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RESEARCH ARTICLE

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The feasibility and value of assessing patient-reported outcomes in pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vascular disease that negatively impacts health-related quality of life (HRQOL). The PAH-symptoms and impact (PAH-SYMPACT) questionnaire is a validated disease-specific patient-reported outcome (PRO) instrument that assesses a patient's symptoms and the impact of PAH and its treatment on well-being. We performed a single-center prospective cohort study of patients with PAH to determine the feasibility of assessing PROs in clinical practice and to determine the association between PAH-SYMPACT domains and clinical characteristics and outcomes. One hundred and ten patients completed the 1-day version of the PAH-SYMPACT questionnaire which consists of 22 Likert-scale questions that assess HRQOL across four domains: cardiopulmonary (CP) symptoms, cardiovascular (CV) symptoms, physical impact (PI), and cognitive and emotional (CE) impact. Higher scores indicate worse HRQOL. Patients were predominantly female ($n = 86$, 78%) with a mean age of 57.8 ± 16.2 years. While several patient characteristics were associated with CP and PI domains, few were associated with CV and CE domains. PI and CE impact scores were associated with recent hospitalizations and mortality and CE impact score was independently associated with an increased risk of death after adjustment for disease severity (hazard ratio: 3.29, 95% confidence interval: 1.56–6.91, $p = 0.002$). In conclusion, the assessment of PROs in clinical practice using the PAH-SYMPACT questionnaire is both feasible and valuable. PAH-SYMPACT scores have independent prognostic value and are not adequately reflected by traditional measures of disease severity. These findings underscore the importance of assessing HRQOL in clinical practice.

KEYWORDS
PAH-SYMPACT, patient-reported outcomes, pulmonary arterial hypertension, quality of life

INTRODUCTION

Pulmonary arterial hypertension (PAH), despite recent therapeutic advances, is a chronic and progressive pulmonary vascular disease associated with impaired health-related quality of life (HRQOL) and survival.[1,2] HRQOL, defined as an individual's perceived physical and mental well-being, is an important prognostic measure that is strongly associated with PAH outcomes and survival.[1,2] PAH negatively impacts HRQOL across physical, social, and emotional domains.[1,2] HRQOL is also increasingly recognized as an important endpoint in clinical trials, but there is incomplete understanding regarding the specific determinants of HRQOL.[3] Prior studies have found that impaired HRQOL as measured by the physical component summary of the Short-Form-36 questionnaire, a generic measurement of HRQOL, is associated with worse survival in PAH, independent of disease severity.[1] HRQOL as assessed by the EMPHASIS-10 score, a PAH disease-specific patient-reported outcome (PRO) tool, has also been associated with mortality.[4,5] Despite its importance, HRQOL is rarely assessed routinely in clinical practice.

Experts at the 6th World Symposium on Pulmonary Hypertension (PH) emphasized the value of incorporating the patient perspective into PAH management, but current treatment guidelines and algorithms do not include PROs.[3,6,7] Treatment decisions are driven primarily by pulmonary hemodynamics, physician-assessed functional class (FC), and laboratory test results rather than how a patient subjectively feels and functions in their daily lives.[6] Although current PAH therapies delay disease progression and improve exercise capacity and pulmonary hemodynamics, they are not curative and are commonly associated with adverse effects, which may negatively impact HRQOL.

The PAH-symptoms and impact (PAH-SYMPACT) questionnaire is a PAH disease-specific PRO instrument that was recently developed and validated in accordance with Food and Drug Administration guidelines to assess the impact of PAH and its treatment on an individual's HRQOL.[8,9] PAH-SYMPACT assesses HRQOL across four domains: cardiopulmonary (CP) symptoms, cardiovascular (CV) symptoms, physical impact (PI), and cognitive and emotional (CE) impact.[9,10] Importantly, the instrument is sensitive to change[9] and thus can detect the effect of specific interventions on HRQOL. Although the PAH-SYMPACT tool is a validated disease-specific instrument, there is limited literature regarding its use outside of clinical trials. In this study, we sought to define the feasibility and utility of assessing PROs in clinical practice and to determine the association between PAH-SYMPACT domains and clinical characteristics and outcomes.

METHODS

Study design

We performed a single-center prospective cohort study at Mayo Clinic Rochester, a tertiary academic medical center and accredited Pulmonary Hypertension Association Care Center (PHCC).[11]

Subjects

The Mayo Clinic PH clinic schedule was screened to identify eligible patients. Patients aged 18 years or older with a clinical classification of Group 1 PAH and the ability to complete the PAH-SYMPACT questionnaire verbally or in writing were eligible for participation. For patients with an unclear diagnosis or PH classification, a PH specialist physician reviewed the medical record to determine clinical classification and eligibility. Patients with comorbidities, such as chronic lung disease, were classified according to current guidelines.[12] Patients with the incident and prevalent PAH were included. The date of diagnostic right heart catheterization was considered the date of diagnosis. Patients with Groups 2–5 PH were excluded.

Study testing

Patients were approached by research study personnel or clinical providers at the time of their clinical appointment and invited to participate in the study. Verbal informed consent was obtained. Patients were preferentially asked to complete the questionnaires before discussion of clinical test results when feasible. For practical use in the clinical setting, patients completed the 1-day version of the PAH-SYMPACT questionnaire.[10] The PAH-SYMPACT questionnaire, licensed for study use by Mapi research trust, consists of 22 Likert-scale questions that assess HRQOL across four domains: CV symptoms, CP symptoms, PI, and CE impact. The score of each question within a domain is added and then divided by the total number of questions within the domain to provide a mean domain score. Higher mean scores indicate worse HRQOL. Clinical data, including demographics, FC, recent hospitalization within 6 months before enrollment, vital signs, test results (laboratory testing, echocardiogram, 6-min walk testing,

most recent pulmonary hemodynamics), PAH therapy, and vital status were collected from the medical record. PH physicians and study personnel completed a case report form for each patient to ensure accurate PH classification and to calculate REVEAL 2.0 scores.[13] We used data from the most recent test (laboratory data, 6-min walk distance, echocardiogram, and right heart catheterization) performed within one year and the most recent diffusion capacity for carbon monoxide (DLCO) regardless of timing to calculate REVEAL 2.0 scores.

Statistical analysis

Descriptive statistics are reported as number (percent) for categorical variables and mean ± standard deviation or median (interquartile range [IQR]) for continuous variables. Univariable and multivariable (adjusted for a priori determined variables of age and sex) linear regression analyses were performed to explore the association of clinical characteristics and PAH-SYMPACT domain scores. We assessed the relationship between individual domain scores and 6-min walk distance and FC using Pearson correlation coefficients and analysis of variance, respectively. Cox proportional hazards regression analyses were performed to examine the relationship between PAH-SYMPACT domain scores and survival using unadjusted models and models adjusted for disease severity as assessed by the REVEAL 2.0 risk score. For survival analysis, patients were followed from enrollment (questionnaire completion) to death, defined as all-cause mortality, or last follow-up. Vital status was assessed on 12/31/20 with follow-up censored on this date. Kaplan–Meier survival curves stratified by median domain scores for the cohort were generated for illustrative purposes. In all cases, two-tailed $p < 0.05$ were considered statistically significant. Statistical analysis was performed in SAS, version 9.4.

RESULTS

Patient characteristics

One hundred and seventeen patients with PAH were invited to participate in the study between March 2019 and June 2020, of whom 110 (94%) agreed to participate with complete (100%) follow-up of all patients. Patients were predominantly female ($n = 86$, 78%) and white ($n = 98$, 96%) with a mean age of 57.8 ± 16.2 years (Table 1). The majority of patients had a diagnosis of idiopathic or connective tissue disease-associated PAH, but there was a comprehensive distribution of PAH

TABLE 1 Patient characteristics and PAH-SYMPACT domain scores

Characteristic	*n*	Summary statistics
Age	110	57.8 ± 16.2
Female Sex	110	86 (78%)
Race	102	
White		98 (96%)
Other		4 (4%)
PAH Etiology	110	
Idiopathic		43 (39%)
Heritable		6 (5%)
Associated with drug/toxin use		3 (3%)
Associated with connective tissue disease		42 (38%)
Associated with human immunodeficiency virus		1 (1%)
Associated with portal hypertension		1 (1%)
Associated with congenital heart disease		13 (12%)
Pulmonary veno-occlusive disease		1 (1%)
Comorbidities	110	
Obstructive sleep apnea		17 (15%)
Chronic obstructive pulmonary disease		18 (16%)
Asthma		5 (5%)
Interstitial lung disease		14 (13%)
Hypertension		10 (9%)
Diabetes mellitus		8 (7%)
Hypothyroidism		6 (5%)
Atrial fibrillation		5 (5%)
Time from diagnosis to enrollment, months	105	41.0 (14.0–109.0)
Oxygen use	110	61 (55%)
Hospitalizations in last 6 months	110	15 (14%)
Functional class	107	
I		15 (14%)
II		46 (43%)
III		39 (36%)
IV		7 (7%)
PAH-SYMPACT domain scores		
Mean cardiopulmonary symptom score	110	1.0 ± 0.6

(Continues)

TABLE 1 (Continued)

Characteristic	*n*	Summary statistics
Mean cardiovascular symptom score	109	0.5 ± 0.6
Mean physical impact score	110	1.2 ± 0.9
Mean cognitive emotional impact score	110	0.8 ± 0.7

Note: Data expressed as *n*, %, mean ± standard deviation or median (25th percentile–75th percentile) as appropriate.

Abbreviation: PAH-SYMPACT, PAH-symptoms and impact.

subclassifications (Table 1). Most patients had FC II or III symptoms (Table 1). Comorbidities and other characteristics are described in Table 1.

PAH-SYMPACT domain scores

The mean scores for each symptom and impact question are depicted in Figure 1. Shortness of breath, fatigue, and lack of energy, had the highest individual symptom scores while walking uphill, walking quickly and carrying things had the highest impact scores. The mean CP domain score was 1.0 ± 0.6, CV score was 0.5 ± 0.6, PI score was 1.2 ± 0.9, and CE score was 0.8 ± 0.7 (Table 1). HRQOL was reduced in the majority of patients with 69% of patients reporting a mean score of >1.0 in at least one domain, indicating more than mild impairment in PAH symptoms or impact.

Test results and PAH risk stratification

Laboratory and other test results and PAH therapy at enrollment are detailed in Table 2. The median 6-min walk distance was 400.8 (IQR: 265.2–531.9) meters. Echocardiographic right ventricular systolic pressure (RVSP) was elevated at 67.0 (IQR: 51.0–85.0 mmHg) with reduced right ventricular (RV) function as measured by RV strain (−20.0%, IQR: −23.0 to −14.0). Pulmonary hemodynamics from the most recent right heart catheterization were consistent with precapillary PH. The majority of patients had treated, prevalent PAH with a median duration of 41 months between PAH diagnosis and enrollment. Seven percent of patients were treatment naïve (incident PAH) at enrollment, 24% were treated with monotherapy and 69% were treated with combination therapy. The median REVEAL 2.0 risk score was 7, consistent with intermediate risk (Table 2).

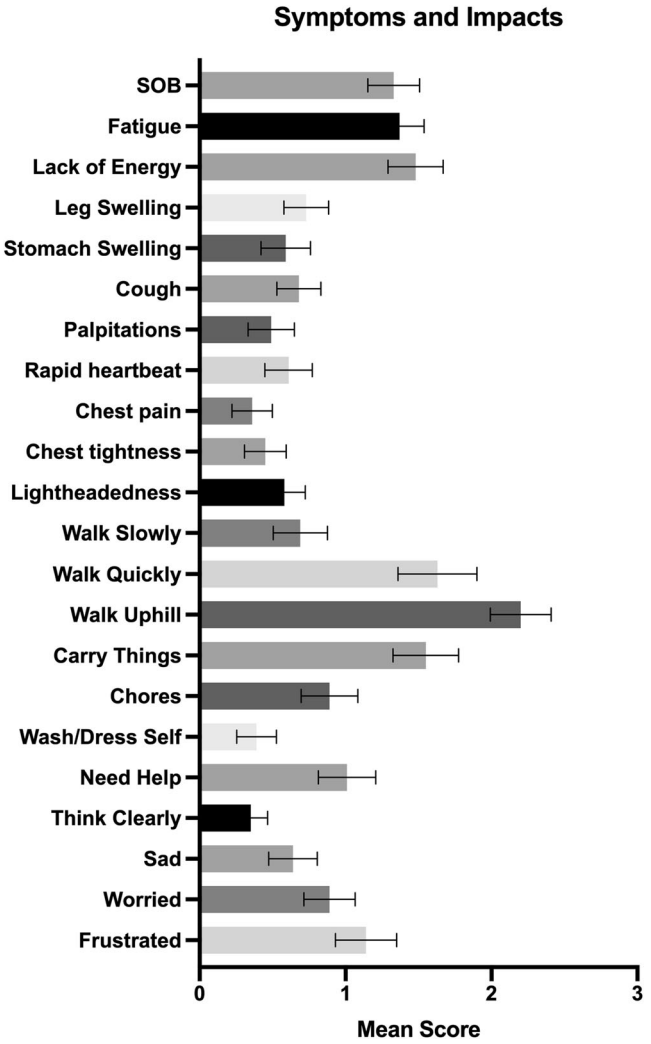

FIGURE 1 Mean scores for individual questions within the PAH-SYMPACT symptom and impact domains. Error bars indicate 95% confidence intervals. Higher scores indicate worse health-related quality of life. PAH-SYMPACT, PAH-symptoms and impact; SOB, shortness of breath.

Associations of PAH-SYMPACT domain scores and clinical variables

The univariable associations between clinical characteristics and PAH-SYMPACT domain scores with their corresponding point estimates, 95% confidence intervals (CIs), and *p*-values are detailed in Table 3. Compared to FC I, higher FC was associated with worse domain scores. Mean individual domain scores across FC are illustrated in Figure 2. Several variables, including older age, race, PAH etiology (less impaired CP symptoms in heritable PAH as compared to idiopathic PAH), supplemental oxygen use, FC, N-terminal pro brain natriuretic peptide (NTproBNP), lower hemoglobin, 6-min walk distance, DLCO < 40% predicted, lower mean pulmonary

TABLE 2 Test results, treatment, and risk stratification

Characteristic	*n*	Summary statistics
Laboratory data		
NTproBNP (pg/ml)	103	362.0 (125.0–1124.0)
Hemoglobin (g/dl)	102	13.3 (11.9–14.4)
Estimated GFR (ml/min/1.73m^2)	103	68.0 (52.0–86.0)
6 min walk distance (m)	88	400.8 (265.2–531.9)
DLCO < 40% predicted	109	25 (23%)
Echocardiogram data		
RVSP (mmHg)	107	67.0 (51.0–85.0)
Right ventricular strain (%)	87	−20.0 (−23.0 to −14.0)
Cardiac output (L/min)	107	5.6 (4.8–6.9)
Cardiac index (L/min/m^2)	107	3.1 (2.7–3.6)
Pericardial effusion	109	33 (30%)
Most recent pulmonary hemodynamics		
RA pressure (mmHg)	107	9.0 (6.0–13.0)
mPAP (mmHg)	108	48.5 (38.0–57.0)
PAWP (mmHg)	108	11.0 (8.0–14.0)
Cardiac index (L/min/m^2)	106	2.6 (1.8–3.2)
PVR (Wood units)	103	7.5 (4.8–13.2)
PAH therapy strategy at enrollment	110	
Treatment naïve at enrollment		8 (7%)
Monotherapy		26 (24%)
Combination therapy		76 (69%)
PAH therapeutic class at enrollment[a]	110	
Calcium channel blocker		11 (10%)
Phosphodiesterase 5 inhibitor		77 (70%)
Soluble guanylate cyclase stimulator		7 (6%)
Endothelin receptor antagonist		67 (61%)
Oral or inhaled prostacyclin pathway agent		31 (28%)
Parenteral prostacyclin		16 (15%)
REVEAL 2.0 risk score	108	7.0 (4.0–10.0)

Note: Data expressed as *n*, %, mean ± standard deviation or median (25th percentile–75th percentile) as appropriate.

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.

[a]Patients may have been treated with more than one PAH therapeutic class.

arterial pressure (mPAP) on most recent right heart catheterization, higher REVEAL 2.0 risk score, obstructive sleep apnea (OSA) and interstitial lung disease (ILD) were associated with higher CP symptom domain scores while only FC, OSA and hypertension were significantly associated with CV symptom domain scores. Older age, PAH etiology (worse PI in connective tissue disease-PAH compared to idiopathic PAH), shorter time from diagnosis to enrollment, supplemental oxygen use, FC, higher NTproBNP, lower hemoglobin, reduced 6 min walk distance, DLCO < 40% predicted, higher RVSP, worse RV function, treatment naive status, higher REVEAL 2.0 risk scores, were associated with higher PI domain scores while only FC, 6 min walk distance, DLCO < 40% predicted, treatment naive status, and higher REVEAL 2.0 score were associated with CE impact domain scores. The relationship between individual domain scores and 6-min walk distance with corresponding correlation coefficients and *p*-values are depicted in Figure 3. Compared to treatment-naïve patients, patients treated with monotherapy and combination therapy had similar CP and CV symptom scores and lower PI and CE impact scores. Excluding treatment naïve patients, route of therapy (parenteral vs. nonparenteral) was not associated with significant differences in domain scores.

Results of multivariable analyses are summarized in Supporting Information: Tables 1–4. After adjusting for age and sex, only FC, PAH etiology, supplemental oxygen use, hemoglobin, 6-min walk distance, DLCO < 40% predicted, *lower* mPAP, and comorbidities (OSA, interstitial lung disease, and hypertension) remained associated with higher CP scores and only FC and comorbidities (OSA and hypertension) were associated with CV scores. After adjustment for age and sex, several variables including FC, time from diagnosis to enrollment, supplemental oxygen use, NTproBNP, 6-min walk distance, DLCO < 40% predicted, right ventricular systolic pressure, right ventricular strain, PAH therapy, REVEAL 2.0 risk score and hypertension remained significantly associated with PI score and only FC, 6-min walk distance, DLCO < 40% predicted, PAH therapy, and REVEAL 2.0 risk score were significantly associated with CE impact score.

Outcomes and prognostic impact of PAH-SYMPACT domains

Fourteen percent of patients reported hospitalizations in the 6 months preceding enrollment. Recent hospitalizations were associated with both PI scores (0.63, 95% CI: 0.16–1.09, $p = 0.009$) and CE impact scores (0.48, 95% CI:

TABLE 3 Associations between PAH-SYMPACT domain scores and clinical characteristics

	Cardiopulmonary Symptom Score		Cardiovascular Symptom Score		Physical Impact Score		Cognitive Emotional Impact Score	
Characteristic	***Estimate (95% CI)***	***P***	***Estimate (95% CI)***	***P***	***Estimate (95% CI)***	***P***	***Estimate (95% CI)***	***P***
Age	0.01 (0.00, 0.02)	0.005	0.00 (−0.01, 0.01)	0.74	0.02 (0.01, 0.03)	<0.001	0.00 (−0.01, 0.01)	0.60
Male sex	0.03 (−0.23, 0.30)	0.81	0.01 (−0.28, 0.29)	0.96	0.12 (−0.28, 0.52)	0.56	0.02 (−0.31, 0.35)	0.90
White race	0.61 (0.04, 1.18)	0.04	0.30 (−0.39, 1.00)	0.39	0.43 (−0.43, 1.29)	0.32	0.54 (−0.11, 1.19)	0.10
PAH Etiology								
Idiopathic	Ref		Ref		Ref		Ref	
Heritable	−0.64 (−1.13, −0.16)	0.01	−0.30 (−0.83, 0.24)	0.28	−0.43 (−1.16, 0.30)	0.24	−0.10 (−0.73, 0.52)	0.74
CTD	0.05 (−0.19, 0.30)	0.66	−0.04 (−0.31, 0.23)	0.76	0.38 (0.01, 0.74)	0.04	0.27 (−0.05, 0.58)	0.10
CHD	−0.26 (−0.61, 0.10)	0.15	−0.01 (−0.40, 0.38)	0.97	−0.28 (−0.81, 0.25)	0.29	0.12 (−0.33, 0.58)	0.59
Other	−0.26 (0.74, 0.23)	0.30	0.04 (−0.50, 0.57)	0.89	0.19 (−0.54, 0.92)	0.61	−0.02 (−0.65, 0.61)	0.95
Time from diagnosis to enrollment	−0.02 (−0.04, 0.00)	0.07	−0.01 (−0.03, 0.01)	0.32	−0.04 (−0.06, −0.01)	0.01	−0.02 (−0.04, 0.01)	0.20
Oxygen use	0.40 (0.20 0.61)	<0.001	0.15 (−0.09, 0.38)	0.21	0.72 (0.42, 1.02)	<0.001	0.17 (−0.10, 0.45)	0.21
Functional class								
I	Ref		Ref		Ref		Ref	
II	0.41 (0.11, 0.70)	0.008	0.24 (−0.11, 0.59)	0.18	0.53 (0.18, 0.88)	0.003	0.01 (−0.40, 0.41)	0.98
III	0.80 (0.49, 1.10)	<0.001	0.50 (0.14, 0.86)	0.008	1.46 (1.10, 1.82)	<0.001	0.57 (0.16, 0.98)	0.007
IV	1.04 (0.58, 1.50)	<0.001	0.58 (0.04, 1.13)	0.04	2.28 (1.74, 2.82)	<0.001	0.45 (−0.17, 1.07)	0.16
Laboratory Data								
Log (NTproBNP)	0.09 (0.02, 0.16)	0.012	0.04 (−0.04, 0.12)	0.34	0.22 (0.12, 0.32)	<0.001	0.06 (−0.03, 0.15)	0.19
Hemoglobin, g/dL	−0.10 (−0.16, −0.05)	<0.001	−0.04 (−0.10, 0.03)	0.24	−0.11 (−0.20, −0.03)	0.01	−0.02 (−0.10, 0.05)	0.59
Estimated GFR, ml/min/1.73m^2	0.06 (0.01, 0.11)	0.07	0.00 (−0.01, 0.01)	0.85	−0.01 (−0.02, 0.00)	0.09	0.00 (−0.01, 0.00)	0.42
6 minute walk distance, per 10–meters	−0.01 (−0.02, −0.01)	<0.001	−0.01 (−0.01, 0.00)	0.16	−0.03 (−0.04, −0.03)	<0.001	−0.01 (−0.02, 0.00)	0.004
DLCO <40% predicted	0.39 (0.13, 0.64)	0.003	−0.10 (−0.38, 0.17)	0.46	0.78 (0.42, 1.15)	<0.001	0.39 (0.07, 0.71)	0.02
Echocardiogram								
RVSP, mmHg	0.00 (0.00, 0.01)	0.21	0.00 (0.00, 0.01)	0.20	0.01 (0.00, 0.02)	0.01	0.01 (0.00, 0.01)	0.07
RV strain, %	0.01 (0.00, 0.03)	0.08	0.01 (−0.01, 0.02)	0.34	0.04 (0.02, 0.07)	<0.001	0.01 (−0.01, 0.04)	0.20
Pericardial effusion	−0.01 (−0.25, 0.23)	0.91	−0.04 (−0.30, 0.22)	0.76	0.14 (−0.22, 0.50)	0.46	−0.12 (−0.42, 0.18)	0.44
Hemodynamics								
RA pressure, mmHg	−0.01 (−0.03, 0.02)	0.59	0.00 (−0.02, 0.02)	0.98	−0.01 (−0.04, 0.03)	0.74	0.00 (−0.03, 0.02)	0.95
MPAP, mmHg	−0.01 (−0.02, 0.00)	0.008	−0.01 (−0.02, 0.00)	0.17	−0.01 (−0.02, 0.01)	0.25	0.00 (−0.01, 0.01)	0.99
PAWP, mmHg	0.00 (−0.03, 0.02)	0.72	−0.01 (−0.03, 0.02)	0.67	−0.01 (−0.05, 0.02)	0.50	−0.01 (−0.03, 0.02)	0.71
Cardiac index, L/min/m^2	0.06 (−0.08, 0.19)	0.39	−0.04 (−0.18, 0.10)	0.58	−0.13 (−0.33, 0.07)	0.19	−0.04 (−0.21, 0.12)	0.60
PVR, Wood units	−0.02 (−0.04, 0.00)	0.07	0.00 (−0.03, 0.02)	0.90	0.01 (−0.02, 0.04)	0.55	0.01 (−0.02, 0.04)	0.48
Treatment								
Treatment naive	Ref		Ref		Ref		Ref	
Monotherapy	−0.10 (−0.56, 0.37)	0.68	−0.12 (−0.61, 0.38)	0.64	−0.84 (−1.51, −0.18)	0.01	−0.68 (−1.25, −0.11)	0.02

TABLE 3 (Continued)

Characteristic	Cardiopulmonary Symptom Score		Cardiovascular Symptom Score		Physical Impact Score		Cognitive Emotional Impact Score	
	Estimate (95% CI)	*P*	*Estimate (95% CI)*	*P*	*Estimate (95% CI)*	*P*	*Estimate (95% CI)*	*P*
Combination therapy	−0.29 (−0.71, 0.14)	0.19	−0.14 (−0.60, 0.31)	0.54	−1.03 (−1.65, −0.42)	0.001	−0.62 (−1.14, −0.10)	0.02
Parenteral Therapy								
Non–parenteral	Ref		Ref		Ref		Ref	
Parenteral	−0.11 (−0.44, 0.21)	0.48	−0.28 (−0.61, 0.05)	0.09	−0.12 (−0.58, 0.34)	0.60	−0.06 (−0.45, 0.33)	0.76
REVEAL 2.0 risk score	0.04 (0.01, 0.06)	0.01	0.02 (−0.01, 0.05)	0.18	0.13 (0.09, 0.16)	<0.001	0.04 (0.01, 0.08)	0.02
Comorbidities								
OSA	0.40 (0.11, 0.70)	0.008	0.44 (0.12, 0.76)	0.007	0.50 (0.05, 0.94)	0.03	0.06 (−0.32, 0.44)	0.74
COPD	0.26 (−0.03, 0.56)	0.08	0.05 (−0.26, 0.37)	0.73	0.64 (0.21, 1.07)	0.004	0.34 (−0.02, 0.71)	0.07
Asthma	0.32 (−0.21, 0.84)	0.23	−0.23 (−0.79, 0.33)	0.42	0.43 (−0.36, 1.21)	0.29	0.10 (−0.56, 0.76)	0.76
ILD	0.43 (0.11, 0.75)	0.009	−0.10 (−0.45, 0.25)	0.58	0.46 (−0.03, 0.94)	0.07	0.06 (−0.36, 0.47)	0.79
Hypertension	0.33 (−0.21, 0.84)	0.08	0.53 (0.14, 0.92)	0.009	0.54 (−0.02, 1.10)	0.06	0.16 (−0.32, 0.64)	0.51
Diabetes Mellitus	0.10 (−0.32, 0.53)	0.63	0.11 (−0.37, 0.58)	0.65	0.04 (−0.59, 0.67)	0.90	0.06 (−0.47, 0.59)	0.82
Hypothyroidism	−0.21 (−0.69, 0.28)	0.40	−0.28 (−0.79, 0.23)	0.28	−0.28 (−1.00, 0.44)	0.44	0.17 (−0.43, 0.78)	0.58
Atrial fibrillation	0.04 (−0.49, 0.57)	0.89	0.06 (−0.49, 0.62)	0.82	0.79 (0.01, 1.56)	0.047	0.05 (−0.61, 0.71)	0.89

Note: For each PAH-SYMPACT domain score separate regression analyses were performed for each characteristic to assess the univariable association of the given characteristic with the given PAH-SYMPACT domain score. Results from these analyses are summarized by presenting the estimate (95% CI) for the regression coefficient. For categorical variables the estimate corresponds to the change in domain score for the given category relative to the reference category. For 6 min walk the estimate corresponds to the change in domain score associated with a 10 meter increase. For all other continuous variables, the estimate corresponds to the change in domain score associated with a 1-unit change in the given characteristic. Bold values indicate statistical significant at $p < 0.05$.

Abbreviations: CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DLCO, diffusion capacity for carbon monoxide; ILD, interstitial lung disease; MPAP, mean pulmonary arterial pressure; NTproBNP, N-terminal pro B-type natriuretic peptide; OSA, obstructive sleep apnea; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RVSP, right ventricular systolic pressure.

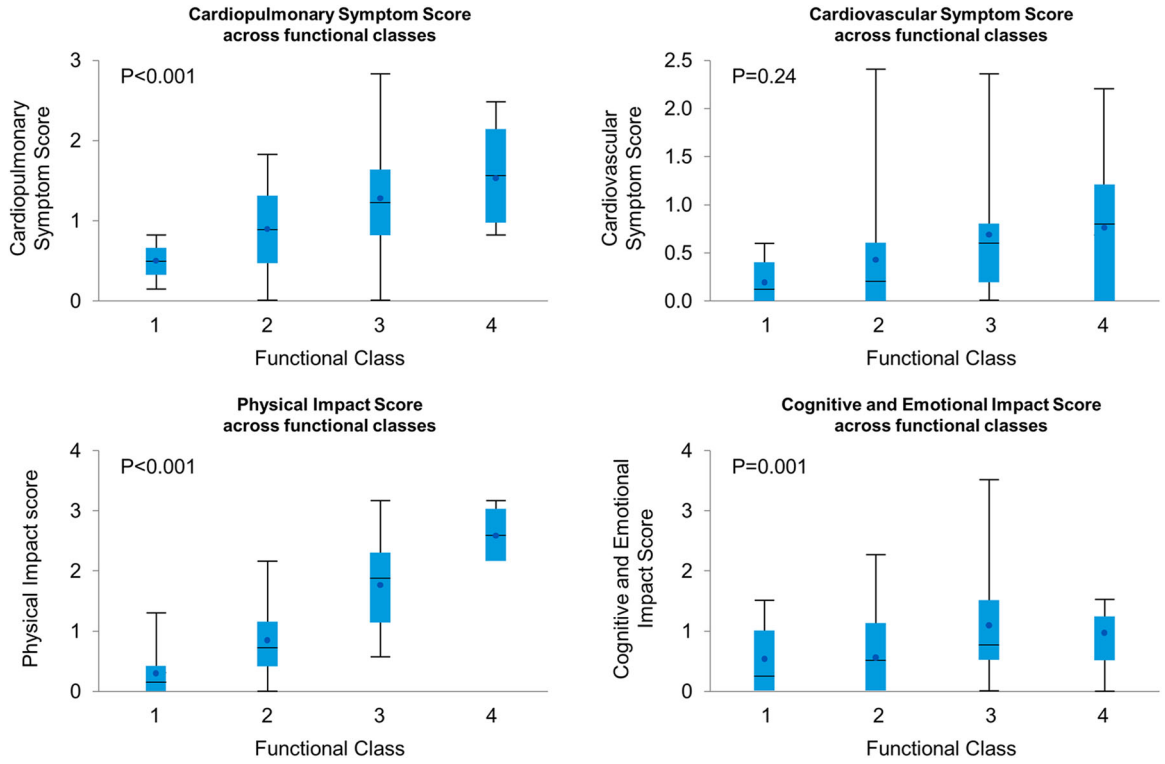

FIGURE 2 Cardiopulmonary symptom, cardiovascular symptom, physical impact, and cognitive emotional impact PAH-SYMPACT domain scores across functional classes. The mean value is indicated by the blue dot while the median is indicated by the line and error bars indicate the range of values. PAH-SYMPACT, PAH-symptoms and impact.

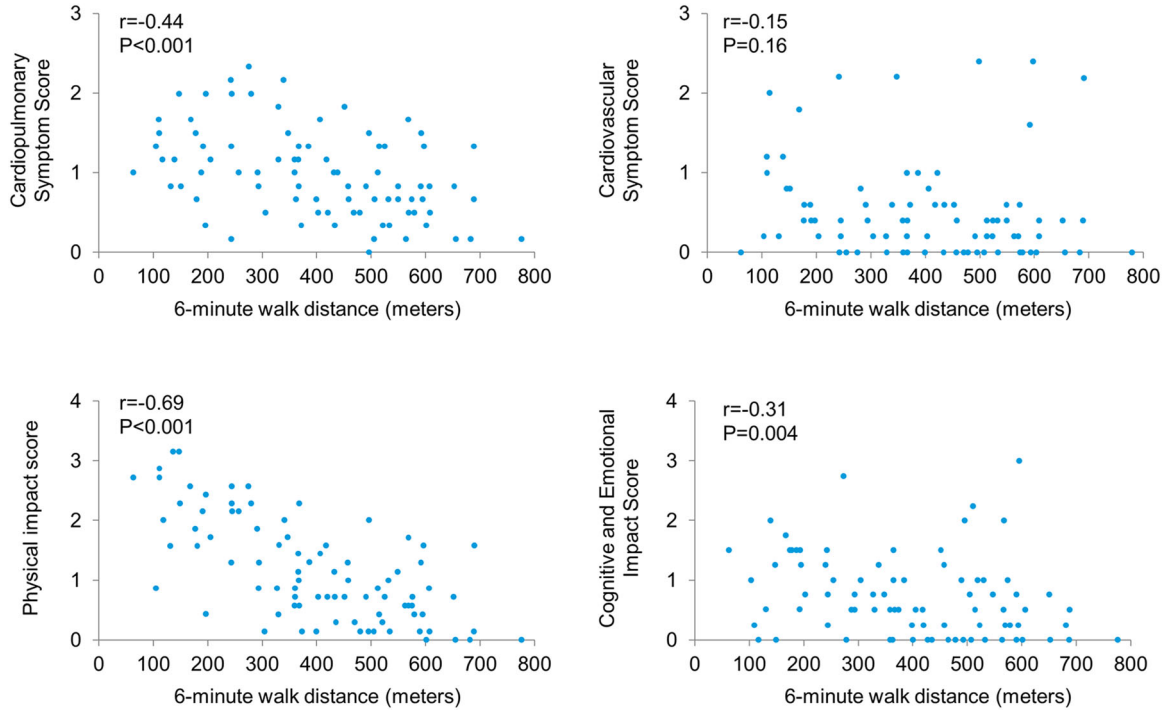

FIGURE 3 Scatter plot demonstrating the relationship between 6-min walk distance and cardiopulmonary symptom, cardiovascular symptom, physical impact, and cognitive and emotional impact domain scores with corresponding correlation coefficients and *p*-values.

0.09–0.87, $p = 0.02$) but neither CP nor CV symptom scores ($p > 0.05$ for both). Twelve out of 110 patients died during the study period (3/1/2019–12/31/2020). In unadjusted analysis, symptom domain scores were not associated with mortality but both impact domain scores (PI and CE impact) were significantly associated with mortality. In multivariate analysis after adjustment for REVEAL 2.0 risk score, only CE impact score remained significantly associated with an increased risk of death (hazard ratio: 3.29, 95% CI: 1.56–6.91, $p = 0.002$) (Table 4). Unadjusted Kaplan–Meier survival curves stratified by median CE score (Figure 4) are shown. Patients with a high CE domain score had worse survival compared to patients with a low CE score (log-rank $p = 0.03$).

DISCUSSION

In this prospective study, we assessed HRQOL using the PAH-SYMPACT questionnaire in real-world clinical practice. We found that (1) three out of four domain scores were associated with FC, 6-min walk distance, DLCO % predicted, and REVEAL 2.0 risk scores, (2) PAH-SYMPACT domain scores, particularly the CV symptom and CE impact domain scores, were poorly associated with traditional indicators of PAH disease severity, such as NTproBNP, RV function, and pulmonary hemodynamics, (3) the CE impact of PAH is independently associated with worse survival, even after adjustment for prognostic risk stratification as assessed by the REVEAL 2.0 score and lastly, (4) routine assessment of HRQOL is feasible and provides valuable insight into the patient experience of living with PAH.

Patient characteristics

The overall demographics and patient characteristics in our study reflect the real-world clinical practice of a tertiary academic center and accredited PHCC. Both treated and untreated patients from the majority of PAH subclassifications were included and reflected in the study patient characteristics. The overall gender and PAH

TABLE 4 Prognostic Impact of PAH-SYMPACT domain-scores

Domain	Hazard ratio (95% CI)	*p*	Adjusted[a] hazard ratio (95% CI)	*p*
Cardiopulmonary symptoms	2.26 (0.94–5.46)	0.07	2.47 (0.86–7.12)	0.09
Cardiovascular symptoms	1.13 (0.48–2.68)	0.78	1.03 (0.41–2.62)	0.94
Physical impact	2.65 (1.34–5.26)	**0.005**	2.03 (0.83–4.98)	0.12
Cognitive and emotional impact	2.70 (1.45–5.03)	**0.002**	3.29 (1.56–6.91)	**0.002**

Note: Bold values indicate statistical significant at $p < 0.05$.

[a]Adjusted for REVEAL 2.0 risk score.

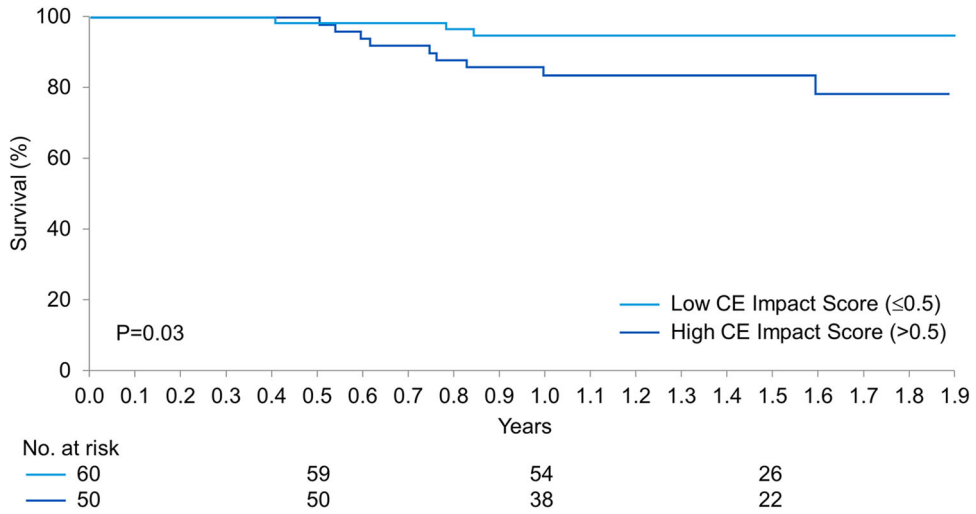

FIGURE 4 Kaplan–Meier survival curves for patients with pulmonary arterial hypertension stratified by median cognitive and emotional impact (CE) score at enrollment (0.5). Patients with high CE scores (indicating worse cognitive and emotional quality of life) had worse survival compared to patients with low CE scores (log-rank $p = 0.03$).

classification distribution in our cohort is similar to other large multicenter PAH registries, such as the REVEAL registry, with slightly higher age and higher prevalence of PAH associated with connective tissue disease in our cohort.[14] One difference between our study and other multicenter PAH registries was our limited racial diversity, which reflects the geographic community we serve. This may limit generalizability as well as conclusions that can be drawn about the association between race and PAH-SYMPACT scores.

PAH-SYMPACT in clinical practice

Few patients (6%) declined to participate in the study, indicating that patients are generally agreeable to completing PRO tools as part of routine clinical practice. Anecdotally, patients also expressed their support for the incorporation of PAH-SYMPACT into their clinical visits, recognizing it as validation of the importance being placed on their HRQOL. Patients also appreciated having the opportunity to discuss the symptoms and impact of PAH on their lives. As PH clinicians, we found that utilizing the PAH-SYMPACT tool provided valuable and unique insight into the patient experience of living with PAH, particularly the cognitive and emotional impact of PAH and its treatment. We hypothesize that there may have been a therapeutic effect of completing the questionnaire as it provided patients the opportunity to bring up concerns they may not have otherwise discussed with their providers.

Although PAH-SYMPACT is a validated disease-specific PRO, there is little peer-reviewed published data regarding mean PAH-SYMPACT domains in clinical trials or in clinical practice. Thus, it is difficult to assess how SYMPACT domain scores in our cohort compare to other PAH patients. Compared to the mean domain scores in the initial published validation of the PAH-SYMPACT questionnaire by Chin et al.[9] (CP: 1.0 ± 0.5, CV: 0.4 ± 0.5, PI: 1.3 ± 0.9, CE 0.9 ± 0.8), domain scores were overall quite similar in our study (CP: 1.0 ± 0.6, CV: 0.5 ± 0.6, PI: 1.2 ± 0.9, and CE 0.8 ± 0.7). As PAH disease-specific PROs are increasingly recognized as important endpoints in clinical trials, studies such as ours defining the mean and standard deviations of PAH-SYMPACT domain scores in clinical practice can be helpful to guide study design.

Associations of clinical characteristics with PAH-SYMPACT domain scores

There is increasing recognition that HRQOL should be a primary PAH treatment goal.[3] As a therapeutic goal, however, it is important to understand the varied factors that influence HRQOL, particularly when novel PRO tools, such as PAH-SYMPACT, are developed. Not surprisingly, FC, an assessment of activity limitation related to PAH, was associated with most domain scores, but there was not a clear worsening in HRQOL with higher FC in the CV symptom and CE impact domains (Figure 2). Three out of four domains were also associated with 6-min walk distance, indicating that HRQOL across multiple domains is associated with impaired exercise capacity. Similar to FC, however, some domains, such as CP and PI domains demonstrated a strong association, while others, such as CV and CE domains, did not. DLCO < 40% predicted was also associated with impaired HRQOL in 3 domains, suggesting that patients with a PAH phenotype associated with severely reduced DLCO have worse HRQOL. Comorbidities, such as obstructive sleep apnea and hypertension, were also associated with worse HRQOL, highlighting the impact of comorbid conditions on PAH-SYMPACT scores. Importantly, we also identified an association between hemoglobin and CP symptoms as well as PI which highlights the importance of considering factors beyond the pulmonary circulation that may influence HRQOL in PAH.

Although the CP symptom and PI domain were each associated with several clinical characteristics often utilized in clinical practice to assess disease severity, the CV symptom, and CE impact domain were not significantly associated with traditional markers of disease severity, such as NTproBNP, RV function, and pulmonary hemodynamics. This emphasizes the value of assessing PROs as they cannot be inferred from clinical test results. Surprisingly, worse pulmonary hemodynamics were not associated with any of the PAH-SYMPACT domain scores, and echocardiographic data were only associated with PI scores. While the lack of association with pulmonary hemodynamics may be related to the time interval between right heart catheterization and assessment of PROs, our findings indicate that some of the variables that clinicians prioritize in routine clinical practice are not strongly associated with PROs. Our findings underscore that HRQOL assessment using validated disease-specific PROs provides valuable and unique information related to a patient's journey of living with PAH.

The effect of varied PAH treatment approaches on HRQOL is poorly understood. Treatment with monotherapy and combination therapy at enrollment (compared to no treatment) was surprisingly not associated with differences in symptom domain scores but was associated with lower PI and CE impact domain scores, suggesting that PAH targeted therapy may have a greater effect on disease impact rather than symptoms.

Prognostic impact of PAH-SYMPACT domain scores

Both PI and CE impact domains were significantly associated with recent hospitalizations as well as increased mortality, but only the CE impact domain was independently associated with increased mortality after adjustment for disease severity. After adjustment for REVEAL 2.0 risk score, an established prognostic risk stratification tool in PAH, the mean CE impact domain score was independently associated with a greater than threefold increased risk of death.[13] The components of this domain, which include just four questions regarding thinking clearly, sadness, worry, and frustration, are not necessarily assessed routinely at PH clinic visits. In fact, the CE impact was the domain least associated with traditional PAH disease severity measures. Although significantly associated with survival, the components of this domain also do not necessarily improve with PAH-specific therapy. This does not make them any less important, however. Although we do not have a specific medication or intervention to improve CE impact in PAH and our findings are merely associations that do not imply causality, our study highlights the importance of understanding and addressing CE concerns, such as sadness, worry, and frustration. Interventions focused on symptom management and coping, such as palliative care or psychotherapy, may be beneficial to address this unmet need, and warrant further study. Our findings also suggest that other domains, such as the PI and CP domains, could be associated with survival but we may have been underpowered to detect significant associations in this single-center observational study. In addition to the importance of PROs to individual patients, the prognostic significance of PAH-SYMPACT domains underscores their value in both clinical practice and research.

Limitations

Limitations include the single-center nature of the study and the limited racial/ethnic diversity of patients included in the study. The patients included in the study also had a variety of comorbid conditions including chronic lung disease which reflects real-world clinical practice. We did not require recent pulmonary function tests for inclusion in the study, but all patients were classified as Group 1 PAH by their PH clinician in accordance with current guidelines, and patients considered to have Group 3 PH were excluded. As this was an exploratory study, we explored the relationship between individual domains and multiple clinical characteristics and did not adjust for multiple testing so it is possible that some of our findings may be due to chance alone. Additionally, as follow-up duration was relatively short and there was a small number of deaths, our ability to adjust for multiple variables in our survival analysis was limited to avoid overfitting.

CONCLUSIONS

In this study, we found that routine assessment of PROs in clinical practice using the PAH-SYMPACT questionnaire is both feasible and valuable. Our findings underscore the importance of assessing HRQOL in routine clinical practice since PAH-SYMPACT domain scores were not adequately reflected by traditional measures of disease severity. Additionally, the CE impact of PAH has significant prognostic value, independent of other well-established risk stratification tools, highlighting the importance of assessing and addressing cognitive and emotional concerns in routine clinic visits.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. The study was approved by our Institutional Research Board (Approval 19-000630).

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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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