RESEARCH ARTICLE

Using PAH-SYMPACT to assess quality of life in patients with pulmonary hypertension associated with chronic lung disease

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Abstract

Chronic lung disease (CLD) is the second leading cause of pulmonary hypertension (PH) and is associated with significant morbidity and mortality. Although PH associated with CLD (PH-CLD) leads to impaired health-related quality of life (HRQOL), there are no validated tools to assess HRQOL in PH-CLD. The Pulmonary Arterial Hypertension–Symptoms and Impact Questionnaire (PAH-SYMPACT) is an HRQOL instrument aimed at assessing the symptoms and impact of PH on overall function and well-being. We performed a single-center prospective cohort study using PAH-SYMPACT scores to compare symptoms, exercise capacity and HRQOL in patients with PAH and PH-CLD. One hundred and twenty-five patients (99 patients with idiopathic/heritable PAH and 26 with PH-CLD) completed the PAH-SYMPACT questionnaire which consists of 22 questions that assess HRQOL across four domains: cardiopulmonary (CP) symptoms, cardiovascular (CV) symptoms, physical impact (PI), and cognitive/emotional (CE) impact. Higher scores indicate worse HRQOL. We compared patients with PAH and PH-CLD using a Wilcoxon rank sum or chi-squared test as appropriate. Multivariate linear regression analysis was used to assess the relationship between PH classification and SYMPACT scores. Compared to PAH, patients with PH-CLD were older, more likely to use oxygen and had worse functional class and exercise capacity. While there was no significant difference between the two groups in CP, CV, or CE domain scores, patients with PH-CLD had significantly worse PI scores by univariate (1.79 vs. 1.13, $p < 0.001$) and multivariate analysis (1.61 vs. 1.17, $p = 0.02$) and overall worse SYMPACT scores (1.19 vs. 0.91, $p = 0.03$). In conclusion, patients with PH-CLD have

worse HRQOL as assessed by the PAH-SYMPACT questionnaire versus patients with PAH. Although PAH-SYMPACT has not been validated in PH-CLD, the results of this study can guide clinicians in understanding the symptoms and impact of PH-CLD relative to PAH.

INTRODUCTION

Pulmonary hypertension (PH) is a heterogeneous group of disorders characterized by high pulmonary arterial pressures caused by several etiologies, most often due to chronic heart and lung disease.[1] Chronic lung disease (CLD) is the second leading cause of PH and is associated with significant morbidity, mortality, reduced functional capacity and impaired health-related quality of life (HRQOL).[2–4] Although advancements in the treatment of chronic lung disease-associated pulmonary hypertension (PH-CLD) have been made, clinical management rests upon an individualized approach to treatment of the underlying lung disease and consideration of approved PH therapy, such as inhaled treprostinil in PH-ILD,[5,6] or the off-label use of treatments approved for pulmonary arterial hypertension (PAH).[7,8]

HRQOL is defined as a person's own perceived physical and mental well-being and has been associated with outcomes and survival in PAH.[9,10] Within the PH community, therapeutic objectives are shifting to focus on morbidity and mortality endpoints as well as HRQOL, and studies demonstrate that an impaired HRQOL is associated with decreased survival in PAH, independent of disease severity.[11] Recently, the 6th World Symposium on Pulmonary Hypertension highlighted the importance of utilizing patient reported outcomes (PROs) and improving strategies for data collection regarding patient experiences to guide PH treatment.[12,13] We recently found that HRQOL assessed by the PAH-SYMPACT questionnaire could be used effectively to assess PROs in clinical practice.[14] Although patients with PH-CLD are known to have increased morbidity and mortality, little is known regarding HRQOL in this population.[14] In addition, there are no validated tools to assess HRQOL in PH-CLD and little is understood about the symptoms and impact of PH in CLD as compared to PAH. HRQOL in patients with PH-CLD is likely influenced by both CLD and PH; general HRQOL measures as well as CLD-specific tools may not capture the true impact of PH-CLD on HRQOL.

The PAH–Symptoms and Impact Questionnaire (PAH-SYMPACT) is a PAH disease-specific HRQOL instrument aimed at assessing the symptoms of PH as well as the impact of the disease on overall function and well-being.[15,16] The PAH-SYMPACT tool assesses HRQOL across four key domains: cardiopulmonary symptoms, cardiovascular symptoms, physical impact and cognitive and emotional impact.[15,16] Although this questionnaire has been validated as a disease-specific tool in assessing HRQOL in PAH, it has not yet been utilized in the PH-CLD population. In this study, we sought to describe PAH-SYMPACT scores in patients with PH-CLD and to compare symptoms, exercise capacity and HRQOL in PH-CLD and PAH.

METHODS

Study design

We performed a single-center prospective cohort study from 03/01/2019 to 01/06/2023 at Mayo Clinic Rochester, a tertiary academic medical center and accredited Pulmonary Hypertension Association Care Center.

Subjects

This study was approved by the Mayo Clinic Institutional Review Board (19-000630). The Mayo Clinic PH clinic schedule was screened on a daily basis to identify eligible patients. Patients aged 18 and above with a clinical diagnosis of PAH or PH-CLD with the ability to complete an English-based questionnaire verbally or in writing were deemed eligible for study participation. Patients with both incident (defined as enrollment within 90 days of diagnostic right heart catheterization) and prevalent PH were included. For our primary analysis, patients with idiopathic and heritable PAH were compared to PH-CLD. We also performed a sensitivity analysis comparing all patients with group 1 PAH to PH-CLD. PH diagnosis

and classification was determined by a PH specialist physician. Patients with group 2, 4, or 5 PH were excluded. Date of diagnosis was defined as the date of diagnostic right heart catheterization.

Study testing

Eligible patients were approached by research study personnel or clinicians following eligibility screening and invited to participate in the study. Informed consent was obtained. Patients completed the 1-day version of the PAH-SYMPACT questionnaire.[17] The PAH-SYMPACT questionnaire consists of 22 Likert-scale questions used to assess HRQOL across the four domains (cardiovascular symptoms, cardiopulmonary symptoms, physical impact and cognitive-emotional impact). The score of each question within a domain was added together and divided by the total number of questions within the domain to provide a mean domain score. Higher mean scores indicate worse HRQOL. A mean summary score was also determined by calculating the sum of the 4 mean domain scores then dividing by 4. Additional clinical data, including demographics, functional capacity, recent hospitalizations within 6 months, vital signs, test results (laboratory testing, echocardiogram, 6-min walk testing (6MWT) and most recent invasive hemodynamics), PH therapy and vital status were collected from the medical record from the most recent clinical visit. Data from testing within 1 year of enrollment (laboratory data, 6MWT, transthoracic echocardiogram and right heart catheterization) and the most recent diffusion capacity for carbon monoxide (DLCO) regardless of timing were utilized.

Statistical analysis

Descriptive statistics are reported as percentages for categorical variables and mean ± standard deviation for continuous variables. PAH and PH-CLD groups were compared using a two-sided t-test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Univariable and multivariable linear regression was performed to assess the relationship between PH Group and PAH-SYMPACT domain scores after adjusting for age and gender as determined a priori. The number of variables in the primary multivariable analysis were limited due to the small sample size to avoid overfitting. We also performed exploratory multivariable analyses to assess whether the relationship between PH group and PAH-SYMPACT domain scores persisted after adjustment for age and gender and other

relevant clinical characteristics that were significant in univariate analyses. The relationships between individual domain scores and markers of PH and lung disease severity [6MWT, NT-proBNP, functional vital capacity (FVC), forced expiratory volume in 1 s (FEV1), total lung capacity (TLC)] were assessed using Pearson correlation coefficients. We also examined whether the relationship between pulmonary hemodynamics and HRQOL varied by PH group by testing for interaction. Survival analysis was performed from date of enrollment (questionnaire completion) to date of death or last known follow-up using Kaplan–Meier methods. In all cases, two-tailed $p < 0.05$ were considered statistically significant. Statistical analysis was performed on SAS, version 9.4 and BlueSky, version 7.4.

RESULTS

Patient characteristics

The study cohort included 125 total patients, 99 with idiopathic or heritable PAH and 26 patients with PH-CLD. Within the PAH group, patients were predominantly female (68.7%) and Caucasian (95.8%) with a mean age of 56.3 ± 17.5 years (Table 1). Patients with PH-CLD were more likely to have incident PH (24% vs. 8.2%, $p = 0.03$), defined as enrollment within 90 days of diagnostic right heart catheterization. Of the PH-CLD group, 46.2% of patients were female and the majority were white (92.3%) with a mean age of 67.8 ± 12.0 years (Table 1). Restrictive lung disease was the most commonly represented PH-CLD subclassification (76.9%) (Table 1). Compared to the PAH cohort, patients with PH-CLD were older ($p < 0.001$), less likely to be female ($p = 0.03$) more likely to have diabetes (30.8% vs. 12.1%; $p = 0.02$), more likely to use supplemental oxygen (92.3% vs. 63.6%; $p = 0.006$) and more likely to have a higher functional class.

Clinical characteristics and test results

Clinical data regarding test results and PH therapy at the time of enrollment are shown in Table 2. Patients with PAH had a mean NT-proBNP of 1546 pg/mL, 6-min walk distance (6MWD) of 406 m, mean pulmonary artery pressure (mPAP) of 48.7 mmHg and pulmonary vascular resistance (PVR) of 9.8 WU (Table 2). Patients with PH-CLD had a mean NTproBNP of 1114.9, 6MWD of 323.9 m, mPAP of 40.8 mmHg and PVR of 6.5 WU. Compared to the PAH group, patients with PH-CLD had significantly worse 6MWD (323.9 ± 96.4 m vs. 406.2 ± 165.9 m; $p = 0.004$), were more likely to have a

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TABLE 1 Patient characteristics and PAH-SYMPACT domains in PAH and PH-CLD.

Characteristic	n	PAH	n	PH-CLD	p-value
Age	99	56.3 ± 17.5	26	67.8 ± 12.0	**<0.001**
Female	99	68 (68.7)	26	12 (46.2)	**0.03**
Race	95		26		0.61
White		91 (95.8)		24 (92.3)	
Other		4 (4.2)		2 (7.7)	
Incident disease	98	8 (8.2)	25	6 (24.0)	**0.03**
PAH etiology	99			N/A	N/A
Idiopathic		89 (89.9)			
Heritable		10 (10.1)			
PH-CLD subtype		N/A	26		N/A
Obstructive lung disease				4 (15.4)	
Restrictive lung disease				20 (76.9)	
Mixed				2 (7.7)	
Comorbidities	99		26		
Obstructive sleep apnea		30 (30.3)		9 (34.6)	0.67
Hypertension		11 (11.1)		4 (15.4)	0.51
Diabetes mellitus		12 (12.1)		8 (30.8)	**0.02**
Atrial fibrillation		5 (5.1)		2 (7.7)	0.63
Oxygen use	77	49 (63.6)	26	24 (92.3)	**0.006**
Hospitalization in the last 6 months	98	12 (12.2)	26	3 (11.5)	0.99
Functional class	93		24		**0.02**
I		18 (19.4)		0 (0.0)	
II		35 (37.6)		8 (33.3)	
III		36 (38.7)		16 (66.7)	
IV		4 (4.3)		0 (0.0)	
PAH-SYMPACT domain scores					
Mean cardiopulmonary symptom score	99	1.10 ± 0.62	26	1.21 ± 0.46	0.40
Mean cardiovascular symptoms score	99	0.52 ± 0.54	26	0.63 ± 0.55	0.39
Mean physical impact score	99	1.13 ± 0.86	26	1.79 ± 0.80	**<0.001**
Mean cognitive/emotional impact score	98	0.79 ± 0.78	25	1.05 ± 0.81	0.14
Mean SYMPACT score	98	0.91 ± 0.58	25	1.19 ± 0.50	**0.03**

Note: Data expressed as *n* (%) or mean ± standard deviation as appropriate. Two-sided *t*-test for independent samples used for continuous variables and Chi-square or Fisher exact test used for categorical variables. **Bold** font for *p*-values indicate *p* < 0.05.

Abbreviations: PAH, pulmonary arterial hypertension; PAH-SYMPACT, symptoms and impact; PH-CLD, chronic lung disease-associated pulmonary hypertension.

DLCO less than 40% (58% vs. 16%; $p < 0.001$), more likely to be treatment naïve at enrollment (38.5% vs. 12.1%; $p = 0.002$) and less likely to be treated with a PDE5 inhibitor, an endothelin receptor antagonist or a parenteral prostacyclin (Table 2). The PH-CLD cohort was noted to have better pulmonary hemodynamics with lower right atrial (RA) pressures (6.7 ± 4.6 mmHg vs. 9.1 ± 5.2 mmHg; $p = 0.05$) and significantly lower mPAP (40.8 ± 10.6 mmHg vs. 48.7 ± 12.5 mmHg; $p = 0.005$) and PVR (6.5 ± 3.0 WU vs. 9.8 ± 6.2 WU, $p = 0.002$).

TABLE 2 Test results and pulmonary hypertension therapy in PAH and PH-CLD.

Characteristic	*n*	PAH	*n*	PH-CLD	*p*-value
Laboratory data					
NTproBNP, pg/mL	97	1546.8 ± 4845.6	25	1114.9 ± 705.6	0.47
Estimated GFR, mL/min/1.73 m^2	96	65.5 ± 20.1	26	64.5 ± 19.0	0.82
6-min walk distance, meters	86	406.2 ± 165.9	22	323.9 ± 96.4	**0.004**
DLCO <40% predicted	98	16 (16.3)	26	15 (57.7)	**<0.001**
Echocardiogram data					
RVSP, mmHg	91	66.8 ± 23.3	23	61.3 ± 19.2	0.29
Right ventricular strain, %	79	-19.2 ± 6.5	25	-19.2 ± 5.6	0.97
Cardiac output, L/min	96	5.7 ± 1.4	25	5.8 ± 2.5	0.91
Cardiac index, L/min/m^2	96	3.0 ± 0.7	23	3.0 ± 1.0	0.72
Pericardial effusion	97	22 (22.7)	22	4 (16.0)	0.59
Most recent pulmonary hemodynamics					
RA pressure, mmHg	97	9.1 ± 5.2	23	6.7 ± 4.6	0.05
mPAP, mmHg	97	48.7 ± 12.5	25	40.8 ± 10.6	**0.005**
PAWP, mmHg	98	10.5 ± 3.4	25	10.4 ± 3.9	0.93
Cardiac index, L/min/m^2	69	2.6 ± 0.9	23	2.6 ± 0.7	0.80
PVR, Wood units	70	9.8 ± 6.2	22	6.5 ± 3.0	**0.002**
PAH therapy at enrollment	99		26		
Treatment naïve		12 (12.1)		10 (38.5)	**0.002**
Phosphodiesterase 5 inhibitor		76 (76.8)		13 (50.0)	**0.007**
Soluble guanylate cyclase stimulator		5 (5.1)		0 (0.0)	0.58
Endothelin receptor antagonist		59 (59.6)		4 (15.4)	**<0.001**
Oral or inhaled prostacyclin pathway agent		29 (29.3)		8 (30.8)	0.99
Parenteral prostacyclin		29 (29.3)		0 (0.0)	**<0.001**

Note: Data expressed as *n*, (%) or mean ± standard deviation. Two-sided *t*-test for independent samples used for continuous variables and Chi-square or Fisher exact test used for catgeorical variables. **Bold** font for *p*-values indicate $p < 0.05$.

Abbreviations: DLCO, diffusion capacity for carbon monoxide; GFR, glomerular filtration rate; MPAP, mean pulmonary arterial pressure; NTproBNP, N-terminal pro B-type natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RVSP, right ventricular systolic pressure.

PAH-SYMPACT domain scores

The mean scores for each PAH-SYMPACT domain are summarized in Table 1. PAH patients had a mean cardiopulmonary (CP) domain score of 1.10 ± 0.62, cardiovascular (CV) score of 0.52 ± 0.54, physical impact (PI) score of 1.13 ± 0.86, cognitive-emotional (CE) score of 0.79 ± 0.78 and mean PAH-SYMPACT summary score of 0.91 ± 0.58. For the PH-CLD group, the mean CP domain score was 1.21 ± 0.46, CV score was 0.63 ± 0.55, PI score was 1.79 ± 0.80, CE score was 1.05 ± 0.81 and mean summary PAH-SYMPACT score was 1.19 ± 0.50 (Table 1). Compared to PAH, patients with PH-CLD had worse HRQOL as assessed by the PAH-SYMPACT

questionnaire with similar CP, CV, and CE domain scores, but significantly higher PI scores ($p = 0.002$) and overall summary PAH-SYMPACT scores ($p = 0.03$). PH-CLD was also associated with significantly higher PI scores after adjustment for age and gender (least square means 1.61, 95% confidence interval [CI]: 1.30–1.93 vs. 1.17, 95% CI: 1.00–1.35, $p = 0.02$) but was no longer associated with higher summary scores. PH-CLD remained associated with higher PI scores in multi-variable models adjusting for age, gender and RVSP (least square means: 1.59, 95% CI: 1.25–1.92 vs. 1.15, 95% CI: 0.97–1.32, $p = 0.02$) and age, gender and functional class (least square means: 1.55, 95% CI: 1.25–1.84 vs. 1.18, 95% CI: 1.03–1.33, $p = 0.03$) with similar trends no longer
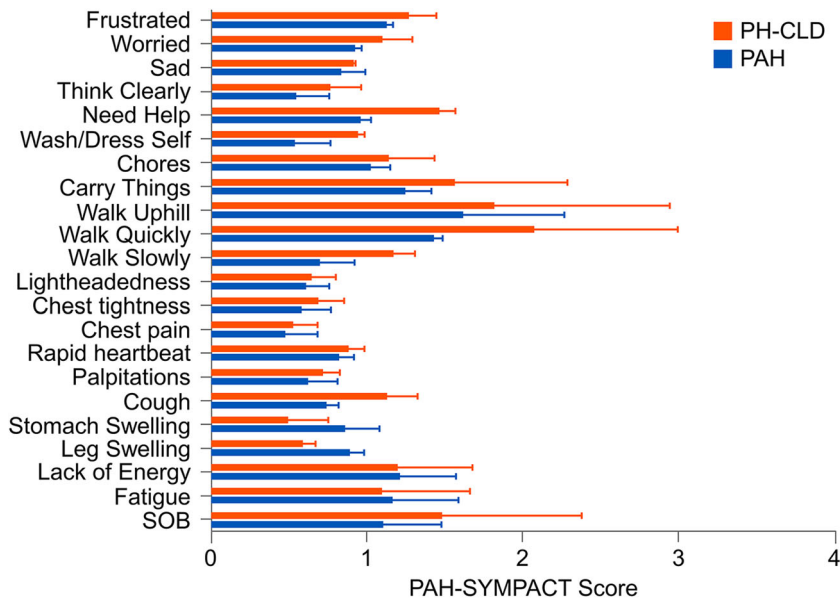
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FIGURE 1 Mean scores for individual questions within the symptom and impact domains of the PAH-SYMPACT questionnaire compared between patients with PAH and PH-CLD. Higher scores indicate worse health-related quality of life. Error bars indicate standard deviation. PAH, pulmonary arterial hypertension; PAH-SYMPACT, PAH-symptoms and impact; PH-CLD, pulmonary hypertension associated with chronic lung disease; SOB, shortness of breath.

achieving statistical significance after adjusting for age, gender and 6MWD (least square means: 1.52, 95% CI: 1.24–1.80 vs. 1.24, 95% CI: 1.10–1.39, $p = 0.09$) and age, gender and incident PH (least square means: 1.50, 95% CI: 1.17–1.82 vs. 1.18, 95% CI: 1.01–1.34, $p = 0.09$). Figure 1 depicts the comparison of responses to individual PAH-SYMPACT questions between patients with PAH and PH-CLD. Overall, patients with PH-CLD had higher mean scores across a majority of the questions with the most notable difference in questions within the PI domain. In our sensitivity analysis comparing patients with all group 1 PAH ($n = 232$) to PH-CLD, results were similar. Patients with PH-CLD had worse HRQOL as indicated by higher overall PAH-SYMPACT summary scores (1.19 ± 0.50 vs. 0.94 ± 0.59, $p = 0.04$) and higher PI domain scores (1.79 ± 0.80 vs. 1.21 ± 0.87, $p = 0.001$) with similar CV, CP, and CE domain scores ($p > 0.05$ for all).

Association of PAH-SYMPACT domain scores and clinical characteristics of PH-CLD patients

Associations between clinical characteristics and PAH-SYMPACT domain scores within the PH-CLD group are detailed in Table 3. Among patients with PH-CLD, female gender was associated with worse CE domain scores (1.46 ± 0.90 vs. 0.67 ± 0.49, $p = 0.01$) but similar CP, CV, and PI domain scores. Higher functional class was associated with worse PI domain scores. 6MWD was significantly associated with all domain scores, and this relationship is depicted in Figure 2 with the corresponding Pearson correlation coefficients. Higher PVR and NTproBNP were

associated with worse CV domain scores but not other individual domain scores. Other hemodynamic variables (RA pressure, mPAP, and CO) were not associated with individual domain scores. The remaining variables including age, RVSP, TLC, FEV1, FVC, and DLCO values were not associated with PAH-SYMPACT domain scores. The interaction terms for PVR and PH group with CV symptom and CE impact domain scores were both significant ($p = 0.04$ and 0.048, respectively), suggesting that the relationship between PVR and HRQOL is different in PH-CLD as compared to PAH (Figure 3). There were no significant interactions between other hemodynamic parameters or domain scores.

Of the 26 patients with PH-CLD, 12% were hospitalized within 6 months before enrollment, this however, was not found to be associated with any of the four domain scores ($p > 0.05$ for all domains) (Table 3).

DISCUSSION

In this study, we utilized the PAH-SYMPACT questionnaire to compare HRQOL between patients with PH-CLD and PAH and to identify clinical characteristics associated with PAH-SYMPACT domain scores in PH-CLD. We found that (1) patients with PH-CLD reported worse HRQOL than patients with PAH, as assessed by both overall PAH-SYMPACT score and PI score, (2) within the PH-CLD group, all four domain scores were associated with exercise capacity as assessed by the 6MWD and (3) using the PAH-SYMPACT questionnaire to assess HRQOL in patients with PH-CLD is feasible and provides insight into the symptoms and impact of PH in CLD.

TABLE 3 Univariate associations between PAH-SYMPACT domain score and clinical characteristics of patients with PH-CLD.

	CP score	CV score	PI score	CE score
Age	$r = 0.02, p = 0.95$	$r = 0.04, p = 0.84$	$r = -0.24, p = 0.23$	$r = 0.07, p = 0.74$
Female gender	$\beta = 0.10, p = 0.60$	$\beta = 0.13, p = 0.56$	$\beta = 0.13, p = 0.68$	$\beta = 0.79, p = \mathbf{0.01}$
Functional Class III/IV	$\beta = 0.26, p = 0.16$	$\beta = 0.21, p = 0.35$	$\beta = 0.77, p = \mathbf{0.01}$	$\beta = 0.64, p = 0.05$
6MWD, meters	$\boldsymbol{r = -0.43, p = 0.046}$	$\boldsymbol{r = -0.47, p = 0.03}$	$\boldsymbol{r = -0.51, p = 0.02}$	$\boldsymbol{r = -0.62, p = 0.003}$
RVSP, mmHg	$r = 0.30, p = 0.15$	$r = 0.22, p = 0.30$	$\boldsymbol{r = 0.41, p = 0.047}$	$r = 0.24, p = 0.26$
RA pressure, mmHg	$r = -0.05, p = 0.83$	$r = 0.18, p = 0.41$	$r = 0.09, p = 0.69$	$r = 0.23, p = 0.28$
mPAP, mmHg	$r = -0.14, p = 0.51$	$r = 0.13, p = 0.54$	$r = 0.17, p = 0.42$	$r = 0.34, p = 0.10$
PVR, wood units	$r = 0.06, p = 0.78$	$\boldsymbol{r = 0.57, p = 0.005}$	$r = 0.20, p = 0.37$	$r = 0.41, p = 0.06$
Cardiac index	$r = 0.18, p = 0.40$	$r = -0.29, p = 0.18$	$r = 0.07, p = 0.76$	$r = 0.02, p = 0.93$
NT-proBNP, pg/mL	$r = 0.31, p = 0.13$	$\boldsymbol{r = 0.42, p = 0.04}$	$r = 0.27, p = 0.19$	$r = 0.30, p = 0.16$
Hospitalization	$\beta = -0.11, p = 0.70$	$\beta = 0.04, p = 0.91$	$\beta = 0.19, p = 0.71$	$\beta = -0.06, p = 0.91$
FVC, %	$r = 0.16, p = 0.46$	$r = 0.00, p = 0.98$	$r = 0.09, p = 0.64$	$r = 0.18, p = 0.34$
FEV1, %	$r = 0.12, p = 0.62$	$r = 0.26, p = 0.23$	$r = 0.02, p = 0.76$	$r = 0.15, p = 0.48$
TLC, %	$r = 0.13, p = 0.61$	$r = 0.09, p = 0.74$	$r = 0.07, p = 0.91$	$r = 0.12, p = 0.54$
DLCO, %	$r = 0.07, p = 0.82$	$r = 0.25, p = 0.32$	$r = 0.20, p = 0.34$	$r = 0.02, p = 0.96$
Oxygen use	$\beta = 0.50, p = 0.14$	$\beta = 0.36, p = 0.38$	$\beta = 1.01, p = 0.09$	$\beta = 0.87, p = 0.15$
Incident PH	$\beta = 0.21, p = 0.30$	$\beta = 0.20, p = 0.42$	$\beta = -0.12, p = 0.75$	$\beta = -0.34, p = 0.38$

Note: Data expressed as β coefficient and *p*-value for categorical data or correlation coefficient (r) and *p*-value for continuous variables. **Bold** font for *p*-values indicate $p < 0.05$.

Abbreviations: DLCO, diffusion capacity adjusted for carbon monoxide; FEV1, forced expiratory volume; FVC, forced vital capacity; 6MWT, 6-min walk test; NT-proBNP, N-terminal pro-terminal brain natriuretic peptide; TLC, total lung capacity.
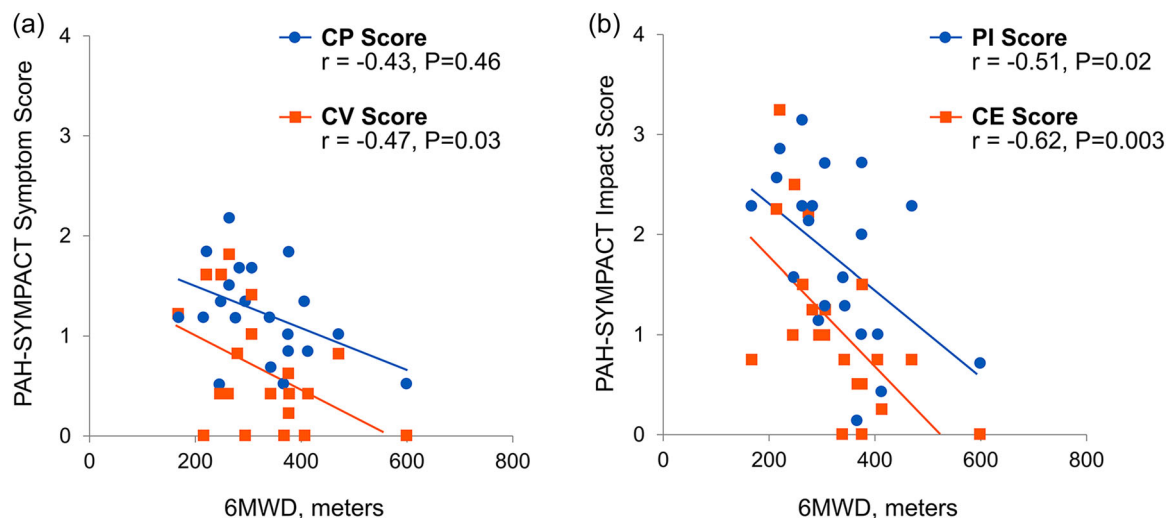

FIGURE 2 Scatter plot showing the relationship between PAH-SYMPACT symptom (a) and impact (b) domain scores and 6-min walk distance among patients with PH-CLD. Corresponding correlation coefficient and *p*-values are also shown. PAH, pulmonary arterial hypertension; PAH-SYMPACT, PAH-symptoms and impact; PH-CLD, pulmonary hypertension associated with chronic lung disease.

The PAH-SYMPACT questionnaire has been used previously to assess HRQOL in patients with PAH,[10,15,16] however this is the first study to assess HRQOL in the PH-CLD population using this tool. Although this questionnaire was not specifically developed for or validated in PH-CLD, it provides important information regarding the impact of PH on HRQOL in PH-CLD. To our knowledge, no studies have previously compared
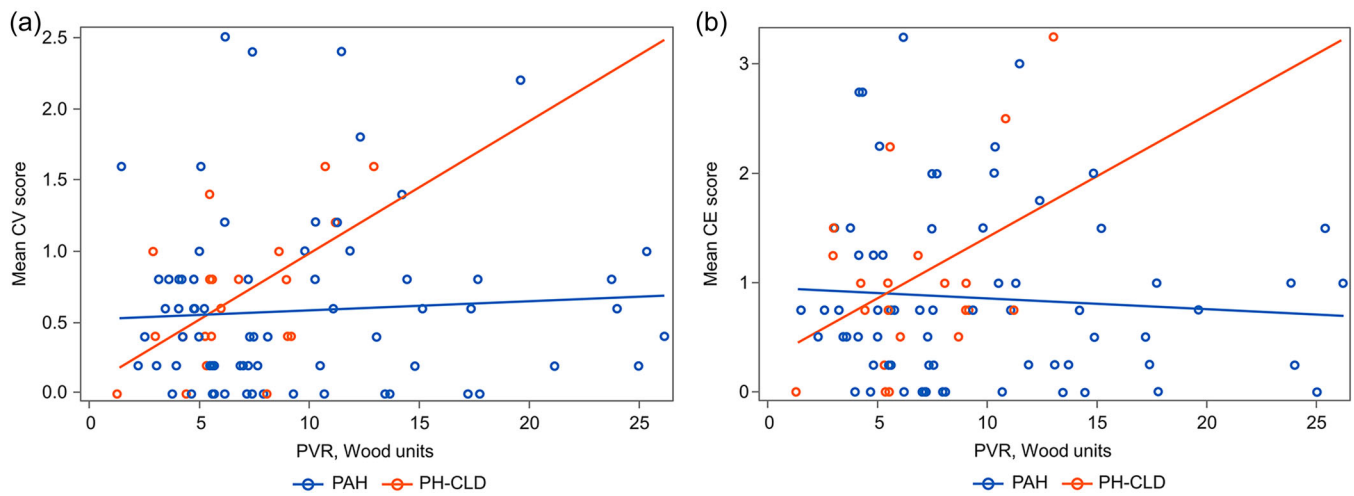
FIGURE 3 Analysis of covariance depicting the relationship between pulmonary vascular resistance and mean cardiovascular symptom domain (a) and cognitive and emotional impact domain (b) scores for patients with pulmonary arterial hypertension and pulmonary hypertension associated with chronic lung disease.

HRQOL in PAH and PH-CLD. Thus, it is not known whether PH and CLD have a synergistic detrimental effect on symptoms, such as dyspnea. We found that patients with PH-CLD had a decreased ability to walk quickly on a flat surface, a decreased ability to walk uphill and worse PI and overall PAH-SYMPACT scores when compared to their PAH counterparts. This relationship with higher PI scores among patients with PH-CLD persisted after adjustment for factors such as functional class but was no longer statistically significant after adjustment for a higher prevalence of incident disease among patients with PH-CLD. There is no established minimal clinically important difference in PAH-SYMPACT scores. Thus, it is not clear whether the differences we observed between PAH and PH-CLD are clinically meaningful. In the SYMPHONY trial validation of PAH-SYMPACT,[16] an improvement in patient global assessment of disease severity was associated with a decrease in PI scores of 0.50, suggesting that the difference in PI scores we observed between groups for PI scores (0.66 in unadjusted models and 0.44 in adjusted models) was similar to changes that were deemed clinically meaningful by patients. Impaired exercise capacity as assessed by 6MWD was significantly reduced in the PH-CLD population as compared to PAH patients and was also strongly associated with individual domain scores.

As research continues to expand into the area of HRQOL, there is recognition that PROs should be primary endpoints and treatment goals in addition to current prognostic indicators such as functional class and 6MWD.[10,18] Although there are many factors which can impact HRQOL, improved understanding of tools to assess HRQOL in varied diseases and classifications of PH can help improve our awareness of the individual patient experience to further guide treatment approaches. Interestingly, female gender was associated with worse CE domain scores in PH-CLD, a relationship that has not been observed in PAH.[10] Unsurprisingly, all four of the PAH-SYMPACT domains were associated with exercise capacity as assessed by the 6MWD. This association is similar to the relationship between 6MWD and PAH-SYMPACT scores in PAH.[10] Functional class was also associated with PI scores in PH-CLD but was not associated with CP, CV, or CE domain scores. In contrast, functional class was more strongly associated with PAH-SYMPACT domain scores among patients with PAH.[10] Last, oxygen use was more prevalent among patients with PH-CLD and was not associated with domain scores whereas prior studies have identified worse CP and PI domain scores associated with supplemental oxygen use among patients with PAH.

Both PH and CLD severity may impact HRQOL in PH-CLD. We found that PH severity, as assessed by NT-proBNP and PVR but not by other hemodynamic parameters, was associated with CV domain scores but not other individual domain scores. Additional domains such as the CP and PI domains may be associated with PH severity, but our study may have been underpowered to detect significant associations given the small sample size. Additionally, there was a unique relationship between PVR and HRQOL among patients with PH-CLD as illustrated in Figure 3, although the clinical implications of this analysis is also limited by the small sample size of the PH-CLD cohort. Interestingly, pulmonary function as assessed by TLC, FEV1, FVC, and DLCO

was not associated with any of the PAH-SYMPACT domains. This suggests that impairments in pulmonary function are not directly related to HRQOL as assessed by the PAH-SYMPACT tool. This could potentially be due to PH severity having a greater impact on HRQOL or to the PH-specific nature of the tool. Interestingly, other studies that have investigated HRQOL with disease specific tools in Chronic Obstructive Pulmonary Disease and ILD also did not identify a significant association between HRQOL and pulmonary function parameters.[19,20]

Taken as a whole, other objective markers of disease severity such as pulmonary hemodynamics, laboratory values and pulmonary function measurements did not directly translate to impairments in HRQOL in PH-CLD. While the lack of association between HRQOL and pulmonary hemodynamics and lung function may be related to the length of time between diagnostic information and PRO assessment, such findings suggest that variables traditionally prioritized for disease assessment in clinical practice are not strongly associated with PROs. Whether PAH-SYMPACT adequately assesses the full range of symptoms and disease impact of PH-CLD on individuals is not known, but our study highlights the importance of assessing PROs in PH-CLD as they provide unique insight into the patient experience of PH-CLD relative to PAH.

LIMITATIONS

Limitations of the study include the single center nature of the study, the relatively small number of patients with PH-CLD, the limited racial diversity and the use of a single tool to assess HRQOL rather than a comparison of multiple tools. Additionally, the validity of PAH-SYMPACT in PH-CLD has not been well-established so our findings are considered exploratory as they attempt to better understand the symptoms and impact of PH-CLD. Last, it is not known how PH therapy impacts HRQOL as assessed by the PAH-SYMPACT domains and whether this would be an effective tool to use as an endpoint in PH-CLD clinical trials.

CONCLUSIONS

In conclusion, patients with PH-CLD have worse HRQOL than their PAH counterparts as assessed by the PAH-SYMPACT questionnaire. HRQOL across PAH-SYMPACT domains was associated with 6MWD but was not associated with pulmonary function. Our study provides insight into the symptoms and impact of PH-CLD relative to PAH and may help clinicians better understand the patient experience of PH-CLD. Future studies are needed to determine the best tool to assess HRQOL in PH-CLD.

AUTHOR CONTRIBUTIONS

All listed authors made a substantial contribution to the project design, data acquisition, analysis and manuscript preparation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

This study was approved by the Mayo Clinic Institutional Review Board and adheres to all institutional ethical standards.

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