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RESEARCH ARTICLE

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Clinical features do not identify risk of progression from isolated postcapillary pulmonary hypertension to combined pre- and postcapillary pulmonary hypertension

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Abstract

Pulmonary hypertension is a common sequelae of left heart failure and may present as isolated postcapillary pulmonary hypertension (Ipc-PH) or combined pre- and postcapillary pulmonary hypertension (Cpc-PH). Clinical features associated with progression from Ipc-PH to Cpc-PH have not yet been described. We extracted clinical data from patients who underwent right heart catheterizations (RHC) on two separate occasions. Ipc-PH was defined as mean pulmonary pressure >20 mmHg, pulmonary capillary wedge pressure >15 mmHg, and pulmonary vascular resistance (PVR) < 3 WU. Progression to Cpc-PH required an increase in PVR to ≥3 WU. We performed a retrospective cohort study with repeated assessments comparing subjects that progressed to Cpc-PH to subjects that remained with Ipc-PH. Of 153 patients with Ipc-PH at baseline who underwent a repeat RHC after a median of 0.7 years (IQR 0.2, 2.1), 33% (50/153) had developed Cpc-PH. In univariate analysis comparing the two groups at baseline, body mass index (BMI) and right atrial pressure were lower, while the prevalence of moderate or worse mitral regurgitation (MR) was higher among those who progressed. In age- and sex-adjusted multivariable analysis, only BMI (OR 0.94, 95% CI 0.90–0.99, $p = 0.017$, $C = 0.655$) and moderate or worse MR (OR 3.00, 95% CI 1.37–6.60, $p = 0.006$, $C = 0.654$) predicted progression, but with poor discriminatory power. This study suggests that clinical features alone cannot distinguish patients at risk for development of Cpc-PH and support the need for molecular and genetic studies to identify biomarkers of progression.

KEYWORDS
biomarker, left heart disease, pulmonary circulation, vascular remodeling

INTRODUCTION

Pulmonary hypertension associated with left heart disease (PH-LHD) is the most common form of PH seen in the clinical setting.[1] PH-LHD is characterized as either isolated postcapillary pulmonary hypertension (Ipc-PH) or combined pre- and postcapillary pulmonary hypertension (Cpc-PH).[2] Ipc-PH is more common and develops from passive transmission of left-sided pressure. Approximately 12%–40% of patients with PH-LHD develop Cpc-PH, which is characterized by pulmonary vascular remodeling as evident by elevated pulmonary vascular resistance (PVR).[3–6] Distinguishing Cpc-PH from Ipc-PH is important because the former group has worse outcomes[7] and therapies targeted at Cpc-PH are only in the preliminary stages.[8–13] Cross-sectional studies have reported the hemodynamic,[5,14] pathologic,[15,16] genetic,[4,17] and cellular changes[18–20] behind the pathophysiology of PH-LHD and Cpc-PH, but it remains unclear why some patients transition from Ipc-PH to Cpc-PH, while others remain with Ipc-PH. Although no prior studies describe a conversion from Ipc-PH to Cpc-PH and the development of Cpc-PH at onset of PH-LHD could be possible, the currently accepted pathophysiology of Cpc-PH begins with long-standing elevation in left-sided pressures, which suggests that development of Ipc-PH should precede Cpc-PH. Longitudinal studies to describe the natural history of Ipc-PH and clinical features associated with transition to Cpc-PH are lacking.

Identifying risk factors for progression to Cpc-PH would be important clinically. Such knowledge may inform surveillance intervals for changes in hemodynamics or right ventricular function and motivate more aggressive risk factor management to reduce adverse events associated with the Cpc-PH phenotype. To address this knowledge gap, we studied patients with PH-LHD referred for right heart catheterization (RHC) at a large tertiary care center. We examined clinical, hemodynamic, and echocardiographic data in a study group with extensive follow-up as a retrospective cohort study with repeated assessments. Based on prior findings from cross-sectional and retrospective studies showing few differences between patients with Cpc-PH and those with Ipc-PH, as well as limited clinical predictors of Cpc-PH,[3,4] we hypothesized that clinical features do not easily distinguish patients who progress from Ipc-PH to Cpc-PH.

METHODS

Study population

Data for this study were extracted from Vanderbilt's Synthetic Derivative, a deidentified version of Vanderbilt's electronic medical record originating in 1995. The design and implementation of the Synthetic Derivative were previously described.[21,22]

Methodology

We queried the medical record for all patients referred for at least two RHC between 1998 (when RHC reports were digitalized) and 2017. Patients with Ipc-PH on the initial RHC with Ipc-PH or Cpc-PH on the repeat RHC were included. For patients with more than two RHCs, the repeat RHC utilized was the next closest RHC performed that was at least 2 weeks apart from the initial. Patients were categorized according to contemporary guidelines by the integrated mean hemodynamic values on the RHC report. Zero-level in the Vanderbilt cardiac catheterization lab is the midthoracic cavity and has been consistent over the study period. In accordance with the World Symposium on Pulmonary Hypertension 2018 consensus recommendations, Ipc-PH was defined as mean pulmonary artery pressure (mPAP) > 20 mmHg, pulmonary capillary wedge pressure (PCWP) > 15 mmHg and PVR < 3 Wood units (WU). Cpc-PH was defined as mPAP > 20 mmHg, PCWP > 15 mmHg, and PVR ≥ 3 WU (Table 1).

Inpatients and outpatients were included in this study, but subjects with a history of cardiac transplant, short interval between the two RHCs (<2 weeks), and involvement in a clinical trial were excluded. After application of the initial exclusion criteria, each of the individual 168 remaining patient charts were manually

TABLE 1 Hemodynamic parameters for pulmonary hypertension subtypes.

	mPAP	PCWP	PVR
No PH	≤20 mmHg	–	–
PAH	>20 mmHg	≤15 mmHg	≥3 WU
Ipc-PH	>20 mmHg	>15 mmHg	<3 WU
Cpc-PH	>20 mmHg	>15 mmHg	≥3 WU

Abbreviations: Cpc-PH, combined pre- and postcapillary pulmonary hypertension; Ipc-PH, isolated postcapillary pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

reviewed to identify the principal indications for each RHC. Clinic notes, inpatient notes, problem lists, and RHC reports were used to make the determination. Each chart was reviewed to verify no diagnosis of PAH or Cpc-PH before the initial RHC identified by our data extraction algorithm. Patients with profound instability (bradycardia, tachycardia, hypertension, hypotension refractory to inotropic support as defined in Supporting Information: Table 1) were also removed from the cohort due to the significant alterations these changes can cause to cardiopulmonary hemodynamics.

Demographic data were extracted from the date of RHC. Comorbidity, medication exposure, and laboratory data closest to the date of each RHC were utilized. We extracted laboratory values that report on disease severity or reflect quantitative measures of comorbidities (e.g., hemoglobin, glomerular filtration rate [GFR], glycosylated hemoglobin [Hgb A1c], lipid profiles, B-type natriuretic peptide [BNP]). Quantitative and semiquantitative echocardiographic data performed within 60 days of the first RHC was included as previously described.[23] Limited echocardiographic data were available at the timing of the repeat RHC and therefore were not included. Nonphysiological data suggestive of entry error (e.g., arterial saturation >100%, negative PVR) were deleted.

We created two groups for analysis in a retrospective cohort design with repeated assessments: patients with Ipc-PH on both the first and second RHC (*persistent Ipc-PH group*) and patients with Ipc-PH on the initial RHC who then progressed to Cpc-PH on the second RHC (*Cpc-PH group*). Characteristics of the two groups at the time of the first RHC were compared as our primary outcomes of interest. Second, the features of the two groups were compared at the time of the second RHC. Within each group, clinical features were compared between the time of the first and second RHC as well.

Statistical analyses

Differences between the Cpc-PH group and Ipc-PH group before progression and after progression were assessed using the Mann–Whitney *U* or Fisher's exact test, as appropriate. For the analysis performed within each group (comparison between baseline and repeat RHC), the Wilcoxon signed-rank test or McNemar's χ^2 test were used. Data are expressed as median [interquartile range] for continuous variables, and absolute value and percent for categorical variables, unless stated otherwise. Limited multivariable logistic regression models adjusting for age, sex, and the variable of interest were used to assess the ability of clinical and laboratory characteristics to identify progression to Cpc-PH. We used a limited number of covariates in the model due to the smaller number of Cpc-PH cases. Results were reported as age- and sex-adjusted odds ratio. For each of the regression models, receiver operating characteristic (ROC) analysis was also performed to determine the diagnostic potential of each variable, with the concordance statistic (C-statistic) reported. Statistical analysis was performed using R (Version 4.0.3; R Foundation for Statistical Computing).[24]

RESULTS

We identified 922 patients referred for two RHCs between 1998 and 2017. Among these, 251 patients met criteria for Ipc-PH at baseline, with a final study group of 153 patients after our exclusion criteria were applied (Figure 1). The patients in this final study group had a median age of 55 (IQR 45, 66), median BMI of 31.9 kg/m^2 (IQR 26.5, 36.8), and 33% were of female sex. The prevalence of Cpc-PH at the second RHC was 33% (50/153) and the repeat RHC was performed after a median time of 0.7 years (IQR 0.2, 2.1). The time interval between the two RHCs was not significantly different between the persistent Ipc-PH group and the Cpc-PH group (0.6 [0.2, 1.8] vs. 0.9 [0.4, 2.7] years, $p = 0.15$). The most common indication for repeat RHC referral was persistent heart failure symptoms ($n = 109$, followed by routine re-evaluation of hemodynamics or as part of cardiac transplant workup, $n = 25$). The indications for repeat RHC were not different between the two groups (Supporting Information: Tables 2 and 3). The proportion of patients with an EF < 50% and heart failure etiology were similar between the two groups (Table 2 and Supporting Information: Table 4). The primary reasons for patient exclusion from the analysis were presence of interval cardiac transplant between the RHCs ($n = 43$) and an interval of fewer than 14 days ($n = 39$) between RHCs (Figure 1).

Table 2 shows baseline variables for each group before progression. The hemodynamics of patients in both groups were not significantly different at the time of the baseline RHC, except for right atrial (RA) pressure, which was lower (9 [6, 15] vs. 12 [9, 17] mmHg, $p = 0.01$) in the Cpc-PH group patients. Patients in the Cpc-PH group had lower body mass index (BMI) (28.7 [24.6, 34.5] vs. 32.7 [27.4, 37.5] kg/m^2, $p = 0.02$) and a trend toward higher high-density lipoprotein (HDL) (40 [29, 46] vs. 35 [28, 44] mg/dL, $p = 0.10$) and BNP (707 [177, 1275] vs. 422 [182, 831] pg/mL, $p = 0.08$) levels at baseline compared with patients in the persistent Ipc-PH group. We observed no differences in any other

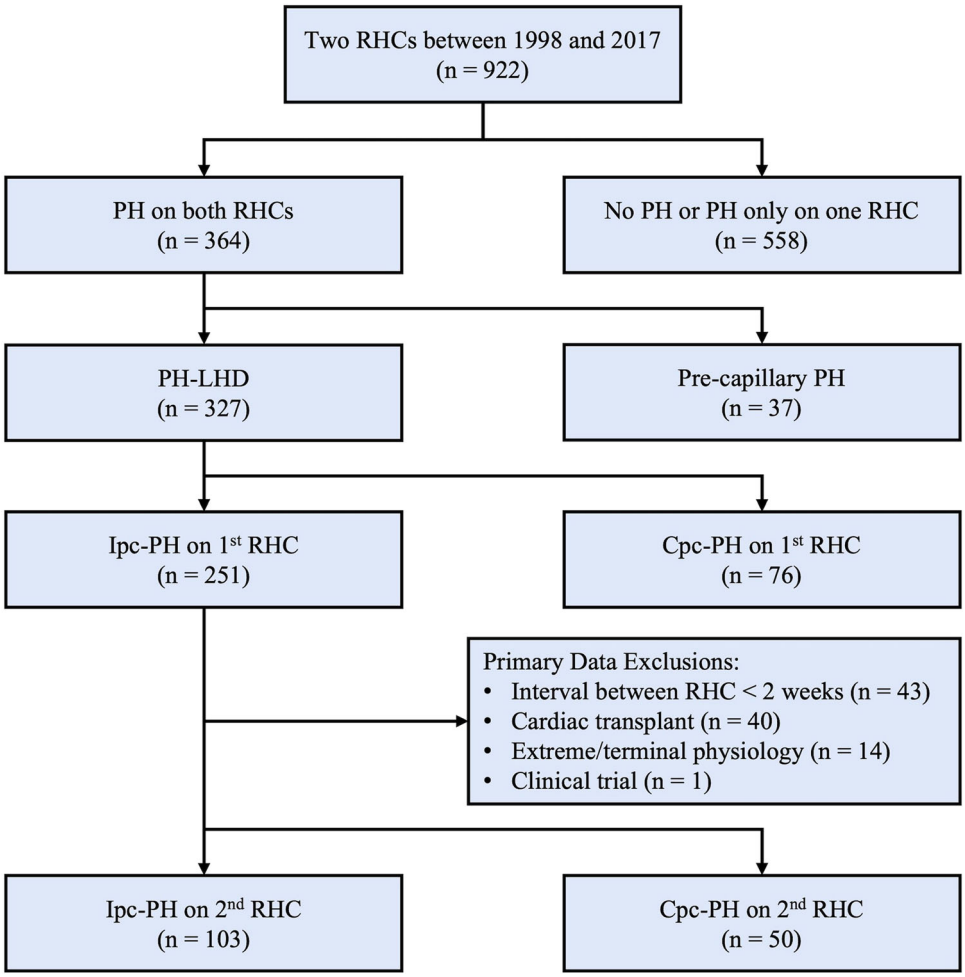

FIGURE 1 Schematic representing the initial data set and subsequent criteria used to create the two comparison groups. Cpc-PH, combined pre- and postcapillary pulmonary hypertension; Ipc-PH, isolated postcapillary pulmonary hypertension; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension due to left heart disease; RHC, right heart catheterization.

demographic or laboratory features, including sex, age, GFR, hemoglobin level, Hgb A1c, low-density lipoprotein (LDL) levels, systolic blood pressure (SBP), and diastolic blood pressure (DBP). The prevalence of diabetes mellitus (DM), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), obesity hypoventilation syndrome (OHS), and end stage renal disease (ESRD) were not different between the two groups, but there was a borderline increased prevalence of atrial fibrillation (44% vs. 28%, $p = 0.09$) in the Cpc-PH group at baseline. There was no difference in prior medication use by medication class. Analysis of echocardiographic data showed a higher prevalence of moderate to severe mitral regurgitation (39% vs. 18%, $p = 0.02$). The results were similar when the two groups were stratified by EF < 50% or EF > = 50% and baseline variables were compared (Supporting Information: Tables 5 and 6). When a minimum interval of 6 months between the two RHCs was utilized as an inclusion criterion, lower BMI (29.3 [25.6, 36.0] vs. 35.1 [30.0, 39.7] kg/m^2, $p = 0.01$) and borderline higher prevalence of moderate to severe mitral regurgitation (14% vs. 33%, $p = 0.05$) were noted in the Cpc-PH group at baseline (Supporting Information: Table 7). In age and sex-adjusted analyses, significant predictors of progression were lower BMI (OR 0.94, 95% CI 0.90–0.99, $p = 0.02$) and higher prevalence of moderate to severe mitral regurgitation (OR 3.00, 95% CI 1.37–6.60, $p < 0.01$). ROC analysis performed on BMI and prevalence of moderate to severe mitral regurgitation yielded *C* statistic values of 0.655 and 0.654, respectively (Figure 2).

With regard to the repeat RHC, BMI was again lower (28.9 [24.0, 33.5] vs. 31.9 [26.3, 37.3] kg/m^2, $p = 0.01$), BNP was higher (925 [265, 1431] vs. 354 [176, 825] pg/mL, $p < 0.01$), triglyceride to HDL ratio was lower (2.8 [1.6, 3.7] vs. 3.8 [2.2, 6.1], $p = 0.03$), and preceding mineralocorticoid receptor antagonist (MRA) use was

TABLE 2 Comparison of patients who remained with Ipc-PH versus those who progressed to Cpc-PH at time of baseline RHC.

	Persistent Ipc-PH group	Cpc-PH group	*p* Value
n	103	50	–
Age (years)	54 [45, 62]	57 [47, 70]	0.10
Female (%)	33.0	34.0	1.00
BMI (kg/m^2)	32.7 [27.4, 37.5]	28.7 [24.6, 34.5]	0.02*
Hemodynamics			
RAP (mmHg)	12 [9, 17]	9 [6, 15]	0.01*
RVSP (mmHg)	45 [40, 52]	49 [43, 56]	0.09
mPAP (mmHg)	32 [28, 38]	33 [29, 37]	0.74
sPAP (mmHg)	45 [40, 54]	47 [40, 55]	0.36
dPAP (mmHg)	22 [19, 26]	22 [19, 26]	0.85
PCWP (mmHg)	22 [19, 27]	22 [19, 27]	0.67
DPG (mmHg)	−1 [−4, 2]	−1 [−3, 2]	0.90
PVR (Wood units)	1.90 [1.17, 2.28]	1.99 [1.63, 2.41]	0.14
CI (L/min/m^2)	2.51 [2.09, 3.04]	2.46 [1.98, 2.91]	0.49
SBP (mmHg)	112 [100, 133]	114 [101, 136]	0.64
DBP (mmHg)	69 [61, 76]	68 [60, 76]	0.85
Co-morbidities			
CAD (%)	64	76	0.19
Atrial fibrillation (%)	28	44	0.08
COPD (%)	16	12	0.74
OSA (%)	24	16	0.34
OHS (%)	1	0	1.00
Hyperlipidemia (%)	64	60	0.76
Diabetes mellitus (%)	35	36	0.82
ESRD (%)	6	2	0.43
Laboratory data			
Hgb A1c (%)	6.4 [5.7, 7.7]	6.4 [5.9, 6.9]	0.51
LDL (mg/dL)	82 [62, 109]	87 [59, 116]	0.88
HDL (mg/dL)	35 [28, 44]	40 [29, 46]	0.10
TG-HDL ratio	3.5 [2.2, 6.1]	3.2 [2.1, 4.2]	0.40
GFR (mL/min)	66 [48, 79]	68 [55, 81]	0.32
Hgb (g/dL)	12.3 [11.0, 13.7]	12.2 [11.3, 13.5]	0.89
BNP (pg/mL)	422 [182, 831]	707 [177, 1275]	0.08
Medication exposure			
Beta blocker (%)	93	86	0.25
ACE inhibitor (%)	73	74	1.00
ARB (%)	31	26	0.65
CCB (%)	34	34	1.00
MRA (%)	47	42	0.72

(Continues)

TABLE 2 (Continued)

	Persistent Ipc-PH group	Cpc-PH group	*p* Value
Statin (%)	70	56	0.13
Anticoagulant (%)	54	54	1.00
Diuretic (%)	90	94	0.64
Echocardiographic data			
EF (%)	25 [17, 49]	30 [18, 52]	0.65
EF < 50% (%)	71	79	0.45
Aortic regurgitation (%)	2	4	0.84
Aortic stenosis (%)	5	4	1.00
Mitral regurgitation (%)	19	38	0.02*
Mitral stenosis (%)	5	0	0.27
RVSP TTE (mmHg)	43 [37, 53]	49 [45, 56]	0.02*
TRV (m/s)	2.90 [2.60, 3.14]	3.17 [2.80, 3.34]	0.14
LA AP diameter (cm)	4.80 [4.43, 5.30]	4.92 [4.28, 5.55]	0.60

Note: Data reflect comorbidities and values at the time of baseline RHC reported as median [interquartile range] or percent.

Abbreviations: ACE, angiotensin converting enzyme; aortic regurgitation, prevalence of moderate to severe aortic regurgitation; aortic stenosis, prevalence of moderate to severe aortic stenosis; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CCB, calcium channel blocker; CI, cardiac index by Fick's formula; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; EF, ejection fraction; EF < 50%, percent of patients with ejection fraction less than 50%; ESRD, end stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoproteins; Hgb, Hemoglobin; Hgb A1c, Hemoglobin A1c; LA AP diameter, left atrial anteroposterior diameter; LDL, low-density lipoproteins; mitral regurgitation, prevalence of moderate to severe mitral regurgitation; mitral stenosis, prevalence of moderate to severe mitral stenosis; mPAP, mean pulmonary artery pressure; MRA, mineralocorticoid receptor antagonist; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; RVSP TTE, right ventricular systolic pressure by echocardiographic measurement; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TG-HDL, triglyceride to HDL ratio; TRV, tricuspid regurgitant velocity.

*$p < 0.05$.

marginally lower (62% vs. 77%, $p = 0.09$) among those who progressed to Cpc-PH (Table 3).

As atrial fibrillation could impact PCWP and PVR measurements, we performed a subgroup analysis of hemodynamics between patients with and without atrial fibrillation in the Cpc-PH group patients, who had a borderline increased prevalence of atrial fibrillation at baseline. At the time of the baseline RHC, PVR was significantly higher in patients with atrial fibrillation compared with patients without atrial fibrillation (2.24 [1.90, 2.44] vs. 1.69 [1.44, 2.30] WU, $p = 0.04$) while PCWP was similar between the subgroups (Supporting Information: Table 8). There was no difference in PVR or PCWP in the Cpc-PH group patients at the time of the repeat RHC (Supporting Information: Table 9).

Table 4 shows the comparison between the data extracted at the baseline RHC and the data extracted at the repeat RHC for the Cpc-PH group. Cardiac index (CI) was unchanged between baseline and repeat RHC (2.24 [1.90, 2.67] vs. 2.46 [1.98, 2.91] L/min/m^2, $p = 0.1$) in those who progressed to Cpc-PH. Conversely, mPAP (33 [29, 37] vs. 40 [33, 44] mmHg, $p < 0.001$), PVR (1.99 [1.63, 2.41] vs. 3.88 [3.49, 4.72] WU, $p < 0.001$), RA pressure (9 [6, 15] vs. 14 [10, 19] mmHg, $p < 0.01$), and the diastolic pressure gradient (DPG, −1 [−3, 2] vs. 4 [1, 7] mmHg, $p < 0.001$) increased in this group. These changes resulted in a 26% increase in mPAP and 11% decrease in CI. GFR and hemoglobin levels were lower, while BNP, BMI, and prevalence of COPD and hyperlipidemia were higher in the Cpc-PH group patients at the time of the repeat RHC compared with at the time of the initial RHC. Increased frequency of exposure to all examined classes of medications except diuretics was also noted between the two time points for the Cpc-PH group.

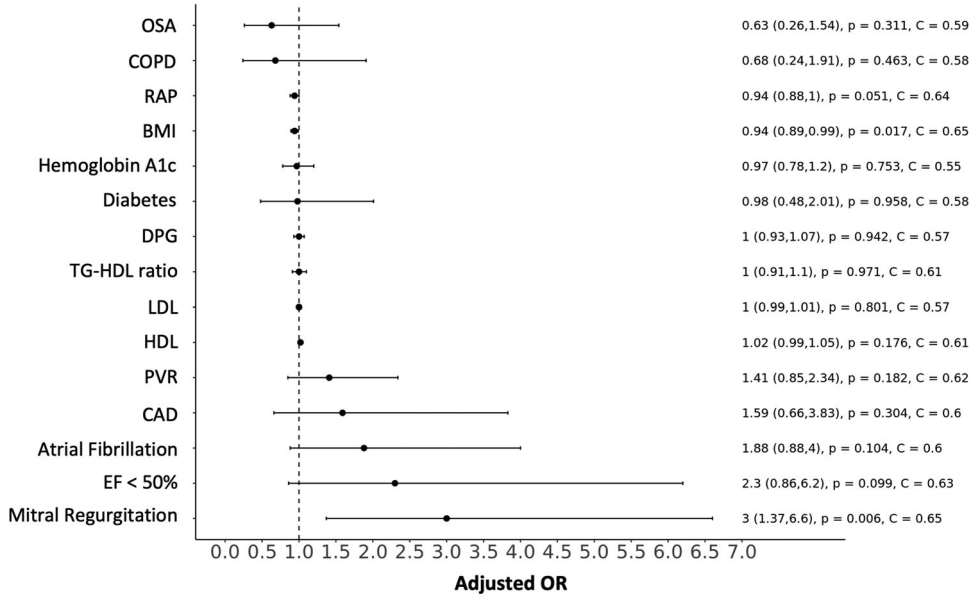

FIGURE 2 Multivariable regression analysis to identify characteristics associated with progression to Cpc-PH. Data reflect comorbidities and values at the time of repeat RHC reported as age- and sex-adjusted odds ratio (95% confidence interval) with respective *p* value and C-statistic. BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; Cpc-PH, combined pre- and postcapillary pulmonary hypertension; DPG, diastolic pressure gradient; EF, ejection fraction; HDL, high-density lipoproteins; LDL, low-density lipoproteins; OSA, obstructive sleep apnea; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; RHC, right heart catheterization; TG-HDL, triglyceride to HDL ratio.

Table 5 shows the comparison between the data extracted at the baseline RHC and the data extracted at the repeat RHC for the persistent Ipc-PH group. There were no hemodynamic differences noted between baseline and repeat RHC in the persistent Ipc-PH group patients. The prevalence of atrial fibrillation, COPD, OSA, CAD, and DM increased, while BMI and GFR decreased in the group that did not progress to Cpc-PH between the two RHCs. Similar to the Cpc-PH group, there was increased exposure to most medication classes, except for beta blockers and diuretics.

DISCUSSION

The primary objective of this study was to determine whether clinical features can distinguish patients who progress from Ipc-PH to Cpc-PH. Our data provide new information on this question, which has not been published previously. We found that lower BMI and higher prevalence of moderate to severe mitral regurgitation were possible predictors of progression to Cpc-PH. However, AUC analysis resulted in a C statistic of less than 0.7 for both parameters, suggesting these features cannot be meaningfully used to predict progression to Cpc-PH. Secondary outcomes of interest were the differences between the two study groups at repeat RHC and the comparison within each group (initial RHC vs. repeat RHC). Compared with persistent Ipc-PH patients, Cpc-PH patients have higher mPAP, PVR, and BNP values, and continued to exhibit lower BMI. For the in-group comparisons between the two RHCs, we observed an increase in prevalence of co-morbidities, increase in medication exposure, and decrease in renal function at the time of the repeat RHC. Notably, the patients in the Cpc-PH group were found to have an increase in BMI while patients in the persistent Ipc-PH group had a decrease in BMI at the repeat RHC.

The results of our study align with established knowledge and understanding of PH. While there is a higher prevalence of metabolic factors such as hypertension, obesity, diabetes, and hyperlipidemia in individuals with World Health Organization Group II (postcapillary) PH compared with individuals with Group I (precapillary) PH,[25] given the shared initial pathogenesis of elevated left-sided pressures, we would not necessarily expect differences in metabolic factors between Cpc-PH and Ipc-PH to be appreciable in patients before progression. Cpc-PH patients might reasonably be expected to demonstrate clinical characteristics somewhere between postcapillary PH and precapillary PH patients. The lower BMI and marginally higher HDL we observed in the Cpc-PH patients at the baseline RHC does fall between what has been observed in PAH patients and Ipc-PH

TABLE 3 Comparison of patients who remained with Ipc-PH versus those who progressed to Cpc-PH at time of repeat RHC.

	Persistent Ipc-PH group	Cpc-PH group	*p* Value
n	103	50	–
Age (years)	55 [46, 63]	59 [48, 72]	0.12
Female (%)	33.0	34.0	1.00
BMI (kg/m^2)	31.9 [26.3, 37.3]	28.9 [24.0, 33.5]	0.01*
Hemodynamics			
RAP (mmHg)	13 [9, 17]	14 [10, 19]	0.56
RVSP (mmHg)	47 [39, 54]	54 [47, 64]	<0.001*
mPAP (mmHg)	33 [28, 38]	40 [34, 44]	<0.001*
sPAP (mmHg)	47 [40, 54]	58 [52, 66]	<0.001*
dPAP (mmHg)	23 [19, 27]	26 [20, 32]	<0.01*
PCWP (mmHg)	23 [20, 28]	22 [19, 28]	0.24
DPG (mmHg)	−1 [−4, 2]	4 [1, 7]	<0.001*
PVR (Wod units)	1.82 [1.42, 2.41]	3.88 [3.49, 4.72]	<0.001*
CI (L/min/m^2)	2.44 [1.99, 3.08]	2.24 [1.90, 2.67]	0.10
SBP (mmHg)	113 [105, 124]	113 [100, 130]	0.98
DBP (mmHg)	69 [61, 75]	66 [60, 74]	0.25
Co-morbidities			
CAD (%)	70	82	0.16
Atrial fibrillation (%)	44	52	0.43
COPD (%)	28	28	1.00
OSA (%)	31	24	0.47
OHS (%)	1	0	1.00
HLD (%)	75	78	0.81
Diabetes mellitus (%)	48	44	0.65
ESRD (%)	10	10	1.00
Laboratory data			
Hgb A1c (%)	6.3 [5.7, 7.7]	6.3 [5.9, 6.9]	0.79
LDL (mg/dL)	82 [59, 108]	78 [55, 102]	0.45
HDL (mg/dL)	36 [29, 42]	38 [30, 46]	0.18
TG-HDL ratio	3.8 [2.2, 6.1]	2.8 [1.6, 3.7]	0.03*
GFR (mL/min)	58 [39, 75]	54 [42, 67]	0.55
Hgb (g/dL)	12.1 [10.8, 13.3]	12.0 [10.7, 12.9]	0.51
BNP (pg/mL)	354 [176, 825]	925 [265, 1431]	<0.01*
Medication exposure			
Beta blocker (%)	98	98	1.00
ACE (%)	79	88	0.24
ARB (%)	38	42	0.75
CCB (%)	43	50	0.50
MRA (%)	77	62	0.09

	Persistent Ipc-PH group	Cpc-PH group	*p* Value
Statin (%)	78	68	0.28
Anticoagulant (%)	72	70	0.96
Diuretic (%)	95	96	1.00

Note: Data reflect comorbidities and values at the time of repeat RHC reported as median [interquartile range] or percent.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CCB, calcium channel blocker; CI, cardiac index by Fick's formula; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; ESRD, end stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoproteins; Hgb, Hemoglobin; Hgb A1c, Hemoglobin A1c; LDL, low-density lipoproteins; mPAP, mean pulmonary artery pressure; MRA, mineralocorticoid receptor antagonist; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TG-HDL, triglyceride to HDL ratio.

*$p < 0.05$.

patients.[4,25] Although obesity has been linked to metabolic dysfunction in several other disease processes and therefore could be expected to enhance pulmonary vascular remodeling, higher BMI was found to correlate only with elevated pulmonary pressures and not with pulmonary vascular remodeling in patients with PAH or PH-LHD.[26] Further, insulin resistance in PAH patients was not correlated with increased BMI,[27] with evidence instead supporting right ventricle dysfunction as a driver of metabolic derangements.[28] Right ventricle dysfunction has also been found to be associated with lower BMI and cardiac cachexia.[29]

There are no prior longitudinal studies examining development of Cpc-PH. However, one comparable analysis by Gerges et al.[3] examined clinical and echocardiographic risk factors for Cpc-PH in separate retrospective and prospective cohorts, and showed that younger age, valvular heart disease, and lower tricuspid annular plane systolic excursion to systolic pulmonary artery pressure ratio (TAPSE/sPAP) are associated with Cpc-PH in patients with diastolic heart failure, while COPD and lower TAPSE/sPAP were associated with Cpc-PH in systolic heart failure patients. In contrast, our study did not find a difference in age or in prevalence of COPD and aortic valve disease of PH-LHD patients before progression even after stratifying by heart failure type, though we did find an increased prevalence of moderate to severe mitral regurgitation. This discrepancy may be in part due our more limited subgroup analysis of diastolic and systolic heart failure as this study had a fewer number of subjects. Nonetheless, the higher prevalence of moderate to severe mitral regurgitation was a key finding of this study and supports previous data noting that HFpEF patients with mitral regurgitation have more severe pulmonary vascular disease, and specifically greater PVR, than HFpEF patients without mitral regurgitation. Patients in the cohort with HFpEF and mitral regurgitation also were found to have lower BMI than patients without mitral regurgitation, which also is similar to the findings of our study.[30] Other cross-sectional studies have sought to distinguish Ipc-PH from Cpc-PH through more focused echocardiographic analyses. The echocardiographic pulmonary to left atrial ratio (ePLAR),[31] echocardiographic pulmonary to left atrial global strain ratio (ePLAGS),[32] doppler estimates of PVR,[33] and an echocardiographic scoring system[34] all have shown the ability to distinguish between precapillary and postcapillary PH at the time of baseline RHC. Parameters related to minute ventilation versus carbon dioxide production (VE/VCO_2) were also found to be strong predictors of precapillary PH in patients with PH-LHD.[35]

Cross-sectional comparison performed at the time of repeat RHC (i.e., after development of Cpc-PH) revealed that patients with Cpc-PH have a similar prevalence of medical co-morbidities as patients with Ipc-PH. We did find that Cpc-PH patients had lower BMI at the time of the repeat RHC, which bears semblance to PAH patients. The hemodynamic differences (higher RVSP and mPAP) and higher BNP in Cpc-PH compared with Ipc-PH have been previously described and exhibits similarity to PAH.[4,36–38] As expected, the analysis of Cpc-PH patients (baseline vs. repeat RHC) revealed significantly increased PVR and mPAP at the time of the repeat RHC. Given that PVR = (mPAP − PCWP)/(cardiac output) and PCWP was unchanged, the increase in PVR could be driven by an increase in mPAP or by a decrease in RV systolic function. However, the degree of change of mPAP

TABLE 4 Comparison of patient characteristics between the baseline and repeat RHC for the Cpc-PH group.

	Baseline RHC	Repeat RHC	*p* Value
BMI (kg/m^2)	28.7 [24.6, 34.5]	28.9 [24.0, 33.5]	<0.01*
Hemodynamics			
RAP (mmHg)	9 [6, 15]	14 [10, 19]	<0.01*
RVSP (mmHg)	49 [43, 56]	54 [47, 64]	<0.01*
mPAP (mmHg)	33 [29, 37]	40 [34, 44]	<0.001*
sPAP (mmHg)	47 [40, 55]	58 [52, 66]	<0.001*
dPAP (mmHg)	22 [19, 26]	26 [20, 32]	<0.01*
PCWP (mmHg)	22 [19, 27]	22 [19, 28]	0.66
DPG (mmHg)	−1 [−3, 2]	4 [1, 7]	<0.001*
PVR (Wood units)	1.99 [1.63, 2.41]	3.88 [3.49, 4.72]	<0.001*
CI (L/min/m^2)	2.46 [1.98, 2.91]	2.24 [1.90, 2.67]	0.10
SBP (mmHg)	114 [101, 136]	113 [100, 130]	0.47
DBP (mmHg)	68 [60, 76]	66 [60, 74]	0.67
Co-morbidities			
CAD (%)	76	82	0.25
Atrial fibrillation (%)	44	52	0.13
COPD (%)	12	28	0.01*
OSA (%)	16	24	0.14
OHS (%)	0	0	1.00
HLD (%)	60	78	0.01*
Diabetes mellitus (%)	36	44	0.13
ESRD (%)	2	10	0.14
Laboratory data			
Hgb A1c (%)	6.4 [5.9, 6.9]	6.3 [5.9, 6.9]	0.89
LDL (mg/dL)	87 [59, 116]	78 [55, 102]	0.19
HDL (mg/dL)	40 [29, 46]	38 [30, 46]	0.37
TG-HDL ratio	3.2 [2.1, 4.2]	2.8 [1.6, 3.7]	0.03*
GFR (mL/min)	68 [55, 81]	54 [42, 67]	<0.001*
Hgb (g/dL)	12.2 [11.3, 13.5]	12.0 [10.7, 12.9]	<0.01*
BNP (pg/mL)	707 [177, 1275]	925 [265, 1431]	0.03*
Medications			
Beta blocker use (%)	86	98	0.04*
ACE (%)	74	88	0.02*
ARB (%)	26	42	0.01*
CCB (%)	34	50	0.01*
MRA (%)	42	62	<0.01*
Statin (%)	56	68	0.04*
Anticoagulant (%)	54	70	0.01*
Diuretic (%)	94	96	1.00

Note: Data reflect comorbidities and values reported as median [interquartile range] or percent.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CCB, calcium channel blocker; CI, cardiac index by Fick's formula; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; ESRD, end stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoproteins; Hgb, Hemoglobin; Hgb A1c, Hemoglobin A1c; LDL, low-density lipoproteins; mPAP, mean pulmonary artery pressure; MRA, mineralocorticoid receptor antagonist; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TG-HDL, triglyceride to HDL ratio.

*$p < 0.05$.

(26% increase) relative to the degree of change in cardiac output (11% decrease) suggests that the rise in PVR appears to be more strongly influenced by progression of pulmonary vascular remodeling than by right ventricular impairment. The DPG increased between the baseline and repeat RHC in Cpc-PH patients, but the repeat value remains only modestly elevated for a population with precapillary disease. Specifically, a DPG ≥ 7 mmHg in PH-LHD patients has been associated with significant pulmonary vascular remodeling and increased mortality.[16] While our study cohort generally did not demonstrate severe precapillary disease as indicated by this metric, the hemodynamic profile of this cohort resembled those in other large observational cohorts with left heart disease.[39,40] Indeed, the World Symposium on Pulmonary Hypertension notes that the typical

TABLE 5 Comparison of patient characteristics between the baseline and repeat RHC for the persistent Ipc-PH group.

	Baseline RHC	Repeat RHC	*p* Value
BMI (kg/m^2)	32.7 [27.4, 37.5]	31.9 [26.3, 37.3]	0.04*
Hemodynamics			
RAP (mmHg)	12 [9, 17]	13 [9, 17]	0.48
RVSP (mmHg)	45 [40, 52]	47 [39, 54]	0.81
mPAP (mmHg)	32 [28, 38]	33 [28, 38]	0.58
sPAP (mmHg)	45 [40, 54]	47 [40, 54]	0.25
dPAP (mmHg)	22 [19, 26]	23 [19, 27]	0.41
PCWP (mmHg)	22 [19, 27]	23 [20, 28]	0.12
DPG (mmHg)	−1 [−4, 2]	−1 [−4, 2]	0.52
PVR (Wood units)	1.90 [1.17, 2.28]	1.82 [1.42, 2.41]	0.31
CI (L/min/m^2)	2.51 [2.09, 3.04]	2.44 [1.99, 3.08]	0.61
SBP (mmHg)	112 [100, 133]	113 [105, 124]	0.81
DBP (mmHg)	69 [61, 76]	69 [61, 75]	0.62
Co-morbidities			
CAD (%)	64	70	0.04*
Atrial fibrillation (%)	28	44	<0.001*
COPD (%)	16	28	<0.001*
OSA (%)	24	31	0.02*
OHS (%)	1	1	1.00
HLD (%)	64	75	<0.01*
Diabetes mellitus (%)	35	48	<0.001*
ESRD (%)	6	10	0.13
Laboratory data			
Hgb A1c (%)	6.4 [5.7, 7.7]	6.3 [5.7, 7.7]	0.27
LDL (mg/dL)	82 [62, 109]	82 [59, 108]	0.54
HDL (mg/dL)	35 [28, 44]	36 [29, 42]	0.51
TG-HDL ratio	3.5 [2.2, 6.1]	3.8 [2.2, 6.1]	0.60
GFR (mL/min)	66 [48, 79]	58 [39, 75]	<0.01*
Hgb (g/dL)	12.3 [11.0, 13.7]	12.1 [10.8, 13.3]	0.20
BNP (pg/mL)	422 [182, 831]	354 [176, 825]	0.84
Medications			
Beta blocker (%)	93	98	0.07
ACE (%)	73	79	0.04*
ARB (%)	31	38	0.02*
CCB (%)	34	43	<0.01*
MRA (%)	47	77	<0.001*
Statin (%)	70	78	0.01*
Anticoagulant (%)	54	72	<0.001*
Diuretic (%)	90	95	0.07

Note: Data reflect comorbidities and values reported as median [interquartile range] or percent.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CCB, calcium channel blocker; CI, cardiac index by Fick's formula; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pressure gradient; ESRD, end stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoproteins; Hgb, Hemoglobin; Hgb A1c, Hemoglobin A1c; LDL, low-density lipoproteins; mPAP, mean pulmonary artery pressure; MRA, mineralocorticoid receptor antagonist; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; RHC, right heart catheterization; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TG-HDL, triglyceride to HDL ratio.

*$p < 0.05$.

hemodynamics of PH-LHD include a mildly elevated mPAP (25–40 mmHg), a low CI (≤2.5 L/min/m^2), a normal DPG (<3 mmHg), and a PVR between 3 and 4.9 WU. Low or negative DPG values were noted to be particularly prevalent in patients with atrial fibrillation.[41] In this cohort, 28% of Cpc-PH patients at the initial RHC and 44% of Cpc-PH patients at the repeat RHC had atrial fibrillation, which could therefore contribute to the lower DPG values observed. Another observation from the in-group analysis was increased exposure to almost every class of medication included in this study in both the persistent Ipc-PH and Cpc-PH patients. As the majority of RHCs were performed for progression of heart failure, interval escalation of therapy is not surprising. This suggests that progression to Cpc-PH occurred in many patients despite escalation in medical therapy.

Future directions

Further longitudinal studies using factors we did not include in our study are indicated to identify characteristics predictive of progression from Ipc-PH to Cpc-PH. Genomic

and proteomic analysis should be prioritized to better understand the pathophysiology and predict progression. Particularly, elaboration of the role of endothelin, NOS, and ID2 is warranted as they have been found to be differentially expressed in Cpc-PH.[42–45] However, initial trials with phosphodiesterase type 5 inhibitors and endothelin receptor antagonists have not shown consistent clinical benefit in Cpc-PH patients[8,9,11,12] suggesting the existence of alternative biochemical pathways and molecular biomarkers with regard to Cpc-PH. Identification of risk factors, additional molecular pathways, and genes associated with Cpc-PH may allow for early identification of patients at risk for progression and the creation of novel targeted therapies.

Study limitations

The most important source of bias in our study derives from the decision to refer patients for RHC on two separate occasions. We attempted to mitigate this source of selection bias by manually reviewing patient records to identify the reasons for repeat RHC referral, most of which were related to persistent symptoms. Hemodynamic tracings and echocardiographic images were not available for review. Therefore, it is possible that individual patients were mislabeled due to errors in the computer-generated hemodynamic values on the RHC and echocardiographic reports. However, as previously noted, there is strong agreement between the manual and computer-generated integrated mean PCWP in this database[36] and low error rate in echocardiographic data extraction.[23] The subgroup analysis of patients with atrial fibrillation raises the small possibility of less accurate hemodynamic measurements in these patients. PVR was noted to be elevated in the atrial fibrillation patients, which could have resulted in potential exclusion of appropriate patients from the initial overall cohort due to a falsely elevated PVR measurement. The majority of the subjects included in the study had heart failure, and more specifically, heart failure with reduced ejection fraction. Therefore, these results may be less generalizable to Cpc-PH and Ipc-PH patients without heart failure or with heart failure with preserved ejection fraction. It is also quite possible that co-morbidities in the HFpEF population uniquely are more prevalent and contribute to the development of Cpc-PH. Echocardiographic data for this cohort was also limited to the time of the baseline RHC and only included several simple measurements. Subjects did not all have the same set of echocardiographic measurements recorded, which prevented us from reporting parameters more representative of RV dysfunction. Specifically, we were unable to include TAPSE and TAPSE/sPAP in our analyses due to insufficient TAPSE measurements, which did not become a routine measurement at our institution until several years ago. The Cpc-PH patients in this cohort also did not exhibit severe precapillary disease as indicated by the PVR and DPG values at the repeat RHC. Thus, these findings may not be applicable to PH-LHD patients with more significant precapillary disease.

CONCLUSIONS

Clinical, demographic, or laboratory features of patients with PH-LHD alone cannot clearly distinguish those at risk for progression from Ipc-PH to Cpc-PH. Cross-sectional comparison after the development of Cpc-PH redemonstrated minimal differences between Ipc-PH and Cpc-PH populations by clinical data. Our findings suggest the need for molecular and genetic studies to identify risk factors for progression of pulmonary vascular disease in patients with PH-LHD, as well as targets for therapeutic intervention.

AUTHOR CONTRIBUTIONS

Gautam Babu and Evan L. Brittain conceived and designed research. Gautam Babu, Evan L. Brittain, and Jeffrey S. Annis extracted data, analyzed data, and interpreted results of analysis. Gautam Babu and Evan L. Brittain drafted manuscript. Gautam Babu, Evan L. Brittain, Jeffrey S. Annis, Jonah D. Garry, Anna R. Hemnes, and Matthew S. Freiberg edited and revised manuscript. Gautam Babu and Evan L. Brittain approved final version of manuscript.

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CONFLICT OF INTEREST STATEMENT

Anna Hemnes serves as a consultant for United Therapeutics, Janssen, GossamerBio, and Merck. She holds stock in Tenax Therapeutics. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

This study was approved by the Vanderbilt University Institutional Review Board as nonhuman subjects research because all data are deidentified. Consent is waived for nonhuman subjects research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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