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Revised Precapillary Pulmonary Hypertension Criteria and Their Prognostic Value in IPF Transplant Waitlist Survival

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a leading indication for lung transplantation. Pulmonary hypertension (PH), a common comorbidity in IPF, has gained renewed attention following the updated ESC/ERS guidelines, which redefine diagnostic thresholds for PH. This study evaluates the impact of the revised PH criteria on transplant waitlist outcomes among IPF patients. Specifically, we assessed the prevalence of PH under the new guidelines and its association with waitlist survival. We conducted a retrospective analysis using the OPTN/SRTR database, including 14,156 IPF candidates listed for lung transplantation. Survival analyses were performed using Kaplan–Meier and multivariate models to examine the influence of revised mPAP and PVR thresholds on waitlist mortality. The prevalence of PH, defined by the revised criteria, was significantly higher compared to the prior definition. Kaplan–Meier analysis demonstrated worse waitlist survival for patients with PH under both diagnostic thresholds. However, multivariate analysis revealed that mPAP and PVR thresholds were not independently predictive of mortality. Instead, clinical parameters, including 6MWD, functional status, BMI, FVC, PaCO2, and double lung transplant preference, were significant predictors of waitlist mortality. In conclusion, while the revised PH diagnostic criteria increase PH prevalence in IPF patients, their independent prognostic utility for waitlist survival is limited. This national transplant database study underscores the importance of comprehensive clinical evaluation and timely referral for transplantation in managing IPF with PH.

1 | Introduction

Idiopathic pulmonary fibrosis (IPF) is a form of chronic, progressive fibrosing interstitial pneumonia with an unknown etiology [1, 2]. IPF is associated with a histopathologic and/or radiographic pattern of usual interstitial pneumonia, and the prognosis is grim, with a mean survival of about 2.5–5 years post-diagnosis [2, 3]. Despite recent therapeutic advancements, IPF remains the leading cause of lung transplantation [4, 5]. According to the 2021 annual report from the Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR), individuals with

Abbreviations: 6MWD, 6-min walk distance; BMI, Body mass index; CO, Cardiac output; ESC, European Society of Cardiology; ERS, European Respiratory Society; FVC, Functional vital capacity; HR, Hazard ratio; ILD, Interstitial lung disease; IPF, Idiopathic pulmonary fibrosis; mPAP, Mean pulmonary artery pressure; OPTN, Organ Procurement and Transplantation Network; PAWP, Pulmonary artery wedge pressure; PH, Pulmonary hypertension; PVR, Pulmonary vascular resistance; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing; US, United States; WU, Wood units.

restrictive lung disease constituted the highest proportion undergoing lung transplants, ranging from 129.5 to 150.3 transplants per 100 patient-years, with IPF emerging as the predominant condition among restrictive lung diseases [6].

Pulmonary hypertension (PH) is acknowledged as a significant comorbidity in the IPF population, with retrospective studies reporting a prevalence ranging from 14% to 84% [7–12]. Studies suggest that the coexistence of PH with IPF is not benign, correlating with increased mortality, even in cases of mild PH [7, 10, 12]. In 2022, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) updated the definition of PH. It is now characterized by a mean pulmonary artery pressure (mPAP) > 20 mmHg at rest, while precapillary PH is defined by a pulmonary vascular resistance (PVR) > 2 Wood units (WU) and a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg [13]. These updated guidelines would significantly increase the number of patients meeting the diagnostic criteria for PH with IPF. However, the clinical significance of these updated PH thresholds with regard to transplant waitlist mortality of IPF patients is uncertain. The objective of our study is to determine the prevalence of PH among IPF patients listed for lung transplant and to assess the impact of the more inclusive PH criteria on lung transplant waitlist mortality compared to a previous, more stringent definition among patients with IPF listed for lung transplant.

We hypothesize that the more inclusive definition of precapillary PH under the new ESC/ERS criteria will continue to predict waitlist mortality among IPF patients compared to those who do not have PH.

2 | Methods

Participants: This retrospective review encompasses consecutive lung transplant candidates drawn from the SRTR national database, spanning the period from May 2005 to November 2022, after the implementation of the Lung Allocation Score (LAS). Data was directly collected by the OPTN under the supervision of the United Network for Organ Sharing (UNOS). The analysis was limited to adult lung transplant candidates, aged 18 and above, diagnosed with IPF and listed for lung transplant, with no history of prior transplantation. The diagnostic code 1604: LU:IIP: IDIOPATHIC PULMONARY FIBROSIS (IPF) was used to identify eligible patients. Individuals listed for heart-lung transplantation were excluded from the study.

Data collection: Candidate baseline characteristics, such as age, sex, race, body mass index (BMI), and comorbidities, were collected. Additionally, clinical data essential for determining organ allocation were obtained, encompassing age, blood type, BMI, functional vital capacity (FVC), partial pressure of arterial carbon dioxide (PaCO2), creatinine, 6-min walk distance (6MWD), mPAP, oxygen requirement, single versus double lung transplant preference and functional status at the time of listing. Precapillary PH was categorized into the following groups: no PH (mPAP < 20 mmHg and PVR < 2 WU), precapillary PH based on the new criteria (mPAP 20–25 mmHg and PVR 2–3 WU), and precapillary PH based on the old criteria (mPAP > 25 mmHg and PVR > 3WU).

The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the US Government. This study used data from the SRTR. The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the OPTN. The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The proposed study was approved by the SRTR.

Statistical analysis: Statistical analysis was performed comparing patients with IPF without PH and IPF with PH. All continuous variables were presented as mean ± SD or median (IQR) unless otherwise stated. Kaplan–Meier survival curves were used to compare survival probabilities among IPF patients based on combined mPAP and PVR criteria: mPAP < 20 mmHg and PVR < 2 WU, mPAP 20–25 mmHg and PVR 2–3 WU, and mPAP > 25 mmHg and PVR > 3 WU. Log-rank tests were employed to assess differences in survival between these groups. Patients who underwent lung transplantation were censored at the time of transplant. Cox regression analysis was performed to evaluate the risk of waitlist mortality associated with different mPAP and PVR groupings, using mPAP < 20 mmHg and PVR < 2 WU as the reference group. Univariate analyses assessed associations between various clinical variables and waitlist mortality. Multivariable analysis was conducted to control for these variables and identify independent and significant predictors of transplant waitlist mortality. Statistical analyses were performed using IBM SPSS Statistics, Version 25. A p-value of < 0.05 was considered statistically significant.

3 | Results

Between May 2005 and November 2022, a total of 14,156 patients with IPF were listed as candidates for lung transplantation, with 13,291 patients having sufficient data for analysis (Figure 1). One thousand eight hundred and six patients had mPAP < 20 mmHg and PVR < 2 WU (group 1), 1972 patients had PH based on the new criteria with mPAP 20–25 mmHg and PVR 2–3 WU (group 2), and 9513 patients had PH based on the older criteria with mPAP ≥ 25 mmHg and PVR ≥ 3 WU (group 3). The baseline demographic and clinical characteristics of this population are detailed in Table 1.

Kaplan–Meier analysis was performed to compare survival probability between the three groups based on mPAP and PVR and revealed a significant difference in survival probability between the three groups (log-rank $p < 0.001$) (Figure 2). Both groups of patients with PH appear to have significantly worse waitlist survival probability than those without PH. Cox regression analysis was performed to compare the risk of waitlist mortality between groups, with group 1 (mPAP < 20 mmHg and PVR < 2 WU) as the reference. The analysis demonstrated that both other mPAP and PVR groupings had a significantly increased risk of waitlist mortality. Specifically, Group 2 (mPAP 20–25 mmHg and PVR 2–3 WU) had a hazard

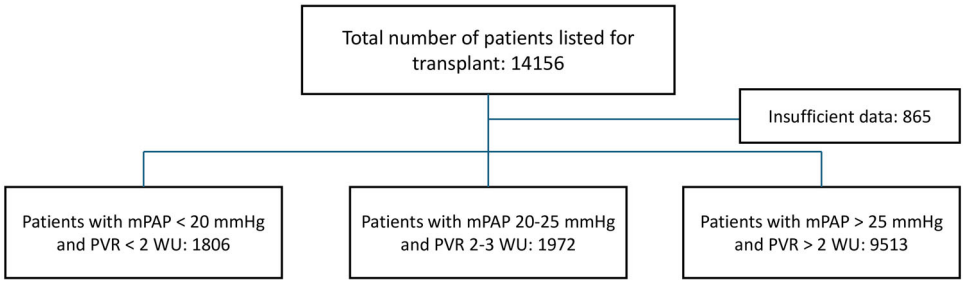

FIGURE 1 | Patient distribution across different PH cohorts.

TABLE 1 | Patient characteristics.

Characteristic		mPAP < 20 mmHg and PVR < 2 WU (1806)	mPAP 20–25 mmHg and PVR 2–3 WU (1972)	mPAP > 25 mmHg and PVR > 2 WU (9513)
Age, years		62.62 ± 8.07	62.95 ± 7.78	62.04 ± 8.39
Female, *n* (%)		460 (25.45)	480 (24.35)	2668 (28.04)
Race, *n* (%)	White	1496 (82.8)	1639 (83.11)	7466 (78.48)
	Black	59 (3.2)	84 (4.25)	662 (6.95)
	Asian	47 (2.6)	52 (2.63)	277 (2.91)
	Hispanic	192 (10.6)	182 (9.22)	943 (9.91)
Blood Type, *n* (%)	A	679 (37.5)	781 (39.6)	3639 (38.2)
	B	198 (10.9)	218 (11)	1085 (11.4)
	AB	89 (4.9)	85 (4.3)	364 (3.8)
	O	840 (46.5)	888 (45)	4405 (46.3)
Height, cm		171.8 ± 17.67	172.4 ± 11.24	170.53 ± 21.13
BMI, Kg/m^2		26.28 ± 3.02	27.82 ± 5.67	27.68 ± 6.07
FVC, % pred		50.39 ± 16.34	50.71 ± 16.94	53.09 ± 18.80
FEV1, % pred		53.70 ± 15.69	54.18 ± 16.47	55.05 ± 17.63
6 min walk, ft		931.40 ± 649.51	847.63 ± 520.32	749.63 ± 579.50
Resting Oxygen, L/min		5.55 ± 8.42	6.27 ± 10.55	7.91 ± 12.49
PaCO2, mmHg		42.52 ± 7.69	44.55 ± 9.97	49.35 ± 16.87
PA systolic, mmHg		32.60 ± 6.13	37.96 ± 4.14	63.03 ± 17.61
PA mean, mmHg		16.83 ± 3.06	22.64 ± 1.27	43.99 ± 17.74
PCW, mmHg		9.99 ± 6.93	8.66 ± 2.55	9.87 ± 5.79
PVR, WU		1.11 ± 1.32	2.49 ± 0.27	6.99 ± 3.79
CO, L/min		6.08 ± 1.52	5.65 ± 0.99	5.19 ± 1.29
Creatinine, mg/dL		0.93 ± 0.24	0.79 ± 0.20	0.85 ± 0.37
Double lung preference		72 (3.9)	74 (3.7)	7641 (80.3)

ratio (HR) of 5.81 (95% CI: 1.26–26.7, $p < 0.001$). Similarly, Group 3 (mPAP > 25 mmHg and PVR > 3 WU) showed an HR of 2.71 (95% CI: 1.22–6.00, $p < 0.001$).

Univariate Cox proportional hazard regression was conducted to examine the association between various predictors and waitlist mortality. The analysis revealed that as FVC increased, the risk of waitlist mortality was significantly reduced (HR 0.98, 95% CI 0.97–0.99, $p < 0.001$). Similarly, greater 6MWD was associated with a decreased risk of waitlist mortality (HR 0.98, 95% CI 0.97–0.99, $p < 0.001$). In contrast, higher oxygen requirements (HR 1.01, 95% CI 1.004–1.02, $p = 0.001$) and pulmonary artery systolic pressure (HR 1.007, 95% CI 1.004–1.01, $p < 0.001$) were associated with an increased risk of waitlist mortality (Table 2).

Multivariable analysis was conducted using all available variables included in the LAS (now Composite Allocation Score) model to identify independent predictors of waitlist mortality. Notably, Group 2 (mPAP 20–25 mmHg and PVR 2–3 WU, HR 4.44, 95% CI 0.57–9.92, $p = 0.75$, and Group 3 (mPAP ≥ 25 mmHg and PVR ≥ 3 WU, HR 7.64, 95% CI 0.49–9.87,

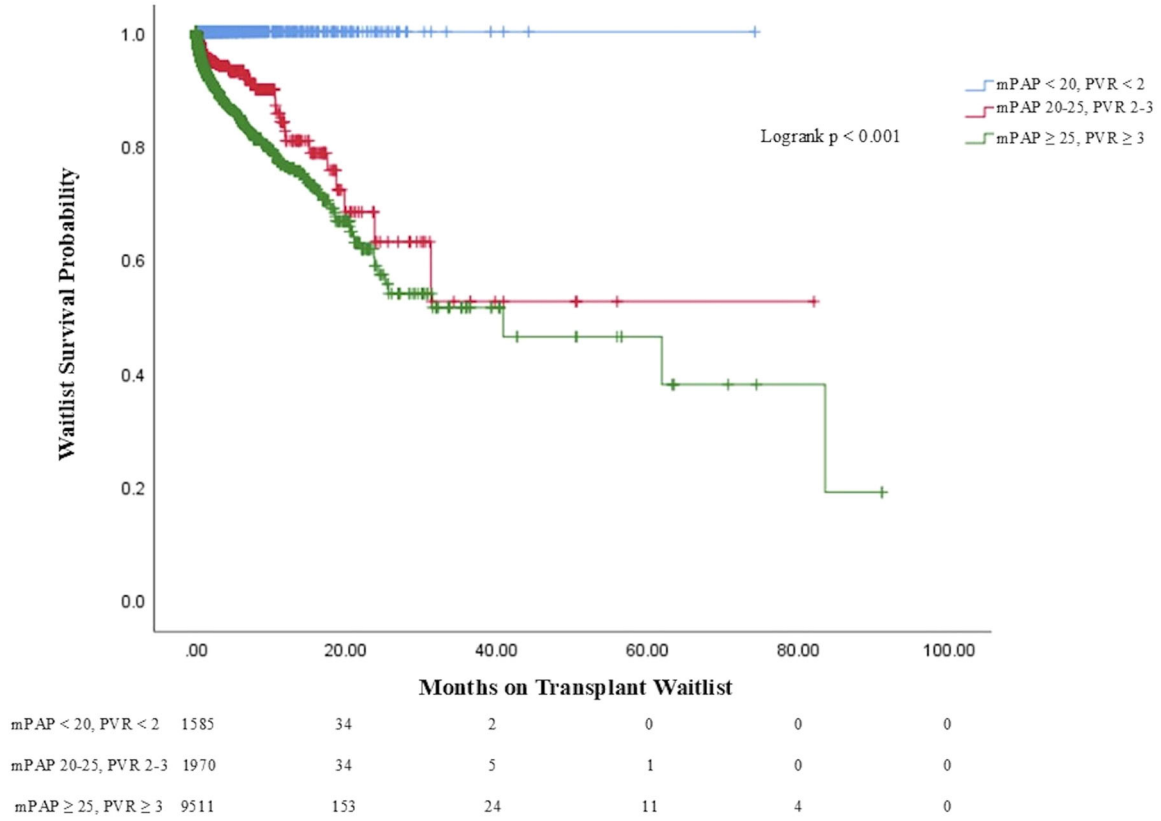

FIGURE 2 | Kaplan–Meier survival analysis plot.

TABLE 2 | Univariate analysis for clinical parameters affecting mortality.

Variable	HR	95% CI	*p* value
FVC (% pred)	0.98	0.97–0.99	$p < 0.001$
6MWD (ft)	0.98	0.97–0.99	$p < 0.001$
Oxygen Requirement (L/min)	1.01	1.004–1.02	$p = 0.001$
PASP (mmHg)	1.007	1.004–1.01	$p < 0.001$

Note: Univariate Cox proportional hazard regression was conducted to examine the association between various predictors and waitlist mortality. The analysis revealed that FVC was significantly associated with reduced risk of mortality (HR 0.98, 95% CI 0.97–0.99, $p < 0.001$). Similarly, a greater 6-min walk distance was associated with a decreased risk of waitlist mortality (HR 0.98, 95% CI 0.97–0.99, $p < 0.001$). In contrast, higher oxygen requirements (HR 1.01, 95% CI 1.004–1.02, $p = 0.001$) and pulmonary artery systolic pressure (HR 1.007, 95% CI 1.004–1.01, $p < 0.001$) were associated with an increased risk of mortality.

$p = 0.73$) were not independently and significantly associated with waitlist mortality. Among other predictors, age, blood type, creatinine, requirement of some assistance and oxygen requirement, showed no significant independent effect on waitlist mortality. However, 6MWD (HR 0.98, 95% CI 0.97–0.99 m $p < 0.001$) and FVC (HR 0.98, 95% CI 0.97–0.99, $p = 0.04$) remained significantly associated with a reduced risk of mortality. Additionally, double lung transplant preference (HR 2.59, 95% CI 1.07–6.28, $p = 0.04$), PaCO2 (HR 1.04, 95% CI 1.02–1.06, $p = 0.002$), requirement of significant assistance (HR 8.28, 95% CI 1.07–64.05, $p = 0.04$), and BMI (HR 1.02, 95% CI 1.01–1.04, $p < 0.001$) were significantly associated with an increased risk of mortality (Table 3).

4 | Discussion

Our study investigated the impact of updated PH definition on IPF patients awaiting lung transplant. According to the new ESC/ERS guidelines, which define PH as mPAP > 20 mmHg, the prevalence of PH in our study cohort was 86.4%. This is a significant increase compared to the prevalence of 71.5% when using the old PH definition criteria of mPAP > 25 mmHg. This prevalence is notably higher than previously reported values in similar studies using the prior PH definition of mPAP > 25 mmHg [7]. Compared to those without PH, patients with mPAP 20–25 mmHg and PVR 2–3 WU and patients with mPAP ≥ 25 mmHg and PVR ≥ 3 WU had worse waitlist survival probability. However, the mPAP and PVR criteria were not independent and significant predictors of mortality, with both 6MWD and FVC serving as stronger predictors of waitlist mortality among patients with IPF and PH listed for lung transplantation.

Recent large studies indicate an increased mortality risk associated with PH in IPF patients listed for lung transplantation [7, 10, 12]. Our study is the first to investigate the impact of the updated ESC/ERS PH definitions on transplant waitlist outcomes among IPF patients. Our findings elucidate that the impact of the lowered mPAP and PVR thresholds for PH in IPF transplant waitlist mortality may effectively predict waitlist outcomes.

The 2022 ESC/ERS guidelines were revised based on robust evidence suggesting that an mPAP > 20 and PVR > 2 were associated with increased mortality and significantly poor

TABLE 3 | Multivariate analysis for clinical parameters affecting mortality.

Variable		HR	95% CI	*p* value
mPAP 20–25 mmHg, PVR 2–3 WU		4.44	0.57–9.92	$p = 0.75$
mPAP > 25 mmHg, PVR > 3 WU		7.64	0.49–9.87	$p = 0.73$
FVC (% pred)		0.98	0.97–0.99	$p = 0.04$
6MWD (ft)		0.98	0.97–0.99	$p < 0.001$
Oxygen requirement (L/min)		0.99	0.98–1.02	$p = 0.96$
PaCO2 (mmHg)		1.04	1.02–1.06	$p = 0.002$
Creatinine (mg/dL)		0.35	0.10–1.17	$p = 0.09$
Functional status	Some assistance	3.29	0.42–26.04	$p = 0.26$
	Total assistance	8.28	1.07–64.05	$p = 0.04$
Blood type	AB	0.80	0.42–1.45	$p = 0.98$
	B	1.08	0.38–3.09	$p = 0.89$
	O	0.64	0.31–1.34	$p = 0.24$
Double lung preference		2.59	1.07–6.28	$p = 0.04$

Note: In the multivariate analysis, which adjusted for potential confounders, the association of mPAP and PVR groups with waitlist mortality was no longer significant. Specifically, Group 2 (mPAP 20–25 mmHg, PVR 2–3 WU) had an HR of 4.44 (95% CI: 0.57–9.92, $p = 0.75$), and Group 3 (mPAP > 25 mmHg, PVR > 3 WU) had an HR of 7.64 (95% CI: 0.49–9.87, $p = 0.73$). Among other predictors, PASP, O2 requirement, and FVC showed no significant independent effect on waitlist mortality with HRs of 1.03 (95% CI: 0.97–1.09, $p = 0.38$), 0.99 (95% CI: 0.98–1.02, $p = 0.96$), and 0.98 (95% CI: 0.97–0.99, $p = 0.04$), respectively. However, 6MWD remained significantly associated with a reduced risk of mortality, with an HR of 0.98 (95% CI: 0.97–0.99, $p < 0.001$).

outcomes [14]. One particularly important study supporting these revisions was a large retrospective study involving over 20,000 participants. In this extensive study, Maron et al demonstrated that assessing mPAP as a continuous variable resulted in a significantly increased risk of mortality, beginning at 19 mmHg. Similar to our study, they stratified the total cohort based on referent (mPAP ≤ 18 mmHg), borderline PH (19–24 mmHg), and PH (mPAP ≥ 25 mmHg) status. They showed that the borderline PH group was associated with an increased risk of mortality, even when high-risk subgroups such as those with PVR ≥ 3 WU were excluded. However, only 0.68% of the total enrolled population in this study reported interstitial lung disease (ILD) as a comorbidity, and therefore, it does not necessarily represent patients with IPF, the subject group of our study [15].

Our study findings suggest that IPF patients listed for lung transplant with mPAP > 20 mmHg and PVR > 2 WU have a significantly increased waitlist mortality compared to patients without PH based on the new criteria. However, its significance with regard to waitlist mortality risk was not seen in a multivariable analysis controlling for other pertinent factors that can contribute to outcomes in patients with IPF and PH. The lack of significance may, in part, be explained by not stratifying the data for severe PH (PVR > 5 WU) to account for the physiological effects of severe vasculopathy, which may indeed impact survival in these patients. This concept was also demonstrated by Hayes et al., where severe PH was associated with significantly reduced survival compared to those without PH among patients with IPF [7].

Our study demonstrated that 6MWD and FVC are independent predictors of mortality in IPF, adding to the expanding literature supporting these findings [16–21]. Mura et al showed that 6MWD ≤ 72% predicted was an independent predictor of mortality among newly diagnosed IPF patients (HR 3.27, 95% CI 1.25–8.82, $p = 0.01$). Similarly, Hallstrand et al evaluated the role of the timed walk test (TWT), a modified 6MWT, in predicting severity and survival in IPF and showed that walk distance was independently associated with survival (HR 0.89, 95% CI 0.81–0.97, $p = 0.01$). Importantly, Bois et al. not only showed that 6MWD was an independent predictor of mortality in IPF patients but also demonstrated that baseline 6MWD < 250 m was independently associated with a two-fold increase in the risk of 1-year mortality (HR 2.12, 95% CI 1.15–3.92; $p = 0.02$) and a 24-week decrement in 6MWD > 50 m was independently associated with a nearly three-fold increase in the risk of mortality at 1 year (HR 2.73, 95% CI 1.60–4.66; $p < 0.01$). Similarly, various studies have demonstrated the crucial role of FVC in predicting disease severity and mortality. Bois et al. showed that FVC % pred and 24-week change in FVC % pred were important predictors of 1-year mortality among patients with a baseline FVC ≤ 50% (HR 6.86, 95% CI 1.99–23.60, $p < 0.01$) and among patients with a ≥ 10% decline in FVC at 24 weeks (HR 5.86, 95% CI 3.33–10.81, $p < 0.01$). Jegal et al. showed that 6-month change in FVC was an independent predictor of survival (HR 0.925, 95% CI 0.893–0.958, $p < 0.001$).

Importantly, 6MWD serves not only as a predictor of mortality in IPF but also as a well-established marker for disease progression and mortality in PH, often serving as an endpoint in clinical trials for PH treatments [13, 22, 23]. Analysis of patients from the REVEAL registry highlighted that a 6MWD < 165 m was associated with increased mortality among PAH patients [23]. Christopher et al addressed the significant impact of PH in IPF, demonstrating its association with increased mortality. The patients with PH had a significantly lower 6MWD compared to those without PH in this study [23]. In contrast to this, Lederer et al. found that 6MWD independently predicted mortality among IPF patients even after adjusting for PH, although their study used the previous definition of PH based on mPAP > 25 mmHg and did not account for PVR or severe PH [24]. This raises the question of whether our finding of an association between 6MWD and increased mortality reflects the impact of

parenchymal disease secondary to IPF, the presence of PH or a combination of both.

Our study also demonstrated that elevated PaCO2 is associated with increased waitlist mortality among IPF patients, a finding well-established in the literature, as hypercapnia is a recognized marker of end-stage ILD [12, 25]. Similarly, elevated BMI and the need for significant functional assistance can, in part, be attributed to the severity of the underlying lung disease [26]. It is therefore unsurprising that these factors significantly impact waitlist mortality. The significant association between these variables highlights their importance in the CAS score, which is critical for identifying patients who should be prioritized for transplantation.

Our finding that double lung transplant preference is associated with increased waitlist mortality underscores the overall scarcity of organ availability and consequently longer wait times [27]. Additionally, patients listed for double lung transplantation may have underlying severe conditions, such as PH, which necessitate listing for double lungs rather than a single lung [28]. These factors likely contribute to the higher waitlist mortality observed in this cohort.

Our investigation advocates for the timely identification of PH in individuals with IPF, emphasizing the need to prioritize the most critically affected patients in organ allocation processes. Our findings can help guide physicians in timing of lung transplant referral. While earlier studies have delved into systematic approaches for timely PH detection in IPF, ongoing debates revolve around the optimal timing for screening and challenges associated with limited accessibility to diagnostic modalities such as right heart catheterization [13]. While many clinical factors play a role in determining outcomes in patients with IPF and PH, earlier detection of pre-capillary PH, with more lenient thresholds as defined by the 2022 ESC/ERS guidelines, can guide decision-making and prompt referral for lung transplantation evaluation.

Our study has several strengths. Firstly, the study's robustness is evident in its extensive sample size, sourced from multiple institutions over an extended duration. Additionally, the application of updated guidelines makes it a valuable and pioneering contribution to the existing body of knowledge. Our application of the mPAP and PVR allowed for the identification of precapillary pH, providing a more comprehensive and accurate assessment of the hemodynamic burden on pulmonary circulation. However, it is important to acknowledge the limitations, including the retrospective collection of data from a registry, which introduces potential uncertainties in the accuracy of right heart catheterization values and other key variables. Moreover, the study does not entirely capture the influence of therapies, such as the administration of antifibrotics and PH medications, during the pre-transplantation period. Our study also captures the era of the LAS, which has now been revolutionized by the CAS. The CAS utilizes a more comprehensive assessment by incorporating additional factors to better predict transplant outcomes and ensure fairer organ allocation, which was not captured in our study. Our study highlights the need for future studies to validate these findings in diverse cohorts, assess long-term survival impact both pre and post-transplant, and investigate the role of PH-directed therapeutic interventions, functional tests like 6MWD, and the new Composite Allocation Score in improving patient management. Nonetheless, our findings with regard to the signal towards prognostic efficacy of reduced PH threshold in terms of waitlist mortality in a large cohort of IPF patients is significant and can help guide the care of patients, particularly in regard to timely lung transplant referral and evaluation.

Author Contributions

Zehra Dhanani: Manuscript writing and editing, data collection and analysis. **Michael J Nicholson:** Manuscript writing. **Shameek Gayen:** Manuscript writing and editing, data collection and analysis, idea conceptualization. Zehra Dhanani is the guarantor of the study and takes responsibility for the integrity and accuracy of the data.

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The authors have nothing to report.

Disclosure

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Data Availability Statement

SRTR and OPTN database.

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