, Imperial College, London, UK

[4]Advanced Lung Disease and Transplant Program, Inova Heart and Vascular Institute, Falls Church, Virginia, USA

[5]Department of Internal Medicine, Division of Pulmonology, Medical University of Graz, Graz, Austria

[6]University of Rome La Sapienza, Cardiovascular and Respiratory Science, Rome, Italy

[7]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland, USA

[8]Department of Internal Medicine, Division of Pulmonology, Medical University of Graz, Graz, Steiermark, Austria

[9]Corewell Health and Michigan State University College of Human Medicine, Grand Rapids, Michigan, USA

[10]Global Clinical Development, Bayer AG, Berlin, Germany

Correspondence
P. Vitulo, Department of Pulmonary Medicine, IRCCS Mediterranean Institute for Transplantation and Advanced Specialized, Therapies, Palermo, Sicilia, Italy.
Email: pvitulo@ismett.edu

Funding information
None

Abstract

Pulmonary hypertension (PH) is a frequent complication of chronic lung disease (CLD). However, PH is difficult to diagnose early since accompanying symptoms overlap and are similar to those of the underlying CLD. In most cases the PH is mild to moderate and therefore physical signs may be absent or subtle. This consensus paper provides insight into the clues that might suggest the presence of occult PH in patients with CLD. An overview of current diagnostic tools and emerging diagnostic technologies is provided as well as guidance for the work-up and diagnosis of PH in patients with CLD.

KEYWORDS
chronic lung disease, diagnosis, imaging, pulmonary hypertension, screening

INTRODUCTION

Pulmonary hypertension (PH) frequently complicates the course of patients with interstitial lung disease (ILD) and chronic obstructive lung disease (COPD). Once it occurs, it is associated with increased morbidity and mortality. There are no guidelines pertaining to whom and when to screen for PH in patients with these disparate forms of chronic lung disease (CLD). The goal of this review is to summarize the criteria that should raise suspicion for PH in the setting of CLD and to suggest when to perform a diagnostic RHC.

SIGNS AND SYMPTOMS OF PH IN COPD AND ILD

There is a significant overlap in symptomatology of ILD and COPD with concomitant PH, which may lead to delay in the diagnosis of the pulmonary vasculopathy.[1–3] There are currently no standardized methods to screen for PH in the setting of CLD. However, there are several harbingers and strategies that have been suggested to monitor these patients for the development of PH.[4–8]

Patients with CLD typically suffer from breathlessness which may be accompanied by cough, the latter being mostly due to their underlying disease. Over time, there may be the development and progression of PH with severe dyspnea which may be attributed to progression of the underlying CTD.[9] In a registry analysis comparing patients with PH-COPD and idiopathic pulmonary arterial hypertension (PAH),[10] there was a higher proportion of patients in WHO functional class (WHO-FC) IV in the COPD group (especially in those with severe PH), despite these patients having significantly better hemodynamic profiles.

As PH progresses, patients may suffer symptoms related to a low cardiac output such as dizziness, palpitations, and chest pain, which may often be taken for signs of possible ischemic or nonischemic heart disease, given the high prevalence of systemic hypertension and the fact that patients with COPD and idiopathic pulmonary fibrosis (IPF) are often either current or exsmokers and are at a significantly increased risk for cardiovascular complications.[11,12] In patients with ILD there is a potential confounding overlap of symptoms related to ILD and PH and consideration of PH may not occur until very advanced stages when peripheral edema, parasternal heave, and jugular distension are present.[13] In patients with COPD, edema may also be caused by mechanisms other than heart failure alone, such as reduced thoracic blood return due to increased intrathoracic pressure, activation of renin, cortisol, and other neurohormonal processes.[14–16] Furthermore, in COPD, hypercapnia may cause a reduction in systemic blood pressure and contribute to maintenance of normal cardiac output due to its vasodilating properties, despite an increase in right-sided heart pressures. While there are reports attesting to the correlation of PH in CLD with functional impairment and World Health Organization Functional Class (WHO-FC), there is a lack of data evaluating clinical symptoms and signs of PH in CLD.[17] It is unclear whether exacerbations of COPD contribute to the development or progression of PH, but it is known that the inverse is true: one of the strongest predictors of hospitalization for acute exacerbations in patients with COPD is elevation of the mean pulmonary artery pressure (mPAP), even with pressures below the current diagnostic threshold for PH.[18] Interestingly, in the CHAMPION trial using a continuous monitoring device of pulmonary artery pressures (PAP) in COPD and non-COPD patients, careful heart failure management resulted in a 62% reduction of "respiratory" hospitalization rates in the COPD group but not in the control group.[19] Furthermore, severe PH is associated with a high prevalence of hospitalizations for exacerbations: whether this is a cause or an effect of the severe hemodynamic compromise is not known.[20] A higher rate of exacerbations has also been described in IPF patients with PH.[21]

FIRST LEVEL DIAGNOSTIC PROCEDURES (PFTS, 6MWT, CPET)

Pulmonary function testing (PFT) is used commonly in the diagnosis and assessment of CLD. Unfortunately, the severity of restriction in ILD and obstruction in COPD does not correlate with the presence or severity of PH.[1,22] On the other hand, severe exertional hypoxemia and reduction in the diffusion capacity (DL_{CO}), especially with relatively preserved lung volumes, have been shown to correlate both with the incidence of PH, and overall outcomes once PH has developed.[1,10,17,23–28] In a retrospective cohort of patients with IPF, a $DL_{CO} < 30\%$ of predicted was associated with a twofold increase in the likelihood of PH.[1] A recent multivariate analysis of patients with both ILD and COPD found the DL_{CO} to be the only PFT variable predictive of mortality with 1- and 5-year survival rates of patients with $DL_{CO} < 32\%$ of 68% and 13%, respectively, as compared to 84% and 60% for those with $DL_{CO} \geq 32\%$.[29] However, another analysis of a group of 151 patients with fibrosing IIP and severe PH showed that total lung capacity (TLC) and not DL_{CO} was associated with mortality.[30] In a further cohort of 93 patients with newly diagnosed ILD, a $TLCO/DL_{CO}$ index >1.67 was most predictive of echocardiographically detected PH.[5] Serum N-terminal

pro-brain natriuretic peptide (NT-ProBNP) or BNP measurements may be useful in detecting severe PH in patients with COPD and ILD,[31,32] although an elevation in these parameters may also correspond with post-capillary PH or left heart failure without PH.

Cardiopulmonary exercise test (CPET) can be useful to raise suspicion of PH in CLD. Maximal oxygen consumption and workload are reduced in PH-CLD compared with CLD without PH.[33,34] With increasing pulmonary vascular dysfunction (PVD), there is a circulatory limitation to exercise characterized by reduced oxygen consumption at the anaerobic threshold and a reduced maximal oxygen pulse.[35,36] In COPD patients PH contributes to a significantly reduced maximal workload and peak oxygen consumption independent of the ventilatory impairment and dynamic hyperinflation that typically accompany the more advanced stages of COPD.[37] Ventilatory inefficiency as gauged by the ventilatory equivalent for CO_2 production (Ve/VCO_2) slope and Ve/VCO_2 at the anaerobic threshold is elevated in ILD patients with PH relative to those without PH.[34,35] Markers of wasted ventilation as an indicator of PH in COPD are more variable.[33,38] These findings on CPET may help in deciding when to proceed to a diagnostic right heart catheterization (RHC).

In patients with COPD, PH should be suspected when there is worsening of symptoms, increased oxygen requirements, and/or reduced exercise tolerance without a concomitant worsening of pulmonary function and/or of emphysema. Some patients may exhibit milder airflow obstruction but very profound gas exchange impairment and may be categorized as the pulmonary vascular phenotype of COPD.[39,40]

Similarly, in ILD, a reduced exercise tolerance, worsening oxygenation, and a decrease in the $DL_{CO,}$ especially when disproportionately lower than the FVC% predicted, may all indicate the presence of underlying PH. A clinical conundrum is to differentiate between the pulmonary vascular phenotype of COPD or ILD and idiopathic PAH with concomitant COPD or ILD, respectively.[40] The relationship between lung function impairment, profound hypoxemia, and the degree of hemodynamic compromise are key features to distinguish between these: in COPD, hypoxemia may be a better indicator of a pulmonary vascular phenotype than the FEV_1.[3] The 6-min walk test (6MWT) has several parameters that might provide "clues" to the presence of underlying PH in patients with CLD. These include not only a reduced distance but also increased desaturation and reduced heart rate recovery (HRR) all of which have been shown to correlate with decreased survival in ILD, as well as with the presence and severity of PH.[26,41–45] One study showed that mPAP correlated with both the 6MWT distance (6MWD) and the distance saturation product.[45]

ECHOCARDIOGRAPHY IN THE IDENTIFICATION OF PH IN CLD

Transthoracic echocardiography (TTE) allows noninvasive measurement of the cardiac chambers and flow velocity within the heart, and, in the presence of tricuspid regurgitation (TR), an estimate of right ventricular (RV) systolic pressure using a simplified Bernoulli formula. To improve the diagnostic accuracy of echocardiography, the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines recommend combining the TR flow velocity with other indirect signs of RV dysfunction to estimate the probability of PH.

The algorithm provided by these guidelines identifies a low probability of PH (normal TR velocity (TRV) < 2.8 m/s and no indirect signs of PH), a high probability of disease (an elevated TRV > 3.6 m/s with or without the presence of indirect PH signs), and an intermediate probability (normal TRV with indirect signs of PH or a TRV between 2.8 and 3.6 m/s without indirect signs of PH).

Even though TTE seems to play a major role in suggesting PH associated with CLD, the criteria based on TRV (and indirect signs) for PH probability in PAH have not as yet been validated in CLD patients. Furthermore, in CLD Doppler TTE has specific limitations.[46] In a recent series of 265 ILD subjects that underwent concomitant RHC and TTE, the positive predictive value for peak TRV > 3.4 m/s combined with RV dilatation/dysfunction was 86%. However, the negative predictive value for excluding PH with a TRV that is unmeasurable or < 2.8 m/s combined with a normal RV was only 60%, with 40% of patients misclassified as low probability when PH was confirmed at subsequent RHC.[47]

In a series of 63 patients with severe emphysema subjected to RHC before lung volume-reduction surgery, TTE estimates of PAP correlated very weakly with hemodynamically derived values, and the test characteristics (e.g., sensitivity, specificity, etc.) of echocardiographic assessments were poor.[48]

Other observations confirmed that in this subset of patients, TTE has good specificity but poor sensitivity in providing a reliable systolic PAP estimation. Additionally, the indirect TTE signs of RV dysfunction, suggesting the probability of PH in addition to TRV measurement, have not yet been validated in CLD.

Despite these limitations, due to its diagnostic accuracy along the spectrum of PH severity in CLD, Doppler TTE has the ability to identify most of the patients with significant pulmonary hypertension. In a recent retrospective study of 210 patients with ILD and sarcoidosis, a TTE-based algorithm for identified patients with severe PH (mPAP ≥35 mmHg) with a sensitivity of 89% and a specificity of 71%.[49] TTE may also detect or exclude

conditions secondarily affecting the pulmonary circulation; specifically, patients with CLD often have risk factors for cardiovascular diseases, and the presence of concomitant left heart disease is frequent in both PH-COPD and PH-ILD patients.[50]

HOW TO STUDY THE RIGHT VENTRICLE IN PATIENTS WITH CLD

The past decade has been marked by a greater understanding of RV function in PH.[51] The concept of pulmonary vascular remodeling leading initially to adaptive and then maladaptive changes and RV failure was introduced in 2013.[51,52] Whether the transition of the RV from adapted to maladapted is the same across all groups of PH etiologies and specifically if it occurs in CLD-PH is currently unknown. Therefore, various TTE imaging techniques that explore novel indices of RV dysfunction (such as speckle tracking derived strain analysis or RV ejection fraction) have been investigated (Table 1). Interestingly, some of these studies suggest that early RV systolic and diastolic dysfunction is present even in patients with early or mild parenchymal disease.

The gold-standard evaluation of RV function, the so-called "load-independent technique," might be especially sensitive in the detection of early RV dysfunction;

TABLE 1 Advanced right ventricular dysfunction imaging in PH-ILD.

Study	Patients	Imaging modality • Key parameter	Key findings
Sonaglioni 2022[59]	N = 60; IPF	TTE • EaI was calculated as the ratio of end-systolic pressure to stroke volume index	EaI correlated to forced vital capacity; EaI was independently associated with outcome
Cobra 2021[60]	N = 123; IPF	TTE • RV GLS	RV GLS alterations were detected in 37% of non-advanced IPF patients
Buonauro 2020[61]	N = 33, fibrotic IPF	TTE • RV GLS • 3D RVEF	RV GLS alterations were observed in IPF indicative of early cardiac damage
D'Andrea 2019[1,62]	N = 50, early stage IPF	TTE • RV GLS • RV LWLS	Impaired RV LWLS is already present at rest in early-stage IPF and worsens during exertion
Tello 2019[58]	N = 172, 55% IPF	TTE • TAPSE/sPAP	TAPSE/sPAP as noninvasive surrogate of ventriculo-arterial coupling differentiate between the haemodynamic phenotypes and associates with prognosis
Amsallem 2017[63]	N = 192, 53% IPF	TTE • RA & RA Volume • RV LWLS	High frequency of right heart enlargement and dysfunction in ILD patients irrespectively from presence of PH
Zhu 2017[64]	N = 90; ILD	TTE • RV LWLS • sPAP	Correlation of the extent of ILD detected by lung ultrasound with RV function
D'Andrea 2016[65]	N = 55, IPF	TTE • RV LWLS	Early impairment of RV function was present; RV LWLS was associated with prognosis
D'Andrea 2016[66]	N = 52, IPF	TTE • RV early diastolic peak velocity • RV GLS • RV LWLS	Impaired RV diastolic and systolic myocardial function were present even in IPF patients without PH
Kato 2015[67]	N = 76, ILD	cMRI • RVEF	RVEF was associated with outcome

Abbreviations: cMRI, cardiac magnetic resonance imaging; EaI, arterial elastance index; GLS, global longitudinal strain; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; LWLS, lateral wall longitudinal strain; PH, pulmonary hypertension; RA, right atrial; RV, right ventricular; RVEF, right ventricular ejection fraction; sPAP, systolic pulmonary arterial pressure; TTE, transthoracic echography; TAPSE/sPAP, tricuspid annular plane excursion/systolic pulmonary arterial pressure.

however, this requires invasive, time-demanding, expensive, and challenging generation of pressure-volume loops.[51] This allows the assessment of the ratio of end-systolic to arterial elastances (Ees/Ea) which ultimately defines the mechanical properties of the RV as ventricular-arterial coupling.[53,54] The ideal approach should be a noninvasive, simple, and easily repeatable technique mirroring the complex mechanism of ventricular-arterial coupling. The current literature has focused on surrogate approaches such as the TAPSE/sPAP (tricuspid annular plane excursion/systolic pulmonary arterial pressure) ratio,[54] the myocardial work assessed by cardiac MRI,[55,56] or simplified calculations derived from RHC.[57] Even though cardiac MRI results in a more detailed study of the RV, in clinical practice TTE is more practical and more readily available.

In particular, TAPSE/sPAP does not require geometric assumption and has been investigated in several forms of PH.[54] One recent study exploring the TAPSE/sPAP role in CLD-PH showed that the ratio is a straightforward and clinically relevant measurement to distinguish between hemodynamic phenotypes with differing survivals.[58]

Other noninvasive measurements of arterial elastance (Ea) have been suggested in IPF.[59] Further research exploring the continuum of RV function decline and the impact of novel image modalities in the evaluation of RV function in different forms of CLD-PH populations are strongly encouraged (Table 1).

MULTIMODALITY INVESTIGATIONS THAT MIGHT INDICATE PH IN CLD

The individual parameters that might suggest the presence of PH can serve to reinforce one another and increase the likelihood of PH in individual patients. Ideally, these could be used in concert in a multiparametric manner to more accurately predict the presence of PH. While some of the same parameters can indicate PH in both ILD and COPD, their use together in scoring systems is different.

When there is suspicion for PH in CLD, a TTE can further inform as to whether or not to proceed with a confirmatory RHC. Conversely, the predictive power of TTE in determining the likelihood of PH in ILD may be enhanced by PFTs (ratio of FVC%/DLCO%), 6MWT and computerized tomography (CT) scan (main pulmonary artery/aorta ratio (PA/Ao)) parameters.[68–70] Pulmonary artery enlargement (a PA:Ao ratio of >1), as detected by CT and depicted in Figure 1, is associated with severe exacerbations of COPD[71] and poor outcome in patients with IPF.[72]

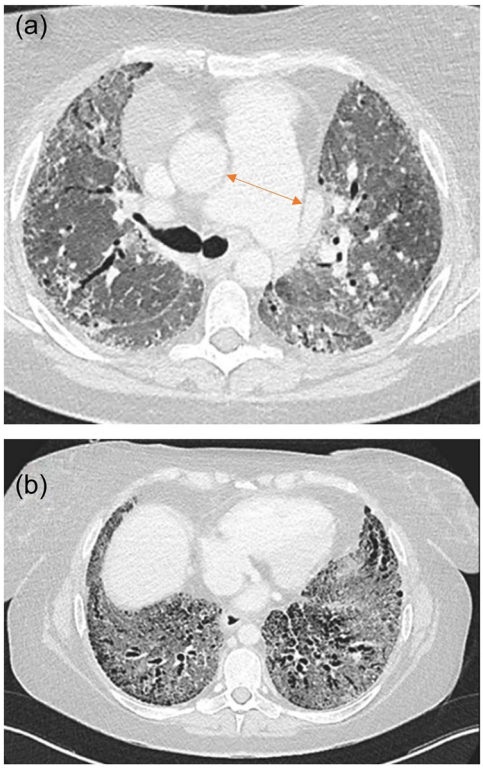

FIGURE 1 A case of ILD with severe PH demonstrating enlargement of the pulmonary artery (a) in the context of severe fibrotic disease (b).

The decision to proceed with RHC needs to be framed in the context of the information obtained and the likelihood of an actionable finding that would be of benefit to the patient. For example, the threshold to obtain a RHC might be lower in ILD patients in countries where there is an approved and available treatment for PH-ILD. Even in countries where there is no approved therapy, there might be benefit to the patient; for example, in those who are transplant candidates since pulmonary hemodynamics weigh into the allocation score in many countries for listed patients. It is conceivable that occult HFpEF might be found, especially given that this is generally an elderly patient population prone to comorbidities. In some patients, the severity of PH might be such that consideration is given to the implementation of individualized PAH therapy. It should be understood and accepted that not all RHCs will elicit PH, and such "negative studies" should not be regarded as futile since prognostic information is important to both patients and their providers Figure 2.

SCORING SYSTEMS

All clinical scoring systems proposed so far for PH-CLD have some limitations that reduce their clinical application. Lung function was not associated to severe

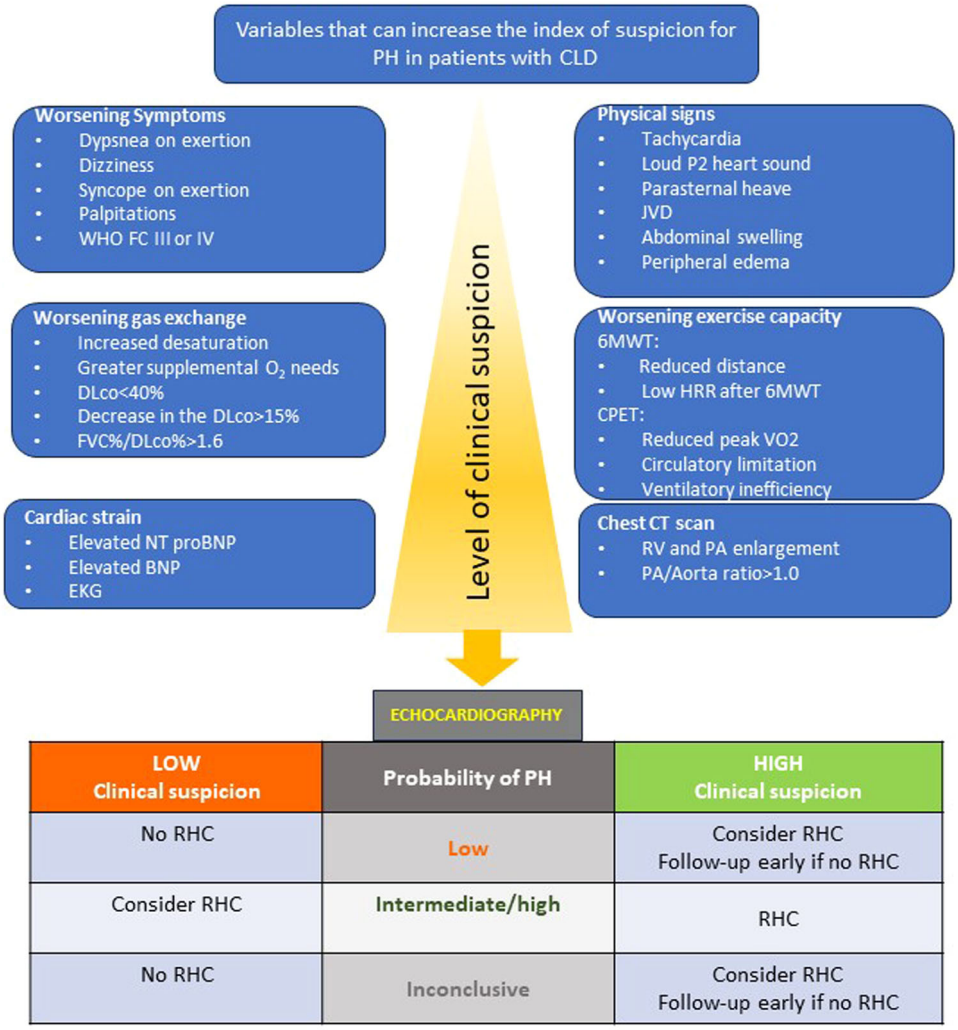

FIGURE 2 Highlights the cumulative contribution of clinical features and test parameters in risk stratifying the probability of PH detection, and thereby to confirm the diagnosis. While this is a suggested algorithm, the final decision to proceed with RHC should be based on the individual patient characteristics and the likelihood that the results will change management. Legend: 6MWT = 6-min walk test; BNP, brain natriuretic peptide; DLco, single breath diffusing capacity for carbon monoxide; FVC, forced vital capacity; JVD, jugular venous distension; NT-proBNP, N terminal proBNP; O_2, oxygen; P2-second pulmonic heart sound; RV, right ventricle; VO2, maximal oxygen consumption; WHO FC, World Health Organization functional class.

PH but to prognosis and this was independent of the prognostic impact of severe PH, therefore, a recently proposed noninvasive scoring system for the detection of severe PH in COPD (mPAP $\geq$ 35 mmHg or mPAP 25–34 mmHg + CO $\leq$ 2.0 L/min) does not include any lung function parameter, gas exchange or exercise variables, and rather includes the estimation of sPAP on TTE, serum NT-ProBNP and the PA/Ao ratio on CT scan of the thorax.[22] However, despite its limitations (retrospective, single-center study), the parameters included in the combined index are linked to the pathophysiological mechanism of PH, and it is not surprising that they may contribute to improving the predictive performance of PH in this patient group. A recent stepwise composite TTE score predicting severe PH proposed by Bax et al. has been applied to ILD patients.[49,69] It is based on the measurement of TVR velocity, right atrial area, RV fractional area change, RV:LV ratio, and eccentricity index. This approach is applicable if there is a good acoustic window allowing the measurement of the required ultrasound parameters. However, this algorithm does not address milder forms of PH which are also important to recognize. Based on their evaluation of a cohort of 93 patients with newly diagnosed ILD, a scoring system incorporating age, 6MWT and TLC/DL_{CO} ratio was proposed by Sobiecka et al.[5] for the prediction of PH suspected by TTE. The authors found that a TLC/DLCO ratio >1.67 increased the probability of PH assessed by TTE fourfold. Another group analyzed multimodality variables in

a cohort of 273 patients with IPF and showed that a clinical scoring system incorporating $DL_{CO} < 50\%$ predicted, PA/Ao≥0.9 on CT and arterial oxygen tension (PaO_2) < 80 mmHg to predict elevation of mPAP had an area under curve (AUC) for the receiver operating characteristic (ROC) of 0.757 (95% CI 0.682–0.833).[17] Another early PH-ILD detection tool incorporating medical history, examination, 6-min walk distance, DLCO, chest imaging, and cardiac biomarkers creating an eight-component score was found to have both a high sensitivity (86.5%) and specificity (86.3%) with an AUC of 0.920 in a retrospective analysis of 154 patients with ILD.[6] All the above scoring systems were retrospective single-center studies and require external validation in independent larger cohort of patients. A recent study developed the FORD score using the cohort of the ARTEMIS randomized controlled trial as a derivation sample for the multivariate analysis (AUC: 0.75; 95% CI: 0.660.82); the score, which includes demographic and functional data, oxygenation and 6MWD, was subsequently validated on an external cohort of IPF patients (AUC: 0.69; 95% CI: 0.56–0.81).[73] Finally, a Delphi consensus statement recommended further research on how to best identify patients with ILD who develop concomitant PH and offered a screening algorithm based on and incorporating previously published data.[8] There is an ongoing prospective study evaluating noninvasive parameters in the prediction of PH in patients with ILD (PHinder study, NCT05776225).

RECOMMENDATIONS FOR RHC IN PH ASSOCIATED WITH CHRONIC LUNG DISEASES

RHC is recommended in the evaluation of CLD patients in whom the results might change management (level of evidence: IC).[40,74] For example, lung transplant candidates require RHC since hemodynamics factor into allocation scoring systems. The availability of an approved therapy that the patient may be a candidate for represents another situation which may warrant a RHC. If no approved therapy is available, but there is suspicion for PH of sufficient severity to warrant off-label PH therapy, then RHC should be performed; especially if the pulmonary hypertension is deemed likely to be more symptom-limiting than the lung disease itself.[74] Another indication might be for confirmation of the presence of heart failure with preserved ejection fraction as contributing to the patients' symptoms and any underlying pulmonary hypertension. It is important to note that if PH is suspected, but that documentation thereof will not change management, then a RHC need not be performed.

There are no comprehensive guidelines or recommendations to advise specifically on the practical aspects of RHC performance in patients with PH-CLD. RHC in patients with PH-CLD is technically challenging and should be performed only in expert centers. The recent interest in PH-CLD pathophysiology and in hemodynamic phenotyping of PH-CLD, together with the published data on treatments targeting PH-ILD, have set the stage for RHC as a more commonly performed procedure in this patient population. It is important to note that correct timing of RHC for the assessment of PH requires the absence of an acute exacerbation, and compensated heart function and should be obtained with a targeted peripheral oxygen saturation (SpO2) of >90%.

RHC in chronic lung diseases: Procedural approach

Particular caution and a comprehensive risk/benefit assessment should be undertaken in patients with respiratory insufficiency with high O_2 requirement or rapid worsening of respiratory conditions. These patients are particularly fragile and even a catheter-induced arrhythmia can destabilize them. Respiratory failure often makes it difficult to lie flat on the table during the procedure; consequently increased work of breathing and associated changes in intra-thoracic pressure can affect pulmonary haemodynamics. However, it is noteworthy that many patients with severe CLD who are being evaluated for lung transplant undergo RHCs routinely without many issues lying flat or with an increased incidence of complications.

Site

Jugular, brachial, or femoral venous routes can be utilized depending on operator and patient preference. For patients with apical bullous disease, a jugular approach should be approached with caution and is best performed under ultrasonic guidance.

Complications

The complications of RHC are mostly related to the venous access and to the RHC procedure independent from the primary lung disease. Although RHC complications are uncommon, on very rare occasions they can be fatal. Patients affected by PH-ILD may be particularly unstable due to the combined ventilatory and hemodynamic derangement and RHC should only be performed in experienced centers. Complications occurring

in patients with a reduced respiratory reserve, or cardiovascular comorbidities may have a greater clinical impact even if considered minor in other contexts (e.g., catheter-induced supraventricular and ventricular arrhythmias).

Acute vasoreactivity testing

The latest recommendations from the ESC/ERS 2022 guidelines reinforce the previous 2015 suggestions not to perform acute vasoreactivity testing in PH-CLD.[74] However, it has been suggested that in patients with severe PH associated with ILD some vasoreactivity when exposed to inhaled nitric oxide or inhaled prostanoids may exist, even in those without overt PH.[75,76] Observational data in CLD patients has reported a positive test in 17%–41% of cases, but without a significant effect on other hemodynamic parameters and no implications for treatment or subsequent survival.[77] More studies are needed to evaluate the true prevalence of vasoreactivity in PH-CLD patients and its implications for treatment strategies and long-term outcomes. At this time, routine acute vasoreactivity testing is only recommended for research purposes.

RHC pitfalls & practical issues in CLD

Zero levelling

Zero levelling is one of the most important and unrecognized pitfalls in the hemodynamic evaluation of pulmonary hypertension, the correct positioning of the transducer being a crucial element for the assessment of pulmonary pressures during RHC.[78] Based on current recommendations, the zero reference level should be set at the mid-thoracic level in supine patients, which represents the level of the left atrium.[78–80] This approach allows for the correct evaluation of right heart and PAP, including PAWP which is of crucial importance in the evaluation of CLD-PH patients, who are often elderly with comorbidities that increase the risk for left heart disease.[79]

Pressure measurements with respect to the respiratory cycle

The ESC/ERS guidelines recommend that in PAH all pressures are recorded as the mean of 3–5 measurements obtained at the end of normal expiration (avoiding breath holding or Valsalva maneuver).[74] However there has been significant debate around the question of respiratory swings in patients with CLD and how to assess intrathoracic pressures. Specifically, in patients with significant bronchial obstruction and in morbidly obese patients, the end of normal expiration and the start of inspiration may occur simultaneously, precluding a time space for measurement.[81] Patients with ILD demonstrate reduced compliance[77] which translates into increased elastic recoil[82] and lower intrathoracic pressure during both inspiration and expiration.[83] In addition, in chronic lung diseases (especially in COPD) large swings in intrathoracic pressure may affect intracardiac pressures significantly.[79,84] Due to these considerations, the 2022 ESC/ERS guidelines[74] confirmed the recommendation that PAWP should be averaged during several respiratory cycles to minimize the effects of changes in intrathoracic pressures on the tracings in patients with lung disease. We also recommend reporting the method used to record PAP in each hemodynamic study.

LV diastolic dysfunction in CLD

Left ventricular dysfunction may be reasonably ruled out by TTE assessment; however, the presence of diastolic dysfunction is not routinely evaluated in CLD. Thus, the hemodynamic evaluation during cardiac catheterization may well be the first diagnostic test during which diastolic dysfunction is suspected or detected. Despite some available evidence on the prevalence of cardiovascular comorbidities in ILD,[85] there is little data on the prevalence of diastolic dysfunction in ILD-PH patients. In 2015 Raghu et al. showed that 4% of patients with IPF had post-capillary PH.[26] More recently Teramachi et al. described 1152 patients with ILD diagnosed with PH using RHC, 20% of whom demonstrated post-capillary PH.[86] More data on cardiovascular comorbidities are available in the COPD population. A recent systematic review reported a high prevalence range for systemic hypertension (17%–65%), coronary artery disease (20%–48%), diabetes (10-45%), chronic heart failure 8%–28%), and arrhythmias (14%–24%).[87] Post-capillary PH has been shown to be present in about 20% of COPD patients listed for lung transplantation.[88] Being aware that this is a highly select population, the prevalence is likely higher in broader groups of COPD patients.[89] In cases where diastolic dysfunction is clinically suspected, an exercise, fluid, or nitric oxide challenge test during RHC may be helpful in ruling out a diastolic component, especially in those patients who present with PAWPs in the range of 12–15 mmHg.[89]

Hemodynamic follow-up

There are no recommendations or guidelines for repeating RHC in patients with PH-CLD. We suggest

obtaining a repeat RHC only if this potentially changes the patient management. For example, repeated RHC may be obtained in patients listed for lung transplant, since worsening hemodynamics will increase their lung allocation score. The need for repeat RHCs to assess the effect of pulmonary vasodilators in ILD-PH is not clear and indeed if a repeat procedure is warranted at all. The question of which parameter is more representative in the hemodynamic follow-up of ILD-PH patients and how to assess a positive response to treatment remains unknown. Indeed, there is no definitive data demonstrating that PVR-directed therapeutic strategies may affect mortality in PH-CLD. A retrospective study of sildenafil and statistical modeling of the INCREASE data set do suggest potential mortality benefits to sildenafil and inhaled treprostinil in PH-ILD patients.[90,91] The 2022 ESC/ERS guidelines identify a PVR cut-off > 5WU as a criterion for defining severe PH in CLD.[74] However, this threshold requires validation and should not be used as the sole criteria to decide on the initiation of therapy, especially given the poor prognosis of CLD with even mild to moderate PH. Indeed, recent data show that in PH-ILD, PVR > 2 has an unfavorable impact on survival.[92] In addition, another post-hoc analysis of the INCREASE data set suggests a potential benefit of therapy in PH-ILD patients with PVRs as low as 3–4 wood units.[93] Nonetheless, it is imperative to continue to prospectively study patients with lower PVRs within clinical trials to determine which phenotypes benefit most from potential therapeutic interventions.

CONCLUDING REMARKS

As with all forms of PH, the diagnosis of PH in the context of CLD requires an RHC. There are no established guidelines as to when and in whom RHC should be performed. The decision to proceed with RHC is predicated by individual risk assessment for underlying PH. This risk stratification relies on a combination of symptoms, oxygen needs, clinical signs, and data from routinely available testing including PFTs, 6MWT, imaging, and biomarkers. While there are a number of scoring systems, these require further refinement and validation. If the diagnosis of PH will result in a possible change in management, for example, availability of an approved therapy, then the threshold to proceed with a RHC should be lowered. Attention to technical detail is critical to obtain reliable RHC data. There are multiple areas where further research is needed and some of these are outlined below.

OPPORTUNITIES AND QUESTIONS FOR FUTURE RESEARCH IN THE DIAGNOSIS OF PH IN CLD

1. The significance of pulmonary vasoreactivity in PH-CLD in terms of prognostic significance and whether this has treatment implications remains to be elucidated.
2. The prognosis and treatment implications of PH in CLD under the guise of lower mPAP and PVR thresholds remains unknown. In addition, how PH progresses in CLD requires further study.
3. Further prospective studies are needed to validate and refine existing scoring systems to predict PH in CLD. In addition, future scoring systems remain to be developed which might include additional novel parameters such as from cardiac MRI.
4. Molecular research is strongly encouraged to endotype CLD patients at risk of developing PH.
5. AI-based algorithms in assisting the diagnosis and prognostication of PH-CLD patients could have a substantial impact on future clinical practice.[89]

GUARANTOR

All authors agree to be accountable for the overall content of the manuscript.

AUTHOR CONTRIBUTIONS

Dr. Vitulo and Dr. 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.

ACKNOWLEDGMENTS

PH-Group 3 workstream members: Steven Abman, Brian Allwood, Katerina Antoniou, Irina Petrache, Mitchell Psotka, Prakash Sista, Norman Stockbridge; Khodr Tello, George Washko. PVRI and IDDI leads: Karen Osborn, Paul Corris, Raymond Benza, Peter Fernandes and Luke Howard. The authors did not receive financial support for the scientific work, authorship, and/or publication of this article.

CONFLICT OF INTEREST STATEMENT

Dr. Vitulo has consulted for MSD and AOP and has received support for attending congresses from MSD, Janssen all of which not related to this manuscript. Dr. Piccari has received research funding from and served as

a speaker for Janssen and Ferrer, advised Janssen, Ferrer and United Therapeutics as well as received support for attending congresses from Janssen, MSD and Ferrer, all of which not related to this manuscript. Dr. S. John Wort received honoraria from Janssen, MSD, Bayer, Ferrer and Acceleron for advisory boards, received honoraria from Janssen for educational activity, received unrestricted research grants from Janssen, Ferrer and Bayer, and travel grants, conference registration and accommodation from Janssen and Ferrer. Dr. Shlobin has consulted for UT, Bayer, ALtavant, Aerovate, Jenssen&Jenssen Jenssen& Jenssen and Merck, and is on the speaker bureau for UT, Bayer, and J&J; Dr. Stockbridge has no conflict of interest. Dr. Kovacs reports personal fees and nonfinancial support from Actelion, Janssen, Bayer, GSK, MSD, Boehringer Ingelheim, Novartis, Chiesi, Vitalaire, Ferrer, and AOP outside the submitted work. Dr. Vizza has no conflict of interest regarding this topic. Dr. Hassoun serves on a scientific advisory board for Merck, an activity unrelated to the current work. Dr. Olschewski received funding from Actelion, AOP, Astra Zeneca, Bayer, Boehringer, Chiesi, GSK, Iqvia, Janssen, Menarini, MSD, Novartis, Ludwig Boltzmann Society, Ferrer, MedUpdate, and Mondial not related to this work. Dr. Girgis received honoraria from Boehringer Ingelheim and research funding from UT. Dr. Nikkho is an employee of Bayer AG.Dr. Nathan is a consultant for United Therapeutics, Bellerophon, Third Pole, Roche, Boehringer-Ingelheim, Insmed, Roivant, Merck and Daewoong. He is on the speakers bureau for United Therapeutics and Boehringer-Ingelheim. He is also on the Gossamer Bio Board of Directors.

ETHICS STATEMENT

Not applicable.

ORCID

P. Vitulo http://orcid.org/0000-0003-1699-0208
L. Piccari http://orcid.org/0000-0002-2241-7523
S. J. Wort http://orcid.org/0000-0003-4287-1173
O. A. Shlobin http://orcid.org/0000-0003-4131-8499
G. Kovacs https://orcid.org/0000-0003-3709-2183
C. D. Vizza https://orcid.org/0000-0002-3540-4983
P. M. Hassoun http://orcid.org/0000-0003-0601-4975
H. Olschewski http://orcid.org/0000-0002-2834-7466
R. E. Girgis http://orcid.org/0000-0001-7656-6199
S. M. Nikkho http://orcid.org/0000-0003-1245-2656
S. D. Nathan http://orcid.org/0000-0002-6270-1617

REFERENCES

1. Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest. 2007;131:657–63. https://doi.org/10.1378/chest.06-2485
2. Braganza M, Shaw J, Solverson K, Vis D, Janovcik J, Varughese RA, Thakrar MV, Hirani N, Helmersen D, Weatherald J. A prospective evaluation of the diagnostic accuracy of the physical examination for pulmonary hypertension. Chest. 2019;155:982–90. https://doi.org/10.1016/j.chest.2019.01.035
3. García AR, Piccari L. Emerging phenotypes of pulmonary hypertension associated with COPD: a field guide. Curr Opin Pulm Med. 2022;28:343–51. https://doi.org/10.1097/mcp.0000000000000890
4. King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease. Chest. 2020;158:1651–64. https://doi.org/10.1016/j.chest.2020.04.046
5. Sobiecka M, Lewandowska K, Kober J, Franczuk M, Skoczylas A, Tomkowski W, Kuś J, Szturmowicz M. Can a new scoring system improve prediction of pulmonary hypertension in newly recognised interstitial lung diseases? Lung. 2020;198:547–54. https://doi.org/10.1007/s00408-020-00346-1
6. Parikh R, Konstantinidis I, O'Sullivan DM, Farber HW. Pulmonary hypertension in patients with interstitial lung disease: a tool for early detection. Pulm Circ. 2022;12:e12141. https://doi.org/10.1002/pul2.12141
7. Zisman DA, Karlamangla AS, Kawut SM, Shlobin OA, Saggar R, Ross DJ, Schwarz MI, Belperio JA, Ardehali A, Lynch JP, Nathan SD. Validation of a method to screen for pulmonary hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2008;133:640–5. https://doi.org/10.1378/chest.07-2488
8. Rahaghi FF, Kolaitis NA, Adegunsoye A, de Andrade JA, Flaherty KR, Lancaster LH, Lee JS, Levine DJ, Preston IR, Safdar Z, Saggar R, Sahay S, Scholand MB, Shlobin OA, Zisman DA, Nathan SD. Screening strategies for pulmonary hypertension in patients with interstitial lung disease. Chest. 2022;162:145–55. https://doi.org/10.1016/j.chest.2022.02.012
9. Nikkho SM, Richter MJ, Shen E, Abman SH, Antoniou K, Chung J, Fernandes P, Hassoun P, Lazarus HM, Olschewski H, Piccari L, Psotka M, Saggar R, Shlobin OA, Stockbridge N, Vitulo P, Vizza CD, Wort SJ, Nathan SD. 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. Pulm Circ. 2022;12:e12127. https://doi.org/10.1002/pul2.12127
10. Vizza CD, Hoeper MM, Huscher D, Pittrow D, Benjamin N, Olsson KM, Ghofrani HA, Held M, Klose H, Lange T, Rosenkranz S, Dumitrescu D, Badagliacca R, Claussen M, Halank M, Vonk-Noordegraaf A, Skowasch D, Ewert R, Gibbs JSR, Delcroix M, Skride A, Coghlan G, Ulrich S, Opitz C, Kaemmerer H, Distler O, Grünig E. Pulmonary hypertension in patients with COPD. Chest. 2021;160:678–89. https://doi.org/10.1016/j.chest.2021.02.012
11. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-

analysis. Lancet Respir Med. 2015;3:631–9 https://doi.org/10.1016/s2213-2600(15)00241-6
12. Oh CK, Murray LA, Molfino NA. Smoking and idiopathic pulmonary fibrosis. Pulm Med. 2012;2012:808260. https://doi.org/10.1155/2012/808260
13. Nikkho SM, Richter MJ, Shen E, Abman SH, Antoniou K, Chung J, Fernandes P, Hassoun P, Lazarus HM, Olschewski H, Piccari L, Psotka M, Saggar R, Shlobin OA, Stockbridge N, Vitulo P, Vizza CD, Wort SJ, Nathan SD. 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. Pulm Circ. 2022;12:e12127. https://doi.org/10.1002/pul2.12127
14. Anand IS, Chandrashekhar Y, Ferrari R, Sarma R, Guleria R, Jindal SK, Wahi PL, Poole-Wilson PA, Harris P. Pathogenesis of congestive state in chronic obstructive pulmonary disease: studies of body water and sodium, renal function, hemodynamics, and plasma hormones during edema and after recovery. Circulation. 1992;86:12–21. https://doi.org/10.1161/01.cir.86.1.12
15. Kawut SM, Poor HD, Parikh MA, Hueper K, Smith BM, Bluemke DA, Lima JAC, Prince MR, Hoffman EA, Austin JHM, Vogel-Claussen J, Barr RG. Cor pulmonale parvus in obstructive pulmonary disease and emphysema. J Am Coll Cardiol. 2014;64:2000–9 https://doi.org/10.1016/j.jacc.2014.07.991
16. Hohlfeld JM, Vogel-Claussen J, Biller H, Berliner D, Berschneider K, Tillmann HC, Hiltl S, Bauersachs J, Welte T. Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial. Lancet Respir Med. 2018;6:368–78 https://doi.org/10.1016/s2213-2600(18)30054-7
17. Hurdman J, Condliffe R, Elliot CA, Swift A, Rajaram S, Davies C, Hill C, Hamilton N, Armstrong IJ, Billings C, Pollard L, Wild JM, Lawrie A, Lawson R, Sabroe I, Kiely DG. Pulmonary hypertension in COPD: results from the ASPIRE registry. Eur Respir J. 2013;41:1292–301. https://doi.org/10.1183/09031936.00079512
18. Kessler R, Faller M, Fourgaut G, MENNECIER B, WEITZENBLUM E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;159:158–64.
19. Krahnke JS, Abraham WT, Adamson PB, Bourge RC, Bauman J, Ginn G, Martinez FJ, Criner GJ. Heart failure and respiratory hospitalizations are reduced in patients with heart failure and chronic obstructive pulmonary disease with the use of an implantable pulmonary artery pressure monitoring device. J Card Failure. 2015;21:240–9. https://doi.org/10.1016/j.cardfail.2014.12.008
20. Dauriat G, Reynaud-Gaubert M, Cottin V, Lamia B, Montani D, Canuet M, Boissin C, Tromeur C, Chaouat A, Degano B, Bergot E, Sanchez O, Prevot G, Sitbon O, Thabut G, Belhadi D, de Beauregard YC, Bencherif A, Humbert M, Simonneau G, Laouenan C, Mal H. Severe pulmonary hypertension associated with chronic obstructive pulmonary disease: a prospective French multicenter cohort. J Heart Lung Transplant. 2021;40:1009–18. https://doi.org/10.1016/j.healun.2021.04.021
21. Judge EP, Fabre A, Adamali HI, Egan JJ. Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis. Eur Respir J. 2012;40:93–100. https://doi.org/10.1183/09031936.00115511
22. Kovacs G, Avian A, Bachmaier G, Troester N, Tornyos A, Douschan P, Foris V, Sassmann T, Zeder K, Lindenmann J, Brcic L, Fuchsjaeger M, Agusti A, Olschewski H. Severe pulmonary hypertension in COPD. Chest. 2022;162:202–12. https://doi.org/10.1016/j.chest.2022.01.031
23. King CS, Nathan SD. Pulmonary hypertension due to interstitial lung disease. Curr Opin Pulm Med. 2019;25:459–67. https://doi.org/10.1097/mcp.0000000000000599
24. Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, Nagao T, Mishima M, Kitaichi M, Izumi T. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest. 2007;131:650–6. https://doi.org/10.1378/chest.06-1466
25. Nadrous HF, Pellikka PA, Krowka MJ, Swanson KL, Chaowalit N, Decker PA, Ryu JH. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest. 2005;128:2393–9. https://doi.org/10.1378/chest.128.4.2393
26. Raghu G, Nathan SD, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Wells AU, Shao L, Zhou H, Henig N, Szwarcberg J, Gillies H, Montgomery AB, O'Riordan TG. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. Eur Respir J. 2015;46:1370–7. https://doi.org/10.1183/13993003.01537-2014
27. Furukawa T, Kondoh Y, Taniguchi H, Yagi M, Matsuda T, Kimura T, Kataoka K, Johkoh T, Ando M, Hashimoto N, Sakamoto K, Hasegawa Y. A scoring system to predict the elevation of mean pulmonary arterial pressure in idiopathic pulmonary fibrosis. Eur Respir J. 2018;51:1701311. https://doi.org/10.1183/13993003.01311-2017
28. Girgis RE, Hoeper MM. Pulmonary hypertension in fibrosing idiopathic interstitial pneumonia: uncertainties, challenges and opportunities. J Heart Lung Transplant. 2021;40:872–81. https://doi.org/10.1016/j.healun.2021.03.004
29. Rose L, Prins KW, Archer SL, Pritzker M, Weir EK, Misialek JR, Thenappan T. Survival in pulmonary hypertension due to chronic lung disease: influence of low diffusion capacity of the lungs for carbon monoxide. J Heart Lung Transplant. 2019;38:145–55. https://doi.org/10.1016/j.healun.2018.09.011
30. Hoeper MM, Behr J, Held M, Grunig E, Vizza CD, Vonk-Noordegraaf A, Lange TJ, Claussen M, Grohé C, Klose H, Olsson KM, Zelniker T, Neurohr C, Distler O, Wirtz H, Opitz C, Huscher D, Pittrow D, Gibbs JSR. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. PLoS One. 2015;10:e0141911. https://doi.org/10.1371/journal.pone.0141911
31. Leuchte HH, Neurohr C, Baumgartner R, Holzapfel M, Giehrl W, Vogeser M, Behr J. Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. Am J Respir Crit Care Med. 2004;170:360–5. https://doi.org/10.1164/rccm.200308-1142OC

32. Leuchte HH, Baumgartner RA, Nounou ME, Vogeser M, Neurohr C, Trautnitz M, Behr J. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. Am J Respir Crit Care Med. 2006;173:744–50. https://doi.org/10.1164/rccm.200510-1545OC
33. Torres-Castro R, Gimeno-Santos E, Vilaró J, Roqué-Figuls M, Moisés J, Vasconcello-Castillo L, Orizaga T, Barberà JA, Blanco I. Effect of pulmonary hypertension on exercise tolerance in patients with COPD: a prognostic systematic review and meta-analysis. Eur Respir Rev. 2021;30:200321. https://doi.org/10.1183/16000617.0321-2020
34. Gläser S, Obst A, Koch B, Henkel B, Grieger A, Felix SB, Halank M, Bruch L, Bollmann T, Warnke C, Schäper C, Ewert R. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis—the predictive value of exercise capacity and gas exchange efficiency. PLoS One. 2013;8:e65643. https://doi.org/10.1371/journal.pone.0065643
35. Boutou AK, Pitsiou GG, Trigonis I, PAPAKOSTA D, KONTOU PK, CHAVOUZIS N, NAKOU C, ARGYROPOULOU P, WASSERMAN K, STANOPOULOS I. Exercise capacity in idiopathic pulmonary fibrosis: the effect of pulmonary hypertension. Respirology. 2011;16:451–8. https://doi.org/10.1111/j.1440-1843.2010.01909.x
36. Boerrigter BG, Bogaard HJ, Trip P, Groepenhoff H, Rietema H, Holverda S, Boonstra A, Postmus PE, Westerhof N, Vonk-Noordegraaf A. Ventilatory and cardiocirculatory exercise profiles in COPD. Chest. 2012;142:1166–74. https://doi.org/10.1378/chest.11-2798
37. Blanco I, Valeiro B, Torres-Castro R, Barberán-García A, Torralba Y, Moisés J, Sebastián L, Osorio J, Rios J, Gimeno-Santos E, Roca J, Barberà JA. Effects of pulmonary hypertension on exercise capacity in patients with chronic obstructive pulmonary disease. Archivos de Bronconeumología (English Edition). 2020;56:499–505. https://doi.org/10.1016/j.arbres.2019.10.015
38. Neder JA, Berton DC, Arbex FF, Alencar MC, Rocha A, Sperandio PA, Palange P, O'Donnell DE. Physiological and clinical relevance of exercise ventilatory efficiency in COPD. Eur Respir J. 2017;49:1602036. https://doi.org/10.1183/13993003.02036-2016
39. Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducoloné A, Ehrhart M, Kessler R, Weitzenblum E. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172:189–94. https://doi.org/10.1164/rccm.200401-006OC
40. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, Weissmann N, Seeger W. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53:1801914. https://doi.org/10.1183/13993003.01914-2018
41. Hallstrand TS. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J. 2005;25:96–103. https://doi.org/10.1183/09031936.04.00137203
42. Flaherty KR, Andrei AC, Murray S, Fraley C, Colby TV, Travis WD, Lama V, Kazerooni EA, Gross BH, Toews GB, Martinez FJ. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med. 2006;174:803–9. https://doi.org/10.1164/rccm.200604-488OC
43. Lettieri CJ, Nathan SD, Browning RF, Barnett SD, Ahmad S, Shorr AF. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med. 2006;100:1734–41. https://doi.org/10.1016/j.rmed.2006.02.004
44. Minai OA, Santacruz JF, Alster JM, Budev MM, McCarthy K. Impact of pulmonary hemodynamics on 6-min walk test in idiopathic pulmonary fibrosis. Respir Med. 2012;106:1613–21. https://doi.org/10.1016/j.rmed.2012.07.013
45. Swigris JJ, Olson AL, Shlobin OA, AHMAD S, BROWN KK, NATHAN SD. Heart rate recovery after six-minute walk test predicts pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16:439–45. https://doi.org/10.1111/j.1440-1843.2010.01877.x
46. Ni JR, Yan PJ, Liu SD, Hu Y, Yang KH, Song B, Lei JQ. Diagnostic accuracy of transthoracic echocardiography for pulmonary hypertension: a systematic review and meta-analysis. BMJ Open. 2019;9:e033084. https://doi.org/10.1136/bmjopen-2019-033084
47. Keir GJ, Wort SJ, Kokosi M, George PM, Walsh SLF, Jacob J, Price L, Bax S, Renzoni EA, Maher TM, MacDonald P, Hansell DM, Wells AU. Pulmonary hypertension in interstitial lung disease: limitations of echocardiography compared to cardiac catheterization. Respirology. 2018;23:687–94. https://doi.org/10.1111/resp.13250
48. Fisher MR, Criner GJ, Fishman AP, Hassoun PM, Minai OA, Scharf SM, Fessler HE. Estimating pulmonary artery pressures by echocardiography in patients with emphysema. Eur Respir J. 2007;30:914–21. https://doi.org/10.1183/09031936.00033007
49. Bax S, Bredy C, Kempny A, Dimopoulos K, Devaraj A, Walsh S, Jacob J, Nair A, Kokosi M, Keir G, Kouranos V, George PM, McCabe C, Wilde M, Wells A, Li W, Wort SJ, Price LC. A stepwise composite echocardiographic score predicts severe pulmonary hypertension in patients with interstitial lung disease. ERJ Open Res. 2018;4:00124–2017. https://doi.org/10.1183/23120541.00124-2017
50. Lepida D, Papathanasiou A, Galiatsou E, Nakos G, Goudevenos I, Koulouras V. The contribution of left heart disease in COPD patients with pulmonary hypertension. Hell J Cardiol. 2018;59:160–5 https://doi.org/10.1016/j.hjc.2018.02.001
51. Naeije R, Richter MJ, Rubin LJ. The physiological basis of pulmonary arterial hypertension. Eur Respir J. 2022;59:2102334. https://doi.org/10.1183/13993003.02334-2021
52. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, Naeije R, Newman J, Oudiz RJ, Provencher S, Torbicki A, Voelkel NF, Hassoun PM. Right heart adaptation to pulmonary arterial Hypertension. J Am Coll Cardiol. 2013;62:D22–33. https://doi.org/10.1016/j.jacc.2013.10.027
53. Richter MJ, Hsu S, Yogeswaran A, Husain-Syed F, Vadász I, Ghofrani HA, Naeije R, Harth S, Grimminger F, Seeger W, Gall H, Tedford RJ, Tello K. Right ventricular pressure-volume loop shape and systolic pressure change in pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol. 2021;320:L715–25 https://doi.org/10.1152/ajplung.00583.2020
54. Tello K, Wan J, Dalmer A, Vanderpool R, Ghofrani HA, Naeije R, Roller F, Mohajerani E, Seeger W, Herberg U,

Sommer N, Gall H, Richter MJ. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. Circ Cardiovasc Imaging. 2019;12:e009047 https://doi.org/10.1161/circimaging.119.009047

55. Butcher SC, Fortuni F, Montero-Cabezas JM, Abou R, El Mahdiui M, van der Bijl P, van der Velde ET, Ajmone Marsan N, Bax JJ, Delgado V. Right ventricular myocardial work: proof-of-concept for non-invasive assessment of right ventricular function. Eur Heart J Cardiovasc Imaging. 2021;22:142–52 https://doi.org/10.1093/ehjci/jeaa261
56. Tello K, Dalmer A, Vanderpool R, Ghofrani HA, Naeije R, Roller F, Seeger W, Wilhelm J, Gall H, Richter MJ. Cardiac magnetic resonance imaging-based right ventricular strain analysis for assessment of coupling and diastolic function in pulmonary hypertension. JACC: Cardiovasc Imaging. 2019;12:2155–64 https://doi.org/10.1016/j.jcmg.2018.12.032
57. Vanderpool RR, Puri R, Osorio A, Wickstrom K, Desai AA, Black SM, Garcia JGN, Yuan JXJ, Rischard FP. Express: surfing the right ventricular pressure waveform: methods to assess global, systolic and diastolic RV function from a clinical right heart catheterization. Pulm Circ 2019. 2019;10:2045894019850993. https://doi.org/10.1177/2045894019850993
58. Tello K, Ghofrani HA, Heinze C, Krueger K, Naeije R, Raubach C, Seeger W, Sommer N, Gall H, Richter MJ. A simple echocardiographic estimate of right ventricular-arterial coupling to assess severity and outcome in pulmonary hypertension on chronic lung disease. Eur Respir J. 2019;54:1802435. https://doi.org/10.1183/13993003.02435-2018
59. Sonaglioni A, Caminati A, Nicolosi GL, Lombardo M, Harari S. Incremental prognostic value of arterial elastance in mild-to-moderate idiopathic pulmonary fibrosis. Int J Cardiovasc Imaging. 2022;38:1473–85. https://doi.org/10.1007/s10554-022-02541-y
60. Cobra SB, Rodrigues MP, de Melo FX, Ferreira NMC, Passini VV, Amado VM, Melo-Silva CA. Right ventricular dysfunction in patients with non-severe idiopathic pulmonary fibrosis: a cross-sectional prospective single-center study. Expert Rev Respir Med. 2021;15:249–56 https://doi.org/10.1080/17476348.2021.1834856
61. Buonauro A, Santoro C, Galderisi M, Canora A, Sorrentino R, Esposito R, Lembo M, Canonico ME, Ilardi F, Fazio V, Golia B, Sanduzzi Zamparelli A, Bocchino ML. Impaired right and left ventricular longitudinal function in patients with fibrotic interstitial lung diseases. J Clin Med. 2020;9:587. https://doi.org/10.3390/jcm9020587
62. D'Andrea A, Stanziola AA, Saggar R, Saggar R, Sperlongano S, Conte M, D'Alto M, Ferrara F, Gargani L, Lancellotti P, Bossone E, Bossone E, Gargani L, Naeije R, Ferrara F, Armstrong WF, Kolias TJ, Bossone E, Ferrara F, Caliendo L, Cocchia R, Citro R, Bellino M, Radano I, Cittadini A, D'Alto M, Argiento P, D'Andrea A, Carbone A, Sperlongano S, Dellegrottaglie S, De Luca N, Grazia MM, Rozza F, Russo V, Di Salvo G, Ghio S, Grunig E, Marra A, Guazzi M, Bandera F, Labate V, La Gerche A, Limongelli G, Pacileo G, Verrengia M, Kasprzak JD, Wierzbowska Drabik K, Kovacs G, Lancellotti P, Moreo A, Casadei F, De Chiara B, Naeije R, Ostenfeld E, Pieri F, Pratali L, Saggar R, Saggar R, Selton-Suty C, Huttin O, Venner C, Serra W, Stanziola A, Martino M, Caccavo G, Szabó I, Varga A, Agoston G, Voilliot D, Vriz O, Galzerano D, Scalese M, Carannante L. Right ventricular functional reserve in early-stage idiopathic pulmonary fibrosis. Chest. 2019;155:297–306. https://doi.org/10.1016/j.chest.2018.11.015
63. Amsallem M, Boulate D, Kooreman Z, Zamanian RT, Fadel G, Schnittger I, Fadel E, McConnell MV, Dhillon G, Mercier O, Haddad F. Investigating the value of right heart echocardiographic metrics for detection of pulmonary hypertension in patients with advanced lung disease. Int J Cardiovasc Imaging. 2017;33:825–35. https://doi.org/10.1007/s10554-017-1069-3
64. Zhu WW, Li YD, Li H, Lu XZ, Kong LY, Ye XG, Cai QZ, Sun LL, Jiang W, Wang L. Integrative cardiopulmonary ultrasound for interstitial lung disease assessment: correlation between lung ultrasound performance and cardiac involvement. Ultrasound Med Biol. 2017;43:744–52. https://doi.org/10.1016/j.ultrasmedbio.2016.11.004
65. D'Andrea A, Stanziola A, D'Alto M, Di Palma E, Martino M, Scarafile R, Molino A, Rea G, Maglione M, Calabrò R, Russo MG, Bossone E, Saggar R. Right ventricular strain: an independent predictor of survival in idiopathic pulmonary fibrosis. Int J Cardiol. 2016;222:908–10. https://doi.org/10.1016/j.ijcard.2016.07.288
66. D'Andrea A, Stanziola A, Di Palma E, Martino M, D'Alto M, Dellegrottaglie S, Cocchia R, Riegler L, Betancourt Cordido MV, Lanza M, Maglione M, Diana V, Calabrò R, Russo MG, Vannan M, Bossone E. Right ventricular structure and function in idiopathic pulmonary fibrosis with or without pulmonary hypertension. Echocardiography. 2016;33:57–65. https://doi.org/10.1111/echo.12992
67. Kato S, Sekine A, Kusakawa Y, Ogura T, Futaki M, Iwasawa T, Kirigaya H, Gyotoku D, Iinuma N, Iguchi K, Nakachi T, Fukui K, Kimura K, Umemura S. Prognostic value of cardiovascular magnetic resonance derived right ventricular function in patients with interstitial lung disease. J Cardiovasc Magn Reson. 2015;17:10. https://doi.org/10.1186/s12968-015-0113-5
68. Bax S, Jacob J, Ahmed R, Bredy C, Dimopoulos K, Kempny A, Kokosi M, Kier G, Renzoni E, Molyneaux PL, Chua F, Kouranos V, George P, McCabe C, Wilde M, Devaraj A, Wells A, Wort SJ, Price LC. Right ventricular to left ventricular ratio at CT pulmonary angiogram predicts mortality in interstitial lung disease. Chest. 2020;157:89–98. https://doi.org/10.1016/j.chest.2019.06.033
69. Sonti R, Gersten RA, Barnett S, Brown AW, Nathan SD. Multimodal noninvasive prediction of pulmonary hypertension in IPF. Clin Respir J. 2019;13:567–73 https://doi.org/10.1111/crj.13059
70. Yagi M, Taniguchi H, Kondoh Y, Ando M, Kimura T, Kataoka K, Furukawa T, Suzuki A, Johkoh T, Hasegawa Y. CT-determined pulmonary artery to aorta ratio as a predictor of elevated pulmonary artery pressure and survival in idiopathic pulmonary fibrosis. Respirology. 2017;22:1393–9. https://doi.org/10.1111/resp.13066

71. Wells JM, Washko GR, Han MK, Abbas N, Nath H, Mamary AJ, Regan E, Bailey WC, Martinez FJ, Westfall E, Beaty TH, Curran-Everett D, Curtis JL, Hokanson JE, Lynch DA, Make BJ, Crapo JD, Silverman EK, Bowler RP, Dransfield MT. Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med. 2012;367:913–21. https://doi.org/10.1056/NEJMoa1203830
72. Shin S, King CS, Puri N, Shlobin OA, Brown AW, Ahmad S, Weir NA, Nathan SD. Pulmonary artery size as a predictor of outcomes in idiopathic pulmonary fibrosis. Eur Respir J. 2016;47:1445–51. https://doi.org/10.1183/13993003.01532-2015
73. Nathan SD, Chandel A, Wang Y, Xu J, Shao L, Watkins TR, Diviney J, King CS, Han L. Derivation and validation of a noninvasive prediction tool to identify pulmonary hypertension in patients with IPF: evolution of the model FORD. J Heart Lung Transplant. 2024;43:547–53. https://doi.org/10.1016/j.healun.2023.11.005
74. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023;61:2200879. https://doi.org/10.1183/13993003.00879-2022
75. Blanco I, Ribas J, Xaubet A, Gómez FP, Roca J, Rodriguez-Roisin R, Barberà JA. Effects of inhaled nitric oxide at rest and during exercise in idiopathic pulmonary fibrosis. J Appl Physiol. 2011;110(1985):638–45. https://doi.org/10.1152/japplphysiol.01104.2010
76. Olschewski H, ARDESCHIR GHOFRANI H, Walmrath D, SCHERMULY R, TEMMESFELD-WOLLBRÜCK B, GRIMMINGER F, SEEGER W. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med. 1999;160:600–7. https://doi.org/10.1164/ajrccm.160.2.9810008
77. Awerbach JD, Stackhouse KA, Lee J, Dahhan T, Parikh KS, Krasuski RA. Outcomes of lung disease-associated pulmonary hypertension and impact of elevated pulmonary vascular resistance. Respir Med. 2019;150:126–30. https://doi.org/10.1016/j.rmed.2019.03.004
78. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013;62:D42–50. https://doi.org/10.1016/j.jacc.2013.10.032
79. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings: how to handle the problems of zero leveling and respiratory swings. Am J Respir Crit Care Med. 2014;190:252–7. https://doi.org/10.1164/rccm.201402-0269PP
80. Kovacs G, Avian A, Olschewski A, Olschewski H. Zero reference level for right heart catheterisation. Eur Respir J. 2013;42:1586–94. https://doi.org/10.1183/09031936.00050713
81. Olschewski H, Zeder K, Douschan P, Sassmann T, Foris V, Olschewski A, Kovacs G. Let's talk about respiratory swings! Am J Respir Crit Care Med. 2023;208:1338–40. https://doi.org/10.1164/rccm.202309-1637LE
82. O'Donnell DE, Elbehairy AF, Berton DC, Domnik NJ, Neder JA. Advances in the evaluation of respiratory pathophysiology during exercise in chronic lung diseases. Front Physiol. 2017;8:82. https://doi.org/10.3389/fphys.2017.00082
83. Cheah R, Chirnaksorn S, Abdelrahim AH, Horgan L, Capstick T, Casey J, Peckham D, Boland A, Sutherland TJT, Beirne P, Lee AS, DeVault KR, Houghton LA. The perils and pitfalls of esophageal dysmotility in idiopathic pulmonary fibrosis. Am J Gastroenterol. 2021;116:1189–200. https://doi.org/10.14309/ajg.0000000000001202
84. LeVarge BL, Pomerantsev E, Channick RN. Reliance on end-expiratory wedge pressure leads to misclassification of pulmonary hypertension. Eur Respir J. 2014;44:425–34. https://doi.org/10.1183/09031936.00209313
85. Margaritopoulos GA, Antoniou KM, Wells AU. Comorbidities in interstitial lung diseases. Eur Respir Rev. 2017;26:160027. https://doi.org/10.1183/16000617.0027-2016
86. Teramachi R, Taniguchi H, Kondoh Y, Kimura T, Kataoka K, Yokoyama T, Furukawa T, Yagi M, Sakamoto K, Hashimoto N, Hasegawa Y. Impact of post-capillary pulmonary hypertension on mortality in interstitial lung disease. Respir Investig. 2021;59:342–9 https://doi.org/10.1016/j.resinv.2020.12.010
87. Santos NC, Miravitlles M, Camelier AA, Almeida VDC, Maciel RRBT, Camelier FWR. Prevalence and impact of comorbidities in individuals with chronic obstructive pulmonary disease: a systematic review. Tuberc Respir Dis. 2022;85:205–20. https://doi.org/10.4046/trd.2021.0179
88. Nathan SD, Barnett SD, King CS, Provencher S, Barbera JA, Pastre J, Shlobin OA, Seeger W. Impact of the new definition for pulmonary hypertension in patients with lung disease: an analysis of the United Network for Organ Sharing database. Pulm Circ. 2021;11:2045894021999960. https://doi.org/10.1177/2045894021999960
89. Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE. Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med. 2002;166:314–22. https://doi.org/10.1164/rccm.2107027
90. Dawes TJW, McCabe C, Dimopoulos K, Stewart I, Bax S, Harries C, Samaranayake CB, Kempny A, Molyneaux PL, Seitler S, Semple T, Li W, George PM, Kouranos V, Chua F, Renzoni EA, Kokosi M, Jenkins G, Wells AU, Wort SJ, Price LC. Phosphodiesterase 5 inhibitor treatment and survival in interstitial lung disease pulmonary hypertension: a Bayesian retrospective observational cohort study. Respirology. 2023;28:262–72. https://doi.org/10.1111/resp.14378
91. Nathan SD, Johri S, Joly JM, King CS, Raina A, McEvoy CA, Lee D, Shen E, Smith P, Deng C, Waxman AB. Survival analysis from the INCREASE study in PH-ILD: evaluating the impact of treatment crossover on overall mortality. Thorax. 2024;79:301–6. https://doi.org/10.1136/thorax-2023-220821
92. w?>Piccari L, Wort SJ, Meloni F, Rizzo M, Price LC, Martino L, Salvaterra E, Scelsi L, López Meseguer M,

Blanco I, Callari A, Pérez González V, Tuzzolino F, McCabe C, Rodríguez Chiaradía DA, Vitulo P. The effect of borderline pulmonary hypertension on survival in chronic lung disease. Respiration. 2022;101:717–27. https://doi.org/10.1159/000524263

93. Weatherald J, Nathan SD, El-Kersh K, Argula RG, DuBrock HM, Rischard FP, Cassady SJ, Tarver J, Levine DJ, Tapson VF, Deng C, Shen E, Das M, Waxman AB. Inhaled treprostinil in patients with pulmonary hypertension associated with interstitial lung disease with less severe haemodynamics: a post hoc analysis of the INCREASE study. BMJ Open Respir Res. 2024;11:e002116. https://doi.org/10.1136/bmjresp-2023-002116

How to cite this article: Vitulo P, Piccari L, Wort SJ, Shlobin OA, Kovacs G, Vizza CD, Hassoun PM, Olschewski H, Girgis RE, Nikkho SM, Nathan SD. Screening and diagnosis of pulmonary hypertension associated with chronic lung disease (PH-CLD): A consensus statement from the pulmonary vascular research institute's innovative drug development initiative—group 3 pulmonary hypertension. Pulm Circ. 2024;14:e70005. https://doi.org/10.1002/pul2.70005