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RESEARCH ARTICLE

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Pulmonary hypertension in patients with interstitial lung disease: a tool for early detection

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Abstract

Pulmonary hypertension (PH) complicates the treatment of interstitial lung disease (ILD) patients resulting in poor functional status and worse outcomes. Early recognition of PH in ILD is important for initiating therapy and considering lung transplantation. However, no standard exists regarding which patients to screen for PH-ILD or the optimal method to do so. The aim of this study was to create a risk assessment tool that could reliably predict PH in ILD patients. We developed a PH-ILD Detection tool that incorporated history, exam, 6-min walk distance, diffusion capacity for carbon monoxide, chest imaging, and cardiac biomarkers to create an eight-component score. This tool was analyzed retrospectively in 154 ILD patients where each patient was given a score ranging from 0 to 12. The sensitivity (SN) and specificity (SP) of the PH-ILD Detection tool and an area-under-the-curve (AUC) were calculated. In this cohort, 74 patients (48.1%) had PH-ILD. A score of ≥6 on the PH-ILD Detection tool was associated with a diagnosis of PH-ILD (SN: 86.5%; SP: 86.3%; area-under-the-curve: 0.920, $p < 0.001$). The PH-ILD Detection tool provides high SN and SP for detecting PH in ILD patients. With confirmation in larger cohorts, this tool could improve the diagnosis of PH in ILD and may suggest further testing with right heart catheterization and earlier intervention with inhaled treprostinil and/or lung transplant evaluation.

KEYWORDS
idiopathic pulmonary fibrosis, interstitial lung disease, prostacyclin, pulmonary hypertension, treprostinil

Abbreviations: 6MWD, 6-min walk distance; 6MWT, 6-min walk test; AUC, area-under-the-curve; BNP, B-type natriuretic peptide; CTD, connective tissue disease; DLCO, diffusion capacity for carbon monoxide; ICD-10, International Classification of Diseases 10th Revision; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; JVP, jugular venous pressure; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal proBNP; P2, pulmonic component of the second heart sound; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PA:A, pulmonary artery to aorta ratio; PFT, pulmonary function test; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; ROC, receiver operating characteristics; SAPH, sarcoidosis-associated pulmonary hypertension; SN, sensitivity; SP, specificity; WHO, World Health Organization.

BACKGROUND

Pulmonary hypertension (PH) is a frequent complication in patients with interstitial lung disease (ILD) and is associated with poor functional status, need for supplemental oxygen, and worse outcomes.[1–5] Over 40 studies have reported concomitant PH in idiopathic pulmonary fibrosis (IPF) patients; prevalence ranges from 3% to 86%.[6,7] This variability in prevalence depends on when PH was investigated during the ILD course, as well as the method of diagnosis. Mean pulmonary artery pressure (mPAP) is elevated in 8%–15% of patients when IPF is initially diagnosed; the prevalence increases with the progression of lung disease, complicating up to 30%–50% of advanced cases and more than 60% of end-stage disease.[8–11] PH can also develop in other ILDs, besides IPF, and a severe phenotype of PH-ILD including depressed cardiac index has been described by large European studies.[12,13] The development of PH in ILD patients is associated with decreased survival and increased morbidity with Song et al.[14] reporting 1-year mortality of 61.2% for patients with IPF and PH detected on echocardiogram compared to 19.9% in those without PH. Similarly, Nadrous et al.[15] reported a median survival of 0.7 years for patients with IPF and PA systolic pressure >50 mmHg on echocardiogram.

Thus, early recognition of PH in ILD is important in planning diagnostic tests, initiating therapy, and considering referral for lung transplantation. For example, in regard to therapy, results from the INCREASE trial demonstrated clinical and functional improvement with inhaled treprostinil in PH-ILD patients, thus increasing the importance of making the diagnosis of PH.[16] However, no standard currently exists regarding which patients to screen for PH-ILD nor the optimal method to do so.[17] Furthermore, the diagnosis of PH in the context of ILD is often difficult because of the overlap in symptoms and diagnostic testing.[18] To obviate these issues, there have been multiple attempts to incorporate various noninvasive parameters into a clinical prediction tool, but none has been widely adopted.[19–21] Currently, the most common recommendation is an echocardiogram annually or sooner if there is a significant change in symptoms.[17]

In an attempt to address these problems, our study determined whether a PH-ILD Detection tool incorporating eight common variables could provide useful information for screening for PH in ILD patients. To this end, we developed a simple, noninvasive tool based on patient history and symptoms, physical exam, 6-min walk test (6MWT), pulmonary function tests (PFTs), chest imaging, and cardiac biomarkers, all of which are routinely monitored in ILD patients.

METHODS

We performed a retrospective analysis of 162 ILD patients who underwent evaluation between October 2016 and February 2022 at Hartford Hospital (Hartford, CT). Patients were identified by the International Classification of Diseases 10th Revision (ICD-10). Of these 162 patients, 8 patients receiving background PH therapy were excluded. Consequently, we examined a total of 154 ILD patients.

Development of the PH-ILD Detection tool

We developed a PH-ILD Detection tool that incorporated patient history and symptoms, physical exam, 6MWT results, PFTs, chest imaging, and cardiac biomarkers to create an eight-component score. Physical exam findings included increased jugular venous pressure (JVP), pedal edema, ascites, accentuated pulmonic component of the second heart sound (P2), and/or parasternal heave. Six-min walk distance (6MWD) in meters (m) and the need for supplemental oxygen were also included in the PH-ILD Detection tool. For 6MWD, we used the cut-point of 350 m to delineate decreased exercise capacity. For PFTs, we used a diffusion capacity for carbon monoxide (DLCO, % predicted) cut-point of 40%. We also incorporated a history of syncope, concomitant diagnosis of connective tissue disease (CTD) or sarcoidosis, elevated B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) levels, and abnormal findings on computed tomography scan of the chest (CT chest) such as pulmonary artery (PA) to aorta ratio (PA:A) >0.9 or PA enlargement >30 mm.

Based on multivariate analysis, the candidate variables that were significantly associated with the PH-ILD subgroup were a physical exam, 6MWD < 350 m, and DLCO < 40%. Based on the regression coefficients of the covariates in the multivariate model, we assigned a weighted score of 2 points to each of these covariates as well as to oxygen supplementation because of its high combined sensitivity (SN) and specificity (SP). We assigned 1 point to the other four covariates: syncope, CTD or sarcoidosis, elevated cardiac biomarkers, and PA enlargement on CT chest. The individual points were totaled to obtain a composite score ranging from 0 to 12 (Table 1).

The PH-ILD Detection tool was designed for use in patients with an established diagnosis of ILD. Depending on the total score for a given patient, patients were then stratified into low, intermediate, or high-risk with the assumption that low-risk patients were unlikely to have PH-ILD and intermediate and high-risk patients had a greater probability of PH-ILD (Table 2). Continued risk assessment at follow-up visits would be recommended for

TABLE 1 Metrics of the detection tool for screening for PH in ILD patients

Clinical finding	Score
6MWD < 350 m	2
Physical exam for PH[a]	2
DLCO < 40%	2
Supplemental oxygen	2
Elevated BNP or NT-ProBNP[b]	1
Syncope or presyncope	1
PA enlargement on CT chest[c]	1
CTD or sarcoidosis	1

Abbreviations: 6MWD, 6-min walk distance; BNP, B-type natriuretic peptide; CTD, connective tissue disease; DLCO, diffusion capacity for carbon monoxide; ILD, interstitial lung disease; NT-ProBN, N-terminal proBNP; PA, pulmonary artery; PH, pulmonary hypertension.

[a]Increased JVP, peripheral edema, ascites, accentuated P2, TR murmur, parasternal heave.

[b]BNP > 50 pg/ml, NT-ProBNP > 300 pg/ml.

[c]Ratio of pulmonary artery (PA) to aorta (A) > 0.9, enlargement of main PA > 30 mm.

TABLE 2 Low-, intermediate-, and high-risk category scores and clinical recommendations

Score	Risk category	Recommendations
≤3	Low	Reassess during follow-up visit
4–5	Intermediate	Echocardiogram and short-term reassessment
≥6	High	Echocardiogram and immediate referral to PH center for RHC

Abbreviations: PH, pulmonary hypertension; RHC, right heart catheterization.

low-risk patients and further screening with an echocardiogram for intermediate-risk patients. For high-risk patients, an echocardiogram and immediate referral to a PH specialist for further evaluation and management, including right heart catheterization (RHC), would be recommended.

Statistics

After evaluating continuous data for normality of distribution, descriptive statistics comprised means and standard deviations. Categorical data were presented as frequencies, using percentages. Inferential statistics comprised a Student's *t*-test, for comparisons of continuous variables between ILD and ILD-PH groups, and a χ^2 test, for comparisons of categorical variables. Variables that showed statistically significant differences upon univariate testing were included in a forward, conditional logistic regression model. A receiver operating characteristics (ROC) curve was generated, and an area-under-the-curve (AUC) was calculated from the values of SN and SP. All analyses were conducted with SPSS v. 26 (IBM) using an a priori α level of 0.05.

RESULTS

Patients

Patient demographics and other clinical data, dichotomized by the presence or absence of PH, are shown in Table 3. The average duration between the evaluation of all components of the PH-ILD Detection tool and RHC was 6 months.

Patients underwent RHC to determine the presence or absence of PH. PH was diagnosed by RHC with an mPAP ≥ 20 mmHg, pulmonary capillary wedge pressure (PCWP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >3 Wood units. The diagnosis of ILD was confirmed by the identification of diffuse parenchymal lung disease on the CT chest.

In the cohort, PH was diagnosed in 74 patients (48.1%) with a mean age of 73.2 years; 47.3% ($n = 35$) were female. The most common cause of ILD was IPF in both the PH-ILD ($n = 32$; 43.2%) and non-PH ILD ($n = 31$; 38.8%) cohorts. There was a significantly larger portion of patients with nonspecific interstitial pneumonia in the non-PH ILD group ($n = 32$; 40.0%) compared to the PH-ILD group ($n = 14$; 18.9%) and conversely, a higher prevalence of combined pulmonary fibrosis and emphysema in the PH-ILD group ($n = 16$; 21.2%) versus the non-PH ILD cohort ($n = 6$; 7.5%).

Results of individual components to predict PH-ILD

Four of the eight components had a combined SN and SP greater than 1.4; however, the two highest components, 6MWD and physical exam, had a much higher SP than SN (Table 4). The component with the highest SN was supplemental oxygen, although that did not contribute significantly to the multivariate model in comparison to 6MWD, physical exam, and DLCO.

Accuracy and validation of the PH-ILD Detection tool

We created a cumulative graph and plotted the risk scores using the ROC curve. A score of ≥6 was associated with the

TABLE 3 Baseline characteristics

Characteristic	All	ILD	PH-ILD	*p* Value
Sample size—number (%)	154	80 (51.9)	74 (48.1)	—
Female sex—number (%)	78 (50.6)	43 (53.8)	35 (47.3)	**0.424**[a]
Age, years (mean ± SD)	70.0 ± 12.1	67.0 ± 11.5	73.2 ± 12.0	**0.001**[b]
Race—number (%)				
White	85 (55.2)	32 (40.0)	53 (71.6)	**0.001**[b]
Black/African American	21 (13.6)	13 (16.3)	8 (10.8)	
Asian	2 (1.3)	2 (2.5)	0 (0.0)	
Other (undefined)	46 (29.9)	33 (41.3)	13 (17.6)	
Hispanic/Latinx—number (%)	49 (31.8)	36 (45.0)	13 (17.6)	**<0.001**[b]
Cause of lung disease—number (%)				
Idiopathic pulmonary fibrosis	63 (40.9)	31 (38.8)	32 (43.2)	**0.014**[b]
Nonspecific interstitial pneumonia	46 (29.9)	32 (40.0)	14 (18.9)	
Combined pulmonary fibrosis and emphysema	22 (14.3)	6 (7.5)	16 (21.2)	
Post-Coronavirus-2019 lung disease	8 (5.2)	5 (6.3)	3 (4.1)	
Respiratory bronchiolitis with ILD	4 (2.6)	3 (3.8)	1 (1.4)	
Cryptogenic organizing pneumonia	4 (2.6)	3 (3.8)	1 (1.4)	
Drug-related lung disease	3 (1.9)	0	3 (4.1)	
Sarcoidosis-related lung disease	2 (1.3)	0	2 (2.7)	
Occupational lung disease	1 (1.0)	0	1 (1.4)	
Pulmonary Langerhans cell histiocytosis	1 (1.0)	0	1 (1.4)	
Antifibrotic therapy—number (%)				
No therapy	136 (88.3)	75 (93.8)	61 (82.4)	**0.029**[b]
On therapy	18 (11.7)	5 (6.3)	13 (17.6)	
Left heart dysfunction—number (%)	22 (14.2)	10 (12.5)	12 (16.2)	

Note: Values in bold are statistically significant at $p < 0.05$.

[a]χ^2.

[b]Student's *t*-test.

TABLE 4 Sensitivity and specificity for each scoring tool component

Component	SN (%)	SP (%)	SN + SP
6MWD < 350 m	78.4	90.0	1.684
Physical exam for PH	52.7	95.0	1.477
DLCO < 40%	71.6	71.3	1.429
Supplemental oxygen	85.1	55.0	1.401
NT-ProBNP >300 pg/ml	75.7	61.3	1.369
Syncope or presyncope	29.7	86.3	1.160
PA enlargement on CT chest	36.5	78.8	1.152
CTD or sarcoidosis	35.1	60.0	0.951

Abbreviations: 6MWD, 6-min walk distance; CTD, connective tissue disease; DLCO, diffusion capacity for carbon monoxide; NT-ProBN, N-terminal proBNP; PA, pulmonary artery; SN, sensitivity; SP, specificity.

greatest likelihood that a patient would have a diagnosis of PH-ILD (Figure 1). The SN was 86.5% and SP was 86.3%, resulting in an AUC of 0.920 (95% confidence interval [CI]: 0.878–0.962, $p < 0.001$). Using the detection tool to identify cases of PH-ILD, the resulting false positives were 11 (7.1%) and false negatives were 10 (6.5%).

Prognostic implications of the PH-ILD Detection tool

A score of ≥8 on the PH-ILD Detection tool resulted in an AUC of 0.680 (95% CI: 0.581–0.778, $p < 0.001$) for mortality with SN of 53.3% and SP of 82.6% (Figure 2), suggesting a score on the risk assessment tool below this cut-off was a strong identifier of patients who survived.

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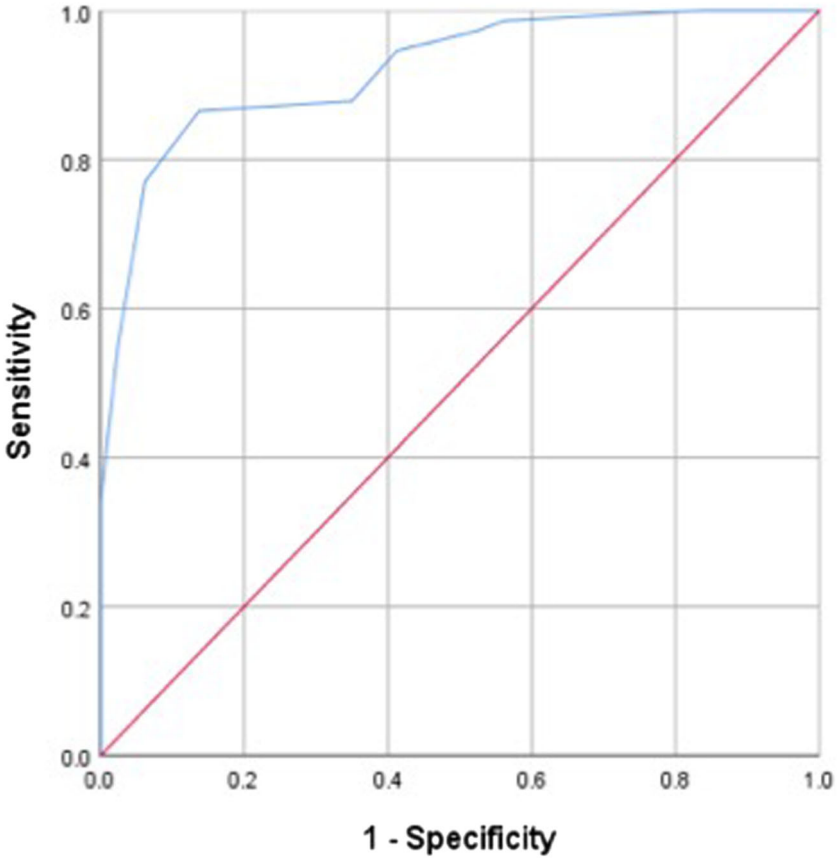

FIGURE 1 ROC curve for scoring tool to identify PH-ILD. ILD, interstitial lung disease; PH, pulmonary hypertension; ROC, receiver operating characteristics.

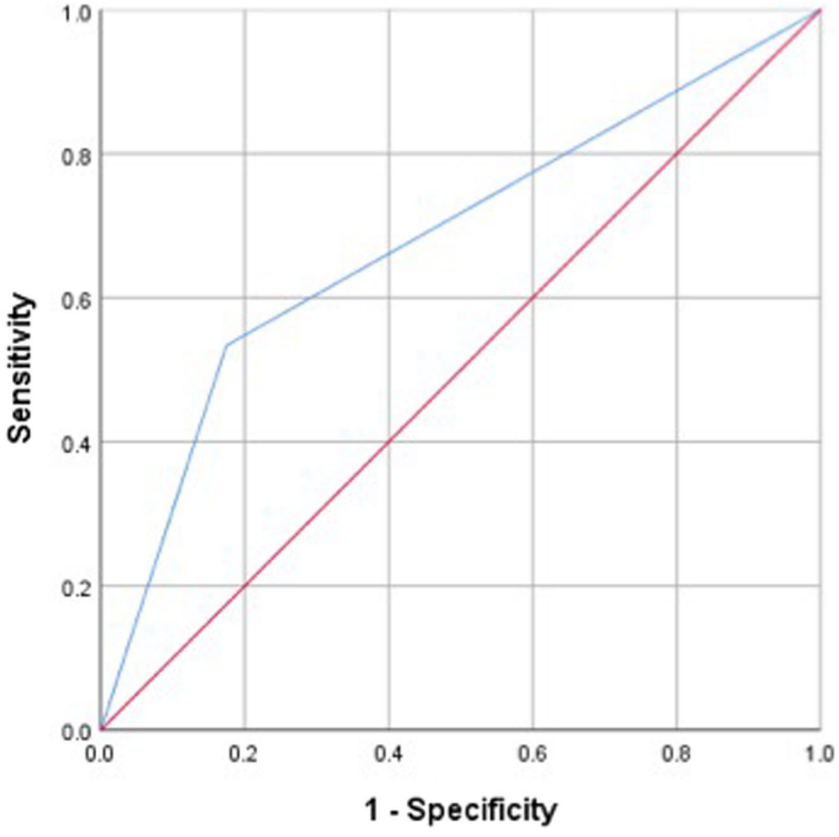

FIGURE 2 ROC curve for scoring tool to identify mortality. ROC, receiver operating characteristics.

Summary of PH-ILD Detection tool metrics

A score of ≥6 using the metrics in the PH-ILD Detection tool was associated with a high likelihood of PH and a score of ≥8 was associated with poorer survival.

DISCUSSION

The presence of PH exerts a significant negative impact on survival in ILD patients.[6,22–24] A study from the Giessen registry demonstrated that patients with World Health Organization (WHO) Group 3 PH had a worse prognosis than patients with WHO Group 1 pulmonary arterial hypertension (PAH).[25] Early detection of PH-ILD is important because even mild elevations in mPAP can be a significant predictor of mortality in patients with ILD.[26,27]

PH commonly intercedes at various stages of ILD so a regular, noninvasive, and affordable screening tool is imperative for the ongoing management and decision-making in these patients. Although RHC is the gold standard to diagnose PH, it is not a convenient screening tool because it is invasive, time-consuming, costly, and the risk of moderate sedation is higher in those with baseline hypoxemia.[19] There have been several unsuccessful attempts to develop a reliable screening tool for PH-ILD and most have used components of PFTs and/or oxygen saturation; as such, recent authors have concluded that noninvasive testing alone is not sufficiently accurate to screen these patients.[20,28–30]

Justification for eight components of PH-ILD Detection tool

In our study, eight variables routinely monitored in ILD patients were incorporated into the PH-ILD Detection tool in an attempt to create a useful and reliable method for screening for PH in this population. Each individual component has previously been utilized in the evaluation and prognostication of PH patients.

6MWD < 350 m

The development of concomitant PH poses an additional burden on exercise capacity in ILD patients.[31] In ILD or PH patients individually, the 6MWT has proven to be highly reproducible and easy to perform while providing information on functional capacity and need for supplemental oxygen with exertion.[32] Multiple studies have demonstrated that patients with PH-ILD have a lower 6MWD than ILD patients without PH.[10,11,13,19,33] Not only does a reduced 6MWD suggest the diagnosis of concomitant PH in ILD patients, but it is also associated with decreased survival.[2] However, there is conflicting data demonstrating that shorter distances on a 6MWT were actually not predictive of PH in ILD.[20]

Physical exam findings suggestive of PH

Physical exam findings, including increased JVP, pedal edema, ascites, P2, and/or parasternal heave are suggestive of right heart dysfunction associated with PH.[34] In fact, ILD patients are often evaluated for concomitant PH only after such signs are detected; at that point, pulmonary vascular disease (PVD) may have significantly progressed.[35,36] However, there is no consensus whether physical exam findings alone have sufficient SN to predict PH-ILD accurately.[34]

Percent predicted DLCO < 40%

Decreased DLCO reflects fibrosis of the alveoli and perfusion inhomogeneity in ILD and PH patients, respectively.[37,38] Studies have proposed that PH should be suspected when DLCO is disproportionately low compared with functional and radiological impairment in ILD patients.[3] Several reports have suggested that DLCO ranging from 30% to 45% can predict PH.[10,18,39,40] Additionally, worsening DLCO in the setting of preserved lung volumes could suggest the possibility of underlying PVD.[17] Therefore, forced vital capacity to DLCO ratio has been incorporated into a multicomponent scoring tool to improve the accuracy of PH prediction.[19,28–30,41] The fact that DLCO not only serves as a diagnostic clue in ILD patients who develop concomitant PH, but also as a prognosticator denotes the potential importance of this metric in this subset of patients.[2,28,29,39,42]

Supplemental oxygen

The need for supplemental oxygen has been evaluated as a predictor of PH in ILD patients.[10] In ILD and sarcoidosis, recent studies suggest that the need for oxygen supplementation is an independent predictor of PH.[10,11,40,43] Hypoxic pulmonary vasoconstriction, an innate physiologic response to alveolar hypoxia resulting in constriction of intrapulmonary arteries and diversion of blood to better oxygenated lung areas, explains why

supplemental oxygen would be predictive of underlying PH in chronically hypoxemic patients.[10,44]

Elevated cardiac biomarkers

Although cardiac biomarkers, such as BNP and NT-proBNP, are controversial as independent predictors of PH in ILD patients, the bulk of available data suggests that they are potentially very useful.[31] For example, Sonti et al.[19] found a statistically significant difference in BNP levels between PH-ILD patients (738 pg/ml) and non-PH ILD patients (263 pg/ml). Other studies have not only shown the potential diagnostic utility of these biomarkers, but also a prognostic value as well. To wit, BNP values have correlated with transplant-free survival in ILD patients and cardiac biomarker levels have been predictive of prognosis in this subset of patients as well.[31,36,45–47] And, a cross-sectional study demonstrated that BNP levels were able to detect PH in IPF patients and not only showed a correlation of BNP with invasive hemodynamics, but also a significant association with WHO functional class and 6MWD.[31]

Yet, there are several factors that make the measurements unreliable on their own including left heart dysfunction, renal failure, and obesity.[36,48] Therefore, other authors have suggested that the predictive value of cardiac biomarkers in newly diagnosed ILD is overall low.[48]

Syncope or presyncope

Syncope in PH patients suggests depressed right heart function.[49] The REVEAL registry further highlighted the incidence and clinical implications of syncope in the PH population.[50] Although the effect of syncope in PH-ILD has not been extensively evaluated, there is hemodynamic evidence to suggest that syncope is a poor prognostic indicator in this entity as well.[13,14]

PA enlargement on CT chest

PA enlargement on CT chest can be due to a variety of conditions including PH. A normal PA diameter has been designated as <27–29 mm.[51] Along with PA dilation, the PA:A ratio has been utilized to suggest PVD.[19] Several studies have evaluated the utility of PA diameter in ILD patients to predict PH; many have shown that a PA:A >0.9 or >1.1 was predictive of an mPAP > 20 mmHg as well as predictive of decreased survival.[30,52] Others have shown that a PA:A ratio >1.0 can predict PH in COPD and IPF patients.[20,30,52,53] King et al. incorporated this ratio into a multi-score predictor tool to establish an association with increased PVR and mortality in patients with ILD.[54] As such, it has been suggested that PA:A combined with other metrics could improve the accuracy of PH prediction in ILD patients.[19] However, other authors remain skeptical about the overall utility of PA size in predicting PH-ILD and in a cross-sectional study of 65 IPF patients, there was no correlation between PH and increased PA diameter or PA:A ratio.[55,56]

CTD or sarcoidosis

The existence of CTD, especially scleroderma, or sarcoidosis can often cloud the clinical picture in PH-ILD.[3,47] Scleroderma is associated with both PAH and ILD individually.[57] Differentiating the contribution of PVD and parenchymal lung disease in scleroderma patients who have both PAH and ILD is challenging.[17,47] Nevertheless, the presence of PAH or ILD are two major causes of morbidity and mortality in patients with scleroderma.[58] Even in CTD patients with WHO Group 1 PAH, the presence of minor parenchymal lung disease affects survival.[59] However, it remains difficult to determine the contributory role of ILD in the development of PH in CTD patients since they are already at risk for WHO Group 1 PAH independent of parenchymal lung disease.[60]

The prevalence of PH in sarcoidosis ranges from 6% to 74% with a 5-year survival of 50%–60%.[5,43,61] The complex mechanisms of sarcoidosis-associated PH (SAPH) include lung fibrosis and obliteration of pulmonary vessels, extrinsic compression of pulmonary vasculature by lymphadenopathy or fibrosing mediastinitis, pulmonary veno-occlusive disease, granulomatous involvement of pulmonary vessels, left ventricular dysfunction, and portopulmonary hypertension.[61] However, despite these complexities, the need for supplemental oxygen was shown to be an independent predictor of PH in a multivariate analysis, suggesting that hypoxic pulmonary vasoconstriction is a major contributor to the pathophysiology.[47,62] This is further suggested by the fact that advanced stage disease has a higher prevalence of both hypoxemia and concomitant PH.[63]

Clinical implications of PH-ILD detection tool

Our study assessed the accuracy of a PH-ILD Detection tool, incorporating eight independent factors to predict

PH-ILD. In this cohort, the PH-ILD Detection tool stratified PH-ILD patients by level of risk for PH; surprisingly, it also seemingly was able to predict prognosis in this subset of patients. From these data, we would suggest that for low-risk individuals (i.e., lower score), reassessment at follow-up visits is warranted unless another metric develops in the interim. Those patients in the intermediate-risk category should be considered for further evaluation including screening echocardiogram and closer follow-up. ILD patients classified as high-risk warrant prompt evaluation for concomitant PH, including echocardiogram and referral to a PH specialist where PH can formally be evaluated and RHC performed.

Strengths and limitations of this study

The present study has several limitations: (1) this was a single-center, retrospective study; (2) there were 12 patients (16.2%) in the PH-ILD group with depressed ejection fraction and/or abnormal diastolic indices on echocardiogram; however, during RHC, PCWP was ≤15 mmHg in these patients and therefore, they were included in the study; (3) eight metrics were tested and incorporated into the PH-ILD Detection tool but other potential risk factors, such as age, were not included; and (4) the PH-ILD Detection tool was validated internally, but does require external validation with an independent cohort of patients.

The strengths of our study are that it is a relatively large cohort of patients with a diverse demographic background that was investigated over a several-year period. Moreover, the effectiveness of this detection tool is quite plausible since many of the individual variables have been independently associated with the development of PH in ILD patients.

CONCLUSION

There is currently no available detection tool widely accepted to suggest PH-ILD. Our study developed a noninvasive detection tool that not only incorporated several variables recently published in a consensus statement for PH screening in ILD but also had both a high SN and SP for detecting PH in ILD within our study cohort.[64]

The development of the PH-ILD Detection tool and its further refinement has important implications in the evaluation and treatment of ILD patients in clinical practice: concomitant PH may be diagnosed sooner and more accurately in these patients, allowing for earlier interventions such as initiation of inhaled therapies or referral for lung transplant evaluation.

AUTHOR CONTRIBUTIONS

Raj Parikh: Conceptualization, data curation, investigation, methodology, validation, writing–original draft, writing–review & editing, guarantor. **Ippokratis Konstantinidis**: Conceptualization, data curation. **David M. O'Sullivan**: Conceptualization, data curation, formal analysis, methodology, writing–original draft, writing–review & editing. **Harrison W. Farber**: Conceptualization, investigation, methodology, validation, writing–original draft; writing–review & editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

This study was approved by the Hartford HealthCare Institutional Review Board (HHC-2022-0014).

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