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Antifibrotic therapy combined with pulmonary vasodilator therapy may improve survival in patients with pulmonary fibrosis and pulmonary hypertension: a retrospective cohort study

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Abstract

Background: Pulmonary fibrosis is a severe, progressive form of interstitial lung disease associated with increased morbidity and mortality. Pulmonary hypertension often accompanies severe pulmonary fibrosis and is also associated with worse outcomes. Antifibrotic therapy and pulmonary vasodilator therapy have demonstrated clinical benefits in pulmonary fibrosis and pulmonary hypertension, respectively. However, the benefit of combined antifibrotic and pulmonary vasodilator therapy in patients with both pulmonary fibrosis and pulmonary hypertension is less established.

Objectives: We aimed to determine the effectiveness of a combination pulmonary vasodilator and antifibrotic therapy with regard to transplant-free survival and six-minute walk distance improvement in patients with pulmonary fibrosis and pulmonary hypertension.

Design: This was a retrospective cohort study of patients with pulmonary fibrosis (idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, and other fibrotic interstitial lung disease) and pulmonary hypertension diagnosed via right heart catheterization. Patients received antifibrotic therapy with or without pulmonary vasodilator therapy.

Methods: Patients who received combination antifibrotic therapy and pulmonary vasodilator therapy were compared to those prescribed antifibrotic therapy alone. Transplant-free survival and change in six-minute walk distance were compared between the two groups. Multivariable Cox regression was performed to determine predictors of transplant-free survival.

Results: Patients who received antifibrotic and pulmonary vasodilator therapy had significantly improved transplant-free survival (log rank $p = 0.001$). Treatment with antifibrotic and pulmonary vasodilator therapy was significantly and independently associated with reduced risk of death or lung transplantation (HR 0.24, 95% CI 0.06–0.93, $p = 0.04$). These patients had worse pulmonary hemodynamics than those receiving antifibrotic therapy alone.

Conclusion: We found a potential survival benefit when pulmonary vasodilator therapy was given in combination with antifibrotic therapy in patients with pulmonary fibrosis and pulmonary hypertension. This may be reflective of a pulmonary vascular phenotype among those with pulmonary fibrosis and pulmonary hypertension. Further trials are needed to better elucidate which patients benefit from combination therapy.

Keywords: antifibrotic therapy, pulmonary fibrosis, pulmonary hypertension, pulmonary vasodilator therapy, transplant-free survival

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Introduction

Interstitial lung disease (ILD) is a heterogeneous group of lung diseases frequently characterized by progressive parenchymal and alveolar destruction.[1] Prognosis varies widely between subtypes of ILD. Idiopathic pulmonary fibrosis (IPF) is the most extensively studied phenotype. It represents a specific form of chronic, progressing, fibrosing interstitial pneumonia and is associated with high mortality.[2] In patients with IPF not treated with antifibrotics, median post-diagnosis survival has been shown to be between 3 and 4 years.[3] Other forms of ILD may also develop progressive pulmonary fibrosis despite the identification and treatment of the underlying disease. For patients with these fibrotic phenotypes, such as IPF or progressive-fibrosing ILD, approved treatment options include antifibrotic therapies such as nintedanib and pirfenidone.[4,5] Both medications have been shown to significantly reduce the rate of functional vital capacity (FVC) decline when compared to placebo alone.[4,6–8]

Sequelae of chronic lung disease can often include pulmonary hypertension, which can develop as a result of impaired gas exchange and remodeling of pulmonary vasculature (PH-ILD).[1,9,10] Clinical manifestations of PH-ILD include poorer functional status, greater need for supplemental oxygen, and decreased survival.[9,11,12] Due to its significant impact on morbidity and mortality, the diagnosis of and treatment for PH-ILD has gained increasing recognition in recent years. Noninvasive testing can aid clinicians in screening for PH, but the gold standard for diagnosis relies on objective hemodynamic criteria obtained via right heart catheterization (RHC). The 2022 ESC/ERS guidelines for the definition and management of PH proposed new hemodynamic definitions for pre-capillary PH to include a resting mPAP >20 mmHg, PAWP ≤ 15 mmHg, and PVR >2 WU and for severe PH to include PVR >5 WU.[13] The classification of severe PH as PVR >5 WU is based on several studies demonstrating decreased survival in patients with chronic lung disease and PH at higher PVR cut-offs.[14,15]

Studies demonstrating the efficacy of pulmonary vasodilators in IPF or other pulmonary fibrosis with PH are limited. The INCREASE trial demonstrated that inhaled treprostinil improved the six-minute walk distance (6MWD) in patients with confirmed PH in the setting of ILD.[16] Studies specifically examining the use of dual antifibrotic and pulmonary vasodilator therapy are even more scarce.

We hypothesize that the addition of pulmonary vasodilator therapy to antifibrotic therapy improves outcomes in patients with pulmonary fibrosis and pulmonary hypertension compared to antifibrotic therapy alone. Our primary objective was to determine whether combination therapy is associated with improved transplant-free survival. Secondary outcomes analyzed include the impact of combination therapy on functional exercise capacity as measured by 6MWD and lung function as measured by pulmonary function testing.

Materials and methods

Study design and definitions

This was a retrospective cohort study of adult patients with pulmonary fibrosis and PH diagnosed via RHC at our institution from 2011 to 2024. Patients greater than 18 years of age who were diagnosed with pulmonary fibrosis and PH and received treatment with antifibrotic therapy were included. Patients not treated with antifibrotic therapy or those with a lung disease separate from pulmonary fibrosis were excluded. We also excluded patients with PH not related to lung disease, such as those with left-sided heart disease as the cause of PH or idiopathic pulmonary arterial hypertension (PAH), as well as those with severe systemic illnesses that could affect mortality, such as active malignancy. Pulmonary fibrosis was diagnosed via pulmonary function testing (PFT) and computed tomography (CT). Lung disease diagnoses included IPF, other fibrotic ILD, and combined pulmonary fibrosis and emphysema (CPFE). Pulmonary hypertension was defined as mPAP >20 mmHg via RHC and was stratified according to the 2022 ESC/ERS guidelines for PH, including severe PH defined as PVR >5 WU. RHC was performed on baseline oxygen requirements. Patient characteristics, comorbidities, and clinical characteristics—including RHC values, spirometry, 6MWD, diffusing capacity of the lungs for carbon monoxide (DLCO), oxygen requirements, and brain natriuretic peptide (BNP)—at the time of PH diagnosis were collected. The outcomes of mortality without lung transplantation (LTx), lung transplant recipients, living without LTx,

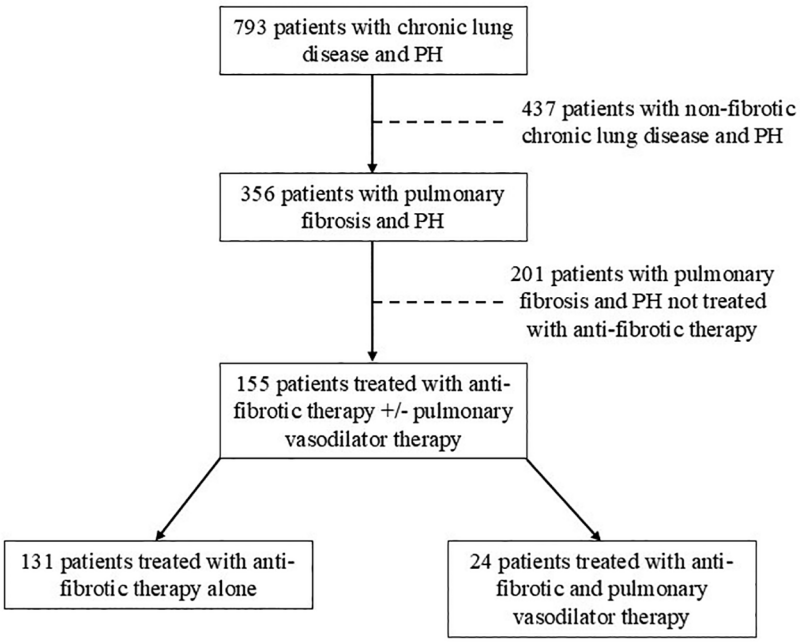

Figure 1. Patient selection flowsheet.
Patient cohort stratified by underlying lung disease initially to identify those with pulmonary fibrosis as underlying lung disease and pulmonary hypertension diagnosed via right heart catheterization. Patients further selected by treatment; those who did not receive antifibrotic therapy were excluded.

and time to an outcome were collected as well. These variables were compared between patients with ILD and PH who received antifibrotic therapy alone versus antifibrotic therapy and pulmonary vasodilator therapy (combination therapy) in the entire cohort. The decision to treat PH was made at the discretion of the individual pulmonary physicians providing care for these patients. The authors used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist in the preparation of this manuscript.[17]

Statistical analysis

Statistical analysis was performed by comparing antifibrotic therapy alone versus antifibrotic therapy and pulmonary vasodilator therapy in the entire cohort. All continuous variables were presented as the mean ± standard deviation unless stated otherwise. Categorical variables were compared using the Pearson chi-squared test or Fisher exact test where applicable. Continuous variables were compared between groups using the Mann–Whitney *U* test given the lack of normal distribution of data. Kaplan–Meier survival analysis was performed to compare the transplant-free survival probability from the time of PH diagnosis to the time of the last follow-up between the antifibrotic therapy alone and the combination therapy groups. Multivariable Cox regression was performed to determine independent and significant associations with the outcome of death or LTx. Patient and disease characteristics known to impact outcomes among patients with pulmonary fibrosis and PH in addition to treatment with both antifibrotic and pulmonary vasodilator therapy were included in the multivariable Cox regression model. The statistical analysis was performed using IBM SPSS Statistics, Version 25 (IBM Corp, Armonk, NY).

Results

We identified 155 patients with pulmonary fibrosis and PH who received antifibrotic therapy with or without pulmonary vasodilator therapy. Among the cohort, 131 patients were prescribed antifibrotic therapy alone, and 24 patients were prescribed pulmonary vasodilator therapy in addition to antifibrotic therapy (Figure 1). There were no significant differences in demographic or comorbid conditions between the two groups (Table 1).

Table 1. Patient baseline and demographic characteristics.

Characteristic	Antifibrotic therapy alone ($n=131$)	Antifibrotic and pulmonary vasodilator therapy ($n=24$)
Age, years (SD)	67.9 (7.5)	65.1 (12.1)
BMI, kg/m^2 (SD)	29.0 (4.7)	28.5 (5.2)
Gender		
Male, *n* (%)	99 (75.6)	18 (75.0)
Female, *n* (%)	32 (24.4)	6 (25.0)
Race		
White, *n* (%)	101 (77.1)	16 (66.7)
Black, *n* (%)	12 (9.2)	2 (8.3)
Other, *n* (%)	18 (13.7)	6 (25.0)
Diabetes, *n* (%)	36 (27.5)	2 (8.3)
Cardiac disease, *n* (%)	6 (4.6)	3 (12.5)

BMI, body mass index.

The proportion of underlying fibrotic lung disease was similar between the two groups. Patients prescribed antifibrotic and pulmonary vasodilator therapy had significantly worse pulmonary hemodynamics via RHC than those prescribed antifibrotic therapy alone (Table 2). A significantly higher proportion of those prescribed both antifibrotic and pulmonary vasodilator therapy had severe PH than those prescribed antifibrotic therapy alone (50% vs 25.2%, $p=0.02$). Lung function, 6MWD, and BNP were similar between the two groups. Prescribed pulmonary vasodilator therapy is described in Supplemental Table 1.

Transplant-free survival was significantly lower among patients who received antifibrotic therapy alone compared to those who received antifibrotic and pulmonary vasodilator therapy (2.3% vs 25.0%, $p<0.001$). The duration of transplant-free survival from RHC was significantly longer among patients who received both antifibrotic and pulmonary vasodilator therapy (19.1 months vs 9.4 months, $p=0.002$, Table 3). There was a trend toward 6MWD improvement, though not statistically significant, in those receiving antifibrotic and pulmonary vasodilator therapy compared to those receiving antifibrotic therapy alone (Table 3).

Kaplan–Meier survival analysis demonstrated improved transplant-free survival probability among those treated with antifibrotic therapy and pulmonary vasodilator therapy than those treated with antifibrotic therapy alone (log rank $p=0.001$, Figure 2). Multivariable Cox regression to determine independent and significant predictors of mortality or transplant evaluated the following variables: combined antifibrotic and pulmonary vasodilator therapy, PVR, BNP, initial FVC % predicted, initial DLCO % predicted, initial 6MWD, and oxygen requirement (Table 4). Combined antifibrotic and pulmonary vasodilator therapy (HR 0.24, 95% CI 0.06–0.93, $p=0.04$) was significantly and independently associated with reduced risk of death or LTx compared to antifibrotic therapy alone when controlling for PVR, lung function, and other markers of clinical severity. As oxygen requirement increased, the risk of death or transplant significantly increased (HR 1.10, 95% CI 1.03–1.25, $p=0.04$), and as DLCO increased, the risk of death or transplant significantly decreased (HR 0.94, 95% CI 0.89–0.98, $p=0.004$).

Discussion

We demonstrated that among patients in our cohort with pulmonary fibrosis and PH, those

Table 2. Clinical characteristics.

Characteristic	Antifibrotic therapy alone (*n* = 131)	Antifibrotic and pulmonary vasodilator therapy (*n* = 24)
Underlying lung disease		
IPF, *n* (%)	64 (48.9)	11 (45.8)
CPFE, *n* (%)	41 (31.3)	7 (29.2)
Other fibrotic ILD, *n* (%)	26 (19.8)	6 (25.0)
Right heart catheterization		
RAP, mmHg (SD)*	4.6 (3.8)	7.0 (5.8)
PASP, mmHg (SD)*	44.4 (12.4)	57.8 (17.6)
mPAP, mmHg (SD)*	27.4 (7.3)	35.0 (10.0)
PCWP, mmHg (SD)	9.5 (5.2)	11.8 (5.8)
CO, L/min (SD)	4.9 (1.3)	4.8 (1.2)
CI, L/min/m^2 (SD)	2.5 (0.7)	2.4 (0.7)
PVR, WU (SD)*	4.1 (2.1)	5.3 (3.2)
Pre-capillary PH, 2015 ESC/ERS definition, *n* (%)	68 (51.9)	17 (70.8)
Pre-capillary PH, 2022 ESC/ERS definition, *n* (%)	111 (84.7)	17 (70.8)
Severe PH, 2015 ESC/ERS definition, *n* (%)*	30 (22.9)	14 (58.3)
Severe PH, 2022 ESC/ERS definition, *n* (%)*	33 (25.2)	12 (50.0)
PFT		
FEV 1% predicted, % (SD)	61.5 (17.9)	65.6 (16.4)
FVC % predicted, % (SD)	60.6 (19.6)	65.8 (16.7)
DLCO % predicted, % (SD)	23.3 (14.1)	28.9 (19.0)
6MWD, m (SD)	265.8 (113.2)	279.4 (112.5)
BNP, pg/dL (SD)	227.9 (445.8)	524.8 (1078.1)
Oxygen requirement, L/min (SD)	7.5 (4.8)	5.6 (4.3)

*$p < 0.05$.
6MWD, 6-minute walk distance; BNP, B-type natriuretic peptide; CI, cardiac index; CO, cardiac output; DLCO, diffusing capacity of the lung for carbon monoxide; ERS, European Respiratory Society; ESC, European Society of Cardiology; FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity; mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PFT, pulmonary function test; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

treated with combination therapy with antifibrotics and pulmonary vasodilators may have improved transplant-free survival when compared to those treated with antifibrotic therapy alone, despite the combination therapy group having more severe PH at baseline. Though not statistically significant, there was a trend toward improved 6MWD in those who received both antifibrotic and pulmonary vasodilator therapy. Treatment with both antifibrotic and pulmonary vasodilator therapy was significantly and independently associated with a reduced risk of death

Table 3. Outcomes.

Outcome	Antifibrotic therapy alone ($n = 131$)	Antifibrotic and pulmonary vasodilator therapy ($n = 24$)
Death prior to lung transplant, *n* (%)	17 (13.0)	2 (8.3)
Lung transplantation, *n* (%)	111 (84.7)	16 (66.7)
Transplant-free survival, *n* (%)*	3 (2.3)	6 (25.0)
Transplant-free survival duration, months (SD)*	9.4 (11.2)	19.1 (23.3)
Change in 6MWD, m (SD)	−42.1 (113.1)	11.0 (128.5)
Change in FVC % predicted, % (SD)	−5.7 (22.0)	−8.0 (19.4)

*$p < 0.05$.
6MWD, 6-minute walk distance; FVC, functional vital capacity.

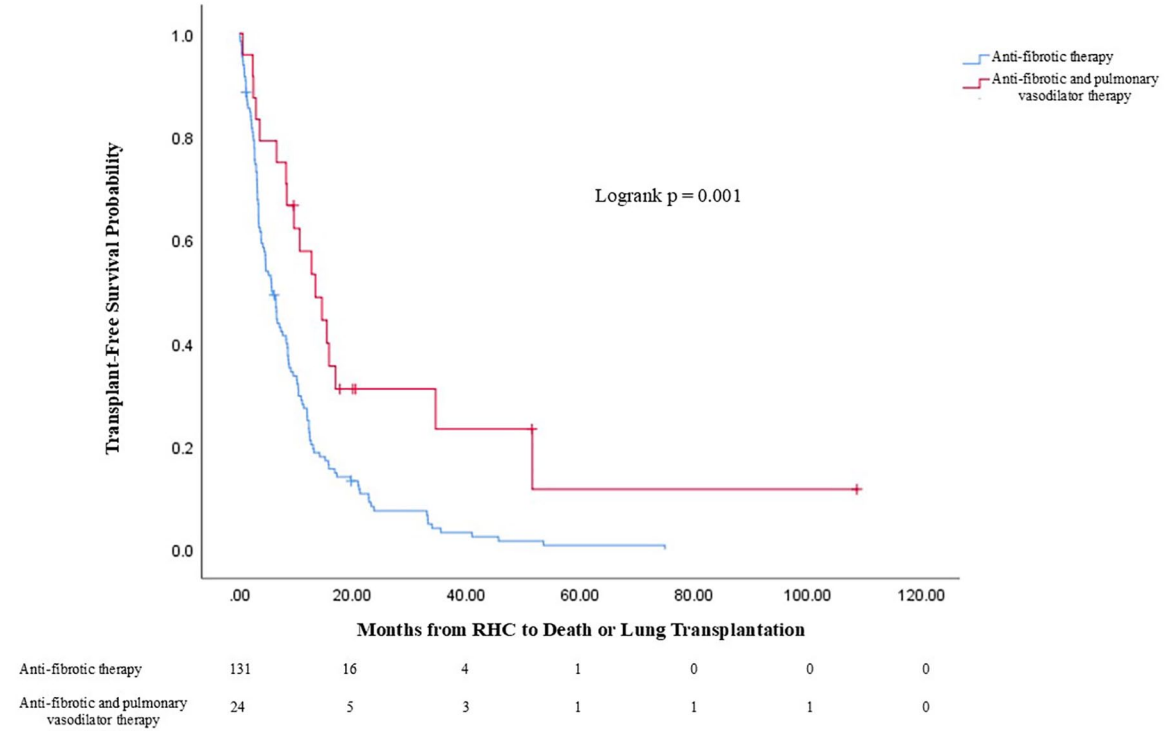

Figure 2. Transplant-free survival probability.
Kaplan–Meier survival analysis comparing patients with pulmonary fibrosis and pulmonary hypertension treated with antifibrotic therapy and pulmonary vasodilator therapy to those treated with antifibrotic therapy alone. A significantly higher transplant-free survival probability seen in those treated with both antifibrotics and pulmonary vasodilators. Number at risk in each group displayed at bottom of graph, with changes in curves due to death or lung transplantation.

or transplant, even when accounting for markers of parenchymal and pulmonary vascular severity.

Our data supports the results of the recent INCREASE trial, which examined the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to ILD; patients on background antifibrotic therapy were included as well. The INCREASE trial was able to demonstrate a statistically significant improvement in

Table 4. Predictors of lung transplantation or death.

Variable	Multivariable Cox regression analysis
Combination antifibrotic and pulmonary vasodilator therapy*	HR 0.24, 95% CI 0.06–0.93, $p = 0.04$
PVR	HR 0.97, 95% CI 0.80–1.18, $p = 0.78$
BNP	HR 1.00, 95% CI 0.99–1.02, $p = 0.42$
FVC % predicted	HR 0.99, 95% CI 0.97–1.03, $p = 0.81$
DLCO % predicted*	HR 0.94, 95% CI 0.89–0.98, $p = 0.004$
Baseline 6MWD	HR 1.00, 95% CI 0.99–1.01, $p = 0.59$
Oxygen requirement*	HR 1.10, 95% CI 1.03–1.25, $p = 0.04$

*Variable independently and significantly associated with composite outcome of death or lung transplantation in multivariable analysis.
6MWD, 6-minute walk distance; BNP, B-type natriuretic peptide; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, functional vital capacity; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

6MWD from baseline when compared to placebo at 16 weeks.[16] Our findings support this result, showing a trend toward improvement in mean 6MWD in the combination therapy group (pulmonary vasodilator and antifibrotic therapy) versus antifibrotic therapy alone; 6WD actually decreased in the antifibrotic therapy group and increased in the combination therapy group.

Change in 6MWD is utilized as an endpoint for clinical and functional improvement in many studies, particularly in PAH trials. While we did not see a statistical significance, the trend toward improvement in the combination therapy group compared to the antifibrotic therapy alone group is encouraging and suggests that combination therapy may enhance exercise capacity in patients with pulmonary fibrosis and pulmonary hypertension.

In addition to improved 6MWD and time to clinical worsening, a post-hoc analysis of the INCREASE trial was able to demonstrate a survival benefit for inhaled treprostinil over 124 weeks in patients with ILD-PH.[18] Although this analysis did not stratify patients based on background antifibrotic therapy, the observed mortality benefit aligns with our findings, which suggest improved transplant-free survival with combination antifibrotic and pulmonary vasodilator therapy.

Interestingly, patients in our study who received pulmonary vasodilator therapies had worse baseline hemodynamics yet similar baseline pulmonary function to the antifibrotic therapy-only group. This observation supports a growing body of literature that suggests the existence of distinct PH phenotypes in patients with comorbid lung disease. Schanz et al. recently proposed that in patients with severe pulmonary hypertension disproportionate to the severity of their chronic lung disease, a distinct pathophysiologic mechanism may be at play, resembling that of PAH.[19] Being able to identify this theorized vascular-predominant phenotype is, therefore, clinically important, as these patients may benefit from a combination of antifibrotic therapy and PAH-targeted pulmonary vasodilator therapy, similar to the cohort observed in our study.

The utility of pulmonary vasodilator therapy in patients with ILD, including pulmonary fibrosis and PH, has not been consistently demonstrated. Behr et al. conducted a study in which patients with IPF at risk for PH received pirfenidone with sildenafil or pirfenidone with a placebo.[20] The addition of sildenafil to pirfenidone did not provide a clinically meaningful benefit compared to pirfenidone alone.[21] These findings contrast with both the INCREASE trial and our study. The discrepancy may be due to the choice of vasodilator therapy; this trial focused on phosphodiesterase-5 inhibitors (PDE5i), whereas patients in the INCREASE trial and many patients in our study received inhaled prostacyclin therapy. Additionally, unlike our study, this study included some patients who did not have PH confirmed by

RHC but rather with echocardiogram findings suggestive of PH; these factors could explain the lack of clinical benefit seen with sildenafil when added to pirfenidone and the importance of appropriately identifying which patients may respond favorably to therapy.

While we were able to observe benefits in exercise capacity and mortality in our patient population, the RISE-IIP trial did not observe similar results in either measure. This trial, which studied the utility and safety of riociguat in patients with idiopathic interstitial pneumonia (IIP) and pulmonary hypertension, was terminated early due to increased mortality and adverse events in the treatment arm.[21] Notably, only 28% of the total patient population within the study was on antifibrotic therapy at the time of enrollment; the lack of antifibrotic therapy may have played a role in increased mortality.

Antifibrotic therapies such as nintedanib and pirfenidone have consistently demonstrated effectiveness in disease management in patients with IPF as well as progressive pulmonary fibrosis aside from IPF.[6,8,22–24] In addition to slowing the rate of FVC decline, antifibrotic therapy has been shown to improve disease progression-free survival and reduce the risk of all-cause mortality in IPF.[26] These trials notably excluded patients with PH and CPFE or did not report data on these conditions. As a result, our patient population likely represents a sicker, real-world cohort with more advanced disease. Nevertheless, we demonstrated a significant improvement in transplant-free survival and a trend toward significance with the change in 6MWD.

We also identified an independent association between oxygen requirement and DLCO impairment with the composite outcome of death or LTx. Hypoxemia and the need for oxygen therapy in the context of interstitial lung disease have consistently been associated with poor prognosis.[25–27] Further, reductions in DLCO have been independently linked to an increased risk of mortality in patients with ILD, both with and without associated pulmonary hypertension.[28,29] It is important to note that impairments in DLCO can be influenced by a multitude of factors. In our patient population, the observed association likely reflects the severity of pulmonary vascular disease or the extent of alveolar surface destruction, although it is difficult to distinguish the primary driver of the measured diffusion limitation.

There are several strengths to our study. Firstly, our data is consistent with the results of the INCREASE trial, supporting the use of pulmonary vasodilators in patients with PH and ILD. Our studied cohort all owned a diagnosis of PH and pulmonary fibrosis, representing subjects with severe disease or significant comorbid conditions. Our study, therefore, helps to fill a gap in existing literature on the utility of combination antifibrotic and pulmonary vasodilator therapy with advanced cardiopulmonary disease, especially by demonstrating improvement in survival.

However, several notable limitations should be acknowledged. The degree of risk reduction associated with pulmonary vasodilator and antifibrotic therapy is very large; most patients in the antifibrotic therapy alone group underwent LTx. The higher rate of LTx is likely a large component of the reduced transplant-free survival seen among patients not treated with pulmonary vasodilator therapy. These patients may have been deemed more "fit" for transplant due to less severe PH and other factors we could not control for. However, transplant-free survival is an important outcome that has been used in studies to determine prognostic factors as well as treatment effects in other cohorts with similar disease states. The retrospective design of this study and small sample size, particularly within the combination therapy group, are additional significant limitations, as selection bias and certain other important factors, such as pulmonary rehabilitation, could not be controlled for. Further, our study was not able to collect repeat RHC data post-treatment, which would be useful to provide further insight into the hemodynamic effects of combination therapy. There was no standardized prescribing of either antifibrotic therapy or pulmonary vasodilator therapy; treatment was at the discretion of the treating pulmonary physician. In fact, it is surprising that such a large proportion of patients with pulmonary fibrosis and pulmonary hypertension in this cohort did not receive antifibrotic therapy. In addition, a large proportion of our patients underwent lung transplant evaluation. These patients tend to have more severe pulmonary disease, both parenchymal and vascular, while also potentially having fewer comorbid conditions that would preclude LTx. Given these considerations, our findings may not be fully applicable to a more general population of patients with pulmonary fibrosis and pulmonary

hypertension. However, the significance of our findings with regard to transplant-free survival is encouraging in potentially improving outcomes in a sick patient population for whom lung transplantation is often the only definitive treatment.

Conclusion

This study suggests that treatment with antifibrotic and pulmonary vasodilator therapy could improve transplant-free survival in patients with pulmonary hypertension related to pulmonary fibrosis. We found increased transplant-free survival probability despite significantly more severe PH at baseline in the patients who received combination therapy compared to patients who received antifibrotic therapy alone, suggesting a pulmonary vascular phenotype even in patients with underlying pulmonary parenchymal disease and pulmonary hypertension. Future prospective, randomized studies are needed to confirm these findings and further explore the long-term outcomes of combination therapy in appropriate patients with pulmonary fibrosis and PH.

Declarations

Ethics approval and consent to participate

Our study met approval for a waiver of informed consent according to the Western Institutional Review Board (Protocol #31795).

Consent for publication

Not applicable.

Author contributions

Christian Cardillo: Data curation; Investigation; Writing – original draft.

Gerard J. Criner: Conceptualization; Supervision; Writing – review & editing.

Shameek Gayen: Conceptualization; Formal analysis; Investigation; Methodology; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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