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Right Heart Catheterization Accurately Diagnoses Pulmonary Hypertension in Patients With Interstitial Lung Disease: Results From a Long-Term Cohort Study

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ABSTRACT

Interstitial lung disease (ILD) can lead to pulmonary hypertension (ILD-PH), worsening prognosis and increasing mortality. Diagnosing ILD-PH is challenging due to the limitations of imaging methods. Right heart catheterization (RHC) is the gold standard for diagnosing PH but is limited to ILD patients considered for lung transplantation. This study assessed the usefulness of RHC in diagnosing ILD-PH in a large cohort of 105 patients followed for at least 72 months, examining hemodynamic parameters for survival analysis. We conducted an ambispective cohort study, diagnosing PH as mean pulmonary artery pressure ≥ 20 mmHg, pulmonary arterial wedge pressure < 15 mmHg, and pulmonary vascular resistance > 2 Wood units by RHC. We registered demographic, biochemical, echocardiographic, respiratory, and hemodynamic parameters for survival analyses. Using RHC, we found a PH prevalence of 84.7% among ILD patients who previously exhibited an intermediate-to-high probability of PH by echocardiography. Thirty-nine ILD-PH patients died, yielding a 5-year survival rate of 35%, whereas ILD patients without PH had a survival rate of 100%. Connective tissue disease-associated ILD and interstitial pneumonia with autoimmune features were the predominant ILD subtypes in ILD-PH patients. The ILD-PH group had worse pulmonary function, lower forced vital capacity, and more severe hypoxemia. Kaplan–Meier analyses showed significantly lower survival rates in ILD-PH patients with a 6-min walking distance < 360 m, tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio < 0.35 mm/mmHg, venous oxygen saturation $< 65\%$, and pulmonary artery compliance < 2.2 mm/mmHg. RHC accurately characterizes ILD-PH and provides long-term survival predictors.

1 | Introduction

Interstitial lung disease (ILD) encompasses a group of over 150 lung diseases that share common functional characteristics, such as restrictive physiology and impaired gas exchange, but exhibit a wide range of causes, clinical manifestations, and outcomes [1]. Common ILDs include idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILD (CTD-ILD), sarcoidosis, interstitial pneumonia with autoimmune features (IPAF), and chronic hypersensitivity pneumonitis [2].

María Berenice Torres-Rojas and Dulce Iliana Navarro-Vergara equally contributed to this work.

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Diagnosing ILD is often delayed and usually occurs in advanced stages [3]. A frequent and severe complication of ILD is the development of pulmonary hypertension (PH) [4]. In ILD-related PH (ILD-PH), vascular loss results from fibrosis and alveolar-septal remodeling, which injures the pulmonary capillary bed and causes intimal proliferation in the pulmonary vasculature [5]. ILD-PH leads to reduced functional capacity, increased oxygen requirements, and high mortality rates of 60%–77% at 3 years [6].

Clinical identification of ILD-PH remains challenging due to the lack of specific symptoms and limitations of detection methods such as transthoracic echocardiogram [7]. ILD-PH is often diagnosed late, upon the appearance of right heart failure, which is associated with poor prognosis, highlighting the importance of timely detection to improve patient survival [7]. Right heart catheterization (RHC) is the gold standard for diagnosing PH [8, 9]. However, RHC is indicated only in ILD patients considered for lung transplantation, which limits its use to assess PH in patients with ILD who do not meet lung transplantation criteria but are still at risk of developing severe PH [10]. Alhamad et al. [11] performed RHC in 340 patients with ILD, finding a PH prevalence of 28%, among whom more than half had severe PH. Likewise, Teramachi and collaborators performed a 1.8-year follow-up to monitor PH progression in 95 IPF patients, finding a significant increase in mean pulmonary artery pressure (mPAP) from 16.8 to 20.2 mmHg at the end of the follow-up [12]. Unfortunately, almost no studies have explored the use of RHC to assess ILD-PH in Latin America, particularly Mexico, where numerous new ILD cases are diagnosed every year with an advanced stage of the disease [13]. Thus, our primary goal was to characterize ILD-PH using RHC, examining hemodynamic parameters that may help predict survival in a large cohort of Mexican patients with a long-term follow-up for at least 72 months.

2 | Materials and Methods

2.1 | Study Design and Selection Criteria

We conducted an ambispective, observational, and analytical cohort study enrolling patients over 18 years with symptoms, imaging evidence, and transthoracic echocardiogram suggestive of ILD-PH who underwent RHC at the Pulmonary Hypertension Clinic of the General Hospital of Mexico between August 2014 and February 2024. The Institutional Review Board of the General Hospital of Mexico approved this study with registration number DIC/11/UME/05/029. The two same medical specialists with specific training in pulmonary hemodynamics performed all RHC under stable conditions if patients showed symptoms suggestive of PH, worsening pulmonary function, or deteriorating oxygenation, along with a transthoracic echocardiogram indicating an intermediate or high probability of PH. We defined PH as a mPAP ≥ 20 mmHg, pulmonary arterial wedge pressure (PAWP) < 15 mmHg, and pulmonary vascular resistance (PVR) > 2 Wood units (WU) through RHC. We excluded patients with other causes of pre-capillary PH, such as group 1, other group 3 phenotypes not caused by ILD, and Group 4, patients with post-capillary PH, recent pulmonary infection, or right-sided heart failure. After diagnosing PH, we followed patients for at least 72 months with a maximum of 10 years, excluding from statistical analyses those participants in whom we could not complete the follow-up. We followed the conventional treatment for ILD considering etiology and disease progression.

2.2 | Demographic, Functional, and Hemodynamic Data

We collected clinical data at the time of PH diagnosis, including age, sex, body mass index (BMI), smoking, comorbidities, ILD subtype, laboratory data, echocardiographic data such as tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic pressure (PASP), fractional area change (FAC), and peak tricuspid regurgitation velocity (TRV). We also registered the modified Medical Research Council (mMRC) dyspnea score and the World Health Organization (WHO) functional class. We collected pulmonary hemodynamic data through RHC. Last, we measured the diameter of the pulmonary artery trunk by chest computed tomography angiography (CT), which we defined as the widest diameter perpendicular to the longitudinal axis of the main pulmonary artery at the bifurcation level. We performed the following respiratory function tests on all enrolled patients: spirometry with bronchodilator challenge, plethysmography, and carbon monoxide (CO) diffusion, as described in the 2021 European Respiratory Society (ERS)/American Thoracic Society (ATS) technical standards [14]. We used standardized techniques to perform transthoracic Doppler echocardiography [15]. We performed the 6MWT following the ATS statement guidelines [16]. We performed RHC using a Swan-Ganz catheter, inserted percutaneously through the right or left jugular vein under ultrasound guidance. We set the external pressure transducer level to zero at the mid-thoracic line while the patient was supine. We measured the hemodynamic parameters mPAP and PAWP at the end of expiration, registering cardiac output by the thermodilution method in triplicate. We took blood samples to assess pulmonary artery oximetry [15]. We diagnosed ILD according to the international consensus of ATS, ERS, and the Latin American Thoracic Association [17]. We categorized ILD patients into two groups: patients with pre-capillary PH and patients without PH [18].

2.3 | Statistics

After assessing the normality of data by the Shapiro–Wilk test, we presented results as mean and standard deviation, median and interquartile range (IQR), absolute numbers, or percentages, as appropriate. We used the Fisher's exact test for analyzing categorical variables and the Student *t*-test or the Mann–Whitney *U*-test for numerical variables to compare data between ILD-PH patients and ILD patients without PH. We assessed survival rates between groups using Kaplan–Meier curves. We analyzed data using SPSS version 25.0 (IBM, Armonk, NY 10504, USA) and the GraphPad Prism 6.01 software (GraphPad Software, La Jolla, CA 92037, USA), considering significant differences when $p < 0.05$.

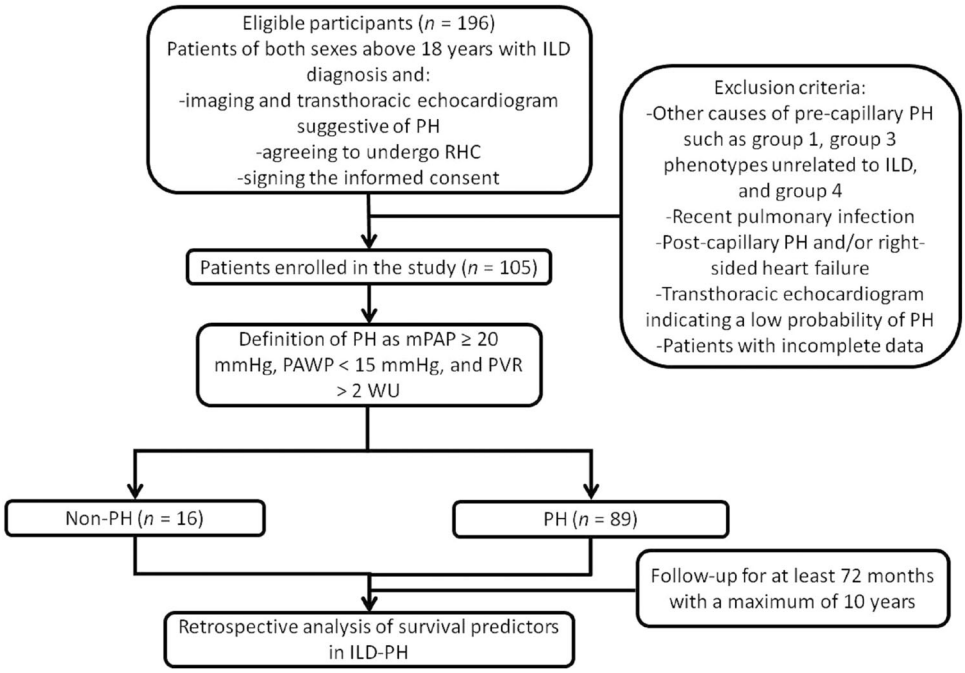

FIGURE 1 | Flowchart illustrating the selection process for the study patients. From a total of 196 eligible participants, we enrolled 105 patients meeting inclusion criteria to follow them for at least 72 months with a maximum of 10 years, performing RHC in all of them without reporting complications or adverse effects. We defined PH as an mPAP ≥ 20 mmHg, pulmonary arterial wedge pressure (PAWP) < 15 mmHg, and PVR > 2 WU through RHC. ILD, interstitial lung disease; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, Wood units.

3 | Results

Figure 1 shows the selection process for the study patients. From a total of 196 eligible participants, we enrolled 105 patients with ILD and followed them for at least 72 months with a maximum of 10 years. We performed RHC in all enrolled patients without reporting complications or adverse effects (Figure 1).

The RHC revealed that 89 patients met the criteria for pre-capillary PH, representing a prevalence of 84.7% among ILD subjects who previously had an intermediate-to-high probability of PH screened by transthoracic echocardiogram (Table 1). The mean age of ILD-PH patients was 60 ± 11.6 years with a higher prevalence of women (52.4%) ($p = 0.003$). There were no significant differences between the ILD-PH group and ILD patients without PH for mMRC dyspnea score ($p = 0.145$), BMI ($p = 0.799$), and WHO function class ($p = 0.25$). In contrast, ILD-PH patients required significantly more oxygen support therapy than patients without PH ($p = 0.004$). Thirty-nine patients within the ILD-PH group mainly died from disease progression, heart failure, and pneumonia, unlike the group of ILD patients without PH, where we did not register any deaths ($p = 0.006$). Notably, Fisher's exact test showed no significant differences when comparing the mortality rate between ILD with severe PH ($n = 17$) and ILD with non-severe PH ($n = 22$) ($p = 0.8293$), suggesting that the drug treatment given according to PH severity did not influence survival in our study population. Systemic arterial hypertension was the most prevalent comorbidity among ILD-PH patients ($p = 0.018$). Smoking was more prevalent among ILD-PH patients than in subjects without PH ($p = 0.049$). Most of laboratory parameters did not show significant differences between the ILD-PH group and ILD patients without PH except for creatinine, glomerular filtration rate (GFR), urea, uric acid, hemoglobin, hematocrit, and indirect bilirubin (Table 1).

The average follow-up of the study patients was 72 months, with a maximum of 10 years (Figure 2A). Overall, ILD-PH patients' estimated survival rates at 1, 3, and 5 years were 66%, 42%, and 35%, respectively. Conversely, the estimated 5-year survival rate was 100% in ILD patients without PH. When examining patients with ILD-PH by the underlying disease, we found higher estimated survival rates in patients with CTD-ILD, followed by those with IPF ($p = 0.001$) (Figure 2B). The ILD-PH subgroup with the statistically highest mortality percentage was IPAF ($p = 0.001$) (Figure 2B).

The main kind of ILD-PH was CTD-ILD (23.6%), followed by IPAF (21.3%), nonspecific interstitial pneumonia (NSIP) (14.6%), fibrotic hypersensitivity pneumonitis (FHP) (13.4%), IPF (8.9%), combined pulmonary fibrosis and emphysema (CPFE) (5.6%), hypersensitivity pneumonitis (HP) (4.4%), and other ILDs (Figure 3A). In ILD patients without PH, CTD-ILD was the most common ILD (75.0%), followed by NSIP (12.5%), FHP (6.2%), and IPAF (6.2%) (Figure 3B).

The partial pressure of oxygen (PaO2) and oxygen saturation of arterial blood (SaO2) reflecting hypoxemia were more severe in the ILD-PH group than in ILD patients without PH ($p < 0.001$ in both cases) (Table 2). We found a lower forced vital capacity (FVC) in the ILD-PH group than in ILD patients without

TABLE 1 | Demographic, clinical, and biochemical characteristics of the study patients.

Variable	Total $n = 105$	ILD		p value
		Non-PH $n = 16$ (15.2%)	PH $n = 89$ (84.7%)	
Age (years)	58.4 ± 12.2	54.3 ± 13.4	60.02 ± 11.6	0.082
Sex (*n*, %)				
Female	71 (67.6%)	16 (100%)	55 (61.7%)	***0.003***
Male	34 (32.4%)	0 (0%)	34 (38.2%)	
mMRC dyspnea score				
mMRC 0	4 (3.8%)	2 (12.5%)	2 (2.2%)	
mMRC 1–2	62 (59%)	10 (62.5%)	52 (58.4%)	0.145
mMRC 3–4	39 (37.1%)	4 (25%)	35 (39.3%)	
WHO FC (*n*, %)				0.125
FC I	29 (27.6%)	8 (50%)	21 (23.6%)	
FC II	42 (40%)	4 (25%)	38 (42.7%)	
FC III	27 (25.7%)	4 (25%)	23 (25.8%)	
FC IV	7 (6.7%)	0 (0%)	7 (7.9%)	
BMI (kg/m^2)	26.6 (23.8–30.5)	26.5 (24.2–30.1)	26.6 (23.5–30.5)	0.799
Oxygen therapy (*n*, %)	72 (71.3%)	6 (5.9%)	66 (65.3%)	***0.004***
Deaths, *n* (%)	39 (37.1%)	0 (0%)	39 (43.8%)	***0.006***
Comorbidities				
Diabetes (*n*, %)	21 (20%)	2 (1.9%)	19 (18.1%)	0.415
SAH (*n*, %)	41 (39%)	2 (1.9%)	39 (37.1%)	***0.018***
Hypothyroidism (*n*, %)	14 (13.3%)	3 (2.9%)	11 (10.5%)	0.489
Smoking index (*n*, %)	4.9 (0.75–25)	0.9 (0.2–1.7)	5.7 (1.3–25)	***0.049***
Laboratory parameters				
Creatinine (mg/dL)	0.76 (0.63–0.92)	0.63 (0.60–0.73)	0.78 (0.66–0.99)	***0.004***
GFR (mL/min/1.73 m^2)	94 (82–104)	105.5 (90.2–113.7)	92 (81–101.7)	***0.011***
Urea (mg/dL)	30.1 (22.7–38.0)	23.3 (19.6–32.9)	32 (23.7–39.6)	***0.027***
Uric acid (mg/dL)	5.4 (4.5–6.8)	4.1 (3.8–5.4)	5.8 (4.9–7.3)	***0.001***
LDH (U/L)	219 (183–264)	199 (173–263)	219 (184–270)	0.265
BNP (pg/mL)	37.6 (14.5–109.5)	37.4 (12.7–53.3)	37.6 (14.5–121.7)	*0.362*
Neutrophils (×10^3/mL)	5.7 ± 2.5	5.2 ± 2.7	6.1 ± 2.5	0.208
Lymphocytes (×10^3/mL)	1.9 (1.3–2.6)	1.5 (0.9–2.3)	1.9 (1.3–2.6)	0.065
N/L index (×10^3/mL)	2.9 (1.7–4.5)	3.2 (2.3–4.8)	2.8 (1.7–4.5)	0.619
Hemoglobin (g/dL)	15.2 ± 2.4	13.2 ± 1.3	15.8 ± 2.4	***< 0.001***
Hematocrit (%)	46.3 ± 7.76	39.9 ± 4.2	48.4 ± 7.5	***< 0.001***
Indirect bilirubin (mg/dL)	0.48 (0.36–0.66)	0.35 (0.29–0.52)	0.50 (0.38–0.76)	***0.009***

Note: We used the Chi-square test for analyzing categorical variables and the Student *t*-test or the Mann–Whitney *U*-test for numerical variables to compare data between ILD-PH patients and ILD patients without PH, using SPSS version 25.0 and GraphPad Prism 6.01 software. We considered significant differences when $p < 0.05$, using bold to highlight.

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; GFR, glomerular filtration rate; ILD, interstitial lung disease; LDH, lactate dehydrogenase; mMRC, modified Medical Research Council dyspnea score; N-L, neutrophil-to-lymphocyte ratio; PH, pulmonary hypertension; SAH, systemic arterial hypertension; WHO FC, World Health Organization functional class.

PH ($p = 0.028$). We measured the diffusing capacity of the lung for carbon monoxide (DLCO) in ILD-PH patients, finding a significant reduction compared to ILD patients without PH ($p = 0.031$). The distance covered in the 6MWD tended to be shorter in the ILD-PH group, although we found no significant differences concerning ILD patients without PH ($p = 0.058$). Conversely, the Nadir oxygen saturation was significantly lower in the ILD-PH group than in ILD patients without

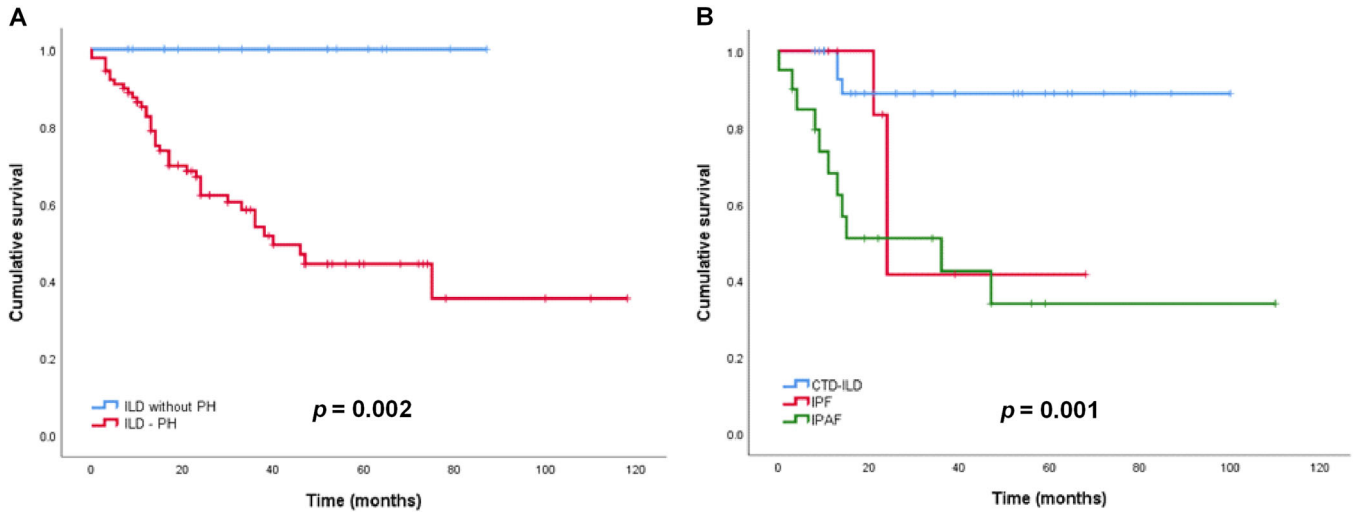

FIGURE 2 | Kaplan–Meier curves for estimated survival rate in the study population. The ILD-PH group exhibited a significantly lower survival rate than ILD patients without PH (A). In ILD-PH patients, CTD-associated ILD showed the highest estimated survival rate, followed by IPF and IPAF (B). We performed survival analyses for up to 10 years using the Kaplan–Meier method with the SPSS version 25.0 and the GraphPad Prism 6.01 software, considering significant differences when $p < 0.05$. CTD-associated ILD, connective tissue disease-associated ILD; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; PH, pulmonary hypertension.

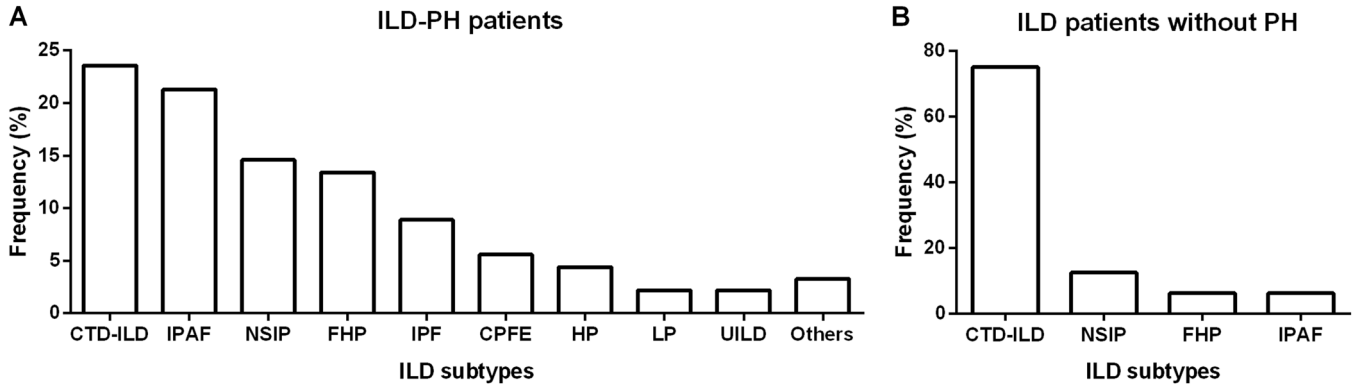

FIGURE 3 | Frequency histograms illustrating the most common ILD subtypes in patients with and without PH. In the ILD-PH group, CTD-ILD was the most frequent ILD (23.6%), followed by IPAF (21.3%), NSIP (14.6%), FHP (13.4%), IPF (8.9%), CPFE (5.6%), HP (4.4%), LP (2.2%), unclassified ILD (2.2%), and other ILD subtypes including post-coronavirus disease-2019 ILD (1.1%), pulmonary alveolar microlithiasis (1.1%), and Hermansky-Pudlak syndrome (1.1%) (A). In ILD patients without PH, CTD-ILD was the most commonly found ILD (75.0%), followed by NSIP (12.5%), FHP (6.2%), and IPAF (6.2%) (B). We performed frequency histograms using the GraphPad Prism 6.01 software. CPFE, combined pulmonary fibrosis and emphysema; CTD-associated ILD, connective tissue disease-associated ILD; FHP, fibrotic hypersensitivity pneumonitis; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; LP; lymphoid pneumonia; NSIP, nonspecific interstitial pneumonia; PH, pulmonary hypertension; UILD, unclassified ILD.

PH ($p = 0.008$). Tomographic data revealed a larger main pulmonary artery diameter (MPAD) and pulmonary artery/aorta (PA/Ao) ratio in the ILD-PH group than in ILD patients without PH ($p = 0.001$ and $p = 0.013$, respectively). Echocardiographic findings showed significant increases in tricuspid regurgitation velocity (TRV) and right ventricular dysfunction with poor ventricular-arterial coupling in ILD-PH patients compared to ILD subjects without PH ($p = 0.013$ and $p < 0.001$, respectively). On the contrary, fractional area change (FAC) exhibited a significant decrease in the ILD-PH group compared to ILD patients without PH ($p = 0.041$). Hemodynamic variables revealed that systolic right ventricular pressure (sRVP) and mPAP significantly increased in the ILD-PH group compared to ILD patients without PH ($p < 0.001$ in both cases). Likewise, PVR and systemic vascular resistance (SVR) exhibited significant increments in the ILD-PH group compared to patients without PH ($p < 0.001$ and $p = 0.026$, respectively). Conversely, the ILD-PH group showed significant decreases in venous oxygen saturation (SvO2) and pulmonary artery compliance (PAC) compared to that found in ILD patients without PH ($p = 0.001$ and $p < 0.001$, respectively) (Table 2).

Figure 4 illustrates variables with the most promissory function in predicting survival in the cohort of ILD patients with and without PH. After performing the long-term follow-up, our findings indicated that a 6MWD < 360 m, tricuspid annular

TABLE 2 | Pulmonary function, tomographic, echocardiographic, and hemodynamic characteristics of ILD patients with and without PH.

Variable	ILD		*p* value
	Non-PH *n* = 16	PH *n* = 89	
Pulmonary function parameters			
PaO2 (mmHg)	67.9 ± 12.8	54.0 ± 15.3	***< 0.001***
SaO2 (%)	94 (91.4–95.9)	87.5 (83.3–91.2)	***< 0.001***
FVC (%)	74.7 ± 25.1	60.5 ± 22.9	***0.028***
FEV1 (%)	76.6 ± 25.6	65.3 ± 22.3	0.075
DLCO (%)	62.9 ± 20.2	45.4 ± 25.4	***0.031***
FVC/DLCO (%)	1.18 (0.99–1.66)	1.45 (0.98–2.3)	0.255
6MWD (m)	431.5 (338–489)	365 (233–423)	0.058
Nadir SaO_2 (%)	82.4 ± 9.3	75.6 ± 9.1	***0.008***
Tomographic parameters			
MPAD (mm)	29.8 ± 4.3	34.2 ± 4.6	***0.001***
PA/Ao Ratio (mm)	1.01 ± 0.11	1.11 ± 0.14	***0.013***
Echocardiographic parameters			
TRV (m/s)	2.6 ± 0.6	3.2 ± 0.8	***0.013***
TAPSE (mm)	20.5 (19–24.7)	19.5 (17–22)	0.154
PASP (mmHg)	38.3 ± 16.6	55.8 ± 17.3	***< 0.001***
TAPSE/PASP (mm/mmHg)	0.58 (0.46–0.89)	0.34 (0.27–0.46)	***< 0.001***
FAC (%)	41.2 ± 7.4	35.8 ± 9.1	***0.041***
Hemodynamic variables			
HR (bpm)	78.1 ± 12.9	84.7 ± 14.8	0.082
RAP (mmHg)	3.5 (2.0–4.0)	3.0 (2.0–5.0)	0.767
sRVP (mmHg)	28 (24.5–31)	47 (40–61)	***< 0.001***
dRVP (mmHg)	3 (2–5)	4 (3–6)	0.292
mPAP (mmHg)	17 (16–18.7)	28 (24–39)	***< 0.001***
PAWP (mmHg)	3 (2–8)	5 (3-8)	0.112
CO (L/min)	5.5 (4.5–6.5)	5.1 (4.0–6.4)	0.301
CI ($L/min/m^2$)	3.4 (2.9–3.8)	3.1 (2.5–3.9)	0.191
SVI (mL/m^2)	47.0 ± 11.3	40.3 ± 13.7	0.069
PVR (WU)	2.3 (1.4–2.9)	4.5 (3.5–7.0)	***< 0.001***
SVR (WU)	15.7 (13.8–19.3)	19.4 (15.5–24.0)	***0.026***
SvO2 (%)	73.3 ± 6.3	65.4 ± 11.3	***0.001***
PAC (mL/mmHg)	3.3 (2.7–4.1)	1.9 (1.2–2.8)	***< 0.001***

Note: We used the Chi-square test for analyzing categorical variables and the Student *t*-test or the Mann–Whitney *U*-test for numerical variables to compare data between ILD-PH patients and ILD patients without PH, using SPSS version 25.0 and GraphPad Prism 6.01 software. We considered significant differences when $p < 0.05$, using bold to highlight.

Abbreviations: CI, cardiac index; CO, cardiac output; DLCO, diffusing capacity for carbon monoxide; FAC, fractional area change; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HR, heart rate; ILD, interstitial lung disease; MPAD, main pulmonary artery diameter; mPAP, mean pulmonary arterial pressure; 6MWD, 6-min walking distance; PA/Ao, pulmonary artery/aorta; PAC, pulmonary artery compliance; PaO2, partial pressure of oxygen; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO2, oxygen saturation of arterial blood; sRVP, systolic right ventricular pressure; SVI, systolic volume index; SvO2, venous oxygen saturation; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity.

plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio < 0.35 mm/mmHg, SvO2 < 65%, and PAC < 2.2 mm/mmHg accurately predicts survival in ILD-PH patients at 10 years (Figure 4A–D, respectively).

4 | Discussion

Different subtypes of ILD have a risk of developing PH, with prevalence ranging between 14% and 73% [19]. Herein, we

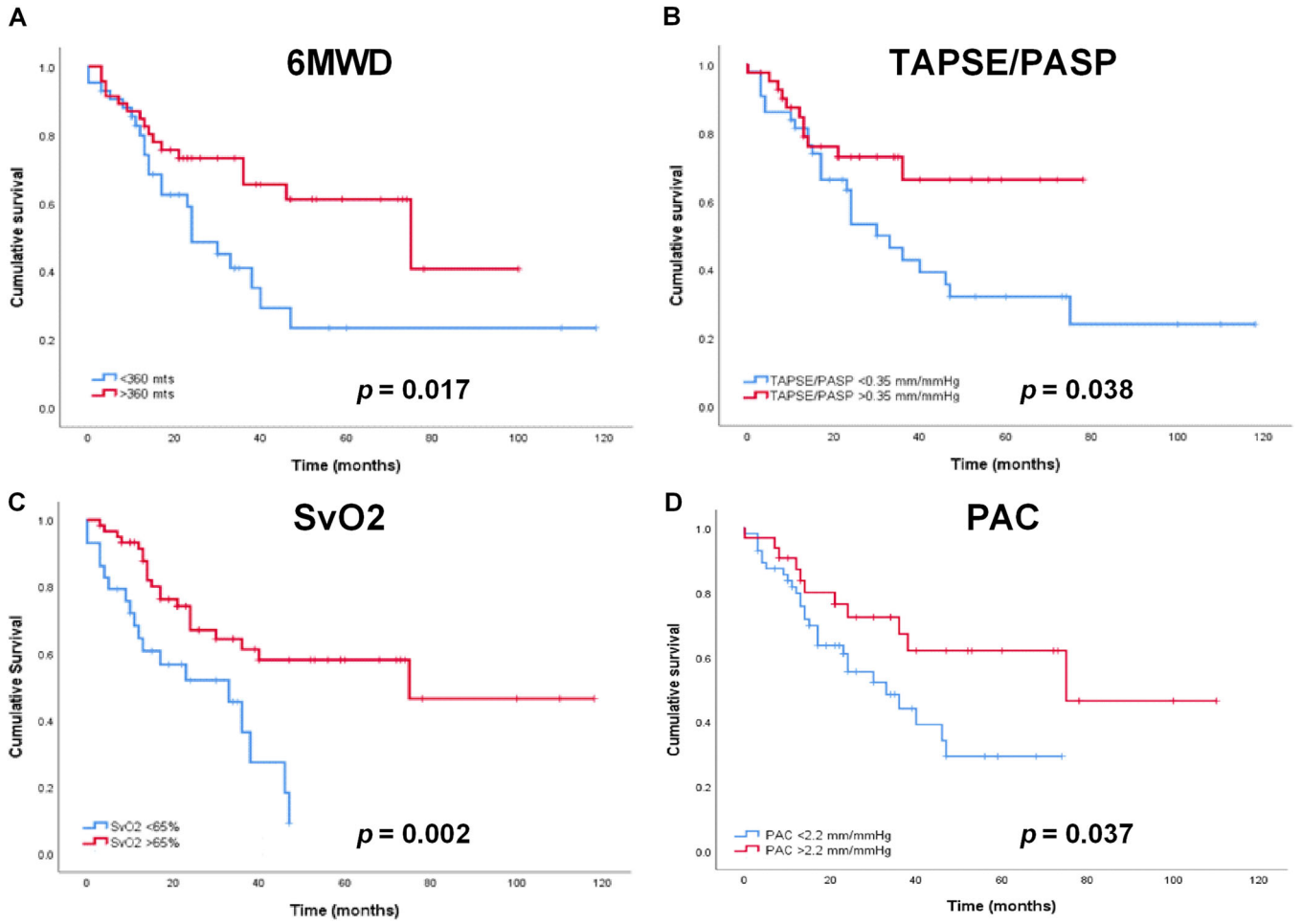

FIGURE 4 | Pulmonary function, echocardiographic, and hemodynamic parameters for estimated survival rates in ILD-PH patients. A 6MWD < 360 m denotes a significantly lower survival rate in ILD-PH patients (A). A TAPSE/PASP ratio < 0.35 mm/mmHg characterizes a significantly lower survival rate in ILD-PH patients (B). A SvO2 < 65% represents a significantly lower survival rate in ILD-PH patients (C). A PAC < 2.2 mm/mmHg denotes a significantly lower survival rate in ILD-PH patients (D). We performed survival analyses for up to 10 years using the Kaplan–Meier method with the SPSS version 25.0 and the GraphPad Prism 6.01 software, considering significant differences when $p < 0.05$. ILD, interstitial lung disease; 6MWD, 6-min walking distance; PAC, pulmonary artery compliance; PASP, tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio; PH, pulmonary hypertension; TAPSE/SvO2, venous oxygen saturation.

report a PH prevalence of 84.7% in ILD patients who previously exhibited an intermediate-to-high probability of PH evidenced by transthoracic echocardiogram, with nearly 35% showing severe PH (> 5 WU) and significantly reduced survival rates as previously reported [10, 19, 20]. Thus, we cannot extrapolate the PH prevalence that we found in our study population to all ILD patients before conducting a study performing RHC on patients with both low and intermediate-to-high probability of PH by echocardiography.

The prevalence of PH in ILD varies widely across studies, depending on the population studied, the clinical criteria used, and diagnostic methods. A study reported a prevalence of up to 86%, though this estimate varies among different types of ILD [21]. Most studies have focused on describing PH prevalence in patients with IPF, the most diagnosed ILD. In this way, the prevalence of PH in IPF patients ranges from 8% to 15% in early stages to over 60% in advanced disease [10, 20]. One key finding of our study is the high prevalence of PH we found by RHC. Previous studies have attributed the wide prevalence ranges to variations in echocardiographic parameters used to diagnose PH [22, 23]. In contrast to works reporting IPF as the leading cause associated with PH [19, 24], our study shows that CTD-ILD is the most common ILD subgroup, whereas IPF is the fifth PH cause. These data support using RHC to explore PH in ILD patients for the first time, opening a potentially alternative method to ILD-PH diagnosis different from the mere echocardiographic assessment.

Despite its limitations, echocardiogram remains the most essential tool for PH screening [18]. The 2022 ESC/ERS guidelines recommended measuring TRV and assessing other echocardiographic parameters to estimate PH [18]. The diagnostic accuracy of the echocardiogram to measure pulmonary artery systolic pressure (PASP) in ILD is poorly sensitive and should be used as a mere screening tool [18]. Furthermore, TRV is an operator-dependent variable, and heart position alteration, RV dilation, and interstitial lung damage can influence the tricuspid regurgitant flow velocity, leading to misinterpretation [25]. Arcasoy et al. reported only a moderate correlation

between PASP measured by echocardiogram or RHC in chronic lung diseases [26]. More recently, Keir et al. [27] evaluated the screening echocardiogram's utility in 265 ILD patients, finding that the TRV threshold recommended by ESC/ERS in 2015 has an accurate positive predictive value of 86% for PH detection. Surprisingly, this study revealed that 40% of patients with PH confirmed by RHC were incorrectly categorized as low probably PH with TRV < 2.8 m/s when using the transthoracic echocardiogram [27]. In our study, RHC demonstrated that echocardiography had inaccurately classified 15% of the cohort patients as intermediate-to-high probability of PH.

Adapting RV function to increased afterload (RV-arterial coupling) is critical in PH prognosis [28]. Non-invasive methods that allow the assessment of RV function, such as echocardiogram and magnetic resonance imaging, are valuable and safe because they do not involve radiation, enabling monitoring of the pulmonary function's evolution across time in the same patient. Although widely used in clinical practice due to their greater availability and lower cost, especially echocardiogram, non-invasive methods only offer an indirect measure of RV contractility because of their dependence on afterload. Our findings show that patients with ILD-PH have lower RV function, indicating poor RV adaptation to increased afterload [29]. Low RV-arterial coupling, denoted by a TAPSE/PSAP < 0.35 mm/mmHg, was a determinant of poor prognosis in patients who died from ILD-PH. Here, we report for the first time that RV-arterial coupling can be a prognostic parameter of survival in ILD-PH. Other studies have previously documented that RV-arterial coupling also has a predictive value in chronic thromboembolic pulmonary hypertension (CTEPH) [28, 30].

PAC measures arterial distensibility and provides information about the pulsatile load on the RV. PAC and PVR have an inverse hyperbolic relationship, and in the early stages of the disease, PAC can decrease even when PVR shows minimal changes. Therefore, PAC has gained increasing attention as a useful hemodynamic marker in PH because of its utility in predicting relevant clinical outcomes [31]. PAC provides information about the distensibility of the total pulmonary circulation, pulsatile load, and RV function [32]. Our results show that patients with ILD-PH have low PAC values < 2.2 mL/mmHg with relevant prognostic implications. Recently, Wang and colleagues explored the clinical relevance of PAC in a large number of patients undergoing RHC who had mild PH (mPAP 19–24 mmHg) [33]. They observed that PAC ≥ 3 mL/mmHg had a strong relationship with survival in all PH patients exhibiting mPAP ≥ 20 mmHg. Similarly, PAC ≥ 3 mL/mmHg was protective in subjects with PVR ≥ 2.2 WU and individuals with normal PVR < 2.2 WU. The authors even questioned whether PAC should be incorporated into the hemodynamic definitions of PH. Other hemodynamic and gas exchange parameters with a promissory role in ILD-PH were sRVP, mPAP, PVR, SvO2, PAC, PaO2, and SaO2. Our findings align with previous studies showing that cardiac complications linked to right ventricular dysfunction are an essential survival marker in ILD-PH, especially poor ventricular-arterial coupling. Indeed, the International Society for Heart and Lung Transplantation guidelines recommend including IPF patients with PH as lung transplant candidates [34], a notion supported by our findings.

PH associated with CTD is a well-recognized complication classified in group 1 of PH, even though it can have several causes, particularly systemic sclerosis [35]. The patient group with the highest prevalence of ILD-PH was that showing CTD, with systemic sclerosis as the most frequent condition. Based on respiratory function tests, imaging studies, and RHC information, we can speculate that ILD was the leading cause of PH. IPAF accounts for 20%–30% of ILD patients [36]. According to echocardiographic parameters, the PH prevalence in IPAF patients is 10.7% [37]. Although numerous reports have documented IPF as the most common cause of PH among ILDs, we found it was only the fifth most common cause in our group of patients. These data suggest we should examine causal entities of PH, such as IPAF or IPF, in a population-specific way, incorporating echocardiographic parameters with RHC evidence for better ILD recognition.

This study has several strengths and limitations. Strengths include the characterization of a large, consecutive cohort of ILD patients with and without PH confirmed by RHC, followed for at least 72 months with a maximum of 10 years. The same two medical specialists trained in lung hemodynamics performed RHC within 14–21 days after establishing the ILD diagnosis. The study's limitations include enrolling patients from a single center, which makes us proceed with caution regarding extrapolating our findings to other patients with ILD-PH from different countries. In this sense, the low percentage of IPF we observed among ILD patients may be linked to the fact that we enrolled patients from a single center. Conducting a multicenter study might help us describe more precisely the most frequent forms of ILD in Mexican patients. Furthermore, we performed RHC only in patients previously screened for an intermediate-to-high probability of PH by transthoracic echocardiogram, which does not allow us to extrapolate the PH prevalence we found in our study subjects to all patients living with ILD.

5 | Conclusion

This work describes for the first time the characterization of ILD-PH by RHC in a large cohort of Mexican patients to identify hemodynamic parameters predicting survival after performing a follow-up for at least 72 months and up to 10 years. RHC allowed us to estimate a PH prevalence of 84.7% among ILD patients with an intermediate-to-high probability of PH by transthoracic echocardiogram. The overall survival of patients with ILD was significantly lower in those developing PH than in patients without PH. However, our study design does not allow us to attribute directly the deaths observed in the ILD-PH group to PH, even after confirming statistically that the presence of PH significantly increased the mortality in the ILD-PH group compared to ILD patients without PH.

Pulmonary function parameters such as FVC and DLCO and hemodynamic variables, including sRVP, mPAP, PVR, and SvO2, were the most important independent factors for adverse outcomes in patients with ILD-PH. These findings support the use of RHC to detect and monitor PH in ILD patients, thus providing an opportune treatment for patients with ILD-PH, particularly those with severe PH. We want to encourage other

colleagues to discuss the potential use of RHC for screening PH in ILD patients, which may offer additional information to Doppler echocardiography. To the best of our knowledge, this is the first report on Mexican patients with ILD describing the prevalence of PH through standardized RHC and estimating survival rates after conducting a long-term follow-up for at least 72 months and up to 10 years.

Author Contributions

María Berenice Torres-Rojas enrolled patients, acquired clinical data, analyzed data, drafted the work, and approved the last version of the manuscript. Dulce Iliana Navarro-Vergara enrolled patients, acquired clinical data, analyzed data, drafted the work, and approved the last version of the manuscript. Marisol García-Cesar analyzed data, drafted the work, and approved the last version of the manuscript. Gustavo Acosta-Altamirano analyzed data and approved the last version of the manuscript. Leslie Marisol González-Hermosillo enrolled patients, analyzed data, drafted the work, and approved the last version of the manuscript. Galileo Escobedo designed the study, analyzed data, drafted the work, and approved the last version of the manuscript. Guillermo Cueto-Robledo conceived the study, enrolled patients, acquired clinical data, analyzed data, and approved the last version of the manuscript.

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Ethics Statement

The Institutional Review Board of the General Hospital of Mexico "Dr. Eduardo Liceaga" that includes the Ethics Committee, the Research Committee, and the Biosafety Committee, approved the study with registration number DIC/11/UME/05/029.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available upon request.

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