Original Research Article

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Health-related quality of life and hospitalizations in chronic thromboembolic pulmonary hypertension versus idiopathic pulmonary arterial hypertension: an analysis from the Pulmonary Hypertension Association Registry (PHAR)

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, morbid, potentially curable subtype of pulmonary hypertension that negatively impacts health-related quality of life (HRQoL). Little is known about differences in HRQoL and hospitalization between CTEPH patients and idiopathic pulmonary arterial hypertension (IPAH) patients. Using multivariable linear regression and mixed effects models, we examined differences in HRQoL assessed by emPHasis-10 (E10) and SF-12 between CTEPH and IPAH patients in the Pulmonary Hypertension Association Registry, a prospective multicenter cohort of patients newly evaluated at a Pulmonary Hypertension Care Center. Multivariable negative binomial regression models were used to estimate incidence rate ratios (IRR) for hospitalization amongst the two groups. We included 461 IPAH patients and 169 CTEPH patients. Twenty-one percent of CTEPH patients underwent pulmonary thromboendarterectomy (PTE) before the end of follow-up. At baseline, patients with CTEPH had significantly worse HRQoL (higher E10 scores) (ß 2.83, SE 1.11, $p = 0.01$); however, differences did not persist over time. CTEPH patients had higher rates of hospitalization (excluding the hospitalization for PTE) compared to IPAH patients after adjusting for age, sex, body mass index, WHO functional class and six-minute walk distance (IRR 1.66, 95%CI 1.04–2.65, $p = 0.03$). CTEPH patients who underwent PTE had improved HRQoL as compared to those who were medically managed, but patients who underwent PTE were younger, had higher cardiac outputs and greater six-minute walk distances. In this large, prospective, multicenter cohort, CTEPH patients had significantly worse baseline HRQoL and higher rates of hospitalizations than those with IPAH. CTEPH patients who underwent PTE had significant improvements in HRQoL.

*Details of PHAR investigators are given in Appendix 1.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by remodeling of the pulmonary arteries resulting from acute and recurrent pulmonary emboli with subsequent development of a pulmonary vasculopathy and elevated pulmonary artery pressures resulting in right heart dysfunction. CTEPH leads to functional impairment and negatively impacts health-related quality of life (HRQoL).[1–3] Surgical treatment with pulmonary thromboendarterectomy (PTE) remains the mainstay of treatment for patients eligible for this procedure; however, 20 to 40% of CTEPH patients have inoperable disease or are not surgical candidates for other reasons.[4] One-third of those who undergo PTE still have residual disease.[5,6] Medical therapies primarily used to treat pulmonary arterial hypertension (PAH) are also used to treat patients with CTEPH; however, the role of medical treatment with or without PTE is not well defined. At the time of this analysis, riociguat remains the only FDA approved therapy for CTEPH.[7]

In contrast to CTEPH, medical therapies have a well-established role in the treatment of PAH with several FDA-approved drug classes. Despite some improvement with medical therapy, patients with PAH continue to experience significantly worse HRQoL than the general U.S. population. Additionally, patients with PAH have considerably higher rates of health care utilization, including up to four times the cost of matched controls, both before and after their diagnosis.[8–10] Clinical studies often group the diagnoses of idiopathic PAH (IPAH) and CTEPH,[11,12] and often vasodilator therapies used in CTEPH are based on extrapolations from PAH.[13] However, there are limited data assessing patient-reported outcomes in CTEPH and comparing them to other PAH patients.[14] The differences in pathogenesis, treatments and outcomes between these patient populations are important to define in a large generalizable population. IPAH is a common subtype of PAH.[15,16] Among patients with PAH, those with IPAH are most likely to be treated with anticoagulation.[17] This is likely due to contraindications to anticoagulation (such as liver disease, cytopenias, etc.) in other PAH subtypes.

We sought to investigate the differences in HRQoL and hospitalizations between patients with CTEPH and IPAH using data from the Pulmonary Hypertension Association Registry (PHAR) – a large, prospective multicenter cohort of pulmonary hypertension patients in the United States.

Methods

Study sample

The PHAR enrolls patients with PAH or CTEPH who were newly evaluated at one of >50 Pulmonary Hypertension Care Centers in the U.S. The registry began enrollment in 2015 with inclusion and exclusion criteria that have been previously described.[18] For this analysis, we included adult patients (>18 years of age) with CTEPH or IPAH enrolled in the registry between January 2015 (inception of registry) and September 2019. This end date of enrollment was chosen to provide at least six months of follow-up before COVID-19-related shutdowns. Patients with both prevalent and incident diagnoses of either CTEPH or IPAH within six months of enrollment were included. CTEPH patients who had already undergone PTE before enrollment in the registry (n = 5) were excluded. All subjects were censored at the time of their last follow-up or March 1st, 2020 (chosen to avoid the impact of COVID-19 shutdown).

Clinical variables

After providing informed consent, demographics, clinical and social history, measurements of exercise performance and hemodynamics via right heart catheterizations were recorded at an initial visit for each patient. Patients were then followed at approximately six-month intervals. At each subsequent visit, patients provided updated demographics, social histories and reported all-cause hospitalizations since their last visit; however, the reason for hospital admission is not recorded in PHAR. Patients also reported symptoms and filled out HRQoL questionnaires described below. In addition, each participating site tracked outcomes, including PTE, lung transplantation and death.[19] At the time of analysis, the registry had not yet started collecting data on pulmonary balloon angioplasty (BPA).

Study outcomes

HRQoL was assessed at the initial visit and longitudinally at all follow-up visits using two questionnaires: the medical outcome short form-12 (SF-12), an abbreviated version of the Medical Outcome Study Short Form-36, and the emPHasis-10 (E10), a pulmonary hypertension specific instrument. The SF-12 consists of a physical component score and mental component score. Each component has scores ranging from 0 to 100, with higher scores, indicating

better HRQoL.[20,21] The E10 score ranges from 0 to 50 with lower scores, indicating better HRQoL.[22]

Statistical analysis

Baseline patient characteristics were summarized using descriptive statistics: numbers and percentages, mean and standard deviations and median and interquartile ranges, as appropriate.

Multivariable linear regression models were used to assess baseline differences in HRQoL scores in the CTEPH group compared to those with IPAH. These models were adjusted for *a priori* selected potential confounders which included age, sex, body mass index (BMI), baseline six-minute walk distance and their baseline World Health Organization (WHO) functional class. These variables were selected because of their known impact on HRQoL and as surrogates for disease severity. We conducted a sensitivity analysis without the surrogate measures of disease severity (WHO functional class and six-minute walk distance) to confirm that our findings were not driven solely by severity of disease. For longitudinal data, mixed effects generalized linear models with random intercept and slopes were fitted to account for the repeated measures of HRQoL over time. These models were adjusted for the same variables, as above and interaction terms for PTE status with time and six-minute walk distance were added to account for the impact of PTE. Negative binomial regression models with an offset for time were used to determine the incidence rate ratios for hospitalization among patients with IPAH and CTEPH, adjusting for PTE status, age, sex, BMI, six-minute walk distance and WHO functional class. For this analysis, admission for PTE was not considered as a hospitalization event. We conducted a sensitivity analysis where we excluded CTEPH patients who underwent PTE from the hospitalization analysis to confirm our findings were not secondary to the PTE. Given that race is a social construct, the primary hypothesis for this study did not focus on exploring racial differences among groups of disease. Additionally, we found no scientific justification to hypothesize that race alone should impact on HRQoL or hospitalizations; therefore, we did not include race as a covariate in our models.[23] Additionally, we ran a sensitivity analysis limiting the dataset to incident IPAH and CTEPH patients (diagnosed within six months of enrollment into the PHAR).

Within the CTEPH subgroup, unadjusted mixed effects generalized linear regression models were used to compare repeat measures of HRQoL between patients who had undergone PTE versus those who were medically managed. Adjusted models for repeat measures were not performed due to the overall small number of patients who underwent PTE in this cohort. All statistical analyses were performed in R version 4.0.4 and RStudio version 1.4.1106.

Results

Clinical characteristics

There were 1361 patients enrolled in PHAR by September 2019, of whom 630 met criteria for inclusion in our analysis (Fig. 1). Of these, 73% had IPAH, and 27% had CTEPH. Table 1 details the baseline characteristics of the study cohort. At the time of enrollment, patients with IPAH were younger with a mean age of 55 years, more likely to be female (76%) and majority non-Hispanic white (71%).

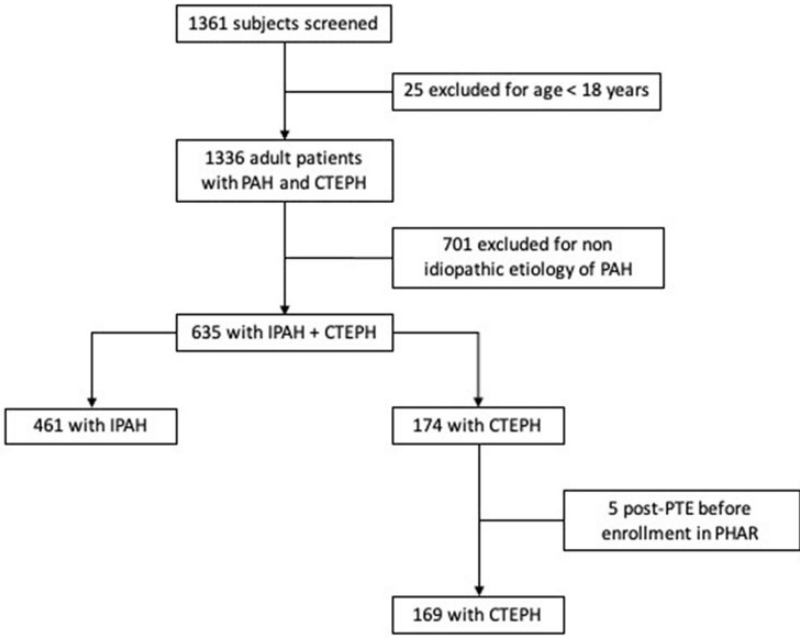

Fig. 1. Flow diagram for study participants.

Table 1. Patient characteristics of the cohort at time of enrollment in PHAR.

	IPAH N = 461	CTEPH N = 169
Age	55 ± 17	58 ± 16
Female sex	348 (76.0)	84 (50.0)
BMI (kg/m^2) (n = 614)	31.0 ± 7.8	31.7 ± 8.5
Race/ethnicity		
Non-Hispanic white	328 (71.1)	111 (65.7)
African American	52 (11.3)	41 (24.3)
Hispanic	47 (10.2)	9 (5.3)
Asian	9 (2.0)	0 (0.0)
Other/multi-racial	25 (5.4)	8 (4.7)
Highest level of education (n = 628)		
Some Schooling	242 (53.0)	88 (52.7)
Completed high school	172 (37.6)	67 (40.1)
College or graduate studies	43 (9.4)	12 (7.2)
Household Income (n = 508)		
<$25,000	100 (26.7)	30 (23.1)
$25,000–50,000	84 (22.5)	34 (26.2)
$50,000–$75,000	58 (15.5)	20 (15.4)
$75,000–$100,000	41 (11.0)	23 (17.7)
>$100,000	91 (24.3)	23 (17.7)
Employment (n = 632)		
Homemaker/retired	320 (69.7)	106 (63.1)
Employed (Full or part time)	126 (27.5)	60 (35.7)
Unemployed	13 (2.8)	2 (1.2)
Marital status		
Married/living with partner	272 (59.0)	95 (56.2)
Widowed/divorced/separated	99 (21.5)	41 (24.3)
Never married	78 (16.9)	30 (17.8)
Did not answer	12 (2.6)	3 (1.8)
Right heart catheterization hemodynamics		
RA pressure (mm Hg)	10 [6, 14]	9 [7, 12]
Mean PA pressure (mm Hg)	51 [42, 60]	45 [37, 53]
PCWP (mm Hg)	11 [7, 14]	11 [8, 16]
Cardiac output (L/min)	4.2 [3.2, 5.1]	4.5 [3.6, 5.4]
Cardiac index (L/min/m^2)	2.1 [1.7, 2.6]	2.3 [1.9, 2.7]
PVR (Wood units)	9.7 [6.7, 14.0]	7.9 [5.4, 10.6]
Incident case	233 (50.7)	85 (50.9)
Pulmonary vasodilators		
PDE5 inhibitors	200 (43.4)	7 (4.1)
ERA	160 (34.7)	8 (4.7)
Parenteral prostacyclin	78 (16.9)	1 (0.6)
Inhaled prostacyclin	5 (1.1)	0 (0.0)
Selexipag	11 (2.4)	2 (1.2)
Riociguat	12 (2.6)	37 (21.9)
Any combination	176 (38.2)	6 (3.6)
Oxygen supplementation	140 (30.4)	38 (22.5)
Anticoagulation at presentation	79 (17.1)	91 (53.8)
Anticoagulation on follow-up	160 (34.7)	160 (94.7)
WHO functional class		
I	50 (11.7)	9 (6.0)
II	144 (33.8)	66 (43.7)
III	206 (48.4)	66 (43.7)
IV	26 (6.1)	10 (6.6)
6MWD (m)	345 ± 141	336 ± 118
Health-related quality of life measures		
emPHasis-10	24 ± 12	26 ± 12
SF-12 physical component	34 ± 7	33 ± 7
SF-12 mental component	49 ± 8	49 ± 9

Note: Data are presented as N (%), mean ± standard deviation, median [Interquartile Range].
6MWD: six-minute walk distance; RA: right atrial; PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; SF: short form; PDE5: phosphodiesterase-5; ERA: endothelin receptor antagonists.

On the other hand, patients with CTEPH were older with a mean age of 58 years, 50% were female and had a higher proportion of African Americans when compared to the IPAH group (24% vs. 11%). There were no differences in levels of education, household income, employment and marital status between groups.

When compared to the IPAH group, patients with CTEPH had lower median mean pulmonary artery pressures (45 vs. 51 mm Hg), lower pulmonary vascular resistance (7.9 vs. 9.7 Woods units) and higher cardiac output (4.5 vs. 4.2 L/min) but similar cardiac indices on their initial right heart catheterization. There were no differences in the WHO functional class or six-minute walk distance between the groups. Patients with CTEPH were most frequently treated with riociguat and anticoagulation therapy, whereas patients with IPAH were most often on phosphodiesterase-5 inhibitors, endothelin receptor antagonists, or a combination of both. At the time of referral to a PHAR enrolling site, only 54% of CTEPH patients were receiving anticoagulation; however, on follow-up, 95% were on anticoagulation therapy. These findings were consistent when analysis was limited to those with incident CTEPH (results not shown).

Health-related quality of life measures

At the time of enrollment, there was no difference in unadjusted mean E10 scores between patients with CTEPH and IPAH (Table 1). However, CTEPH patients had higher E10 scores (worse HRQoL) than patients with IPAH after adjusting for age, sex, BMI, six-minute walk distance and WHO functional class ($\beta = 2.83$, SE = 1.11, $p = 0.01$) (Fig. 2). There were no differences in the baseline mental or physical components of the SF-12 among the two groups even after multivariable adjustment (Fig. 2). Over time, there were no differences in either HRQoL score among the two groups, even after adjustment for PTE status (Fig. 3). Sensitivity analysis excluding surrogate measures of disease severity (six-minute walk distance and WHO functional class) had similar findings. There were no differences in SF-12 scores over time between the two groups.

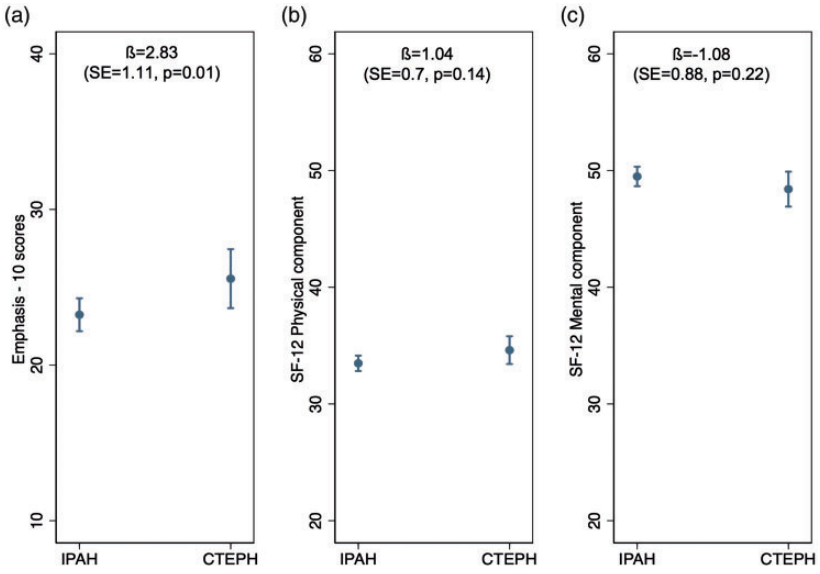

Fig. 2. Expected mean estimates for patients with IPAH vs. CTEPH of (a) emPHasis-10 scores, (b) Short Form-12 physical component and (c) Short Form-12 mental component scores at the time of enrollment adjusted for age, sex, BMI, six-minute walk distance and WHO functional class.

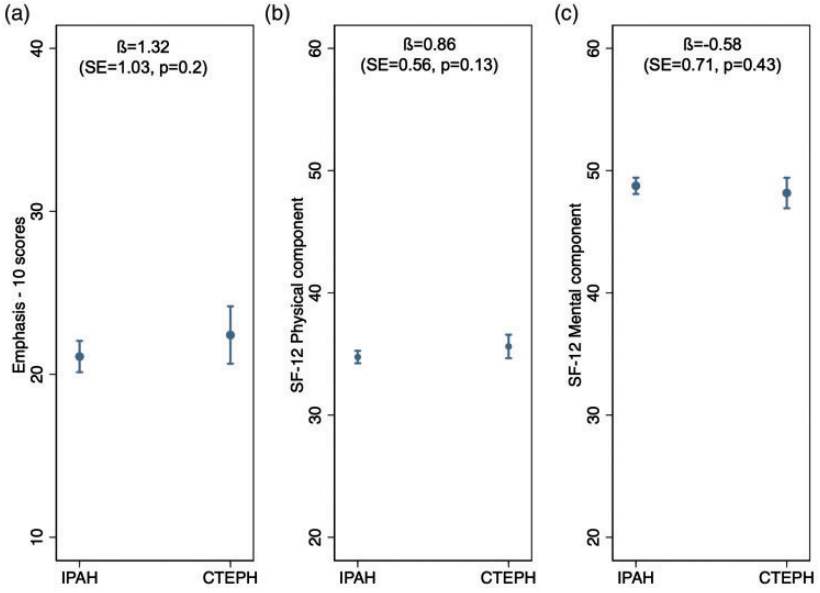

Fig. 3. Expected mean estimates for patients with IPAH vs. CTEPH of (a) emPHasis-10 scores, (b) Short Form-12 physical component and (c) Short Form-12 mental component scores over time adjusted for age, sex, BMI, six-minute walk distance, WHO functional class and pulmonary thromboendarterectomy status.

Hospitalizations

Of the 630 patients included in our study, 515 patients had at least one subsequent follow-up visit. During 1585 person-years of follow-up, there were 939 hospitalizations recorded. Patients with CTEPH had a higher incidence rate ratio of all-cause hospital admissions than patients with IPAH (IRR 1.66, 95%CI 1.04–2.65, p = 0.035) after adjustment for age, sex, BMI, six-minute walk distance, WHO functional class and PTE status (Fig. 4). In sensitivity analysis excluding CTEPH patients who underwent PTE, CTEPH patients were again noted to have increased incidence rates of hospitalizations as compared to IPAH patients (IRR 1.90, 95% CI 1.08–3.40, p = 0.027).

CTEPH subgroup analysis

In PHAR, 63% of patients with CTEPH were referred for surgical evaluation at enrollment. By the end of follow-up,

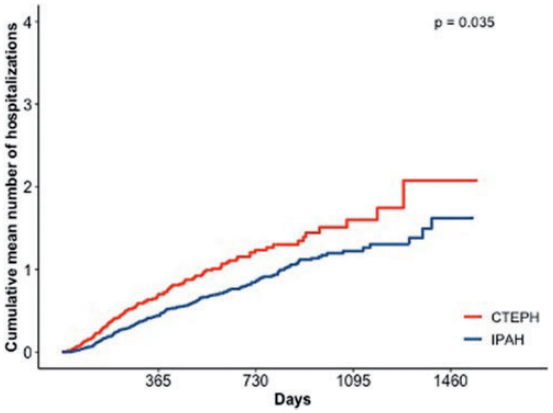

Fig. 4. Cumulative mean hospitalizations over time in patients with chronic thromboembolic pulmonary hypertension (CTEPH) vs. those with idiopathic pulmonary arterial hypertension (IPAH).

22% had undergone PTE and 78% were managed medically. Mean age was 59 years and majority females (69%) among all patients who were medically managed throughout and did not undergo PTE (Table 2). The CTEPH patients who underwent PTE were younger with a mean age of 54 years and more likely to be male (62%). There were no differences in levels of education, household income, employment, or marital status between the two groups (Table 2).

When compared to those that were medically managed, patients who underwent PTE had a higher cardiac output (4.7 vs. 4.3 L/min) and higher E10 scores (worse HRQoL, 29 vs. 24). However, the patients who underwent PTE were less likely to present in WHO functional class IV (3% vs. 6%) and had greater six-minute walk distances (425 vs. 335 m) in comparison to patients who were managed medically. There were no differences in cardiac indices, right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure between the groups and both were most frequently treated with riociguat (Table 2).

Patients who underwent PTE had a decrease in their E10 scores postoperatively indicating improved HRQoL (Fig. 5). Unadjusted mixed effects models showed that patients who underwent PTE had lower E10 scores and higher SF-12 physical component scores, both indicative of better HRQoL (Fig. 6). There were no differences in SF-12 mental component scores between the two subgroups.

Discussion

In a large multicenter prospective cohort of patients with IPAH and CTEPH across the US, patients with CTEPH at enrollment were older, with better hemodynamics (lower pulmonary artery systolic pressure and pulmonary vascular resistance) but worse HRQoL when compared to patients with IPAH after adjustment for baseline variables; however, the difference in HRQoL did not persist over time. Patients with CTEPH had higher hospitalization rates (after excluding hospitalization for PTE) than patients with IPAH. Among CTEPH patients, those who eventually underwent PTE were younger, male, with a higher cardiac output and better six-minute walk distance than those who were medically managed. In addition, patients with CTEPH who underwent PTE had improvement in their HRQoL.

Pulmonary hypertension is a rare debilitating disease that negatively impacts the quality of life of patients and their caregivers. In addition to hemodynamic measurements, laboratory biomarkers and exercise testing, there has been increased recognition of the importance of incorporating patient-centered outcomes into management decisions and clinical trial design.[11,24,25] A patient-reported outcome is a self-assessment of health by patients and frequently includes HRQoL.[26,27] Several studies have demonstrated a strong correlation between patient-reported HRQoL and outcomes such as the six-minute walk distance, hospitalizations and survival in pulmonary hypertension.[3,28,29] Studies exploring differences in HRQoL between patients with CTEPH and IPAH have mixed results with some finding no difference and others showing CTEPH patients having worse HRQoL.[14,30,31] The results from this study demonstrate that patients with CTEPH have higher E-10 scores (worse HRQoL) at referral to a Pulmonary Hypertension Care Center as compared to patients with IPAH, but these differences do not persist over time in a large prospective multicenter cohort. While the differences in scores at baseline is statistically significant, it is smaller than the minimally clinically important difference reported for E-10 scores,[32] which is approximately a six-point change, so the clinical implications of the difference in scores remain to be determined. Among CTEPH patients, similar to what has been previously reported,[31] this study found that patients who undergo PTE have significant improvement in their HRQoL, and the improvement in scores may be more significant in patients without residual disease post-PTE.[4,5]

The worse HRQoL observed in CTEPH patients at referral was not explained by older age as compared to IPAH patients; however, older age may be associated with increased co-morbid conditions, which were not available for us to account for. Over time, with treatment, both groups had similar HRQoL scores. The improvement in the CTEPH group may be driven by improved HRQoL scores in the subgroup of CTEPH patients who underwent PTE. In contrast, medically managed patients with CTEPH and IPAH patients continued to have similar HRQoL. Since most patients with CTEPH in this cohort were medically managed, this may have biased our results towards the null. While this study found differences in E-10 scores, no differences were detected in SF-12 scores among patients with IPAH versus those with CTEPH. The E-10 is a PH-specific instrument[22] and thus may be a more sensitive tool to measure HRQoL in these patient populations.

Table 2. Baseline characteristics of CTEPH patients who were medically managed or subsequently underwent pulmonary thromboendarterectomy (PTE).

	Medical management N = 133	PTE group N = 36
Age	59 ± 16	54 ± 15
Female sex	69 (52.0)	64 (38.0)
BMI (kg/m^2)	31.3 ± 8.0	30 ± 7.7
Race/ethnicity		
Non-Hispanic white	85 (64)	26 (72)
African American	34 (25.6)	7 (19.4)
Hispanic	8 (6.0)	1 (2.8)
Asian	0 (0.0)	0 (0.0)
Other/multi-racial	4 (4.5)	2 (5.6)
Highest level of education		
Some schooling	70 (53)	18 (51)
Completed high school	52 (39)	15 (43)
College or graduate studies	10 (8)	2 (6)
Household income		
<$25,000	24 (24)	6 (21)
$25,000–50,000	25 (25.7)	8 (28)
$50,000–$75,000	12 (11.9)	8 (27.6)
$75,000–$100,000	21 (20.8)	2 (6.9)
>$100,000	18 (17.8)	5 (17.2)
Employment		
Homemaker/retired	85 (64.4)	21 (58.3)
Employed (Full or part time)	45 (34.1)	15 (41.7)
Unemployed	2 (1.5)	0 (0.0)
Marital status		
Married/living with partner	77 (57.9)	18 (50)
Widowed/divorced/separated	32 (24.1)	9 (25)
Never married	21 (15.8)	9 (25)
Did not answer	3 (2.3)	0 (0.0)
Right heart catheterization hemodynamics		
RA pressure (mm Hg)	9 [6, 13]	10 [7, 12]
Mean PA pressure (mm Hg)	45 [37, 54]	45 [42, 51]
PCWP (mm Hg)	11 [8, 16]	11 [7, 14]
Cardiac output (L/min)	4.3 [3.52, 5.4]	4.7 [4.2, 5.5]
Cardiac index (L/min/m^2)	2.22 [1.88, 2.56]	2.29 [1.90, 2.80]
PVR (Wood units)	8 [5, 11]	7 [5, 10]
Pulmonary vasodilators		
PDE5 inhibitors	7 (5.3)	0 (0.0)
ERA	8 (6.0)	0 (0.0)
Parenteral prostacyclin	1 (0.8)	0 (0.0)
Inhaled prostacyclin	0 (0.0)	0 (0.0)
Selexipag	2 (1.5)	0 (0.0)
Riociguat	31 (23.3)	6 (16.7)
Any combination	6 (4.5)	0 (0.0)
Oxygen supplementation	29 (21.8)	9 (25.0)
Anticoagulation at presentation	61 (45.9)	30 (83.3)
Anticoagulation on follow-up	125 (94.0)	35 (97.2)
WHO functional class		
I	9 (7.6)	0 (0.0)
II	55 (46.6)	11 (33.3)
III	45 (38.1)	21 (63.6)
IV	9 (7.6)	1 (3.0)
6MWD (m)	335 ± 138	425 ± 82
Health-related quality of life measures		
emPHasis-10	24 ± 12	29 ± 11
SF-12 physical component	34 ± 7	35 ± 6
SF-12 mental component	49 ± 8	47 ± 9

Note: Data are presented as N (%), mean ± standard deviation, median [Interquartile Range].
6MWD: six-minute walk distance; RA: right atrial; PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; SF: short form; PDE5: phosphodiesterase-5; ERA: endothelin receptor antagonists

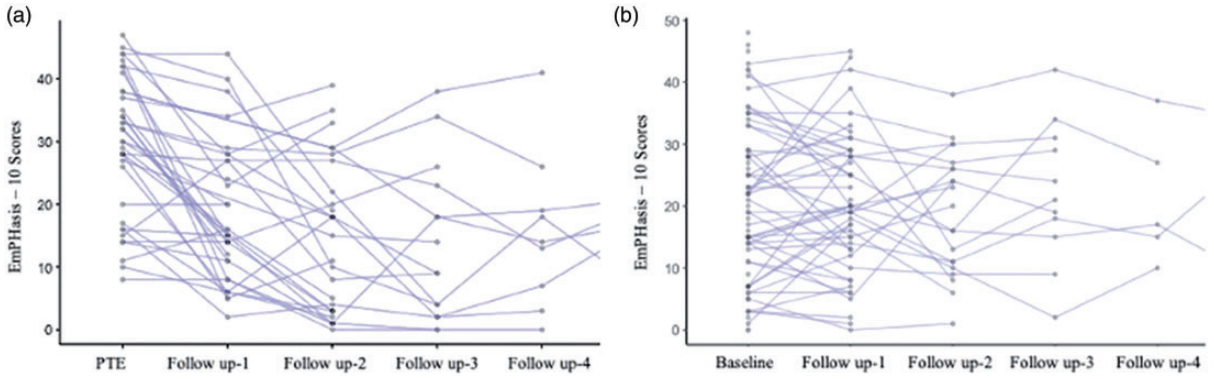

Fig. 5. Spaghetti plot of emPHasis-10 scores for individual patients with chronic thromboembolic pulmonary hypertension (CTEPH) (a) post-pulmonary thromboendarterectomy (PTE) and (b) medical management only.

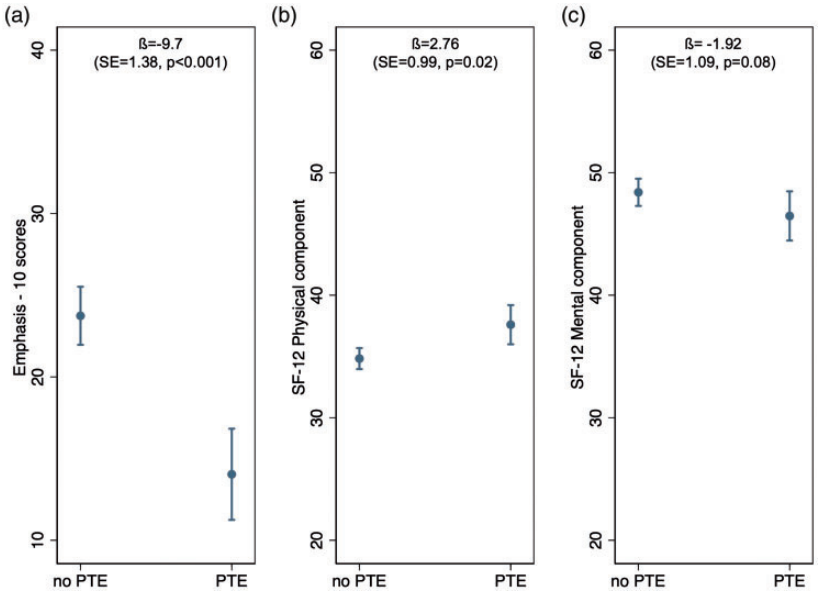

Fig. 6. Expected unadjusted mean estimates for patients with CTEPH who underwent pulmonary thromboendarterectomy (PTE) vs. those who were medically managed of (a) emPHasis-10 scores, (b) Short Form-12 physical component and (c) Short Form-12 mental component scores over time.

PTE is a potentially curative procedure in CTEPH and is recommended as the treatment of choice in this population by the European Society of Cardiology/European Respiratory Society expert consensus guidelines.[33,34] Successful PTE has been associated with lower right atrial pressure, higher cardiac index, better WHO functional class and improved survival.[4,35] In the overall population of patients with CTEPH, it is estimated that PTE is feasible in 63–76% of patients and 71–88% of those who are deemed operable undergo the procedure.[36] At their initial assessment at a Pulmonary Hypertension Care Center, only 63% of patients with CTEPH were referred for surgical evaluation for PTE. The relatively low rate of referral to PTE at enrollment in the PHAR is likely a reflection of their incident case status and referrals often occur after evaluation at one of the Pulmonary Hypertension Care Centers. Of all the CTEPH patients in our cohort, 78% were medically managed, and only 22% underwent PTE. An additional five patients had undergone PTE prior to enrollment in the PHAR and were excluded from our analysis. In our cohort, rates of PTE were significantly lower presumably because patients either declined surgery or had factors that deemed them unsuitable for surgery – such as comorbidities or distribution of clots on imaging. Reasons for no surgical referral and reasons for no PTE after surgical referral were not recorded in the PHAR. Due to the low number of patients who underwent PTE in this cohort, we were unable to examine how hospitalization rates change post PTE.

Pulmonary hypertension is associated with higher health care utilization and costs.[9,10,37,38] Studies of patients with CTEPH found that these patients have up to six times

higher inpatient and outpatient costs and overall health care utilization than matched controls.[8,37] However, we are not aware of prior studies comparing hospitalization rates between IPAH and CTEPH. In our cohort, patients with CTEPH had higher hospitalization rates than those with IPAH (excluding the hospitalization for PTE) even after adjusting for patient demographics and disease severity. It is possible that this may be a reflection of the higher rate of associated co-morbidities in this patient cohort, bleeding-related complications in patients with CTEPH or may include admissions for balloon pulmonary angioplasty, data for which were not collected in PHAR at the time of analysis.

This study has several limitations. Seven percent of patients in this registry were lost to follow-up. Based on the "real-world" registry protocol, patients were seen in follow-up "as clinically needed" in approximately six-month intervals, thus resulting in variable follow-up times for patients. However, this should not lead to a bias due to the non-differential nature of the missing data. Additionally, all of the previously presented longitudinal analyses incorporated patient follow-up times. Details of comorbid conditions and pulmonary vascular imaging were not recorded in the registry, limiting the assessment of surgical eligibility. Additionally, data on balloon pulmonary angioplasty were not collected in this cohort during the study period which limits our ability to investigate whether higher hospitalization rates among CTEPH patients could be partially attributable to patients undergoing balloon pulmonary angioplasty. Finally, the overall rates of PTE were lower in this cohort than those generally reported in the CTEPH population in prior publications and are likely reflective of "real-world" practice across pulmonary hypertension centers where PTE may not be readily accessible; however, we anticipate that the lower rates of PTE would have likely biased our results to the null. Data on the lack of surgical eligibility, patient refusal and balloon pulmonary angioplasty were not captured. To address some of these limitations, the PHAR began prospectively recording data on balloon pulmonary angioplasties starting in June 2020. Future studies will focus on the inclusion of these data for analyses.

In a large, multicenter, prospective cohort, patients with CTEPH were found to have significantly worse HRQoL at initial presentation to pulmonary hypertension specialty centers compared to patients with IPAH; however, these differences did not persist over time. CTEPH patients who underwent PTE experienced significant improvements in HRQoL. The worse baseline quality of life and higher hospitalization rate of CTEPH patients present an opportunity for improvement in clinical management of these patients.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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Contributorship

All authors have participated in the conceptualization, writing and interpretation of the content and have approved the final version of this article. Drs. Minhas, Narasimmal, Pugliese and Al-Naamani were involved in the data collection and analysis of this project.

Guarantor

Minhas and Al-Naamani are guarantors of the paper and take responsibility for the integrity of this work as a whole.

Ethical Approval

This study was approved by the University of Pennsylvania Institutional Review Board (#822830).

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