DOI: 10.1002/pul2.12273

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

The PH-ILD Detection tool: External validation and use in patients with ILD

Raj Parikh[1] | **David M. O'Sullivan**[2] | **Harrison W. Farber**[3]

[1]Division of Pulmonary, Critical Care and Sleep, Hartford Hospital, Hartford, Connecticut, USA

[2]Department of Research Administration, Hartford HealthCare, Hartford, Connecticut, USA

[3]Division of Pulmonary, Sleep and Critical Care Medicine, Tufts Medical Center, Boston, Massachusetts, USA

Correspondence
Raj Parikh, 85 Seymour St. #923, Hartford, CT 06106, USA.
Email: Raj.parikh210@gmail.com

Funding information
None

Abstract

Pulmonary hypertension (PH) results in increased morbidity and mortality in patients with interstitial lung disease (ILD). Early recognition of PH in this population is essential for planning diagnostic testing, initiating therapy, and evaluating for lung transplantation. The previously developed PH-ILD Detection tool has significant potential in the evaluation and treatment of ILD patients; the aim of this study was to validate the tool in an independent, multicenter cohort of patients. We conducted a retrospective review of prospectively collected data from 161 ILD patients. Patients were stratified into low- ($n = 78$, 48.4%), intermediate- ($n = 54$, 33.5%), and high-risk ($n = 29$, 18.0%) groups based on the score obtained with the tool. Intermediate- and high-risk patients underwent follow-up echocardiogram (TTE); 49.4% ($n = 41$) had an abnormal TTE suggestive of underlying PH. These patients underwent right heart catheterization; PH-ILD was diagnosed in 73.2% ($n = 30$) of these cases. The PH-ILD Detection tool has a sensitivity of 93.3%, specificity of 90.9%, and area-under-the-curve of 0.921 for diagnosing PH in ILD patients, validating the findings from the original study and establishing the tool as a fundamental resource for early recognition of PH in ILD patients.

KEYWORDS

combined pulmonary fibrosis and emphysema, idiopathic pulmonary fibrosis, interstitial lung disease, prostacyclin, pulmonary hypertension, risk assessment, treprostinil

Abbreviations: 6MWD, 6-min walk distance; AUC, area-under-the-curve; BNP, B-type natriuretic peptide; CI, cardiac index; CTD, connective tissue disease; DLCO, diffusion capacity for carbon monoxide; EMR, electronic medical record; ePASP, estimated pulmonary artery systolic pressure; eRVSP, estimated right ventricular systolic pressure; ICD-10, international Classification of Diseases 10th Revision; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IVS, interventricular septal; JVP, jugular Venous Pressure; mPAP, mean pulmonary artery pressure; NSIP, nonspecific interstitial pneumonia; P2, pulmonic valve heart sound; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrium; RHC, right heart catheterization; ROC, receiver operating characteristics; RV, right ventricle; SN, sensitivity; SP, specificity; TR, tricuspid regurgitation; TTE, transthoracic Echocardiogram.

BACKGROUND

Pulmonary hypertension (PH) is a significant complication in patients with interstitial lung disease (ILD), resulting in poorer functional status, need for supplemental oxygen, and worse outcomes.[1–5] Mean pulmonary artery pressure (mPAP) is elevated in 8–15% of patients when initially diagnosed with ILD; the prevalence of PH increases as the lung disease progresses.[6–9] The development of PH in ILD patients is associated with increased morbidity and mortality; echocardiographic studies suggest a median survival of less than one year in patients with idiopathic pulmonary fibrosis (IPF) and an estimated pulmonary artery systolic pressure > 50 mmHg.[10,11]

Given the significant morbidity and mortality, early recognition of PH in ILD is vital not only for planning appropriate diagnostic testing but also for initiating therapy and evaluation for lung transplantation. To address this problem, we created a PH-ILD Detection tool from a retrospective review of ILD patients in a single, tertiary academic center (Tables 1 and 2).[12] The tool incorporates eight variables that are routinely monitored in ILD patients; dependent on the score, the tool creates three risk groups for existence of PH: low, intermediate, and high (Table 2). Based on the risk group, suggested treatment is either reassessment at various intervals for low-risk patients, screening with transthoracic echocardiogram (TTE) for the intermediate-risk group, or prompt evaluation including TTE and referral to a PH specialist where PH can be formally evaluated and right heart catheterization (RHC) performed for high-risk patients.

Although this PH-ILD Detection tool is a provocative method for early recognition of this important complication of ILD and has significant potential implications in the evaluation and treatment of such patients, the original iteration was limited by development in a single center. The current study was undertaken to validate the PH-ILD Detection tool in an independent, multicenter cohort of patients and establish it as a fundamental resource for early recognition of PH in ILD patients.

TABLE 1 Scoring system and components of the PH-ILD detection tool.

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; JVP, jugular venous pressure; PH-ILD, pulmonary hypertension-interstitial lung disease; TR, tricuspid regurgitation.

[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 based on PH-ILD detection tool.

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-ILD, pulmonary hypertension-interstitial lung disease; RHC, right heart catheterization.

METHODS

We conducted a retrospective study of prospectively collected data from 199 ILD patients undergoing evaluation from February 2022 to April 2023 at six sites. Patients were identified by the International Classification of Diseases 10th Revision (ICD-10) codes for ILD subtypes (J84). The diagnosis of ILD was confirmed by diffuse parenchymal lung disease on CT chest. An electronic medical record-based smart phrase was developed for the six participating centers, which assisted in patient identification. The study was approved by the Hartford HealthCare Institutional Review Board (IRB; HHC-2022-0014).

Of the 199 patients initially identified, 38 did not have all eight components of the PH-ILD Detection tool available; the most common missing metric was N-terminal pro B-type natriuretic peptide (proBNP) level. Thus, for the current study, we examined a total of 161 ILD patients. 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 PH-ILD groups, and a chi square test, for comparisons of categorical variables. A receiver operating characteristics (ROC)

curve was generated, and an area-under-the-curve (AUC) was calculated from the values of sensitivity (SN) and specificity (SP). All analyses were conducted with SPSS v. 26 (IBM) using an a priori α level of 0.05.

Components of the PH-ILD Detection tool

We originally developed a PH-ILD Detection tool that incorporated patient history and symptoms, physical exam, 6-min walk test results, pulmonary function testing (PFTs), chest imaging, and cardiac biomarkers to create an eight-component score (Table 1).[12]

Physical exam findings included increased jugular venous pressure, pedal edema, ascites, accentuated pulmonic component of the second heart sound (P2), and/or parasternal heave; all of them being suggestive of right heart dysfunction without consensus on whether these findings alone have sufficient SN to predict PH-ILD accurately.[13]

6-min walk distance (6MWD) in meters (m) and need for supplemental oxygen were also included in the PH-ILD Detection tool. Although recognizing that the exact distance is controversial, for 6MWD, we used the cut-point of 350 m to delineate decreased exercise capacity since multiple studies have demonstrated that patients with PH-ILD have a lower 6MWD than ILD patients without PH.[14–19] Meanwhile, the need for oxygen supplementation is an independent predictor of PH.[14,15,20,21]

For PFTs, we used a diffusion capacity for carbon monoxide (DLCO, % predicted) cut-point of 40% because studies have proposed that PH should be suspected when DLCO is disproportionately lower compared with functional and radiological impairment in ILD patients.[3,17,22–25] The fact that DLCO not only serves as a diagnostic clue in ILD patients who develop PH but also as a prognosticator denotes the potential importance of this metric in this subset of patients.[2,23,26–28]

We also incorporated a concomitant diagnosis of connective tissue disease (CTD) or sarcoidosis in the PH-ILD Detection tool. Existence of CTD, especially scleroderma, or sarcoidosis can often cloud the clinical picture in PH-ILD since the concomitant disease can be associated with the development of PH and ILD individually.[3,29,30] Nevertheless, the presence of PH or ILD are major causes of morbidity and mortality in the CTD population while advanced stage sarcoidosis has a higher prevalence of developing PH as well.[31,32]

Along with baseline comorbidities of CTD and sarcoidosis, we included symptoms of severe right ventricular dysfunction including syncope which has significant clinical implications when present in the PH population.[33,34] While 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; therefore, we incorporated it into the PH-ILD Detection tool.[10,16]

Lastly, we included cardiac biomarkers and findings on chest imaging in the detection tool. This included BNP or proBNP, useful markers in ILD patients for PH detection and prognosis.[19,29,35–38] However, their utility as independent predictors of PH in ILD patients remains controversial as there are several factors that make the measurements unreliable on their own including left heart dysfunction, renal failure, and obesity.[36,39] Similarly, 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 were included in the PH-ILD Detection tool given the evidence supporting its use in predicting concomitant PH.[17,18,24,30,40–42]

Each of the 8 parameters included in the PH-ILD Detection tool have an inconsistent ability to predict PH in ILD patients when evaluated independently; nevertheless, they are important factors in increasing the likelihood of concomitant disease. Therefore, combining all these metrics into the composite scoring system resulted in the PH-ILD Detection tool in which the candidate variables that were significantly associated with the PH-ILD subgroup based on multivariate analysis were 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 SN and 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).

RESULTS

Patients

Patient demographics and other baseline clinical data are shown in Table 3. The mean age was 69.8 years and there was a slight male predominance (81 patients; 50.3%). In this cohort, the most common cause of ILD was IPF (68 patients: 42.2%), followed by nonspecific interstitial pneumonia (NSIP; 37 patients: 23.0%).

Echocardiogram and right heart catheterization

The PH-ILD Detection tool was applied to each ILD patient in the cohort. Patients were stratified into low-,

TABLE 3 Baseline characteristics.

Characteristic	All	ILD only	PH-ILD	*p* Value*
Sample size—number	161	131 (81.4%)	30 (18.6%)	–
Gender—number (%)				0.440[a]
Male	81 (50.3)	64 (48.9)	17 (56.7)	
Female	80 (49.7)	67 (51.1)	13 (43.3)	
Age, years (mean ± SD)	69.8 ± 9.4	70.3 ± 9.6	67.6 ± 8.1	0.144[b]
Race—number (%)				0.414[a]
White	123 (76.4)	100 (76.9)	23 (76.7)	
Black/African American	10 (6.2)	7 (5.4)	3 (10.0)	
Asian	2 (1.2)	1 (0.8)	1 (3.3)	
Other (undefined)	25 (15.5)	22 (16.9)	3 (10.0)	
Missing	1 (0.6)	1 (0.8)	0 (0.0)	
Hispanic/Latinx—number (%)	26 (16.1)	23 (17.8)	3 (10.0)	0.296[a]
Cause of lung disease—number (%)				0.332[a]
Idiopathic pulmonary fibrosis	68 (42.2)	55 (42.0)	13 (43.3)	
Nonspecific interstitial pneumonia	37 (23.0)	30 (22.9)	7 (23.3)	
Undifferentiated and drug-related lung disease	15 (9.3)	12 (9.2)	3 (10.0)	
Combined pulmonary fibrosis and emphysema	11 (6.8)	6 (4.6)	5 (16.7)	
Post-Coronavirus-2019 lung disease	8 (5.0)	7 (5.3)	1 (3.3)	
Respiratory bronchiolitis with ILD	6 (3.7)	6 (4.6)	0 (0.0)	
Cryptogenic organizing pneumonia	6 (3.7)	6 (4.6)	0 (0.0)	
Sarcoidosis-related lung disease	6 (3.7)	5 (3.8)	1 (3.3)	
Hypersensitivity pneumonitis	4 (2.5)	4 (3.1)	0 (0.0)	
Antifibrotic therapy—number (%)				0.178[a]
No therapy	108 (67.1)	91 (69.5)	17 (56.7)	1.000[c]
On therapy	53 (32.9)	40 (30.5)	13 (43.3)	
Pirfenidone	38/53 (58.5)	23 (57.5)	8 (61.5)	
Nintendanib	22/53 (41.5)	17 (42.5)	5 (38.5)	
Supplemental oxygen—number (%)				**<0.001**[a]
No oxygen	102 (63.4)	94 (71.8)	8 (26.7)	
On oxygen	59 (36.6)	37 (28.2)	22 (73.3)	

Abbreviations: PH-ILD, pulmonary hypertension-interstitial lung disease; SD, standard deviation.

*Values in **bold** represent statistically significant differences at $p < 0.05$;

[a]chi square;

[b]Student's t;

[c]Fisher's exact.

intermediate-, and high-risk groups based on the score obtained with the tool (Table 4). Twenty-six patients (16.1%) had follow-up assessment with the PH-ILD Detection tool and two (7.7%) of these patients had a change in score, transitioning them from intermediate-risk to high-risk.

Based on recommendations outlined by the PH-ILD Detection tool, the 54 intermediate-risk and 29 high-risk underwent follow-up TTE. Parameters suggestive of underlying PH on TTE included: 1) dilated right atrium (RA) or right ventricle (RV), 2) moderate or severe tricuspid regurgitation (TR), 3) estimated RV systolic

TABLE 4 Risk stratification groups and echocardiogram outcomes.

Score	Risk category	Frequency (*n*, %)	Abnormal TTE	Abnormal RHC (for PH-ILD)
≤3	Low	78, 48.4%	0/78 (0%)	0/0
4-5	Intermediate	54, 33.5%	12/54 (22.2%)	2/12 (16.7%)
≥6	High	29, 18.0%	29/29 (100%)	28/29 (96.6%)

Abbreviations: PH-ILD, pulmonary hypertension-interstitial lung disease; RHC, Right heart catheterization; TTE, transthoracic echocardiogram.

TABLE 5 Echocardiographic findings.

TTE abnormality	Frequency (*n*, %)
Dilated RA/RV	32 (78.0)
Moderate/Severe TR	12 (29.3)
eRVSP ≥ 35 mmHg	32 (78.0)
Pericardial effusion	12 (29.3)
IVS deviation	11 (26.8)
2 TTE abnormalities	7 (17.1)
3 TTE abnormalities	15 (36.6)
4 TTE abnormalities	7 (17.1)

Abbreviations: eRVSP, estimated RV systolic pressure; IVS, Interventricular septal; RA, Right atrium; RV, Right ventricle; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram.

pressure (eRVSP) ≥ 35 mmHg, 4) presence of a pericardial effusion, and 5) interventricular septal (IVS) deviation (Table 5).[43–49] In the cohort of 83 patients in the intermediate- and high-risk groups, 41 (49.4%) patients had an abnormal TTE (Table 4). These 41 patients underwent RHC; PH was defined by a mPAP ≥ 20 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units. Pre-capillary PH was diagnosed in 30 (73.2%) patients (Table 5). These patients subsequently underwent routine testing to evaluate other potential causes of pre-capillary PH including ventilation-perfusion imaging to screen for chronic thromboembolic PH; once other etiologies were excluded, a diagnosis of PH-ILD was established.

PH-ILD Detection tool components and risk groups

Within the low-risk group, the most common finding from the PH-ILD Detection tool components was presence of CTD or sarcoidosis ($n = 26$, 33.3%) followed by symptoms of syncope and presyncope ($n = 16$, 20.5%; Table 6). In the intermediate-risk group, the use of supplemental oxygen ($n = 32$, 59.3%) was most frequent followed by DCLO < 40% ($n = 29$; 53.7%) and presence of CTD or sarcoidosis ($n = 27$; 50%). The most common parameters from the high-risk group as determined by the PH-ILD Detection tool included DLCO < 40% ($n = 26$, 89.7%), 6MWD < 350 m (n = 24, 82.8%), elevated proBNP ($n = 23$, 79.3%), and use of supplemental oxygen ($n = 22$; 75.9%).

Risk and PH-ILD

The risk categorization of the PH-ILD Detection tool was tested for SN and SP to identify PH-ILD. Using the risk score of 0−12, the best cut point (≥ 6, the low boundary of the high-risk group) was used in a dichotomy (i.e., ≥ 6 vs. < 6) to calculate an AUC from these values. The SN was 93.3% and the SP was 90.9%, resulting in an AUC of 0.921 ($p < 0.001$).

Risk and mortality

The risk categorization of the PH-ILD Detection tool also was tested for SN and SP to identify mortality and an AUC was calculated, again using a dichotomy with a best cut point of ≥ 8. The SN was 40% and the SP was 47.3%, resulting in an AUC of 0.397 ($p = 0.188$). A score of ≥ 8 on the PH-ILD Detection tool in the original study 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%, suggesting a score below this cut-off was a strong identifier of patients who survived.[12] However, in this validation cohort, those findings were not confirmed.

DISCUSSION

Clinical implications of PH-ILD Detection tool validation

The recently established PH-ILD Detection tool shows promise as a multi-faceted and convenient method for

TABLE 6 Components from PH-ILD detection tool.

	Low risk ($n = 78$)	Intermediate risk ($n = 54$)	High risk ($n = 29$)	p Value[a] (χ^2)
6MWD < 350 m	14 (17.9%)	22 (40.7%)	24 (82.8%)	**<0.001**
Physical exam for PH	8 (10.3%)	7 (13.0%)	18 (62.1%)	**<0.001**
DLCO < 40%	7 (9.0%)	29 (53.7%)	26 (89.7%)	**<0.001**
Supplemental oxygen	5 (6.4%)	32 (59.3%)	22 (75.9%)	**<0.001**
Elevated proBNP	3 (3.8%)	1 (1.9%)	23 (79.3%)	**<0.001**
Syncope/ presyncope	16 (20.5%)	8 (14.8%)	12 (41.4%)	**0.019**
CTD/Sarcoidosis	26 (33.3%)	27 (50.0%)	13 (44.8%)	0.144

Abbreviations: 6MWD, 6-min walk distance; BNP, B-type natriuretic peptide; CTD, Connective tissue disease; PH-ILD, pulmonary hypertension-interstitial lung disease.

[a]2-df $\chi 2$ to evaluate distribution across all three groups; values in **bold** represent statistically significant differences at $p < 0.05$.

early detection of PH in ILD patients and also reflects expert consensus for PH screening in ILD.[44] In particular, it incorporates eight commonly assessed metrics in ILD patients and creates low-, intermediate-, and high-risk categories that provide clinical recommendations for management of each subset of patients. The tool's accuracy was initially tested among the same cohort of patients yielding a SN of 86.5%, SP of 86.3%, and AUC of 0.92 (95% CI 0.878−0.962, $p < 0.001$).[12] The validation of these findings in this independent cohort of patients demonstrates its accuracy and confirms its usefulness in the identification of PH in ILD patients and their overall management.

Missing variables from the PH-ILD Detection tool

There were 38 patients missing at least one metric from the PH-ILD Detection tool. Because of the study design to compare this validation cohort to the discovery cohort, such patients were not included in the original statistical analysis. However, given the real-world possibility that patients will not always have all 8 metrics available at the time of evaluation, we assessed these 38 patients separately.

Each missing parameter was assigned a score of 0, as if it were not present. Of the 38 patients, all had only one missing metric, except for two patients who had two missing variables. Based on the PH-ILD Detection tool, 22 patients stratified into low-risk, 10 into intermediate-risk, and 6 into high-risk. All 6 patients in the high-risk group did undergo a RHC, which confirmed PH-ILD in all of them.

Invasive hemodynamics

In the 30 patients who were formally diagnosed with PH-ILD, invasive hemodynamic data showed an average mean PAP of 39.3 mmHg, average PVR of 7.8 Wood units, and average Fick-derived Cardiac Index (CI) of 2.2 (Table 7). For comparison, patients enrolled in the INCREASE clinical trial had an average mean PAP of 36.6 mmHg and an average PVR of 6.2 Wood units.[50] This emphasizes the importance of early detection of PH in ILD patients. Use of the PH-ILD Detection tool could ideally result in a standardized process to detect PH early so that patients have ample opportunity to undergo further evaluation with RHC, initiate therapy that may improve quality of life and overall respiratory symptoms, and potentially become better candidates for lung transplant.

Strengths and limitations of this study

The present study has several limitations: (1) this was a retrospective study (although the original data were collected prospectively); (2) there were 38 patients initially screened who had missing metrics for use in the PH-ILD Detection tool; and (3) TTE was utilized as the initial screening test for intermediate- and high-risk patients despite having its limitations in the ILD population.[43,45,51–53] In particular, the study by Weir et al regarding TTE limitations in detecting PH in ILD is difficult to compare with our results given its methodology and study design.[53] Additionally, by the algorithm, patients in the low-risk category did not undergo TTE or

TABLE 7 RHC findings.

RHC measurement	No PH ($n = 7$)	PH-ILD ($n = 30$)	Postcapillary PH ($n = 4$)
PA, mean ± SD (mmHg)	18.0 ± 1.5	39.3 ± 7.1	30.2 ± 2.5
PVR, mean ± SD (Wood units)	2.0 ± 0.2	7.8 ± 2.2	1.8 ± 0.9
Cardiac index fick, mean ± SD	2.5 ± 0.2	2.2 ± 0.3	2.2 ± 0.1

Abbreviations: PA, pulmonary artery; PH-ILD, pulmonary hypertension-interstitial lung disease; PVR, pulmonary vascular resistance; RHC, Right heart catheterization; SD, standard deviation.

RHC, nor did patients with a normal TTE; as such, we cannot determine the false negative rate of TTE in these patients and potentially the false negative predictability of the PH-ILD Detection tool. There are also limitations related to the tool's development itself which were highlighted in the initial pilot study; most importantly, eight metrics were tested and incorporated into the tool but other potential risk factors, such as age, were not included.[12] Lastly, while the purpose of the PH-ILD Detection tool is to establish an early diagnosis of PH, the patients included in this retrospective study were diagnosed fairly late in their disease course based on hemodynamic data. However, since most of these patients were referrals there was no standardized protocol for the timeliness of the referral. To potentially address this issue, the PH-ILD Detection tool can and will be modified and the cut-points altered as studies on metrics predicting PH in this population are published.

Strengths of our study are: (1) it is a large cohort of patients with a diverse demographic background from multiple centers; (2) many of the individual metrics in the tool have been independently associated with development of PH in ILD patients; and (3) most importantly, it confirms findings from the initial iteration of the PH-ILD Detection tool.

Evolution of the PH-ILD Detection tool

To date, there are no consensus guidelines when to screen for PH in ILD patients; some have recommended an annual TTE but this generalized approach fails to take into account the progressive nature of concomitant PH in ILD patients.[22] The PH-ILD Detection tool is a fundamental addition to the growing landscape of PH-ILD as a disease entity. However, as noted above, further refinement of the tool will likely be warranted. Similar to the REVEAL risk assessment tools, the PH-ILD Detection tool will continue to be re-evaluated and its individual metrics constantly refined in an effort to create an evolving early detection method that can adjust as more data become available, potentially even including novel gas-exchange parameters obtained during submaximal exercise testing.[54–56]

CONCLUSION

Until the development of the PH-ILD Detection tool, there was no widely accepted method to predict PH in ILD patients. The current study validates the PH-ILD Detection tool in an independent cohort of patients and establishes it as an indispensable asset for management of these patients. It has important implications in the evaluation and treatment of ILD patients in clinical practice: concomitant PH may be diagnosed earlier in these patients, allowing for 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 and editing; guarantor. **David M. O'Sullivan:** Conceptualization; data curation; formal analysis; methodology; writing—original draft; writing—review and editing. **Harrison W. Farber:** Conceptualization; investigation; methodology; validation; writing—original draft; writing—review and editing

ACKNOWLEDGMENTS

Acknowledgment to the participating centers (Hartford Hospital, Backus Hospital, Hospital of Central Connecticut, Charlotte Hungerford, Midstate Medical Center, Windham Hospital) and the Pulmonary specialists (Meredith Holub, DO; Michael Perkins, MD; Dilpreet Kaur, MD; Maxwell Reback, MD; Tejal Shah, MD; Thinesh Dahanayake, MD, Aashutosh Ramakar, MD).

CONFLICT OF INTEREST STATEMENT

The author declare no conflict of interest.

ETHICS STATEMENT

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

ORCID

Raj Parikh http://orcid.org/0000-0003-3063-6002
Harrison W. Farber http://orcid.org/0000-0002-0297-7902

REFERENCES

1. Nathan SD, Hassoun PM. Pulmonary hypertension due to lung disease and/or hypoxia. Clin Chest Med. 2013;34: 695–705.
2. 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.
3. Caminati A, Cassandro R, Harari S. Pulmonary hypertension in chronic interstitial lung diseases. Eur Respir Rev. 2013;22(129):292–301.
4. Oliveira RKF, Pereira CAC, Ramos RP, Ferreira EVM, Messina CMS, Kuranishi LT, Gimenez A, Campos O, Silva CMC, Ota-Arakaki JS. A haemodynamic study of pulmonary hypertension in chronic hypersensitivity pneumonitis. Eur Respir J. 2014;44(2):415–24.
5. Baughman RP, Shlobin OA, Wells AU, Alhamad EH, Culver DA, Barney J, Cordova FC, Carmona EM, Scholand MB, Wijsenbeek M, Ganesh S, Birring SS, Kouranos V, O'Hare L, Baran JM, Cal JG, Lower EE, Engel PJ, Nathan SD. Clinical features of sarcoidosis associated pulmonary hypertension: results of a multi-national registry. Respir Med. 2018;139:72–8.
6. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. Eur Respir J. 2015;46:1113–30.
7. Andersen CU, Mellemkjær S, Nielsen-Kudsk JE, Bendstrup E, Simonsen U, Hilberg O. Diagnostic and prognostic role of biomarkers for pulmonary hypertension in interstitial lung disease. Respir Med. 2012;106:1749–55.
8. 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(1):1801914.
9. Nathan SD, Shlobin OA, Ahmad S, Koch J, Barnett SD, Ad N, Burton N, Leslie K. Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Resp Int Rev Thor Dis. 2008;76:288–94.
10. Song JW, Song JK, Kim DS. Echocardiography and brain natriuretic peptide as prognostic indicators in idiopathic pulmonary fibrosis. Respir Med. 2009;103(2):180–6.
11. 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(4):2393–9.
12. 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.
13. 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(5):982–90.
14. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006;129(3): 746–52.
15. Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J. 2007;30(4):715–21.
16. Chebib N, Mornex JF, Traclet J, Philit F, Khouatra C, Zeghmar S, Turquier S, Cottin V. Pulmonary hypertension in chronic lung diseases: comparison to other pulmonary hypertension groups. Pulm Circ. 2018;8(2):1–10.
17. Sonti R, Gersten RA, Barnett S, Brown AW, Nathan SD. Multimodal noninvasive prediction of pulmonary hypertension in IPF. Clin Respir J. 2019;13(9):567–73.
18. 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(1):1701311.
19. 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(3):547–54.
20. Patel NM, Lederer DJ, Borczuk AC, Kawut SM. Pulmonary hypertension in idiopathic pulmonary fibrosis. Chest. 2007;132:998–1006.
21. Shorr AF. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. Eur Respir J. 2005;25:783–8.
22. King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease: dilemmas in diagnosis and the conundrum of treatment. Chest. 2020;158:1651–64.
23. 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.
24. Alkukhun L, Wang XF, Ahmed MK, Baumgartner M, Budev MM, Dweik RA, Tonelli AR. Non-invasive screening for pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med. 2016;117:65–72.
25. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, Müller-Ladner U, Pope JE, Vonk MC, Doelberg M, Chadha-Boreham H, Heinzl H, Rosenberg DM, McLaughlin VV, Seibold JR. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis. 2014;73(7):1340–9.
26. Zisman DA, Ross DJ, Belperio JA, Saggar R, Lynch JP, Ardehali A, Karlamangla AS. Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med. 2007;101:2153–9.
27. Trip P, Nossent EJ, de Man FS, van den Berk IAH, Boonstra A, Groepenhoff H, Leter EM, Westerhof N, Grünberg K, Bogaard HJ, Vonk-Noordegraaf A. Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. Eur Respir J. 2013;42:1575–85.
28. 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.
29. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J. 2008;31(6):1357–67.

30. Bazan IS, Mensah KA, Rudkovskaia AA, Adonteng-Boateng PK, Herzog EL, Buckley L, Fares WH. Pulmonary arterial hypertension in the setting of scleroderma is different than in the setting of lupus: a review. Respir Med. 2018;134:42–6.
31. Morrisroe K, Stevens W, Sahhar J, Rabusa C, Nikpour M, Proudman S. Epidemiology and disease characteristics of systemic sclerosis-related pulmonary arterial hypertension: results from a real-life screening programme. Arthritis Res Ther. 2017;19:42.
32. Baughman RP, Engel PJ, Taylor L, Lower EE. Survival in sarcoidosis-associated pulmonary hypertension. Chest. 2010; 138:1078–85.
33. Mar PL, Nwazue V, Black BK, Biaggioni I, Diedrich A, Paranjape SY, Loyd JE, Hemnes AR, Robbins IM, Robertson D, Raj SR, Austin ED. Valsalva maneuver in pulmonary arterial hypertension. Chest. 2016;149:1252–60.
34. Le R, Kane GC, Frantz RP. REVEAL: syncope in pulmonary arterial hypertension. Chest. 2011;30(4):S14–5.
35. 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.
36. 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.
37. Yogeswaran A, Tello K, Faber M, Sommer N, Kuhnert S, Seeger W, Grimminger F, Ghofrani HA, Richter MJ, Gall H. Risk assessment in severe pulmonary hypertension due to interstitial lung disease. J Heart Lung Transplant. 2020;39(10): 1118–25.
38. Andersen C, Mellemkjær S, Hilberg O, Bendstrup E. NT-proBNP < 95 ng/l can exclude pulmonary hypertension on echocardiography at diagnostic workup in patients with interstitial lung disease. Eur Clin Respir J. 2016;3:32027.
39. Andersen KH, Iversen M, Kjaergaard J, Mortensen J, Nielsen-Kudsk JE, Bendstrup E, Videbaek R, Carlsen J. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. J Heart Lung Transplant. 2012;31:373–80.
40. Raymond TE, Khabbaza JE, Yadav R, Tonelli AR. Significance of main pulmonary artery dilation on imaging studies. Ann Am Thorac Soc. 2014;11(10):1623–32.
41. 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(7):1393–9.
42. 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.
43. 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, Schwerzmann M, Dinh-Xuan AT, Bush A, Abdelhamid M, Aboyans V, Arbustini E, Asteggiano R, Barberà JA, Beghetti M, Čelutkienė J, Cikes M, Condliffe R, de Man F, Falk V, Fauchier L, Gaine S, Galié N, Gin-Sing W, Granton J, Grünig E, Hassoun PM, Hellemons M, Jaarsma T, Kjellström B, Klok FA, Konradi A, Koskinas KC, Kotecha D, Lang I, Lewis BS, Linhart A, Lip GYH, Løchen ML, Mathioudakis AG, Mindham R, Moledina S, Naeije R, Nielsen JC, Olschewski H, Opitz I, Petersen SE, Prescott E, Rakisheva A, Reis A, Ristić AD, Roche N, Rodrigues R, Selton-Suty C, Souza R, Swift AJ, Touyz RM, Ulrich S, Wilkins MR, Wort SJ. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731.
44. 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(1):145–55.
45. King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease. Chest. 2020;158: 1651–64.
46. Roberts JD, Forfia PR. Diagnosis and assessment of pulmonary vascular disease by Doppler echocardiography. Pulm Circ. 2011;1(2):160–81.
47. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the european association of cardiovascular imaging. J Am Soc Echocardiogr. 2015;28(1): 1–39.e14.
48. Vaidya A, Golbus JR, Vedage NA. Virtual echocardiography screening tool to differentiate hemodynamic profiles in pulmonary hypertension. Pulm Circ. 2020;10(3):2045894020950225.
49. Chemla D, Castelain V, Humbert M, Hébert JL, Simonneau G, Lecarpentier Y, Hervé P. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. Chest. 2004;126(4):1313–7.
50. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, Allen R, Feldman J, Argula R, Smith P, Rollins K, Deng C, Peterson L, Bell H, Tapson V, Nathan SD. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Eng J Med. 2021;384(4):325–34.
51. Nathan SD, Shlobin OA, Barnett SD, Saggar R, Belperio JA, Ross DJ, Ahmad S, Saggar R, Libre E, Lynch JP, Zisman DA. Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med. 2008;102(9):1305–10.
52. Ruffenach G, Hong J, Vaillancourt M, Medzikovic L, Eghbali M. Pulmonary hypertension secondary to pulmonary fibrosis: clinical data, histopathology and molecular insights. Respir Res. 2020;21(1):303.
53. Keir GJ, Wort SJ, Kokosi M, George PM, Walsh S, 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 (Carlton, Vic.). 2018; 23(7):687–94.
54. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, McGoon MD, Pasta DJ, Selej M, Burger CD, Frantz RP. Predicting survival in patients with pulmonary arterial hypertension. Chest. 2019;156(2):323–37.
55. Moallem N, O'Sullivan DM, Scott V. Submaximal exercise testing in interstitial lung disease: assessing the role of GXCAP to detect concomitant pulmonary hypertension. American Thoracic Society International Conference May 2023. Abstract presentation.
56. Joseph P, Savarimuthu S, Zhao J, Yan X, Oakland HT, Cullinan M, Heerdt PM, Singh I. Noninvasive determinants of pulmonary hypertension in interstitial lung disease. Pulm Circ. 2023;13(1):e12197.

How to cite this article: Parikh R, O'Sullivan DM, Farber HW. The PH-ILD Detection tool: external validation and use in patients with ILD. Pulm Circ. 2023;13:e12273.
https://doi.org/10.1002/pul2.12273