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Zisman, D., Sahay, S., Bandyopadhyay, D. et al. (2026) Screening for pulmonary hypertension in interstitial lung disease: preliminary results from the PHINDER study. Advances in Therapy. ISSN: 0741-238X

https://doi.org/10.1007/s12325-026-03508-4

Adv Ther
https://doi.org/10.1007/s12325-026-03508-4

ORIGINAL RESEARCH

Screening for Pulmonary Hypertension in Interstitial Lung Disease: Preliminary Results from the PHINDER Study

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Received: November 10, 2025 / Accepted: January 23, 2026

ABSTRACT

Introduction: Interstitial lung disease (ILD) is frequently complicated by pulmonary hypertension (PH) resulting in reduced functional capacity, diminished quality of life, and increased mortality. However, standardized screening for PH in ILD is lacking, causing delays in diagnosis and treatment. PHINDER (NCT05776225) is a prospective multicenter study that aims to identify parameters for the detection of PH in ILD.

Methods: Data were collected prospectively in patients with ILD from predefined routine testing, including clinical, physiological, and imaging assessments. Precapillary PH was defined as mean pulmonary arterial pressure > 20 mmHg, pulmonary artery wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 2 Wood units (WU). Investigators estimated probability of precapillary PH based

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-026-03508-4.

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Published online: 10 March 2026

on noninvasive evaluations before confirmation by right heart catheterization (RHC).
Results: Preliminary results included 190 participants; 105 (55%) had precapillary PH and 26 (14%) had severe PH (PVR>5 WU). Notable parameters associated with precapillary PH included supplemental oxygen use (OR 3.6, $p=0.004$), diffusing capacity of the lung for carbon monoxide ([DLCO] OR 0.9, $p=0.005$), forced vital capacity % to DLCO % ratio (OR 1.1, $p=0.008$), tricuspid annular plane systolic excursion to right ventricular systolic pressure ratio (OR 0.8, $p=0.020$), tricuspid regurgitant velocity (OR 4.4, $p=0.006$), pulmonary artery (PA) enlargement (OR 10.6, $p<0.001$), PA/aorta diameter ratio (OR 1.7, $p=0.004$), and right to left ventricle diameter ratio (OR 1.5, $p=0.021$). There was a trend toward higher likelihood of PH with higher clinician suspicion of PH before RHC, but gestalt-based assessment showed limited accuracy relative to hemodynamic confirmation (positive predictive value, 59%; negative predictive value, 68%; accuracy, 60%).
Conclusions: Preliminary findings support the composite use of pulmonary function testing, lung imaging, and echocardiography to improve early detection of precapillary PH in ILD and guide structured screening strategies. The final data set from PHINDER will provide guidance on thresholds for continuous variables with application in diagnosing PH in ILD, facilitating the development of a validated evidence-based screening tool to aid the detection of PH in ILD.
Trail Registration: NCT05776225.

Keywords: Right heart catheterization; Echocardiography; Lung imaging; Detection

Key Summary Points

Despite the significant morbidity and mortality associated with pulmonary hypertension (PH) in interstitial lung disease (ILD), evidence-based PH screening guidelines are lacking in this population; to address this, the ongoing PHINDER study will enroll approximately 300 patients with ILD who undergo noninvasive assessments followed by right heart catheterization (RHC), to identify predictors of PH in ILD.

Preliminary findings from 190 patients, 55% with RHC-confirmed precapillary PH, suggest that supplemental oxygen use, low DLCO, TAPSE/RVSP ratio, TRV, RV/LV diameter ratio, and PA/aorta ratio may be predictive of PH.

Clinician suspicion of PH was largely inaccurate, with precapillary PH confirmed in a third of patients who were deemed low likelihood for PH prior to RHC, underscoring the need for a more objective screening approach.

These preliminary results support a combination of pulmonary function tests, echocardiography, and CT imaging to improve early detection of PH in ILD, rather than relying solely on clinical judgment or echocardiography.

The final dataset from PHINDER will be used to establish prognostic thresholds for noninvasive measurements and to develop a validated PH screening tool to apply in ILD care.

INTRODUCTION

Interstitial lung disease (ILD) encompasses a heterogeneous group of parenchymal lung disorders and is frequently a life-limiting condition characterized by varying degrees of lung inflammation and fibrosis [1, 2]. The clinical trajectory of

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ILD varies among patients, with some patients experiencing slow progression or prolonged stability, while others exhibit rapid functional decline [3–5]. Therapeutic responses are likewise variable and are often influenced by the underlying ILD subtype [6, 7].

Pulmonary hypertension (PH) is a common and serious complication in ILD, associated with worse symptoms, diminished quality of life, and decreased survival [8–10]. Reported prevalence ranges from 3% to 64% [11–13], depending on the diagnostic modality used, ILD subtype, and disease severity. PH in this setting is thought to develop as a result of multiple interacting mechanisms, including alveolar hypoxia, endothelial dysfunction, oxidative stress, immune- and inflammatory-mediated pathways, as well as a genetic predisposition, resulting in vasoconstriction, proliferation, vascular remodeling, and fibrogenesis [9, 14, 15].

PH is commonly diagnosed late in the setting of ILD, often when patients undergo right heart catheterization (RHC) during lung transplant evaluation [1]. Until recently, no therapies were approved for the treatment of ILD-PH (also commonly known as PH-ILD), and consequently there was limited value in clinicians proactively considering the diagnosis of PH. However, the INCREASE trial in patients with ILD-PH met its primary endpoint of change in 6-min walk distance (6MWD) leading to US Food and Drug Administration approval of inhaled treprostinil for the treatment of ILD-PH in the USA in 2021 [16]. Despite this approval and availability of an effective therapy, challenges and delays remain in the detection of ILD and resulting PH. Currently, there are no prospectively validated strategies to aid the diagnosis of ILD-PH. A recent Delphi consensus for screening and detection of ILD-PH described characteristics associated with the presence of PH but highlighted the need to establish evidence-based diagnostic strategies [17]. Although echocardiography is recommended when PH is suspected [7], it is less accurate in patients with lung disease compared to other forms of PH [18], though an analysis of a sophisticated stepwise echocardiographic algorithm demonstrated reasonable diagnostic accuracy in patients with hemodynamically severe PH [19, 20]. Recently, several screening scores have been derived for PH and validated in idiopathic pulmonary fibrosis and ILD populations [21–23]. However, these studies used retrospective chart analyses or post hoc analyses of other clinical trials, limiting their generalizability, introducing potential bias, and limiting inference to association rather than causal interpretation. Additionally, the studies used different definitions of PH. As such, knowledge gaps remain.

The Pulmonary Hypertension Screening in Patients with Interstitial Lung Disease for Earlier Detection Study (PHINDER, NCT05776225) aims to address this gap by prospectively evaluating screening parameters and early detection strategies for PH in patients with ILD. The objective of the PHINDER study is to identify parameters associated with the presence of PH in ILD and develop a PH detection tool to apply in clinical practice. To ensure timely dissemination of clinically relevant insights while the study is ongoing, this preliminary analysis is presented to inform current practice, while the final dataset from PHINDER will be used to establish prognostic thresholds and validate a structured PH screening algorithm.

METHODS

Study Design and Approvals

The PHINDER study is an ongoing, prospective, multicenter, nonrandomized, noninterventional study to evaluate parameters that might be useful in predicting the presence of PH in patients with ILD. Parameters of interest were selected a priori on the basis of previously published research [17, 24–26], and the study design adopted the systematic, stepwise approach of the DETECT study which developed a screening algorithm for PH in patients with systemic sclerosis, with entry criteria added for greater specificity [27]. Data collected were used to identify and weigh clinical parameters according to their predictive significance for RHC-confirmed precapillary PH using the 7th World Symposium definition of precapillary PH (mean pulmonary arterial pressures [mPAP] > 20 mmHg, pulmonary artery wedge pressure [PAWP] ≤ 15 mmHg, and pulmonary vascular resistance [PVR] > 2 Wood units [WU]) [28]. This preliminary analysis included data collected through May 5, 2025.

Ethical oversight for this study was provided by Advarra, serving as the Central Institutional Review Board (IRB) and local IRB approval was obtained for some sites. The study was approved by all participating institutions and site-level IRB approval details can be found in Table S1 of the Online Data Supplement. Written informed consent was obtained from all study participants, and all procedures involving human participants were performed in accordance with the ethical standards of each institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Permission to use proprietary or copyrighted questionnaires was obtained from the copyright holder or licensing authority prior to study initiation where applicable and were administered in accordance with the licensing terms and conditions.

Study Assessments

The ongoing study consists of an initial screening visit (days −28 to 0) and subsequent study visit which occurs up to 14 days after screening (Fig. 1). Participants were assessed for eligibility during the screening visit window on the basis of pulmonary function tests (PFTs), chest high-resolution computed tomography (HRCT), exercise capacity, biomarkers, physical exam features, and echocardiography. If historical PFTs within 90 days of screening or HRCT within 180 days of screening were available, then these historical tests could be submitted for analysis as part of the study. During the subsequent study visit, the following assessments were performed: PFTs, HRCT, echocardiography, physical examination, 6-min walk test, clinical labs including brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), as well as University of California San Diego Shortness of Breath Questionnaire, King's Brief Interstitial Lung Disease Questionnaire, 36-Item Short Form Survey, Pulmonary Hypertension Functional Classification Self-Report, and RHC. If a participant received a PFT, HRCT, or echocardiogram at the screening visit to assess study eligibility, a repeat assessment was not needed at study visit 1. Investigators also completed the Investigator's Suspicion of PH Questionnaire, capturing their subjective pre-test probability of precapillary PH based on the non-invasive findings prior to RHC.

HRCTs, echocardiography, and RHC tracings were centrally read. Qualifying echocardiographic images, HRCTs, and RHC tracings were submitted by sites for quality control, and all data were analyzed in a blinded manner and adjudicated centrally by Medpace (Cincinnati, OH) and the Echo/RHC core lab. Determination of pulmonary artery (PA) enlargement on HRCT was based on a composite evaluation of central pulmonary arteries, trunk diameter > 30–32 mm, PA/aorta ratio > 1, and visual enlargement of the main and interlobular arteries. Formal adverse event monitoring is being conducted throughout this study; however, safety data are not reported here since this is a non-interventional study assessing measurements from standard-of-care procedures.

Participant Selection

Participants were eligible if they were ≥ 18 years of age and had a diagnosis of ILD based on CT, including idiopathic or nonspecific interstitial pneumonia, connective tissue disease-associated ILD with forced vital capacity (FVC) < 70%, hypersensitivity pneumonitis, scleroderma-related ILD, or occupational ILD, and combined pulmonary fibrosis and emphysema. Exclusion criteria included prior RHC with mPAP > 20 mmHg, current use of an US Food and Drug Administration-approved pulmonary arterial hypertension (PAH) medication for the treatment of PAH, diagnosis of chronic obstructive pulmonary disease (combined pulmonary fibrosis and emphysema notwithstanding), uncontrolled or untreated sleep apnea, pulmonary embolism within the past 3 months, or a history of left ventricular ejection fraction < 40%. Participants were also required to meet one or more criteria from at least two of the three predefined PH-enrichment categories (i.e., a minimum of two total criteria across distinct domains) based on the investigator's clinical judgment, within 180 days of screening (Table 1).

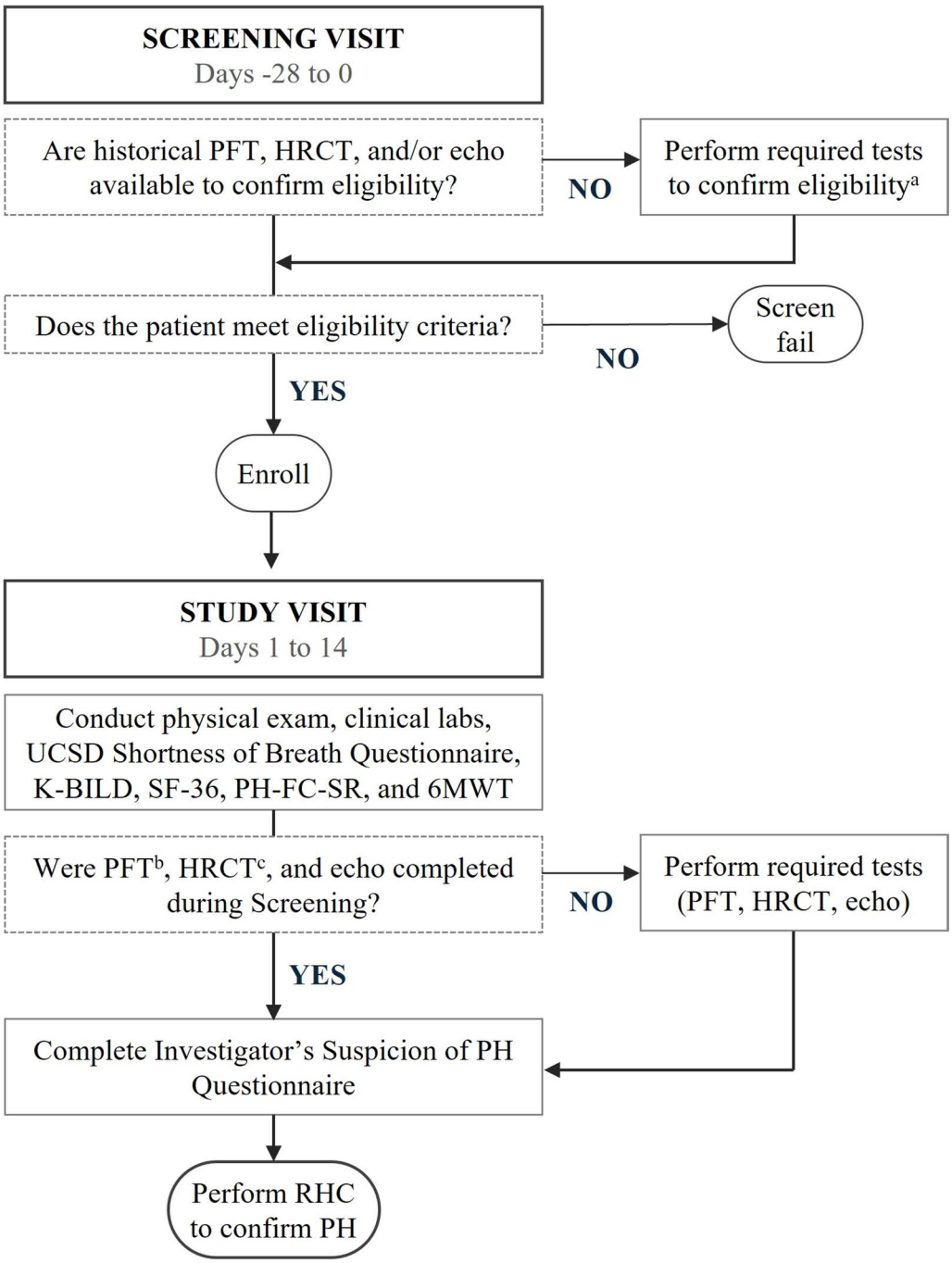

Fig. 1 Study schematic.[a]Echo performed at screening visit must be performed at days −7 to day 0; [b]Historical PFTs can be submitted if acquired within 90 days of screening; [c]Historical HRCT can be submitted if acquired within 180 days of screening. *Echo* echocardiography, *HRCT* high-resolution computed tomography, *K-BILD* King's Brief Interstitial Lung Disease Questionnaire, *PFT* pulmonary function tests, *PH* pulmonary hypertension, *PH-FC-SR* Pulmonary Hypertension Functional Class Self-Report, *RHC* right heart catheterization, *SF-36* 36-Item Short Form Health Survey, *UCSD* University of California San Diego, *6MWT* 6-min walk test

Statistical Analysis

Assuming a PH prevalence rate of 30%, a sample size of 200 participants was estimated to provide 90% sensitivity with a precision of ± 7.5% where sensitivity refers to the probability of correctly identifying precapillary PH in a participant with ILD, as verified by RHC. Following interim analyses, the sample size was increased to approximately 300–350 patients to allow for continued data collection and further subgroup analyses. Descriptive analyses were conducted to describe the study population and summarize assessment measures. Performance metrics for the Investigator's Suspicion of PH Questionnaire results were calculated, including positive predictive value (PPV), negative predictive value (NPV), specificity, sensitivity, and accuracy. To identify which of the assessment measures are independently correlated with precapillary PH, univariate logistic regression was performed to determine the odds ratio and confidence interval (CI) for each variable and test significance at $\alpha = 0.05$. The regression analysis was performed against all patients without precapillary PH and against patients with normal mPAP, PVR, and PAWP on RHC. For continuous variables, measures were modeled continuously, so that each odds ratio (OR) reflects the change in odds of precapillary PH for each one-unit increase in the predictor (or 0.1-unit increase in parameters reported as a ratio), thereby capturing a graded risk relationship rather than a binary threshold. Additional subgroup analyses were performed on an additional seven predefined hemodynamic phenotypes (Table 2): severe precapillary PH [7], isolated postcapillary (Ipc) PH [7], combined pre/postcapillary (Cpc) PH [7], isolated mPAP elevation > 20 mmHg, isolated PAWP elevation, isolated PVR elevation > 2 WU [29], and ILD with normal mPAP, PAWP, and PVR. All statistical analyses were conducted using the latest version of SAS (SAS Institute Inc.; Cary, North Carolina).

RESULTS

Population and Hemodynamic Phenotypes

At the time of this analysis, 41 study sites were activated, of which 37 had enrolled ≥ 1 participant. A total of 190 participants with ILD had RHC data available and were included in the analysis (Fig. 2). The median (interquartile range [IQR]) age was 73 (64–77) years, 54% were male, 81% were white, and the median (IQR) time since ILD diagnosis was 2.5 (1.1–5.4) years (Table 3). Most participants had idiopathic interstitial pneumonia (56%) followed by connective tissue disease-associated ILD (23%; Fig. 3). In total, 105 (55%) participants had precapillary PH confirmed by RHC, while 6 had Ipc-PH, 9 had Cpc-PH, 14 had isolated mPAP elevation, 2 had isolated PAWP elevation, 25 had isolated PVR elevation, and 29 had normal hemodynamics (Table 3). Distribution of underlying ILD subtypes among the different hemodynamic phenotypes is shown in Fig. 3. A complete list of measurements among all groups can be found in Table S2 of the Supplementary Material. The median (IQR) time between noninvasive testing and RHC was 22 (6–55) days for PFTs, 27 (9–83) days for HRCT, and 6 (2–12) days for echocardiography.

Although no statistical analyses for significance were performed to compare these hemodynamic subgroups, the following numerical trends emerged: the precapillary PH group had the lowest diffusing capacity of the lung for carbon monoxide (DLCO) % predicted and absolute value, higher RVSP, and greater signs of enlarged PA; the Ipc-PH and Cpc-PH groups had the lowest 6MWD, forced expiratory volume in one second (FEV1), and FVC as well as higher RVSP, yet higher DLCO. Participants with isolated mPAP elevation had the longest time since ILD diagnosis, the most supplemental oxygen use, the highest FVC%/DLCO% ratio, and the greatest signs of PA enlargement while participants with isolated PVR elevation were less frequently male,

Table 1 Enrichment criteria for study eligibility

Category 1 PFTs and/or HRCT	Category 2 Exercise capacity, oxygenation, biomarkers, and/or physical exam	Category 3 Echocardiography
Pulmonary function testing	*Exercise testing and oxygenation*	• TAPSE < 2 cm
• DLCO < 40%	• Decline in 6MWD ≥ 15%	• RVSP > 35 mmHg
• DLCO decline ≥ 15% based on 2 most recent assessments	• Desaturation on 6MWT disproportionate to ILD severity	• RV dilation or enlargement
• DLCO decline > 10% with FVC decline < 5% (i.e., worsening FVC/DLCO ratio) based on 2 most recent assessments	• Recent worsening desaturation	• RV abnormality
HRCT	*Biomarkers*	
• RV/LV ratio > 1	• BNP > 200 pg/mL	
• PA/aorta ratio > 1	• NT-proBNP > 395 pg/mL	
• Enlarged PA	*Symptoms and physical exam*	
• Enlarged PAs in lung periphery	• Symptoms disproportionate to ILD severity or changes in symptoms not explained by ILD progression	
• Ventricular septal flattening	• ≥ 1 of syncope, JVD, peripheral edema, ascites, loud P2 or S2 heart sound, or hepatomegaly	

BNP B-type natriuretic peptide, *DLCO* diffusing capacity of the lung for carbon monoxide, *FVC* forced vital capacity, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *JVD* jugular venous distention, *LV* left ventricle, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *PA* pulmonary artery, *PFT* pulmonary function test, *RV* right ventricle, *RVSP* right ventricular systolic pressure, *TAPSE* tricuspid annular plane systolic excursion, *6MWD* 6-min walk distance, *6MWT* 6-min walk test

Table 2 Hemodynamic definitions of the analysis phenotypes

	Precapillary PH	Severe precapillary PH	Ipc-PH	Cpc-PH	Elevated mPAP only	Elevated PAWP only	Elevated PVR only	Normal hemodynamics
mPAP, mmHg	> 20	> 20	> 20	> 20	> 20	≤ 20	≤ 20	≤ 20
PVR, WU	> 2	> 5	≤ 2	> 2	≤ 2	≤ 2	> 2	≤ 2
PAWP, mmHg	≤ 15	≤ 15	> 15	> 15	≤ 15	> 15	≤ 15	≤ 15

CPC combined pre- and postcapillary, *IPC* isolated postcapillary, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistance, *WU* Wood units

had the shortest time since ILD diagnosis, the most antifibrotic use, the least peripheral edema yet the highest rate of loud accentuated pulmonary component of the second heart sounds and the lowest TAPSE. Lastly, participants with normal hemodynamics had the least antifibrotic and supplemental oxygen use, as well as the highest 6MWD, FVC, DLCO, and lowest FVC%/DLCO% ratio.

Indicators of Precapillary PH

In the regression analysis of patients with precapillary PH ($n = 105$) against all patients without precapillary PH ($n = 85$) several clinical and imaging variables, though no demographic variables, correlated with the presence of precapillary PH (Table 4). The only medical history variable associated with precapillary PH was the use of supplemental oxygen (OR 2.19, CI 1.22–3.94). Pulmonary function parameters that correlated with the presence of precapillary PH included DLCO % predicted (OR 0.97, CI 0.95–0.99), DLCO absolute value (OR 0.90, CI 0.84–0.96), and FVC%/DLCO% ratio (OR 1.08, CI 1.02–1.14). Echocardiography parameters associated with precapillary PH included right atrial pressure [RAP] (OR 1.17, CI 1.002–1.36), right ventricular systolic pressure [RVSP] (OR 1.03, CI 1.004–1.06), tricuspid annular plane systolic excursion [TAPSE]/RVSP ratio (OR 0.88, CI 0.78–0.998), and tricuspid regurgitant velocity [TRV] (OR 2.12, CI 1.13–4.00). All HRCT parameters were significantly associated with the presence of precapillary PH including right/left ventricular (RV/LV) ratio (OR 1.30, CI 1.03–1.62), having an RV/LV ratio > 1 (OR 2.74, CI 1.33–5.63), PA/aorta ratio (OR 1.42, CI 1.14–1.78), having a PA/aorta > 1 (OR 2.09, CI 1.09–4.03), and PA enlargement (OR 2.98, CI 1.58–5.61).

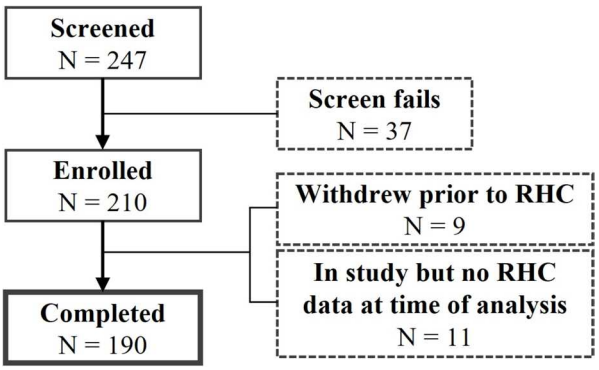

Fig. 2 Patient disposition at the time of the preliminary analysis. Reasons for screen failure included failure to meet eligibility criteria ($N = 25$), inability to schedule study visits ($N = 4$), patient decision to withdraw ($N = 4$), physician decision to withdraw ($N = 1$), death ($N = 1$), adverse event ($N = 1$), and loss to follow-up ($N = 1$)

In the regression analysis against patients with normal hemodynamics ($N = 29$), many of the same parameters emerged but with stronger correlation with the presence of PH (Table 4), including the use of supplemental oxygen (OR 3.65, CI 1.51–8.81), DLCO % predicted (OR 0.96, CI 0.93–0.98), DLCO absolute value (OR 0.89, CI 0.82–0.97), FVC%/DLCO% ratio (OR 1.13, CI 1.03–1.24), RVSP (OR 1.09, CI 1.03–1.15), TAPSE/RVSP ratio (OR 0.82, CI 0.70–0.97), TRV (OR 4.42, CI 1.53–12.83), RV/LV ratio (OR 1.53, CI 1.07–2.20), having an RV/LV ratio > 1 (OR 3.55, CI 1.13–11.16), PA/aorta ratio (OR 1.66,

Table 3 Patient characteristics of the preliminary population and predefined hemodynamic subgroups. Data are reported as median (IQR) or *N* (%)

Characteristic	Total	Precapillary PH	Ipc-PH	Cpc-PH	Elevated mPAP only	Elevated PAWP only	Elevated PVR only	Normal RHC
N	190	105	6	9	14	2	25	29
Medical history								
Age, years	73 (64–77)	74 (64–78)	76 (72–79)	77 (66–78)	73 (67–77)	67.5 (67–68)	73 (66–76)	69 (57–77)
Sex, male	103 (54%)	56 (53%)	4 (67%)	6 (67%)	8 (57%)	2 (100%)	10 (40%)	17 (59%)
Time since ILD diagnosis, years	2.5 (1.1–5.4)	2.6 (1.1–5.8)	2.8 (2.0–5.9)	3.8 (1.4–6.3)	4.6 (2.7–5.2)	1.0 (0.3–1.7)	1.7 (0.4–3.4)	2.1 (1.3–6.2)
Antifibrotic use	64 (34%)	32 (30%)	2 (33%)	5 (56%)	5 (36%)	2 (100%)	14 (56%)	4 (14%)
Supplemental O_2 use	100 (53%)	64 (62%)	3 (50%)	5 (56%)	9 (64%)	0 (0%)	10 (40%)	9 (31%)
6MWD, meters	300 (210–396)	300 (196–389)	264 (225–372)	255 (183–280)	360 (179–460)	416 (375–456)	293 (137–366)	383 (297–454)
NT-proBNP, pg/mL	158 (82–348)	160 (89–497)	102 (50–447)	509 (317–718)	119 (100–280)	43 (41–45)	232 (42–353)	111 (66–269)
Peripheral edema	57 (30%)	30 (29%)	2 (33%)	7 (78%)	5 (36%)	0 (0%)	3 (12%)	10 (35%)
Loud P2/S2	43 (23%)	26 (25%)	0 (0%)	1 (11%)	1 (7%)	1 (50%)	8 (32%)	6 (21%)
Pulmonary function								
FEV1, % predicted	70 (56–83)	68 (55–83)	63 (56–79)	60 (46–74)	78 (70–83)	95 (87–103)	73 (56–82)	73 (53–91)
FEV1, L	1.8 (1.3–2.3)	1.7 (1.3–2.3)	1.7 (1.5–2.1)	1.3 (1.2–1.7)	2.1 (1.8–2.5)	3.0 (2.4–3.5)	1.6 (1.3–2.3)	2.0 (1.5–2.6)
FVC, % predicted	65 (55–78)	63 (55–78)	60 (51–71)	57 (35–75)	71 (61–77)	83 (80–85)	63 (56–70)	72 (47–85)
FVC, L	2.1 (1.6–2.9)	2.0 (1.6–2.9)	2.3 (1.8–2.5)	1.5 (1.4–2.2)	2.4 (2.1–3.2)	3.4 (2.9–3.8)	1.9 (1.5–2.6)	2.4 (1.8–3.3)
DLCO, % predicted	41 (32–52)	38 (30–48)	44 (32–61)	45 (37–49)	41 (34–62)	37.5 (37–38)	43 (36–56)	45 (39–63)
DLCO, mL/min/mmHg	9 (7–13)	8 (6–12)	16 (14–18)	9 (8–11)	11 (8–14)	18 (10–26)	10 (8–14)	11 (9–16)
%FVC/%DLCO	1.6 (1.3–2.0)	1.6 (1.4–2.1)	1.6 (1.2–1.7)	1.4 (1.2–1.8)	1.7 (1.3–2.1)	2.2 (2.2–2.2)	1.3 (1.0–1.8)	1.3 (1.0–1.6)

Table 3 continued

Characteristic	Total	Precapillary PH	Ipc-PH	Cpc-PH	Elevated mPAP only	Elevated PAWP only	Elevated PVR only	Normal RHC
Echocardiography								
RVSP, mmHg	37 (28–46)	40 (31–49)	42 (28–58)	43 (39–64)	35 (23–78)	24 (24–24)[a]	33 (25–40)	30 (27–33)
TAPSE/RVSP ratio	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.7 (0.3–0.8)	0.4 (0.2–0.4)	0.7 (0.7–0.8)	1.0 (1.0–1.0)[a]	0.6 (0.5–0.8)	0.7 (0.6–1.0)
TRV, m/s	2.9 (2.4–3.3)	3.0 (2.5–3.4)	3.1 (2.5–3.7)	3.0 (3.0–3.7)	2.7 (2.2–3.0)	2.3 (2.3–2.3)[a]	2.5 (2.3–3.0)	2.6 (2.4–2.7)
RAP, mmHg	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–8.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)[a]	3.0 (3.0–3.0)	3.0 (3.0–3.0)
Computed tomography								
PA enlargement[b]	77/171 (45%)	53/93 (57%)	2/4 (50%)	4/9 (44%)	7/11 (64%)	0 (0%)	8/25 (32%)	3/27 (11%)
PA/aorta, ratio	0.9 (0.8–1.0)	1.0 (0.9–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	1.0 (0.9–1.0)	0.9 (0.9–1.0)	0.8 (0.8–1.0)	0.9 (0.8–1.0)
PA/aorta ratio > 1	59/171 (35%)	39/93 (42%)	0 (0%)	3/9 (33%)	5/11 (45%)	0 (0%)	5/25 (20%)	7/27 (26%)
RV/LV ratio	0.9 (0.9–1.0)	1.0 (0.9–1.1)	1.0 (0.8–1.2)	0.9 (0.9–1.0)	0.9 (0.9–1.0)	1.0 (0.9–1.0)	0.9 (0.9–1.0)	0.8 (0.8–1.0)
RV/LV ratio > 1	48/165 (29%)	34/89 (38%)	2/4 (50%)	2/8 (25%)	1/11 (9%)	0 (0%)	5/24 (21%)	4/27 (15%)

DLCO diffusing capacity of lungs for carbon monoxide, *FEV1* forced expiratory volume, *FVC* forced vital capacity, *LV* left ventricle, *O2* oxygen, *PA* pulmonary artery, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *RV* right ventricle, *RVSP* right ventricular systolic pressure, *TAPSE* tricuspid annular plane systolic excursion, *6MWD* 6-min walk distance

Precapillary PH = mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR > 2 WU; isolated postcapillary PH (Ipc-PH) = mPAP > 20 mmHg, PAWP > 15 mmHg, and PVR ≤ 2 WU; combined pre- and postcapillary PH (Cpc-PH) = mPAP > 20 mmHg, PAWP > 15 mmHg, and PVR > 2 WU; isolated mPAP elevation = mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR ≤ 2; isolated PAWP elevation = mPAP ≤ 20 mmHg, PAWP > 15 mmHg, and PVR ≤ 2 WU; isolated PVR elevation = mPAP ≤ 20 mmHg, PAWP ≤ 15 mmHg, and PVR > 2 WU; normal RHC = mPAP ≤ 20 mmHg, PAWP ≤ 15 mmHg, and PVR ≤ 2 WU

[a]Only 1 of 2 patients had RVSP and TRV measured

[b]Composite evaluation of central pulmonary arteries integrating trunk diameter > 30–32 mm, PA/Aorta ratio > 1, and subjective enlargement of the main and interlobular arteries

CI 1.18–2.34), and PA enlargement (OR 10.60, CI 2.98–37.69). 6MWD (OR 0.995, CI 0.992–0.999) was uniquely associated with the regression analysis against the normal hemodynamic group. The complete list of all parameters in the regression analyses can be found in Table S3 of the Online Data Supplement.

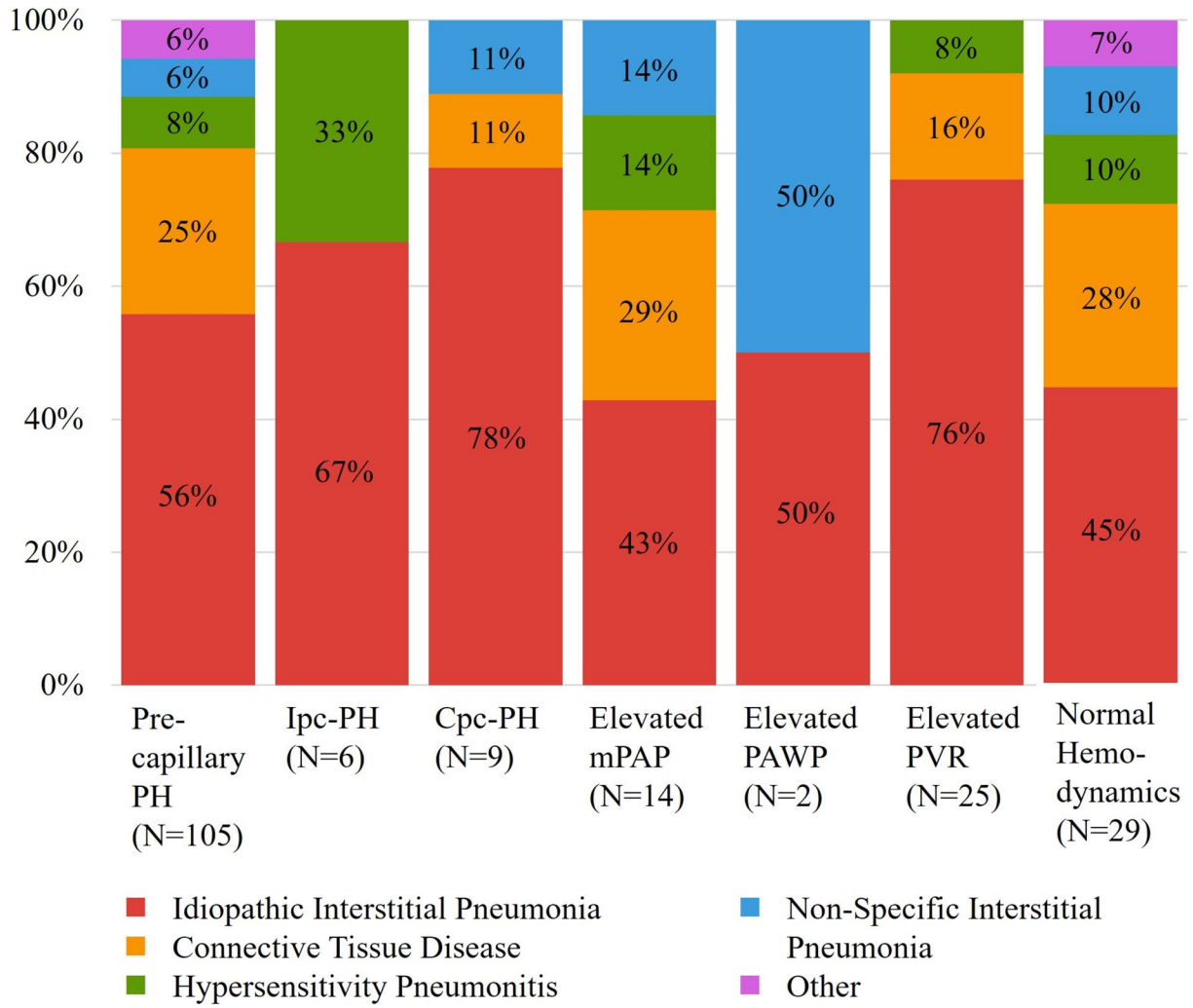

Fig. 3 ILD subtypes among predefined hemodynamic subgroups of interest. Precapillary PH = mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR > 2 WU; Ipc-PH = mPAP > 20 mmHg, PAWP > 15 mmHg, and PVR ≤ 2 WU; Cpc-PH = mPAP > 20 mmHg, PAWP > 15 mmHg, and PVR > 2 WU; Isolated mPAP elevation = mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and PVR ≤ 2; Isolated PAWP elevation = mPAP ≤ 20 mmHg, PAWP > 15 mmHg, and PVR ≤ 2; Isolated PVR elevation = mPAP ≤ 20 mmHg, PAWP ≤ 15 mmHg, and PVR > 2 WU; Normal hemodynamics = mPAP ≤ 20 mmHg, PAWP ≤ 15 mmHg, and PVR ≤ 2 WU. *Cpc* combined pre- and postcapillary, *ILD* interstitial lung disease, *IPC* isolated postcapillary, *mPAP* mean pulmonary artery pressure, *PAWP* pulmonary artery wedge pressure, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistance, *RHC* right heart catheterization, *WU* Wood units

Severe Precapillary PH

Of the 105 participants with RHC-confirmed precapillary PH, a quarter ($n = 26$) had severe precapillary PH defined as PVR > 5 WU. The majority of these patients were female (58%) with idiopathic interstitial pneumonia (54%), connective tissue disease (23%), or hypersensitivity pneumonitis (12%) ILD subtypes. They had a median (IQR) age of 75 (69–78) years,

time since ILD diagnosis of 3.6 (1.2–6.8) years, and a 6MWD of 270 (180–337) m. Many of the same pulmonary function and echocardiography parameters were also correlated with the presence of severe precapillary PH such as DLCO % predicted (OR 0.96, CI 0.92–0.99), DLCO absolute value (OR 0.80, CI 0.68–0.94), RVSP (OR 1.06, CI 1.01–1.11), TAPSE/RVSP ratio (OR 0.02, CI 0.001–0.86), and TRV (OR 5.25, CI 1.61–17.11). Variables that were uniquely associated with severe PH included NT-proBNP (OR 1.63, CI 1.07–2.49) and the presence of peripheral edema (OR 0.25, CI 0.07–0.91).

A summary of hemodynamic results as measured by RHC for all subgroups can be found in Table 5.

Clinician Suspicion of PH vs RHC

After performing all noninvasive assessments but prior to RHC, clinicians recorded their gestalt-based suspicion of precapillary PH as low, medium, or high (Fig. S1). Of the 189 patients who had likelihood of PH assessed by their clinician, 15% were deemed low likelihood, 46% medium likelihood, and 39% high likelihood for PH. Parameters that trended along with suspicion levels and may have driven gestalt-based likelihood for PH, included 6MWD, natriuretic peptide levels, supplemental oxygen requirements, peripheral edema or loud second heart sounds, FEV, FVC, DLCO, FVC/DLCO, RVSP, TRV, PA enlargement, PA/aorta diameter, and RV/LV diameter.

A high level of discrepancy was observed between gestalt-based assessments and RHC-confirmed diagnoses of precapillary PH (Fig. 4). Having medium or high suspicion of precapillary PH resulted in a positive predictive value of 59%, while having a low suspicion resulted in a negative predictive value of 68%; overall, clinician suspicion had a sensitivity of 91%, specificity of 22%, and accuracy of 60%.

DISCUSSION

The ongoing PHINDER study is evaluating clinical, functional, imaging, and echocardiographic parameters to identify variables associated with RHC-confirmed precapillary PH in the setting of ILD. Several significant variables emerged, notably, decreased DLCO (% predicted and absolute value) and elevated FVC%/DLCO% ratio were significant pulmonary function markers associated with precapillary PH. HRCT findings, particularly elevated PA/aorta diameter ratio and RV/LV diameter ratio, demonstrated a strong correlation with the presence of precapillary PH. Echocardiographic parameters, including TRV, RVSP, and TAPSE/RVSP ratio were also significantly associated with the presence of precapillary PH and exhibited graded relationships: higher velocities and lower TAPSE/RVSP ratios corresponded to incrementally greater odds of PH.

Among the various assessments, chest CT appeared particularly valuable. The PA/aorta diameter ratio was a notably strong imaging variable associated with precapillary PH, suggesting that simple CT-based metrics may play a critical role in the early identification of at-risk patients. Recent studies have confirmed the diagnostic accuracy of CT-derived PA diameter in patients with and without ILD, with area under the curve values as high as 0.87 in ILD and 0.83 in non-ILD cohorts, respectively [30]. In addition, multimetric models incorporating PA diameter, right heart morphology, and septal configuration have shown excellent discrimination for PH and may offer prognostic value [31]. Although earlier reports questioned the specificity of PA enlargement in fibrotic lung disease [32], these findings suggest that CT may have a broader application in PH screening than previously appreciated. Interestingly, although NT-proBNP is commonly used to screen for pulmonary hypertension, particularly in earlier stages of disease, our findings suggest that its utility may be limited in detecting mild-to-moderate PH in ILD, as elevations were not consistently observed in patients with PH and were only found to be correlated with severe PH (PVR > 5 WU). This may be a reflection of the less severe myocardial stress seen in patients with earlier disease and milder hemodynamic elevations.

Consistent with previous tools developed to screen for PH in ILD [21–23], our study

Table 4 Regression analysis results for parameters significantly associated with precapillary PH, performed against patients with normal mPAP, PVR, and PAWP, and against all patients without precapillary PH. Results are reported as odds ratio (OR), confidence interval (CI), and *p* value

	Precapillary PH vs normal RHC			Precapillary PH vs all other patients		
	OR	**CI**	***P* value**	**OR**	**CI**	***P* value**
Medical history						
Supplemental O_2 use	3.65	1.51–8.81	0.0040	2.19	1.22–3.94	0.0090
6MWD, meters	0.995	0.992–0.999	0.0141	1.00	1.00–1.00	0.3644
Pulmonary function						
DLCO, % predicted	0.96	0.93–0.98	0.0006	0.97	0.95–0.99	0.0018
DLCO, mL/min/mmHg	0.89	0.82–0.97	0.0045	0.90	0.84–0.96	0.0016
%FVC/%DLCO ratio	1.13	1.03–1.24	0.0080	1.08	1.02–1.14	0.0047
Echocardiography						
RVSP, mmHg	1.09	1.03–1.15	0.0023	1.03	1.004–1.06	0.0247
TAPSE/RVSP ratio	0.82	0.70–0.97	0.0198	0.88	0.78–0.998	0.0466
TRV, m/s	4.42	1.53–12.83	0.0062	2.12	1.13–4.00	0.0200
RAP, mmHg	1.32	0.91–1.92	0.1410	1.17	1.002–1.36	0.0470
Computed tomography						
RV/LV diameter ratio	1.53	1.07–2.20	0.0207	1.30	1.03–1.62	0.0246
RV/LV ratio > 1	3.55	1.13–11.16	0.0299	2.74	1.33–5.63	0.0062
PA/aorta ratio	1.66	1.18–2.34	0.0038	1.42	1.14–1.78	0.0020
PA/aorta ratio > 1	2.06	0.80–5.36	0.1368	2.09	1.09–4.03	0.0268
PA enlargement[a]	10.6	2.98–37.69	0.0003	2.98	1.58–5.61	0.0007

CI confidence interval, *DLCO* diffusing capacity of lungs for carbon monoxide, *FVC* forced vital capacity, *LV* left ventricle, *mPAP* mean pulmonary arterial pressure, *O2* oxygen, *PA* pulmonary artery, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *RV* right ventricle, *RA/RVSP* right atrial/ventricular systolic pressure, *TAPSE* tricuspid annular plane systolic excursion, *TRV* tricuspid regurgitation velocity, *6MWD* 6-min walk distance

[a]Composite evaluation of central pulmonary arteries integrating trunk diameter > 30–32 mm, PA/Aorta ratio > 1, and subjective enlargement of the main and interlobular arteries

identified low DLCO and the need for supplemental oxygen as significantly associated with precapillary PH and in particular severe PH. Our study further builds on earlier models by systematically incorporating echocardiographic markers. Specifically, elevated RVSP, elevated TRV, and reduced TAPSE/RVSP ratio on echocardiography were strongly associated with RHC-confirmed precapillary PH or severe precapillary PH. While these findings suggest that the addition of noninvasive hemodynamic and morphologic assessments may improve the detection of PH in ILD populations, they also suggest that echocardiography alone may not be a sufficient screening tool, and a nonsuspicious echocardiography result should not be used as rationale for ruling out a confirmatory RHC.

Additionally, removing the echocardiography component of the PH enrichment criteria for this study did not have a significant effect on

Table 5 Hemodynamics of the preliminary population by hemodynamic phenotype, confirmed by right heart catheterization

Characteristics[a]	Precapillary PH	Severe precapillary PH[b]	Isolated postcapillary PH	Combined pre/postcapillary PH	Isolated mPAP elevation	Isolated PAWP elevation	Isolated PVR elevation	Normal hemodynamics
N	105	26	6	9	14	2	25	29
mPAP, mmHg	27 (24–31)	32 (27–36)	30 (26–34)	33 (31–39)	23 (22–25)	15 (14–16)	19 (16–20)	16 (13–18)
sPAP, mmHg	44 (39–50)	53 (45–58)	46 (41–50)	53 (50–55)	37 (34–43)	26 (23–29)	31 (27–34)	28 (22–32)
dPAP, mmHg	17 (14–20)	21 (17–25)	19 (17–21)	22 (17–25)	16 (14–18)	10 (5–15)	10 (8–12)	10 (6–12)
CO[c], L/min	4.0 (4.0–5.0)	4.0 (3.0–4.0)	5.5 (5.0–6.0)	5.0 (4.0–6.0)	6.0 (4.0–7.0)	4.5 (3.0–6.0)	4.0 (4.0–5.0)	5.0 (5.0–7.0)
CI, L/min/m^2	2.4 (2.1–2.8)	2.2 (1.9–2.5)	2.9 (2.3–3.2)	2.4 (1.8–2.7)	2.8 (2.1–3.0)	2.5 (2.0–3.0)	2.4 (2.2–2.6)	2.9 (2.5–3.1)
SVI, mL/m^2	37 (32–42)	32 (25–38)	39 (35–46)	34 (22–43)	41 (33–50)	34 (25–43)	35 (31–40)	43 (36–49)
PAWP, mmHg	9 (7–12)	8 (6–10)	21 (16–24)	17 (17–20)	13 (12–13)	16.5 (16–17)	7 (4–7)	8 (5–10)
PVR, WU	3.8 (3.0–5.0)	6.3 (5.6–9.4)	1.6 (1.2–2.0)	3.4 (2.6–4.5)	1.6 (1.1–1.7)	0.9 (0.7–1.2)	2.8 (2.6–3.2)	1.5 (1.0–1.7)
RAP, mmHg	5 (3–8)	4 (2–7)	9 (8–10)	10 (8–13)	8 (7–9)	5.5 (4–7)	2 (1–4)	4 (2–5)

CI cardiac index, *CO* cardiac output, *dPAP* diastolic pulmonary arterial pressure, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *sPAP* systolic pulmonary arterial pressure, *SVI* stroke volume index

[a]Data reported as median (IQR)

[b]Severe PH = PVR > 5 WU

[c]Cardiac output measured by Fick vs thermodilution yielded similar results

identifying patients with PH: among patients who met PH enrichment criteria from any category in Table 1 the precapillary PH rate was 55%, while patients only meeting enrichment criteria from categories 1 and 2 ($N = 106$ without echocardiogram criteria) had a similar precapillary PH rate of 58%.

Findings from previous studies also align with our results in highlighting DLCO < 40%, elevated PA/aorta ratio on CT, and worsening 6MWD as key screening triggers for PH in ILD [17, 24]. However, while those studies emphasized symptom-based and expert-driven suspicion as important components of early detection, our findings suggest limitations in relying solely on clinical judgment. Our study extends prior efforts by quantifying the predictive value of echocardiographic and CT-based structural markers, in addition to pulmonary function and clinical parameters, in risk-stratifying for PH.

Upon comparing characteristics of participants with precapillary PH to those with Ipc-PH,

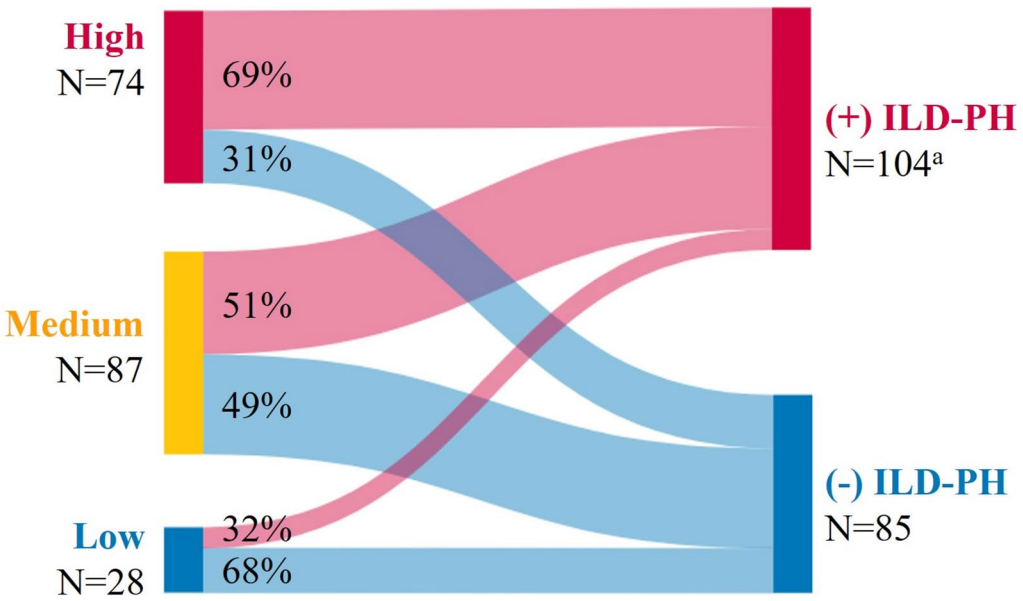

Fig. 4 Investigator suspicion of PH vs RHC-confirmed PH status. Following all noninvasive assessments, investigators were asked to rank their suspicion of PH as low, medium, or high, for each patient prior to right heart catheterization (RHC); the presence precapillary PH was then confirmed by RHC.[a]One patient did not have investigator's suspicion of PH reported prior to RHC. *PH* pulmonary hypertension, *RHC* right heart catheterization

Cpc-PH, as well as isolated mPAP, PAWP, and PVR elevations, the precapillary ILD-PH group had a greater incidence of syncope, worse pulmonary function, and lower TAPSE/RVSP ratio than the other groups. Interestingly, participants with isolated mPAP elevation had the longest time since ILD diagnosis, most supplemental oxygen use, the greatest incidence of jugular venous distention and PA enlargement, but the highest 6MWD. Patients with isolated PVR elevation had the lowest TAPSE, but also the lowest RVSP and TRV, and the least frequent incidence of peripheral edema and enlarged PA. The similarities and complex findings across varying hemodynamic phenotypes emphasize the importance of accurate hemodynamic assessment in this group of patients.

Although gestalt clinical suspicion stratification aligned modestly with RHC-confirmed PH status, substantial discordance across suspicion categories highlighted the need for a more objective approach. Notably, 32% of participants assessed as low suspicion by clinicians and 51% of those with medium suspicion were ultimately found to have precapillary PH on RHC, indicating that deferring RHC based on gestalt alone would have missed a considerable proportion of true cases. These findings underscore the limitations of relying solely on clinical suspicion to assess the risk of precapillary PH, as a substantial proportion of participants, particularly those with low or medium clinical suspicion, may have discordant findings with definitive hemodynamic evaluation. Together, these results emphasize the importance of structured screening for early detection that incorporates objective imaging and functional assessments in addition to clinical suspicion.

This study has several important limitations. First, the rate of precapillary PH confirmed by RHC was arguably higher than expected, with 55% of participants meeting hemodynamic criteria for precapillary PH. This likely reflects the use of enrichment criteria intentionally designed to select participants at higher risk for PH. While this approach was intended to increase the likelihood of identifying meaningful variables for screening model development, it also introduces the possibility of selection bias. As a result, patients with less advanced disease or lower risk

features may be underrepresented, which could limit the generalizability of these findings to the broader ILD population. Nonetheless, selection bias due to the enrichment criteria may not have been that prominent in this preliminary population as 15% of patients were deemed low likelihood for PH by their study clinician and less than half deemed high likelihood; the patients with precapillary PH in this study also had relatively modest elevation of mPAP and PVR compared to previous studies. Moreover, because clinical gestalt is inherently unreliable (as evidenced in our results), the degree of selection bias introduced by referring patients at-risk for PH is uncertain. Importantly, our eligibility criteria mirror real-world clinical practice, as RHC would be unlikely to be pursued in patients without an apparent risk of PH.

As the study is currently ongoing, not all planned participants have completed assessments, which may introduce bias or limit the robustness of preliminary findings. The HRCT and echocardiography imaging were centrally reviewed and interpreted for purposes of this analysis; however, these analyses were performed by a single reviewer per imaging type and did not account for inter- or intra-reader variability. Centralized adjudication and additional inter- and intra-variability analyses are planned for the final dataset to minimize subjectivity. Furthermore, the absence of contrast-enhanced HRCT may have limited the precision of vascular measurements, particularly regarding PA assessment. The statistical analyses may also be limited by the sample size of subgroups and the fact that outliers were not removed. This analysis did not disaggregate outcomes by sex; future studies with appropriately powered male and female cohorts may be needed to explore potential sex-based differences in these outcomes.

And while a univariate model was used for this preliminary data, a more robust multivariate analysis will be performed on the final dataset. Disease progression in the time between noninvasive assessments and RHC should also be considered, although the median times since PFTs, HRCT, and echocardiography were relatively short in this preliminary dataset.

A notable advantage of this prospective study is that all testing is contemporaneous versus prior studies and models where there were highly variable time gaps between the RHC and other testing. This likely impacted the reliability of the results as it is well established that PH can evolve in these patients and sometimes at an accelerated rate [33].

CONCLUSIONS

Preliminary findings from 190 participants suggest that a composite of PFTs, echocardiography, and chest CT should be considered when screening for PH in ILD. The enrollment criteria to the study, based on commonly available medical history, physical exam findings, imaging, and laboratory testing resulted in a significant unmasking of PH and specifically precapillary PH, lending the study's eligibility criteria to be a potential framework for screening while more robust guidance is developed. Patients with ILD who are found to have decreased DLCO on PFTs, elevated RVSP or TRV on echocardiography, and/or elevated PA/aorta diameter ratio or RV/LV diameter on CT may benefit from undergoing RHC to determine if PH is present. Clinical suspicion alone, or lack thereof, was insufficient for accurately identifying and ruling out precapillary PH, as substantial discordance was observed between clinician-assessed suspicion levels and RHC-confirmed diagnoses. These findings support the need for structured screening protocols that integrate objective imaging and functional assessments alongside clinical judgment to improve diagnostic accuracy, as commonly used screening approaches such as gestalt, echocardiography, and natriuretic peptide levels should not be relied upon. These results also suggest that the current threshold for performing RHC in this population may warrant reconsideration; specifically, the data suggest that relying solely on echocardiographic findings and/or the absence of clinical suspicion may be insufficient to rule out PH. Additional data on the remaining PHINDER participants will look to support these findings, provide prognostic cutoff values for continuous variables, and further refine a validated, practical tool to screen for PH in ILD.

ACKNOWLEDGEMENTS

Medical Writing and/or Editorial Assistance. The authors thank Dorothy Keine, PhD, of 3Prime Medical Writing, LLC for support in manuscript preparation, compensated by United Therapeutics Corporation.

Author Contributions. Meredith Broderick, Kevin Maher, Andrew Nelsen, and Claire M. Thrasher contributed to the study protocol; Maral DerSarkissian, David Kiely, Tejaswini Kulkarni, Mary Beth Scholand, Oksana A. Shlobin, and David Zisman are members of the study Steering Committee; Amro Al-Astal, Debabrata Bandyopadhyay, Matthew Hunsucker, Steven Nathan, Raj Parikh, Abhijit Raval, Sandeep Sahay, and David Zisman serve as principal investigators in the study; Franck Rahaghi contributed to the analysis and manuscript. Dasom Lee performed all formal analyses; and Claire M. Thrasher drafted the manuscript with critical review and editorial contributions from all authors.

Funding. This work was supported by United Therapeutics Corporation. The journal's Rapid Service and Open Access fees were funded by United Therapeutics Corporation.

Data Availability. Datasets generated and/or analyzed during the current study will be made available upon request from the corresponding author, after completion of the study and publication of the final dataset. Data access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receiving a signed data-sharing agreement. Data access should comply with local laws and regulations.

Declarations

Conflicts of Interest. Meredith Broderick, Dasom Lee, Kevin Maher, Andrew Nelsen, Franck Rahaghi, and Claire M. Thrasher are employees of the study sponsor, United Therapeutics. Danielle Caudell Stamper, is an employee of the study's clinical research organization contracted by the study sponsor. Hunter Champion has received consulting fees and payment for speakers' bureaus from United Therapeutics. Maral DerSarkissian has received consulting fees from United Therapeutics. David G. Kiely has received funding from NIHR Sheffield Biomedical Research Centre, Janssen, and Ferrer; consulting fees from Janssen, Ferrer, Altavant, MSD, United Therapeutics, Liquidia, Gossamer Bio, and Apollo; payment for presentations, manuscript writing, or events from Janssen, Ferrer, Altavant, MSD, and United Therapeutics; participated in a Data Safety Monitoring or Advisory Board for Janssen, MSD, and Liquidia; and is a member of the Clinical Reference Group for Specialised Respiratory Medicine (NHS England) and leads the UK National Audit of Pulmonary Hypertension. Tejaswini Kulkarni has received consulting fees from and participated in an Advisory Board for United Therapeutics. Steven Nathan has received consulting fees, payment for expert testimony and payment for presentations, manuscript writing, or events from United Therapeutics; participated in a Data Safety Monitoring or Advisory Board for United Therapeutics, AbbVie, and BMS; has stock in and holds a leadership or fiduciary role at Gossamer Bio. Raj Parikh has received payment for presentations, manuscript writing, or events from Janssen and United Therapeutics; and participated in a Data Safety Monitoring or Advisory Board for United Therapeutics and Liquidia. Sandeep Sahay has received funding from Merck, United Therapeutics, Gossamer Bio, Keros, Pulmovant, Liquidia, and Respira; consulting fees from Merck and United Therapeutics; support for meeting attendance or travel from Janssen; participated in Advisory Boards for United Therapeutics, Liquidia, and Data Safety Monitoring Board for NIH-funded trials; and holds a leadership role at ACCP CHEST and PHA. Mary Beth Scholand has received consulting fees from Boehringer Ingelheim, Genentech, Veracyte, Imvaria, and United Therapeutics. Oksana A. Shlobin has received consulting fees from Merck, Insmed, and AllRock; payment for speakers' bureau from United Therapeutics; participated in a Data

Safety Monitoring or Advisory Board for Janssen and GSK; and holds a leadership or fiduciary role at PHA and ACCP CHEST. David Zisman has received funding from the Jean and William Soman Research Fund. Debabrata Bandyopadhyay, Amro Al-Astal, Matthew Hunsucker, and Abhijit Raval have nothing to disclose.

Ethical Approval. Ethical oversight for this study was provided by Advarra, serving as the Central Institutional Review Board (IRB) and local IRB approval was obtained for some sites. The study was approved by all participating institutions and site-level IRB approval details can be found in Table S1 of the Online Data Supplement. Written informed consent was obtained from all study participants, and all procedures involving human participants were performed in accordance with the ethical standards of each institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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