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RESEARCH ARTICLE

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Noninvasive determinants of pulmonary hypertension in interstitial lung disease

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Abstract

Pulmonary hypertension (PH) in interstitial lung disease (ILD) is associated with increased mortality and impaired exertional capacity. Right heart catheterization is the diagnostic standard for PH but is invasive and not readily available. Noninvasive physiologic evaluation may predict PH in ILD. Forty-four patients with PH and ILD (PH-ILD) were compared with 22 with ILD alone (non-PH ILD). Six-min walk distance (6MWD, 223 ± 131 vs. 331 ± 125 m, $p = 0.02$) and diffusing capacity for carbon monoxide (DLCO, $33 \pm 14\%$ vs. $55 \pm 21\%$, $p < 0.001$) were lower in patients with PH-ILD. PH-ILD patients exhibited a lower gas-exchange derived pulmonary vascular capacitance (GX_{CAP}, 251 ± 132 vs. 465 ± 282 mL × mmHg, $p < 0.0001$) and extrapolated maximum oxygen uptake (VO_{2max}) ($56 \pm 32\%$ vs. $84 \pm 37\%$, $p = 0.003$). Multivariate analysis was performed to determine predictors of VO_{2max}. GX_{CAP} was the only variable that predicted extrapolated VO_{2max} among PH-ILD and non-PH ILD patients. Receiver operating characteristic curve analysis assessed the ability of individual noninvasive variables to distinguish between PH-ILD and non-PH ILD patients. GX_{CAP} (area under the curve [AUC] 0.85 ± 0.04, $p < 0.0001$) and delta $ETCO_2$ (AUC 0.84 ± 0.04, $p < 0.0001$) were the strongest predictors of PH-ILD. A CART analysis selected GX_{CAP}, estimated right ventricular systolic pressure (eRVSP) by echocardiogram, and FVC/DLCO ratio as predictive variables for PH-ILD. With this analysis, the AUC improved to 0.94 (sensitivity of 0.86 and sensitivity of 0.93). Patients with a $GX_{CAP} \leq 416$ mL × mmHg had an 82% probability of PH-ILD. Patients with $GX_{CAP} \leq 416$ mL × mmHg and high FVC/DLCO ratio >1.7 had an 80% probability of PH-ILD. Patients with $GX_{CAP} \leq 416$ mL × mmHg and an elevated eRVSP by

Abbreviations: CI, cardiac index; CO, cardiac output; CPET, cardiopulmonary exercise testing; GX_{CAP}, gas exchange derived pulmonary vascular capacitance; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; OUES, oxygen uptake efficiency slope; PAC, pulmonary artery compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle; SV, stroke volume; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.

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echocardiogram >43 mmHg had 100% probability of PH-ILD. The incorporation of GX_{CAP} with either eRVSP or FVC/DLCO ratio distinguishes between PH-ILD and non-PH-ILD with high probability and may therefore assist in determining the need to proceed with a diagnostic right heart catheterization and potential initiation of pulmonary arterial hypertension-directed therapy in PH-ILD patients.

KEYWORDS
cardiopulmonary exercise testing, interstitial lung disease, pulmonary hypertension

INTRODUCTION

Pulmonary hypertension (PH) is a known complication of interstitial lung disease (ILD) and is defined by a mean pulmonary artery pressure (mPAP) >20 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg, and pulmonary vascular resistance (PVR) of >2 Wood units (WU) on right heart catheterization (RHC).[1] Patients with ILD associated PH (PH-ILD) have a significantly worse prognosis than patients without PH.[2,3] However, the exact prevalence of PH in ILD is difficult to ascertain due to the heterogeneity in diagnostic methods, definition of PH used, and the patient population studied.[2]

Accurate and early determination of PH in ILD population is important because recent studies have shown that treatment with PAH targeted therapy, specifically inhaled treprostinil, delays time to clinical worsening[4] and may even improve lung function.[3,5] While RHC remains the reference standard for PH diagnosis, it is invasive, not readily available in non-tertiary centers, and is not commonly used to monitor disease progression. Additionally, resting RHC has little utility in examining the dynamic effects of hemodynamic perturbation that accounts for the exertional and functional limitation seen in PH patients during exercise. Current, commonly employed noninvasive methods used to screen ILD patients for the presence of PH include blood testing for trends in plasma N-terminal (NT)-prohormone-brain natriuretic peptide (NT-proBNP), transthoracic echocardiography (TTE), worsening pulmonary function test (PFT) parameters, and reduced 6-min walk distance (6MWD).[6] Unfortunately, these investigative tests in isolation have inherent limitations as a screening tool for PH-ILD[7–9] and currently there remains no standard approach to assessing patients' risk for PH in ILD.[6] Variations in PH-ILD screening practices could translate into infrequent patient assessment and potentially delayed diagnosis of PH in the ILD population.

In addition to standard diagnostic evaluation, cardiopulmonary exercise testing (CPET) is frequently utilized as an adjunct in the diagnosis and management of patients with PH.[10] We recently demonstrated that unlike conventional TTE measures, several parameters obtained during submaximum CPET are able to unmask the dynamic pulmonary vascular disease (PVD) burden encountered by patients with combined pre- and post-capillary PH.[11] This is particularly relevant in PH-ILD as one the main pathomechanisms of PVD development in ILD involves vasoconstriction, remodeling, and fibrotic ablation of the pulmonary vasculature.[2] These pathophysiological changes imparted on the pulmonary vasculature consequently reduce the ability of the vessels to passively distend to receive antecedent RV stroke volume (SV), which in turn, further increases right ventricular afterload. This aberrant RV-pulmonary vascular interaction is apparent on noninvasive CPET assessment as it results in ventilation perfusion mismatch and therefore abnormalities in gas exchange. In fact, Armstrong et al., showed that PH-ILD patients exhibited greater degree of ventilation-perfusion mismatch characterized by abnormal end tidal carbon dioxide ($ETCO_2$) and VE/VCO_2 (i.e., ventilatory inefficiency) response during maximum CPET in a small cohort of patients with advanced ILD undergoing lung transplant evaluation.[12] However, maximum CPET efforts are not germane to activities of daily living, which are generally accomplished at lower exercise intensities.[13] In submaximum CPET, unlike conventional CPET, a maximal exercise effort is not required, making it an attractive option for PH-ILD patients with baseline cardiopulmonary limitation or patients with preexisting musculoskeletal disorders (e.g., those with connective tissue disease) and elderly patients who often are unable to undergo maximum exercise testing.

Accordingly, in this study we sought to compare the different noninvasive methods that may help distinguish between PH-ILD from non-PH ILD and examine which noninvasive parameter(s) best identifies with the pulmonary

disease burden encountered in PH-ILD population. We hypothesize that owing to its dynamic assessment of ventilation-perfusion (mis)match during exercise, derangement of the different gas exchange variables attained during submaximum CPET would best distinguish between PH-ILD from ILD alone, thus providing a useful adjunct investigative tool in the diagnosis and management of patients with PH-ILD.

METHODS

Study population and design

We enrolled ILD patients referred to our PVD program between January 2019 and May 2022 for either diagnostic resting RHC study for suspected PH or invasive CPET for further investigation of unexplained dyspnea. The study protocol was approved by our Institutional Review Board (IRB 2000024783). Included patients consented to have their clinical and investigative data used for research purposes.

PH was defined as resting supine mPAP >20 mmHg and PVR > 2 WU along with a PAWP ≤ 15 mmHg on RHC study.[1] The different types of ILD in both groups are described in Supporting Information: Table S2.

Submaximum exercise step protocol

It is our standard of practice to have all patients who are capable undergo submaximum exercise step testing (Shape Medical Systems, Inc.) during their ambulatory PVD clinic visit. Our method of performing submaximum CPET has been previously described.[11] Briefly, it consists of a portable unit with a 14 cm high step that patients step up and down for 3 min. The unit is equipped with a portable metabolic cart and a mouthpiece that is connected to a continuous gas exchange analyzer. The entire duration of the test is 6 min: 2 min of rest for baseline monitoring, 3 min of step exercise followed by 1 min of recovery. The test measures submaximum and extrapolated maximum exercise oxygen consumption,[14,15] VO_2 (% predicted), ventilatory efficiency expressed as VE/VCO_2, oxygen uptake efficiency slope (OUES), gas exchange derived estimate of pulmonary vascular capacitance (or GX_{CAP}), $ETCO_2$ at rest and during exercise, heart rate and rhythm, and peripheral oxygen saturation. After the 2 min of baseline measurements, patients are instructed to "begin exercise" by stepping on and off from a platform at the speed indicated by a metronome set by the test administrator. After each minute of exercise, the test administrator increases the metronome speed. After 3 min of exercise, the patient is instructed to stop and stand idle for an additional minute for data collection. Gas exchange parameters, heart rate, and peripheral O_2 saturation are collected throughout the entire 2 min of rest, 3 min of step exercise, and 1 min of recovery.

Right heart hemodynamic assessment

Our method of performing resting supine RHC has been previously described.[11] Briefly, RHC was performed in the supine position with a 6 or 7.5 F Swan-Ganz catheter (Edwards LifeSciences) inserted percutaneously under fluoroscopic and ultrasound guidance into the internal jugular vein. Right atrial pressure, right ventricular pressure, PA pressure, and PAWP along with superior vena cava, right atrial, and pulmonary arterial oxygen (O_2) saturations were measured. When significant respirophasic changes persisted, an electronic average was used.[16] A zero reference was obtained at the mid-thoracic level.[17,18]

PAWP measurement was determined by fluoroscopic confirmation and by characteristic waveform appearance. In addition, PAWP is confirmed to be occlusive either by three attempts of PAWP saturation to achieve occlusion peripheral oxygen saturation (i.e., >90% or within 5% of peripheral arterial saturation)[19] or by demonstration of stasis of contrast on fluoroscopy. Cardiac output (CO) was determined using the thermodilution method. PVR was calculated by (mPAP-PAWP)/CO and expressed in WU. SV was calculated as CO divided by the heart rate. CO and SV were indexed to body surface area to obtain both cardiac index and SV index. PA compliance was calculated as the ratio of SV to pulmonary artery pulse pressure (the difference between systolic PA pressure and diastolic PA pressure) and expressed as mL/mmHg.

Six-min walk test (6MWT)

6MWT was performed in accordance with ATS guidelines.[14] Testing was deferred if patients had a history of unstable angina or myocardial infarction in the prior month, resting heart rate >120 beats per min, or systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg. Testing was discontinued if patients reported chest pain, intolerable dyspnea, leg cramps, or diaphoresis, or exhibited pallor as determined by the supervising respiratory therapist. Our complete 6MWT protocol is included in the Supporting Information: Appendix S1.

Statistical analysis

Unless otherwise stated, values are presented as mean and standard deviation. Comparisons of baseline characteristics, echocardiogram data, PFT data, RHC data, 6MWT data, and submaximum CPET variables between PH-ILD and ILD patients were performed using independent Student *t*-test analysis for normally distributed data and Wilcoxon Rank Sum test for data not normally distributed. Receiver-operating characteristic (ROC) curve analysis was used to assess the ability of the different noninvasive testing variables to distinguish between PH-ILD and ILD without PH. Univariate and multivariate analysis were performed to determine predictors of extrapolated maximum VO_2 on submaximum step test in PH-ILD patients. A probability value of <0.05 was considered significant. Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software; LLC) and SAS 9.4 (SAS Institute Inc.). The decision tree analysis was conducted on variables that were significantly different between PH-ILD and non-PH-ILD patients using the CART algorithm implemented in the rpart (version 4.1.16) for R (version 4.1.2). The complete tree was first constructed and then pruned by choosing the most parsimonious model within one standard error of the minimum cross-validation error.[20] The importance score of all variables was calculated to describe the effect on model improvement, that is, how important each variable is to the constructed decision tree.

RESULTS

Demographic and clinical characteristics

The study included 44 consecutive PH-ILD patients and 22 consecutive ILD patients without PH by RHC. 6MWT data were available in 23 PH-ILD patients and 12 ILD patients. There was no statistical difference in the age, gender, body mass index, hemoglobin concentration, and serum NT-proBNP levels between the groups. The PH-ILD group had significantly lower diffusing capacity for carbon monoxide (DLCO % predicted) ($33 \pm 14\%$ vs. $55 \pm 21\%$, $p < 0.001$) and greater forced vital capacity to DLCO ratio (FVC/DLCO) (2.31 ± 1.1 vs. 1.74 ± 0.9, $p = 0.04$) compared to the ILD group. Additionally, on echocardiogram, the PH-ILD group had greater estimated RV systolic pressure (RVSP) (58 ± 14 vs. 37 ± 9 mmHg, $p < 0.0001$) and reduced tricuspid annular systolic plane excursion to RVSP ratio (TAPSE/RVSP) (0.44 ± 0.26 vs. 0.76 ± 0.22, $p = 0.001$) compared to ILD group. By study design, PH-ILD group had greater mPAP and PVR along with reduced PA compliance compared to ILD group. The baseline characteristics, comorbidities, and PFT, echocardiogram parameters, and resting RHC data are summarized in Table 1.

Exercise testing assessment

PH-ILD patients achieved a lower 6MWD (223 ± 131 vs. 331 ± 125 m, $p = 0.02$) along with a greater degree of peripheral O_2 desaturation ($85 \pm 4\%$ vs. $94 \pm 6\%$, $p = 0.0003$) compared to ILD patients. On submaximum CPET, PH-ILD patients exhibited worse ventilatory efficiency (i.e., greater VE/VCO_2) (48 ± 16 vs. 34 ± 10, $p = 0.001$), delta $ETCO_2$ (-2.8 ± 2.7 vs. 1.1 ± 2.6 mmHg, $p < 0.0001$), GX_{CAP} (232 ± 105 vs. 465 ± 282 mL × mmHg, $p < 0.0001$), oxygen (O_2) pulse (54 [39–82] vs. 99 [69–73] % predicted, $p < 0.0001$), submaximum VO_2 (% predicted) (49 ± 22 vs. $64 \pm 31\%$ predicted, $p = 0.02$), and extrapolated maximum VO_2 (% predicted) ($56 \pm 32\%$ vs. $84 \pm 37\%$ predicted, $p = 0.003$) compared to the ILD group. The 6MWT and submaximum CPET parameters between the groups are summarized in Table 2 and Figure 1.

Distinguishing PH-ILD from ILD without PH using individual noninvasive testing variables

Using the variables from Tables 1 and 2 that help distinguish PH-ILD from ILD without PH, $GX_{CAP,}$ and delta $ETCO_2$ emerged as best predictors on ROC analysis. The area under the curve (AUC) for GX_{CAP} was 0.85 ± 0.04 ($p < 0.0001$) with a sensitivity of 85% and a specificity of 67% at an optimal cut-off point of 345 mL × mmHg. For delta $ETCO_2$, the AUC was 0.84 ± 0.04 ($p < 0.0001$) with a sensitivity of 85% and a specificity of 52% at an optimal cut-off point of 0.3.

The other noninvasive variables, including DLCO (% predicted) (AUC of 0.81 ± 0.06; $p < 0.0001$), VE/VCO_2 (AUC of 0.77 ± 0.06; $p = 0.0004$), FVC/DLCO (AUC of 0.74 ± 0.07; $p = 0.002$), 6MWD (AUC of 0.71 ± 0.09; $p = 0.002$), and O_2 pulse (AUC of 0.66 ± 0.08; $p = 0.04$), provided less discrimination between PH-ILD patients and ILD patients without PH (Figure 2).

Independent predictors of peak VO_2 in PH-ILD and non-PH ILD groups

The determination of peak VO_2 predictors was performed for PH-ILD and non-PH ILD cohorts. For the PH-ILD cohort,

TABLE 1 Baseline demographics.

	PH-ILD ($n = 44$)	Non-PH ILD ($n = 22$)	p Value
Baseline characteristics			
Age (years)	66 ± 13	62 ± 12	0.17
Female gender, *n* (%)	26 (59)	15 (68)	0.47
BMI (kg/m^2)	28 ± 6	27 ± 8	0.58
NT-proBNP (pg/mL)	243 (88–862)	54 (50–143)	0.002
Hemoglobin (g/dL)	12.5 ± 1.9	12.6 ± 1.4	0.76
Comorbidities, *n* (%)			
Diabetes	8 (18)	2 (9)	0.33
Systemic hypertension	19 (43)	7 (33)	0.44
Atrial fibrillation	5 (11)	1 (4)	0.33
Coronary artery disease	10 (23)	0	0.01
Obstructive sleep apnea	7 (15)	7 (31)	0.13
Medications, *n* (%)			
Diuretic	20 (45)	5 (22)	0.07
Beta blocker	15 (34)	3 (14)	0.07
Calcium channel blocker	9 (20)	8 (36)	0.16
ACE inhibitor or ARB	10 (15)	3 (13)	0.38
PDE-5 inhibitor	6 (13)	3 (13)	1.00
Systemic treprostinil	2 (4)	0	0.32
Inhaled treprostinil	3 (4)	0	0.31
Pulmonary function test			
FEV_1 (% predicted)	68 ± 19	82 ± 18	0.01
FVC (% predicted)	67 ± 19	84 ± 20	0.002
FEV_1/FVC (% predicted)	98 ± 14	97 ± 8	0.57
DLCO (% predicted)	33 ± 14	55 ± 21	<0.0001
FVC/DLCO	2.31 ± 1.1	1.74 ± 0.9	0.04
Echocardiogram			
RV systolic pressure (mmHg)	58 ± 14	37 ± 9	<0.0001
TR jet velocity (m/s)	3.2 ± 0.8	2.4 ± 0.5	0.01
TASPE (cm)	2.01 ± 0.4	2.14 ± 0.3	0.45
TAPSE/RV systolic pressure	0.44 ± 0.26	0.76 ± 0.22	0.001
LV ejection fraction (%)	61 ± 1	62 ± 1	0.64
Right heart catheterization			
Right atrial pressure (mmHg)	6 ± 3	6 ± 3	0.72
Cardiac index (L/min/m^2)	2.60 ± 0.7	3.30 ± 1.1	0.001
SV index (mL/min/m^2)	33.1 (28.7–40.3)	43.1 (39.8–48.8)	<0.0001
Mean PA pressure (mmHg)	36 ± 9	22 ± 3	<0.0001
PA wedge pressure (mmHg)	9 ± 2	11 ± 3	0.01

(Continues)

TABLE 1 (Continued)

	PH-ILD ($n = 44$)	Non-PH ILD ($n = 22$)	p Value
PVR (WU)	6.2 ± 2.9	1.9 ± 0.9	<0.0001
PA compliance (mL/mmHg)	1.95 ± 0.9	3.52 ± 1.3	<0.0001

Note: Data presented as no (%) or mean ± SD unless otherwise specified.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; cm, centimeters; DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ILD, interstitial lung disease; LV, left ventricle; m, meters; MWT, minute walk test; NT-proBNP, N-terminal prohormone brain natriuretic peptide; PA, pulmonary artery; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricle; RVSP, right ventricle systolic excursion; SpO_2, blood oxygen saturation; SV, stroke volume; TR, tricuspid regurgitation; WU, woods unit.

TABLE 2 Exercise capacity assessment.

Six-min walk test parameters			
	PH-ILD ($n = 23$)	**Non-PH ILD ($n = 11$)**	**p Value**
Time between 6-MWD and RHC, median (IQR), days	98 (40–162)	86 (8–107)	0.42
Distance covered (m)	223 ± 131	331 ± 125	0.02
Rest SpO_2 (%)	96 ± 2	98 ± 2	0.02
End SpO_2 (%)	85 ± 4	94 ± 6	0.0003
Delta rest-to-end SpO_2 (%)	−10 ± 3	−5 ± 5	0.001
Submaximum CPET parameters			
	PH-ILD ($n = 44$)	**Non-PH ILD ($n = 22$)**	
Time between submaximum CPET and RHC, median (IQR), days	32 (20–99)	76 (19–135)	0.35
Rest $ETCO_2$ (mmHg)	31 ± 6	35 ± 6	0.05
Rest SpO_2 (%)	91 ± 5	95 ± 4	0.002
End SpO_2 (%)	81 ± 8	90 ± 8	0.001
RER	1.08 ± 0.3	0.99 ± 0.1	0.19
VE/VCO_2	48 ± 16	34 ± 10	0.001
Delta $ETCO_2$ (mmHg)	−2.8 ± 2.7	1.1 ± 2.6	<0.0001
GX_{CAP} (mL × mmHg)	232 ± 105	465 ± 282	<0.001
OUES (% predicted)	59 ± 31	75 ± 26	0.06
O_2 pulse (% predicted)	54 (39–82)	99 (69–73)	<0.0001
Submaximum VO_2 (% predicted)	49 ± 22	64 ± 31	0.02
Extrapolated maximum VO_2 (% predicted)	56 ± 32	84 ± 37	0.003

Note: Data presented as no (%) or mean ± SD unless otherwise specified.

Abbreviations: CPET, cardiopulmonary exercise test; $ETCO_2$, end tidal carbon dioxide; GXCAP, gas exchange derived pulmonary vascular capacitance; HR, heart rate; IQR, interquartile range; O_2, oxygen; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; RHC, right heart catheterization; SpO_2, blood oxygen saturation; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.

on univariate analysis, DLCO (% predicted), 6MWD, FVC/DLCO, VE/VCO_2, delta $ETCO_2$, and GX_{CAP} were significantly associated with the extrapolated peak VO_2 (% predicted) (Tables 3a and 3b). For the non-PH ILD group, DLCO (% predicted), 6MWD, VE/VCO_2, delta $ETCO_2$, and GX_{CAP} were significantly associated with the extrapolated peak VO_2 (% predicted). However, on multivariate analysis, only GX_{CAP} was significantly associated with the extrapolated peak VO_2 (% predicted) for both PH-ILD and non-PH ILD cohorts (Tables 4a and 4b).

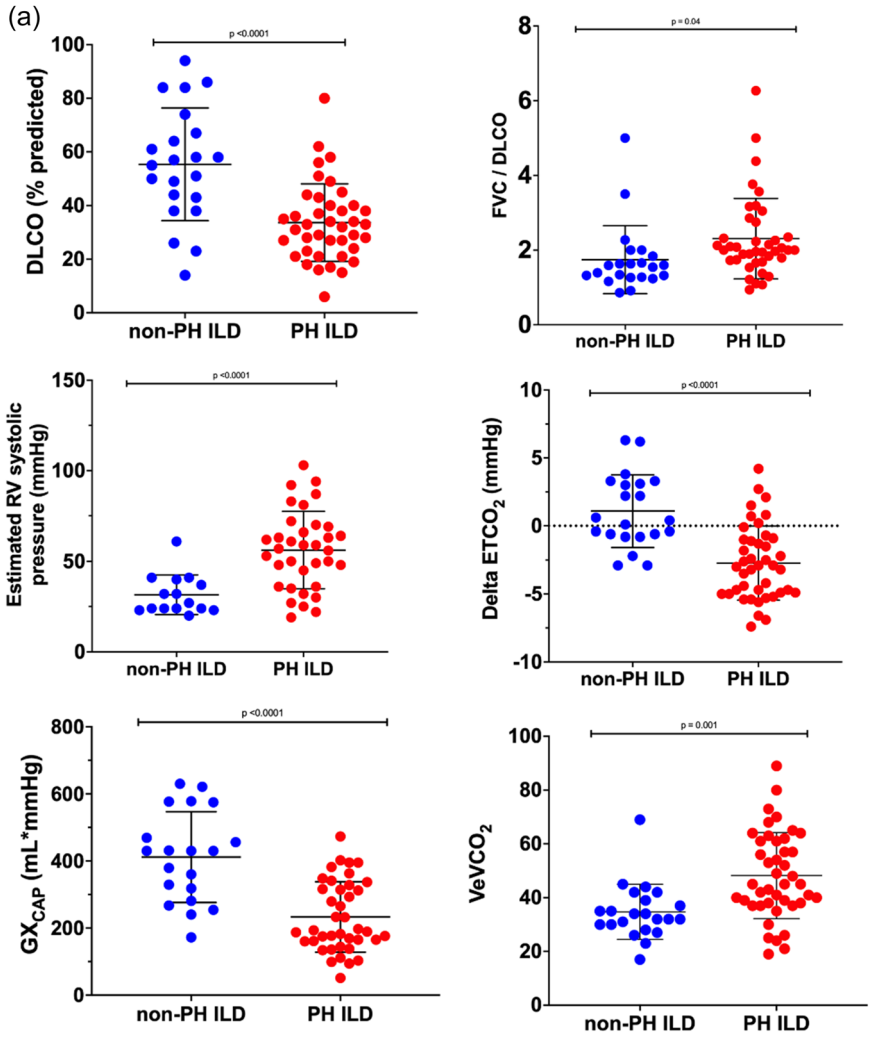

FIGURE 1 (a) Noninvasive parameters in patients with ILD with confirmed pulmonary hypertension on right heart catheterization (PH ILD) compared with patients with ILD without pulmonary hypertension (non-PH ILD). (b) Noninvasive parameters in patients with ILD with confirmed PH ILD compared with patients with non-PH ILD. Data presented as mean ± standard deviation. DLCO, diffusing capacity for carbon monoxide; $ETCO_2$, end-tidal carbon dioxide; FVC, forced vital capacity; GxCAP, gas exchange derived pulmonary vascular capacitance; ILD, interstitial lung disease; O_2, oxygen; PH, pulmonary hypertension; RV, right ventricular; VE/VCO_2, ventilatory efficiency; VO_2, oxygen uptake; 6MWD, 6-min walk distance.

Decision tree analysis

A decision tree analysis using CART selected GX_{CAP}, estimated RVSP, and FVC/DLCO ratio as predictive variables for PH-ILD. The CART derived decision tree was more predictive than individual variables to detect the presence of PH in ILD patients with an improved AUC of 0.94 (sensitivity of 0.86 and specificity of 0.93). GX_{CAP} was the variable with the highest importance score in the constructed decision tree (Supporting Information: Table S1). $GX_{CAP} \leq 416$ mL × mmHg alone was associated with an 82% probability of PH-ILD. $GX_{CAP} \leq 416$ mL × mmHg and FVC/DLCO ratio <1.7 was associated with an 80% probability of PH-ILD. $GX_{CAP} \leq 416$ mL × mmHg and estimated right ventricular systolic pressure (eRVSP) >43 mmHg were associated with a 100% probability of PH-ILD in our studied cohort (Figure 3).

DISCUSSION

This is the first study to investigate different noninvasive resting and exercise variables to help determine the presence of PH in ILD. In the current study, we showed that patients with PH-ILD exhibit further derangements in their PFT, echocardiographic, and noninvasive exercise testing parameters compared to ILD patients without associated PH. We demonstrated that the individual reductions in the submaximum CPET parameters of GX_{CAP} and delta $ETCO_2$ provided the best

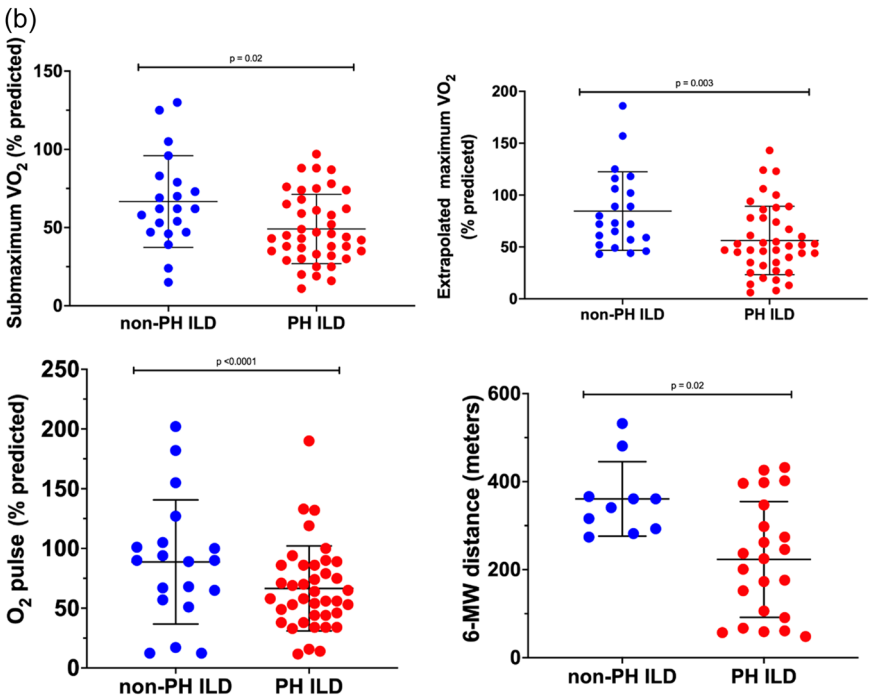

FIGURE 1 (Continued)

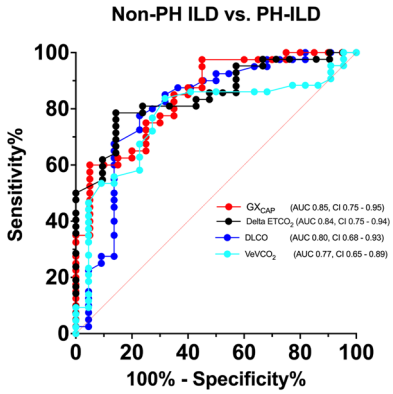

FIGURE 2 Area under receiver operating curve characteristics for noninvasive measures distinguishing between patients with interstitial lung disease (ILD) and pulmonary hypertension (PH-ILD) and patients with ILD without PH (non-PH ILD). DLCO, diffusing capacity for carbon monoxide; eRVSP, estimated right ventricular systolic pressure; FVC, forced vital capacity; GxCAP, gas exchange derived pulmonary vascular capacitance; PH, pulmonary hypertension; 6MWD, six min walk distance.

discrimination to detect the presence of PH in ILD. Additionally, a reduced GX_{CAP} during submaximum exercise was associated with reduced exercise capacity in both PH-ILD and non-PH ILD groups. We further demonstrated that a decision tree incorporating different noninvasive testing including reduced GX_{CAP}, estimated RVSP by TTE, and FVC/DLCO ratio on PFT enabled discrimination of PH-ILD and non-PH-ILD with high probability and with improved sensitivity and specificity compared to individual testing parameters alone.

In the current study, PH-ILD patients exhibited lower 6MWD along with greater systemic O_2 desaturation compared to ILD patients without PH. However, a change in 6MWD in PH-ILD is nonspecific and can reflect worsening parenchymal lung disease, a pulmonary vascular process, and also a range of other pathologies including individual biomechanics.[8] Furthermore, in the current study, on ROC analysis, 6MWD provided less discrimination in predicting presence of PH compared to other noninvasive variables (Figure 2).

There were several abnormal gas exchange parameters on submaximum exercise testing that were more pronounced in PH-ILD (Figure 1 and Table 2). The greater degree of delta $ETCO_2$ abnormality and ventilatory inefficiency (i.e., abnormal VE/VCO_2 slope) in PH-ILD observed in the current study is in keeping with prior reports.[12] VE/VCO_2 shares a close relationship with PVR and is therefore a marker of PVD burden.[11,21] Failure to appropriately increase $ETCO_2$ throughout exercise reflects the inability to augment RV output due to increased afterload imposed by the obliterative pulmonary vasculopathic process observed in PH. This inability to augment RV output is manifested by the greater reduction in O_2 pulse observed in PH-ILD compared to non-PH ILD (Figure 1 and Table 2).

TABLE 3a Univariate model for predicting extrapolated VO_2 (% predicted) in PH-ILD patients using noninvasive diagnostic variables ($n = 44$).

Variable	ß-coefficient	p Value	95% confidence interval
Serum NT-pro-BNP	−7.08	0.27	−19.99 to 5.82
DLCO (% predicted)	10.70	0.001	4.14–17.26
FVC/DLCO	−13.00	0.01	−22.32 to −3.67
TAPSE/RVSP (mm/mmHg)	0.42	0.93	−10.54 to 11.04
Estimated RV systolic pressure (mmHg)	−6.93	0.21	−17.96 to 4.09
6-MW distance (m)	17.11	0.002	6.73−27.50
$VeVCO_2$	−18.17	<0.0001	−26.53 to −9.81
Delta $ETCO_2$ (mmHg)	14.07	0.0003	6.75–21.39
GX_{CAP} (mL × mmHg)	856	<0.0001	4.56–12.57

Abbreviations: DLCO, diffusion capacity for carbon monoxide; $ETCO_2$, end tidal carbon dioxide; FVC, forced vital capacity; GXCAP, gas exchange derived pulmonary vascular capacitance; MW, minute walk; NT-proBNP, N-terminal prohormone brain natriuretic peptide; RV, right ventricle; RVSP, right ventricle systolic pressure; TAPSE, tricuspid annular plane systolic excursion; $VeVCO_2$, ventilatory efficiency; VO_2, oxygen consumption.

TABLE 3b Multivariate model for predicting extrapolated VO_2 (% predicted) in PH-ILD patients using noninvasive diagnostic variables ($n = 44$).

Variable	ß-coefficient	p Value	95% confidence interval
DLCO (% predicted)	−2.86	0.54	−12.44 to 6.77
6-MW distance (m)	5.68	0.95	−6.73 to 18.09
$VeVCO_2$	2.16	0.75	−12.18 to 16.51
Delta $ETCO_2$ (mmHg)	8.27	0.28	−4.94 to 21.48
GX_{CAP} (mL × mmHg)	6.74	0.01	1.68–11.79

Abbreviations: DLCO, diffusion capacity for carbon monoxide; $ETCO_2$, end tidal carbon dioxide; GXCAP, gas exchange derived pulmonary vascular capacitance; MW, minute walk; $VeVCO_2$, ventilatory efficiency; VO_2, oxygen consumption.

TABLE 4a Univariate model for predicting extrapolated VO_2 (% predicted) in ILD patients only using noninvasive diagnostic variables ($n = 22$).

Variable	ß-coefficient	p Value	95% confidence interval
DLCO (% predicted)	13.39	0.01	3.69–23.09
FVC/DLCO	−6.04	0.14	−14.22 to 2.14
TAPSE/RVSP (mm/mmHg)	0.37	0.93	−9.24 to 9.99
Estimated RV systolic pressure (mmHg)	0.56	0.21	−9.22 to 2.10
6-MW distance (m)	16.30	0.002	6.41–26.19
$VeVCO_2$	−11.64	<0.0001	−17.00 to −6.29
Delta $ETCO_2$ (mmHg)	13.79	0.003	6.62–20.96
GX_{CAP} (mL × mmHg)	23.06	<0.0001	12.27–33.85
PA compliance (mL/mmHg)	9.17	0.08	−1.01 to 19.36

Abbreviations: DLCO, diffusion capacity for carbon monoxide; $ETCO_2$, end tidal carbon dioxide; FVC, forced vital capacity; GXCAP, gas exchange derived pulmonary vascular capacitance; MW, minute walk; PA, pulmonary artery; RV, right ventricle; RVSP, right ventricle systolic pressure; TAPSE, tricuspid annular plane systolic excursion; $VeVCO_2$, ventilatory efficiency; VO_2, oxygen consumption.

In the present study, the two noninvasive parameters which offered the best discrimination between PH-ILD, and non-PH ILD were GX_{CAP} and delta $ETCO_2$ (Figure 2). We previously demonstrated that GX_{CAP} correlates with PA compliance obtained during RHC.[11] The pathologic hallmark of precapillary PH implicates a pulmonary arterial vasculopathy process of the distal vasculature which in turn reduces PA compliance.[22] Hence, in precapillary PH, advanced pulmonary vascular remodeling impairs the vessels' ability to initially recruit and later distend, culminating in dynamic worsening of GX_{CAP} during exercise testing. While DLCO may identify diffusion impairment associated with pulmonary vascular remodeling, it is subject to variability due to several factors including the presence of heart failure, intrapulmonary or intracardiac shunt, or worsening parenchymal lung disease, thereby limiting its specificity within precapillary PH.[23] Furthermore, on multivariate analysis, GX_{CAP} emerged as the only predictor of extrapolated maximum VO_2 (% predicted). Maximum VO_2 has been previously shown to be an important prognostic indicator in patients with PAH.[24] Taken together, GX_{CAP} can serve as an important adjunctive diagnostic tool to help screen ILD patients for PH, while also offering a pathophysiological reasoning for the differential exertional intolerance experienced by PH-ILD and non-PH ILD.

TABLE 4b Multivariate model for predicting extrapolated VO_2 (% predicted) in ILD patients only using noninvasive diagnostic variables ($n = 22$).

Variable	β-coefficient	p Value	95% confidence interval
6-MW distance (m)	4.81	0.38	−6.48 to 16.10
Delta $ETCO_2$ (mmHg)	5.70	0.26	4.63–25.93
GX_{CAP} (mL × mmHg)	15.28	0.01	4.63–25.93

Abbreviations: $ETCO_2$, end tidal carbon dioxide; GXCAP, gas exchange derived pulmonary vascular capacitance; MW, minute walk; VO_2, oxygen consumption.

Perhaps unsurprisingly, TTE estimation of RVSP and serum NT-proBNP were greater in PH-ILD (Table 1). While TTE can provide morphological and limited systolic assessment of RV function, in the absence of either, it has limited accuracy in estimating RVSP especially in the setting of ILD and is therefore more commonly used for risk assessment rather than for PH diagnosis.[7,25] An elevated plasma NT-proBNP does not distinguish between pre- and postcapillary PH and falsely reassuring concentrations of NT-proBNP can be observed in obese patients with heart failure.[9,26–28]

Notably, on ROC analysis, while the individual variables of GX_{CAP} and delta $ETCO_2$ were highly

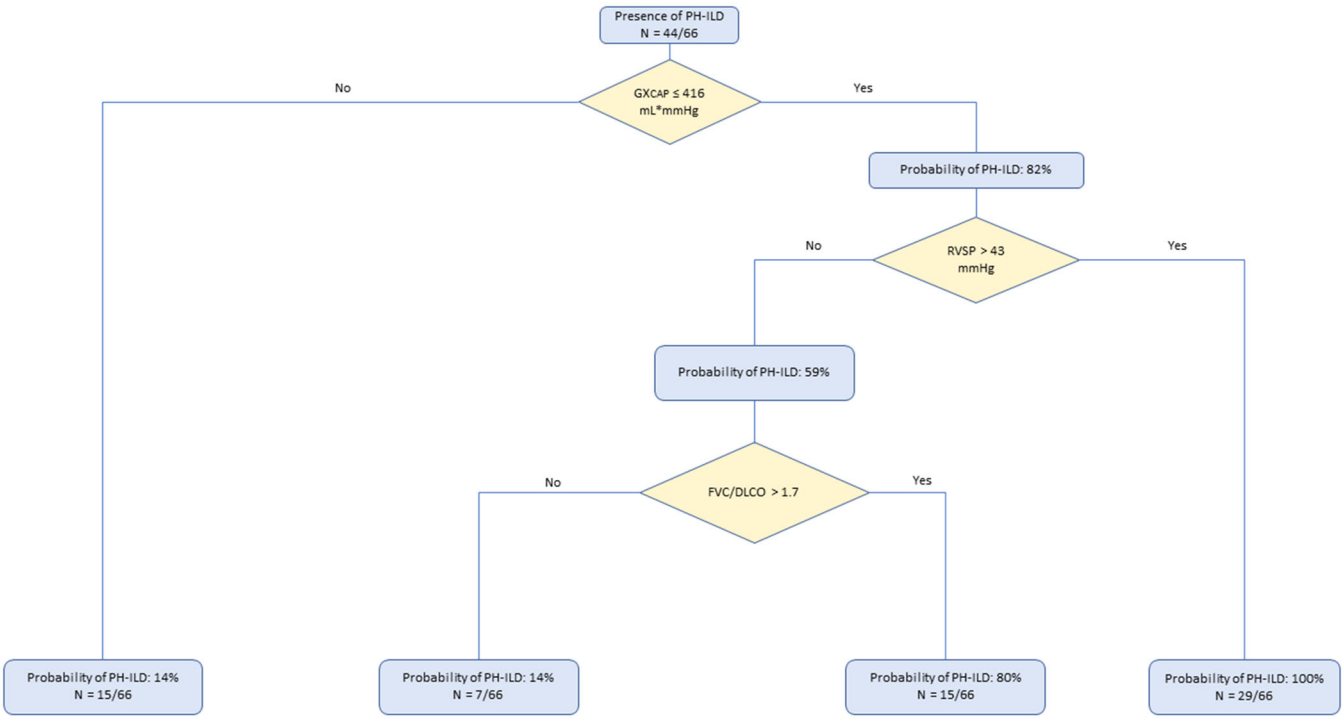

FIGURE 3 Decision tree to predict PH-ILD. DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; GX_{CAP}, gas exchange derived pulmonary vascular capacitance; ILD, interstitial lung disease; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure.

sensitive, they were not specific to help determine the presence of PH in patients with ILD. Accordingly, we performed CART analysis as this would allow the construction of a decision tree incorporating all variables together. The CART analysis selected GX_{CAP}, estimated RVSP, and FVC/DLCO ratio as the final set of predictive variables, with GX_{CAP} having the highest importance score and by itself predicting the presence of PH-ILD with a high probability. A decision tree incorporating these noninvasive variables was superior to each individual variable ROC analysis as demonstrated by an increased AUC of 0.94 (sensitivity 0.86 and specificity 0.93) (Figure 3). Importantly, this final decision tree reflects the combination of variables that are obtained from commonly performed outpatient investigative testing (i.e., submaximum CPET, echocardiogram, and PFTs).

Limitations

Study results need to be interpreted in the context of several limitations. First, only 34 subjects had data available for 6MWT, which may confound our comparison of 6MWT and submaximum CPET. However, the current data set offers a unique opportunity to compare PH-ILD and non-PH ILD. The latter group are often not subjected to the reference standard RHC because low clinical suspicion for presence of PH. In our cohort, the majority of non-PH ILD underwent invasive CPET for further investigation of unexplained dyspnea, allowing us to examine for the various noninvasive determinants of PH in our ILD patients.

Second, there was a time delay between the submaximum CPET and RHC. However, no treatment was instituted or augmented in PH-ILD or non-PH ILD patients in the interim period between their submaximum CPET and RHC. Third, while we did not directly examine how these noninvasive parameters relate to clinical outcome, maximum VO_2 has been shown to confer prognostic significance in PAH.[24] Fourth, the above testing can be used as an adjunct to help identify patients with suspected PH but should not replace the use of RHC as this remains the reference standard of diagnosis.

Lastly, eRVSP represents an important variable that constitutes our decision tree model. As mentioned above, inaccurate estimation of RVSP is common in the setting of ILD and in those with elevated body mass index[7,25] which may limit the applicability of our clinical decision tree model. Nonetheless, even without the incorporation of estimated RVSP, the clinical decision tree model consisting of GX_{CAP} alone and in combination with FVC/DLCO can predict the presence of PH in ILD with high probability (~80%).

CONCLUSION

Mortality amongst ILD patients with concomitant PH remains unacceptably high. As advances in PAH targeted therapeutics for PH-ILD become more readily available, there will be an increasing need for early identification of patients likely to benefit from earlier institution of PAH-directed therapy. In this context, we describe noninvasive diagnostic variables that can be used to discriminate between PH-ILD and non-PH ILD. We demonstrated that readily available and easily executed outpatient noninvasive investigative tests incorporating submaximum CPET derived GX_{CAP}, estimated RVSP by echo, and FVC/DLCO enables for the prediction of PH in ILD with high probability and may therefore assist in determining the need to proceed with diagnostic RHC and potential initiation of PAH targeted treatment in PH-ILD patients. In addition to its noninvasive screening property, submaximum CPET derived GX_{CAP} is also associated with reduced exercise capacity in PH-ILD and non-PH ILD groups. Future studies are needed to understand the utility of long-term submaximum CPET derived parameters in predicting response to therapy and clinical outcomes in PH-ILD.

AUTHOR CONTRIBUTIONS

Stella Savarimuthu, Phillip Joseph, Paul M. Heerdt, and Inderjit Singh contributed to conception and design of the work; interpretation of the data and writing. Inderjit Singh, Hannah T. Oakland, and Stella Savarimuthu contributed to data analysis. Hannah T. Oakland, Inderjit Singh, Marjorie Cullinan, and Phillip Joseph contributed to data acquisition. All authors approved the final version of the manuscript and are accountable for all aspects of the work. Inderjit Singh and Phillip Joseph accept the responsibility for the overall integrity of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

All authors conform to the International Standard for Authors. There are no ethical concerns.

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