EmPHasis-10 as a measure of health-related quality of life in pulmonary arterial hypertension: data from PHAR

Marissa Borgese[1], David Badesch[2], Todd Bull[2], Murali Chakinala[3], Teresa DeMarco[4], Jeremy Feldman[5], H. James Ford[6], Dan Grinnan[7], James R. Klinger[8], Lena Bolivar[9], Oksana A. Shlobin[10], Robert P. Frantz[11], Jeffery S. Sager[12], Stephen C. Mathai[13], Steven Kawut[14], Peter J. Leary[15], Michael P. Gray[16], Rita A. Popat[1] and Roham T. Zamanian[17,18], on behalf of the PHAR Study Group

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Understanding quality of life is critical given the profound impact PAH has on patient lives. This study shows that emPHasis-10 score correlates with demographic and clinical characteristics, and is potentially useful as a clinical trial end-point. https://bit.ly/3k57oaB

Cite this article as: Borgese M, Badesch D, Bull T, *et al.* EmPHasis-10 as a measure of health-related quality of life in pulmonary arterial hypertension: data from PHAR. *Eur Respir J* 2021; 57: 2000414 [https://doi.org/10.1183/13993003.00414-2020].

ABSTRACT

Introduction: While the performance of the emPHasis-10 (e10) score has been evaluated against limited patient characteristics within the United Kingdom, there is an unmet need for exploring the performance of the e10 score among pulmonary arterial hypertension (PAH) patients in the United States.

Methods: Using the Pulmonary Hypertension Association Registry, we evaluated relationships between the e10 score and demographic, functional, haemodynamic and additional clinical characteristics at baseline and over time. Furthermore, we derived a minimally important difference (MID) estimate for the e10 score.

Results: We analysed data from 565 PAH (75% female) adults aged mean±SD 55.6±16.0 years. At baseline, the e10 score had notable correlation with factors expected to impact quality of life in the general population, including age, education level, income, smoking status and body mass index. Clinically important parameters including 6-min walk distance and B-type natriuretic peptide (BNP)/N-terminal proBNP were also significantly associated with e10 score at baseline and over time. We generated a MID estimate for the e10 score of −6.0 points (range −5.0–−7.6 points).

Conclusions: The e10 score was associated with demographic and clinical patient characteristics, suggesting that health-related quality of life in PAH is influenced by both social factors and indicators of disease severity. Future studies are needed to demonstrate the impact of the e10 score on clinical decision-making and its potential utility for assessing clinically important interventions.

This article has an editorial commentary: https://doi.org/10.1183/13993003.04376-2020

This article has supplementary material available from erj.ersjournals.com

Received: 26 Feb 2020 | Accepted: 1 Nov 2020

Introduction

Pulmonary arterial hypertension (PAH) is a rare and progressive cardiopulmonary disorder characterised by pulmonary vascular obliteration and consequent increased pulmonary vascular resistance, leading to right ventricular failure and death [1]. PAH is associated with debilitating symptoms such as breathlessness, lightheadedness and fatigue [2, 3]. The nonspecific nature of these symptoms can lead to patient- and provider-driven delays, resulting in progressive functional limitations and increased anxiety at the time of diagnosis [4].

Once diagnosed, PAH patients can experience a range of emotions from relief in receiving a formal diagnosis [4] to distress upon realising the magnitude of disease and expense, invasiveness and risks of therapies [5]. Knowledge of a poor prognosis and the lack of a cure impose significant emotional burdens on patients already faced with the challenges of PAH-related physical limitations [6]. During a public meeting hosted by the United States Food and Drug Administration (US FDA), patients expressed that not only were they hindered in their ability to complete everyday tasks, but they were often also unable to engage in personally meaningful activities [3]. Patients collectively conveyed a strong desire for less cumbersome therapies that would both improve function and allow for greater flexibility and freedom. Understanding health-related quality of life (HRQoL) in PAH is of critical importance, given the profound impact that the disease has on patients' daily lives. HRQoL measures appear to be a promising method for capturing the trade-offs between gains in functional ability *versus* side-effects with PAH therapies. Most interestingly, HRQoL measures have potential as patient-centred clinical trial end-points.

HRQoL can be measured by generic or disease-specific tools. Generic tools such as the Medical Outcomes Survey Short Form-36 may predict outcomes in PAH [7]. While most clinical trials of novel therapies in PAH have employed generic HRQoL measures as secondary outcomes and shown statistically significant improvements, few have demonstrated clinically relevant changes in these generic measures [8]. Subsequently, several disease-specific, patient-reported outcome instruments have been developed to better quantify the impact of pulmonary hypertension symptoms and therapies on HRQoL, the first being the Minnesota Living with Heart Failure questionnaire [9], and subsequently including the Cambridge Pulmonary Hypertension Outcome Review [10], Living with Pulmonary Hypertension [11], Pulmonary Arterial Hypertension – Symptoms and Impact [12] and emPHasis-10 (e10) questionnaires [13]. The e10 questionnaire is short, simple to score and available free of charge for clinical and academic use through the Pulmonary Hypertension Association UK. Recent studies have demonstrated the association of e10 score with World Health Organization (WHO) functional class [13], patient-reported measures of dyspnoea and emotional distress [14] and mortality [15]. However, these studies were limited to patients within the United Kingdom (UK).

Currently there is an unmet need for research exploring relationships between a comprehensive set of patient characteristics and the e10 score among patients in the United States. The performance of the e10 score as it relates to patient demographic and clinical characteristics, along with determination of e10 score's minimally important difference (MID), may help further elucidate the driving factors of HRQoL in PAH and guide sample size calculations for future research interested in using the e10 score as an end-point. The aims of our study were to explore the relationships between PAH patient characteristics and HRQoL as measured by the e10 score at baseline and over time among patients in the United States, and to determine the MID of the e10 score in a United States-based PAH registry. We hypothesised that

Affiliations: [1]Dept of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA. [2]Division of Pulmonary and Critical Care Medicine, University of Colorado, Denver, CO, USA. [3]Division of Pulmonary and Critical Care Medicine, Washington University at Barnes-Jewish, Saint Louis, MO, USA. [4]Division of Cardiology, University of California San Francisco, San Francisco, CA, USA. [5]Arizona Pulmonary Specialists, Phoenix, AZ, USA. [6]Division of Pulmonary and Critical Care Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [7]Division of Pulmonary and Critical Care Medicine, Virginia Commonwealth University Medical Center, Richmond, VA, USA. [8]Division of Pulmonary and Critical Care Medicine, Brown University, Providence, RI, USA. [9]Patient representative, USA. [10]Inova Fairfax Hospital, Falls Church, VA, USA. [11]Division of Cardiovascular Medicine, Mayo Clinic Rochester, Rochester, MN, USA. [12]Cottage Pulmonary Hypertension Center, Santa Barbara, CA, USA. [13]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, USA. [14]Division of Pulmonary and Critical Care Medicine, University of Pennsylvania, Philadelphia, PA, USA. [15]Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, WA, USA. [16]Pulmonary Hypertension Association, Silver Spring, MD, USA. [17]Division of Pulmonary and Critical Care Medicine, Stanford University School of Medicine, Stanford, CA, USA. [18]Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University School of Medicine, Stanford, CA, USA.

Correspondence: Roham T. Zamanian, 300 Pasteur Dr, Room H3143, Stanford, CA 94305, USA. E-mail: Zamanian@stanford.edu

patients with sociodemographic and behavioural vulnerabilities and clinical indicators of more severe and progressive disease would have higher e10 scores indicating poorer HRQoL.

Methods

Participant selection and data

We used data from the Pulmonary Hypertension Association Registry (PHAR; clinicaltrials.gov identifier NCT04071327), a large, multicentre registry of patients diagnosed with PAH and chronic thromboembolic pulmonary hypertension seen at any of 33 participating accredited pulmonary hypertension care centres (PHCCs) in the United States (supplementary material). We included adults with a PHCC-determined diagnosis of PAH recruited between 2015 and 2018. Patients with pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis, chronic thromboembolic pulmonary hypertension or persistent pulmonary hypertension of the newborn were excluded. The e10 questionnaire consists of 10 items formatted as a semantic six-point differential scale resulting in patient-reported scores ranging from 0 to 50. Patients aged <18 years were excluded, because the e10 questionnaire was developed and validated in adults. The University of Pennsylvania institutional review board approved PHAR protocols and study-related activities (Federal Wide Assurance number FWA00004028). Informed consent was obtained from each patient prior to enrolment.

Haemodynamic parameters were assessed *via* right heart catheterisation and reported at baseline only. All clinical and medication data were collected by clinical research coordinators at each PHCC visit. Quality-of-life questionnaires, care, lifestyle and demographic factors were captured directly from patients using an electronic study tablet (supplementary material). Follow-up frequency was determined by each PHCC and typically occurred once every 3–6 months for clinically stable patients. The e10 score was calculated at each visit according to patient responses on the e10 questionnaire (supplementary figure S1).

Given that nearly half of our cohort only had a B-type natriuretic peptide (BNP) value, while the other half only had an N-terminal proBNP (NT-proBNP) value, we created a BNP/NT-proBNP z-score parameter which included scaled values centred around a mean±SD BNP 246±386 pg·mL^{-1} and mean NT-proBNP 1437±3292 pg·mL^{-1}. REVEAL Registry risk scores [16] were calculated as described in the literature and risk strata represent the following ranges of predicted 1-year survival: <70% (very high risk), 70–<85% (high risk), 85–<90% (moderate high risk), 90–<95% (average risk) and 95–100% (low risk). Refer to the supplementary material for a comprehensive list of and information about the variables collected.

Data analysis

We summarised the study cohort demographic and clinical characteristics at baseline. Continuous parameters were expressed as mean±SD. If data were not normally distributed, we reported the median (interquartile range (IQR)). Categorical parameters were expressed as counts (%). We evaluated data for completeness and applied standard multiple imputation methodology for those with >10% missingness at baseline (supplementary material).

We used linear regression models with e10 score as the dependent variable to evaluate associations of patient demographic and clinical characteristics with e10 score at baseline. Models with a demographic parameter as the predictor were adjusted for age, sex and education level. When the variable of interest was one of these parameters, only the other two were included as covariates. Models with a clinical parameter as the predictor were adjusted for age, sex and body mass index (BMI), with the exception of the model for BMI, which was adjusted only for age and sex.

We used mixed linear regression models with e10 score as the dependent variable to evaluate longitudinal relationships between time-varying patient characteristics and HRQoL. Mixed linear regression models were utilised given their ability to handle both correlated and missing data. For continuous predictors of interest, we used a within-subject centring approach [17] to isolate longitudinal relationships in the form of within-subject effects. A similar approach was used for each categorical predictor of interest where a patient's modal predictor value was used in place of a mean value. This approach was used given the ordinal nature of the categorical parameters measured over time. The covariates added to each model included those present in each predictor's baseline model, in addition to linear and quadratic time parameters and random intercepts for each participant. All analyses were conducted using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and the R package "lme4" [18] was used for the mixed linear regression models. We considered p-values <0.05 to be statistically significant across all analyses.

To determine the MID of the e10 score, we used four different distribution-based approaches [19]: the standard error of measurement, reliable change index, 0.5 SD and effect size approaches. Data from the baseline and first follow-up visits were used in all calculations, the previously reported intraclass correlation β-coefficient of 0.95 [13] was used as an estimate of reliability, and parameters were set to

identify a moderate effect. We repeated the calculations for two subgroups of patients who were diagnosed within 6 months of their baseline visit and patients who were treatment naïve at their baseline visit.

Results

Participant characteristics

Of the 658 total patients enrolled in PHAR between 2015 and 2018, we excluded 93 patients, most of whom were diagnosed with chronic thromboembolic pulmonary hypertension (n=79). We included 565 adult patients with PAH in our analyses (figure 1). Our study cohort had a mean±SD age of 55.6±16.0 years; patients were predominantly female (n=421; 75%) and most identified as non-Hispanic white (n=368; 65%) (table 1). A majority reported having completed a high-school or higher level of education (n=505; 90%) and an employment status of employed (n=155; 27%), on medical leave/disability (n=153; 27%) or retired (n=166; 29%). A significant portion reported having Medicare (n=247; 44%) or private insurance (n=197; 35%) coverage. Half of the patients were diagnosed with PAH within 6 months of PHAR enrolment (n=285) and the most common PAH aetiologies were idiopathic PAH (n=224; 40%) and connective tissue disease-associated PAH (n=181; 32%) (table 2).

Most patients reported WHO functional class II (n=172; 30%) or III (n=276; 49%) symptoms. The mean 6-min walk distance (6MWD) was 335±123 m, which was approximately half that expected in healthy subjects [20]. A majority of the study cohort (n=281; 49.7%) were identified as having a 95–100% chance of 1-year survival according to their REVEAL risk stratum. Furthermore, 14% (n=81) of patients were treatment naïve and 38% used supplemental oxygen (n=214) at the time of their baseline visit (supplementary table S1).

Haemodynamics of our study cohort reflected severe PAH as evidenced by a mean pulmonary artery pressure of 48 (39–58) mmHg, pulmonary artery wedge pressure/left ventricular end-diastolic pressure of 10 (7–14) mmHg and pulmonary vascular resistance of 720 (480–1040) dyn·s·cm^{-5}.

The mean e10 score in our study cohort of 25.4±12.2 (table 2) aligned with the centre of the 0–50-point range of possible scores and the entire e10 score range was represented in our study cohort (figures S2 and S3).

Factors associated with emPHasis-10 at baseline

After adjustment for relevant confounders, older age was associated with higher e10 scores (indicating poorer HRQoL), where each 10-year increase in age was associated with a 0.9-point higher e10 score (95% CI 0.3–1.5; p=0.005) (table 3). Females had a 2.6-point higher e10 score (95% CI 0.3–4.9; p=0.024) than males. Patients who reported less than a high-school education level, being unemployed or on medical leave/disability, having a yearly income below poverty level, a history of illicit stimulant use or a history of smoking tended to have higher e10 scores. Furthermore, we found that higher patient-reported PHCC care ratings were associated with lower e10 scores (β-coefficient −1.4, 95% CI −2.2 to −0.6; p=0.001).

The e10 score was also significantly associated with several clinical parameters after adjustment for relevant confounders (table 4; supplementary table S2). Higher BMI values were associated with higher

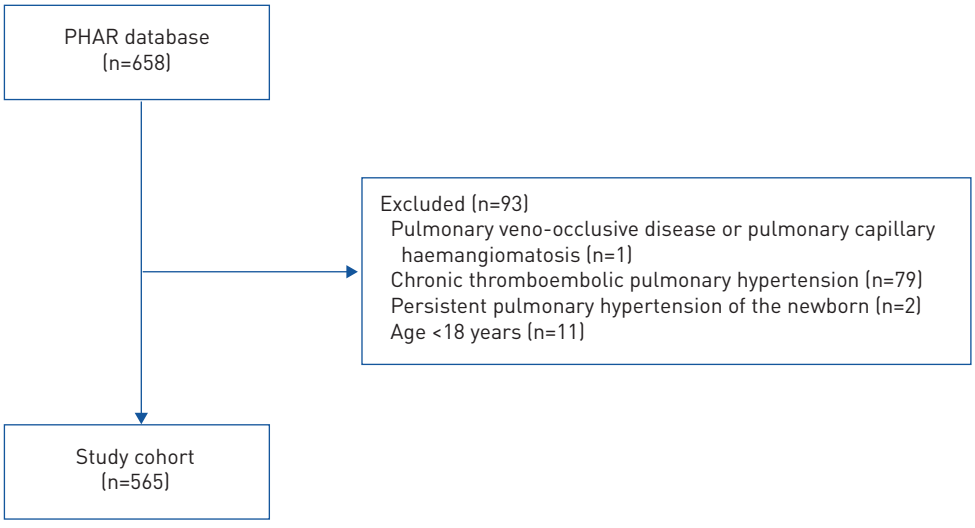

FIGURE 1 Flowchart of patient selection. PHAR: Pulmonary Hypertension Association Registry.

TABLE 1 Baseline patient demographics

Patients	565
Age years	55.6±16.0
Female	421 (74.5)
Race/ethnicity	561
White, non-Hispanic	368 (65.6)
Asian/Pacific Islander	35 (6.2)
Hispanic	69 (12.3)
Black, non-Hispanic	67 (11.9)
Native American	7 (1.2)
Mixed race	15 (2.7)
Highest education level	559
Less than high school	54 (9.7)
High school/GED	322 (57.6)
College or graduate degree	183 (32.7)
Employment status	554
Unemployed	71 (12.8)
Employed	155 (28.0)
Medical leave/disability	153 (27.6)
Student	9 (1.6)
Retired	166 (30.0)
Yearly income level	456
Below poverty level	98 (21.5)
Above poverty, <USD 75 000	225 (49.3)
⩾USD 75 000	133 (29.2)
Marital status	556
Single	154 (27.7)
Married	288 (51.8)
Divorced	76 (13.7)
Widowed	38 (6.8)
Health insurance	560
Uninsured	9 (1.6)
Medicare	247 (44.1)
Medicaid	58 (10.4)
Other government service	49 (8.8)
Private insurance	197 (35.2)

Data are presented as n, mean±SD or n (%). Total number of observations is 565, unless otherwise stated. GED: General Educational Development.

e10 scores, where each 1-kg·m^{-2} increase in BMI was associated with a 0.2-point increase in e10 score (95% CI 0.1–0.4 points; p=0.001). Relative to patients diagnosed with idiopathic PAH, patients with heritable PAH had lower e10 scores, and those with drug/toxin and connective tissue disease-associated PAH had higher e10 scores.

Additionally, we found that indicators of functional limitation were associated with higher e10 scores. Patients in WHO functional class III and IV had 8.7-point (95% CI 5.0–12.4 points; p<0.001) and 11.6-point (95% CI 6.7–16.6 m; p<0.001) higher e10 scores than patients in WHO functional class I. Each 30-m increase in 6MWD was associated with a 1.3-point decrease in e10 score (95% CI −1.6 to −1.0 point; p<0.001). Higher BNP/NT-proBNP z-scores (β=1.7, 95% CI 0.8–2.7; p<0.001) and supplemental oxygen use (β=3.4, 95% CI 1.4–5.4; p=0.001) were both associated with higher e10 scores.

Worse haemodynamics, as evidenced by higher right atrial pressures (per 3 mmHg; β=0.8, 95% CI 0.3–1.4; p=0.001) and pulmonary vascular resistances (per 160 dyn·s·cm^{-5}; β=0.6, 95% CI 0.2–1.0; p=0.004) were associated with higher e10 scores. We found no evidence of associations between the e10 score and mean pulmonary artery pressures or pulmonary artery wedge pressures.

Higher-risk REVEAL strata were associated with higher e10 scores. In addition, patients who reported an emergency room visit (β=4.4, 95% CI 2.4–6.4; p<0.001) or hospitalisation (β=4.1, 95% CI 2.1–6.1; p<0.001) in the 6 months prior to their baseline visit also tended to have greater e10 scores. Unadjusted models for 6MWD, WHO functional class and REVEAL risk stratum indicated that these variables explained the greatest amounts of variation in the e10 score among all parameters assessed (17%, 21% and 8%, respectively) (figure 2).

TABLE 2 Baseline patient clinical characteristics

Patients	565
EmPHasis-10 score (n=554)	25.4±12.2
BMI kg·m^{-2} (n=553)	29.1±7.3
PAH aetiology	
Idiopathic	224 (39.6)
Heritable	19 (3.4)
Drug/toxin-associated	66 (11.7)
CTD-associated	181 (32.0)
HIV-associated	9 (1.6)
PPHTN-associated	36 (6.4)
CHD-associated	30 (5.3)
WHO FC (n=527)	
I	43 (8.2)
II	172 (32.6)
III	276 (52.4)
IV	36 (6.8)
6MWD m (n=484)	335.4±123.2
Laboratory tests	
BNP pg·mL^{-1} (n=331)	130 (50–370)
NT-proBNP pg·mL^{-1} (n=229)	531 (191–2242)
Creatinine mg·dL^{-1} (n=546)	0.9 (0.8–1.1)
Haemodynamics	
Heart rate beats·min^{-1} (n=368)	79 (69–90)
Right atrial pressure mmHg (n=534)	9 (5–13)
mPAP mmHg (n=544)[#]	48 (39–58)
PAWP/LVEDP mmHg (n=536)	10 (7–14)
Cardiac output L·min^{-1} (n=528)	3.9 (3.2–5.1)
PVR dyn·s·cm^{-5} (n=514)	720 (480–1040)
Stroke volume mL (n=359)	50.4 (38.4–67.0)
PAC mL·mmHg^{-1} (n=357)	1.1 (0.8–1.6)
REVEAL risk stratum[¶] (n=527)	
Low risk	281 (53.3)
Average risk	84 (15.9)
Moderate high risk	69 (13.1)
High risk	78 (14.8)
Very high risk	15 (2.8)

Data are presented as n, mean±SD, n (%) or median (interquartile range). Total number of observations is 565, unless otherwise stated. BMI: body mass index; PAH: pulmonary arterial hypertension; CTD: connective tissue disease; PPHTN: portopulmonary hypertension; CHD: congenital heart disease; WHO FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; LVEDP: left ventricular end-diastolic pressure; PVR: pulmonary vascular resistance; PAC: pulmonary artery compliance. [#]: of the 21 patients missing a value for mPAP, 15 were diagnosed with PAH >6 months prior to their baseline visit; [¶]: determined using the REVEAL Registry Risk Score Calculator [16].

Of all included variables, only baseline income level, 6MWD, heart rate, stroke volume and pulmonary artery compliance had >10% missing data. Imputation of missing data for these parameters did not alter our findings (supplementary material).

Factors associated with emPHasis-10 over time

The median (IQR) time between follow-up visits among active participants was 9.6 (6.0–14.5) months. The mean e10 scores among patients seen for their first, second, third or fourth follow-up PHCC visits were lower than the baseline average e10 score (supplementary table S1). Patients lost to follow-up had higher e10 scores and lower income than active study participants. Deceased patients and lung transplant patients had higher e10 scores, were older and had more advanced disease than active study participants.

After isolating within-subject effects, we found that the β-coefficient for WHO functional class was 3.0 (95% CI 1.9–4.0; p<0.001), indicating that for every increase in WHO functional class (relative to their most frequently observed WHO functional class), we would expect a 3.0-point increase in their e10 score (table 5; supplementary table S3). The within-subject β-coefficient for 6MWD was −0.6 (95% CI −0.9 to −0.4; p<0.001), suggesting an expected 0.6-point decrease in e10 score for every 30-m increase in 6MWD

TABLE 3 Associations between patient demographic parameters and emPHasis-10 score at baseline

	Unadjusted			Adjusted[#]		
	Coefficient (95% CI)	R^2	p-value	Coefficient (95% CI)	R^2	p-value
Age per 10 years	1.0 (0.4–1.6)	0.02	0.002	0.9 (0.3–1.5)	0.06	0.005
Female	2.7 (0.4–5.0)	0.01	0.023	2.6 (0.3–4.9)	0.06	0.024
Race/ethnicity		0	0.33		0.06	0.575
White, non-Hispanic (reference)						
Asian/Pacific Islander	−2.4 (−6.8–2.1)			0.7 (−3.8–5.1)		
Hispanic	0.3 (−2.9–3.5)			−0.6 (−4.0–2.9)		
Black, non-Hispanic	0.8 (−2.4–4.0)			−0.4 (−3.6–2.7)		
Native American	8.9 (−0.1–18.0)			8.0 (−0.9–16.8)		
Mixed race	−2.1 (−8.3–4.2)			−1.7 (−7.7–4.4)		
Highest education level		0.04	<0.001		0.06	<0.001
Less than high school (reference)						
High school/GED	−1.2 (−4.7–2.3)			−1.6 (−5.1–1.9)		
College or graduate degree	−6.5 (−10.1–−2.8)			−6.8 (−10.4–−3.1)		
Employment status		0.06	<0.001		0.1	<0.001
Unemployed (reference)						
Employed	−4.4 (−7.8–−1.1)			−3.0 (−6.4–0.4)		
Medical leave/disability	3.3 (−0.1–6.7)			3.8 (0.5–7.1)		
Student	−5.8 (−14.0–2.4)			−3.2 (−11.4–5.1)		
Retired	2.2 (−1.1–5.5)			1.0 (−2.8–4.8)		
Yearly income level		0.03	<0.001		0.08	0.018
Below poverty level (reference)						
Above poverty <USD 75 000	−2.9 (−5.8–0.0)			−3.5 (−6.5–−0.5)		
⩾USD 75 000	−6.6 (−9.8–−3.4)			−4.8 (−8.3–−1.4)		
Marital status		0	0.18		0.06	0.341
Single (reference)						
Married	0.2 (−2.2–2.6)			−0.1 (−2.7–2.4)		
Divorced	3.5 (0.1–6.8)			2.1 (−1.3–5.4)		
Widowed	0.8 (−3.6–5.2)			−2.1 (−6.7–2.6)		
Health insurance		0.03	0.001		0.07	0.132
Uninsured (reference)						
Medicare	−0.7 (−8.7–7.3)			−2.1 (−10.1–5.9)		
Medicaid	−0.7 (−9.1–7.8)			−0.3 (−8.6–8.0)		
Other government service	−2.0 (−10.5–6.5)			−1.5 (−9.9–6.8)		
Private insurance	−5.4 (−13.4–2.6)			−4.4 (−12.3–3.6)		
Patient PHCC care rating (per point)	−1.5 (−2.3–−0.7)	0.02	<0.001	−1.4 (−2.2–−0.6)	0.08	0.001
Drinks alcohol	−2.6 (−4.7–−0.5)	0.01	0.016	−1.6 (−3.7–0.5)	0.06	0.14
History of illicit stimulant use[¶]	4.4 (1.5–7.2)	0.01	0.003	5.5 (2.6–8.3)	0.08	<0.001
Smoking status		0.02	0.005		0.07	0.032
Nonsmoker (reference)						
Ex-smoker	3.3 (1.2–5.4)			2.6 (0.5–4.8)		
Current smoker	3.7 (−0.5–7.9)			3.3 (−0.9–7.5)		
Participates in PH clinical trial	1.4 (−1.4–4.3)	0	0.319	2.0 (−0.8–4.7)	0.06	0.159
Presence of an advance directive	0.7 (−1.5–2.9)	0	0.523	0.4 (−1.8–2.6)	0.06	0.699
United States region		0	0.549		0.06	0.241
Northeast (reference)						
Midwest	1.5 (−2.0–5.0)			1.4 (−2.0–4.8)		
South	1.4 (−1.6–4.3)			1.8 (−1.1–4.7)		
West	2.1 (−0.7–5.0)			2.9 (0.1–5.7)		

GED: General Educational Development; PHCC: pulmonary hypertension care centre; PH: pulmonary hypertension. [#]: adjusted for age, sex and education level except where the predictor of interest was one of these factors, in which case only the other two factors were included as covariates; [¶]: stimulants include cocaine, crack cocaine and methamphetamine.

relative to their personal average across PHCC visits. The β-coefficients for BNP/NT-proBNP z-score (β=2.2; 95% CI 1.0–3.4; p<0.001), frequency of emergency room visits (β=0.3; 95% CI 0.0–0.6; p=0.034) and number of nights spent hospitalised (β=0.1; 95% CI 0.0–0.1; p=0.019) also suggest that within-patient increases in these parameters were associated with increased e10 scores. Finally, we found that the fixed-effects models for 6MWD and WHO functional class explained the greatest amounts of variance in the e10 score over time (19% and 21% respectively) (figure 3).

TABLE 4 Associations between patient clinical parameters and emPHasis-10 score at baseline

	Unadjusted			Adjusted[#]		
	Coefficient (95% CI)	R^2	p-value	Coefficient (95% CI)	R^2	p-value
BMI per kg·m^{-2}	0.2 (0.1–0.4)	0.02	0.001	0.2 (0.1–0.4)	0.04	0.001
Diagnosed within past 6 months	0.6 (−1.4–2.7)	0	0.549	0.3 (−1.7–2.3)	0.04	0.773
PAH aetiology		0.03	0.001		0.06	0.002
Idiopathic (reference)						
Heritable	−7.4 (−13.0–−1.8)			−6.0 (−11.6–−0.3)		
Drug/toxin-associated	4.7 (1.4–8.1)			5.4 (2.0–8.8)		
CTD-associated	2.8 (0.5–5.2)			2.9 (0.5–5.4)		
HIV-associated	1.4 (−7.1–9.9)			4.5 (−4.0–12.9)		
PPHTN-associated	−0.3 (−4.6–4.0)			1.2 (−3.3–5.6)		
CHD-associated	−1.3 (−5.9–3.4)			−0.1 (−4.8–4.5)		
WHO FC		0.21	<0.001		0.21	<0.001
I (reference)						
II	−2.3 (−6.0–1.4)			−2.3 (−6.1–1.4)		
III	9.1 (5.5–12.6)			8.7 (5.0–12.4)		
IV	12.0 (7.1–16.8)			11.6 (6.7–16.6)		
6MWD per 30 m	−1.2 (−1.5–−1.0)	0.17	<0.001	−1.3 (−1.6–−1.0)	0.19	<0.001
Laboratory tests						
BNP/NT-proBNP z-score per SD[¶]	1.6 (0.7–2.6)	0.02	0.001	1.7 (0.8–2.7)	0.06	<0.001
Creatinine per mg·dL^{-1}	1.1 (−0.8–3.1)	0	0.255	0.9 (−1.1–3.0)	0.03	0.386
Haemodynamics						
Heart rate per 10 beats·min^{-1}	0.8 (0.0–1.5)	0.01	0.066	1.0 (0.2–1.8)	0.05	0.017
Right atrial pressure per 3 mmHg	0.9 (0.4–1.4)	0.02	<0.001	0.8 (0.3–1.4)	0.05	0.001
mPAP per 5 mmHg	−0.1 (−0.4–0.3)	0	0.718	0.1 (−0.2–0.5)	0.03	0.481
PAWP/LVEDP per mmHg	0.0 (−0.1–0.2)	0	0.72	0.0 (−0.2–0.1)	0.03	0.788
Cardiac output per L·min^{-1}	−0.7 (−1.2–−0.2)	0.01	0.004	−0.7 (−1.2–−0.2)	0.05	0.004
PVR per 160 dyn·s·cm^{-5}	0.4 (0.0–0.8)	0.01	0.049	0.6 (0.2–1.0)	0.05	0.004
Stroke volume per 5 mL	−0.3 (−0.6–−0.1)	0.02	0.012	−0.4 (−0.7–−0.1)	0.06	0.004
PAC per mL·mmHg^{-1}	−1.0 (−2.2–0.3)	0	0.125	−1.1 (−2.4–0.1)	0.04	0.075
REVEAL risk stratum[+]		0.08	<0.001		0.12	<0.001
Low risk (reference)						
Average risk	4.6 (1.8–7.5)			4.2 (1.4–7.1)		
Moderate high risk	7.1 (4.0–10.2)			7.2 (4.1–10.3)		
High risk	8.8 (5.8–11.7)			9.3 (6.3–12.4)		
Very high risk	9.8 (3.6–16.1)			11.4 (4.8–17.9)		
Visited ER in past 6 months	4.0 (2.0–6.0)	0.02	<0.001	4.4 (2.4–6.4)	0.07	<0.001
Hospitalised in past 6 months	3.9 (1.9–5.9)	0.02	<0.001	4.1 (2.1–6.1)	0.06	<0.001

BMI: body mass index; PAH: pulmonary arterial hypertension; CTD: connective tissue disease; PPHTN: portopulmonary hypertension; CHD: congenital heart disease; WHO FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; LVEDP: left ventricular end-diastolic pressure; PVR: pulmonary vascular resistance; PAC: pulmonary artery compliance; ER: emergency room. [#]: adjusted for age, sex and BMI with the exception of the model for BMI, which was adjusted for age and sex; [¶]: parameter reflects scaled values centred around a 246±386 pg·mL^{-1} mean BNP and 1437±3292 pg·mL^{-1} mean NT-proBNP; [+]: determined using the REVEAL Registry Risk Score Calculator [16].

We repeated our longitudinal analyses within the subgroup of incident patients (diagnosed within 6 months of their baseline visit) and demonstrated generally similar associations (supplementary material).

MID emPHasis-10

We calculated MID estimates for the e10 score using the standard error of measurement (−5.3 points), reliable change index (−7.6 points), 0.5 SD (−5.0 points) and effect-size approaches (−6.1 points) for patients with e10 scores recorded at their baseline and first follow-up visits (supplementary table S4A). The estimates generated for the subgroups of patients who were diagnosed within 6 months of their baseline visit and were on zero medications at their baseline visit were similar to those generated using data from all patients. The average calculated MID for the e10 score was −6.0 points. The mean change in 6MWD among patients whose e10 score decreased by ⩾6.0 points between PHCC visits was 35.0±88.5 m, whereas the distance among patients whose e10 score decreased by <6 points or increased between PHCC visits was only 2.3±82.3 m. Finally, analysis of MID-estimates did not differ across major group 1 PAH

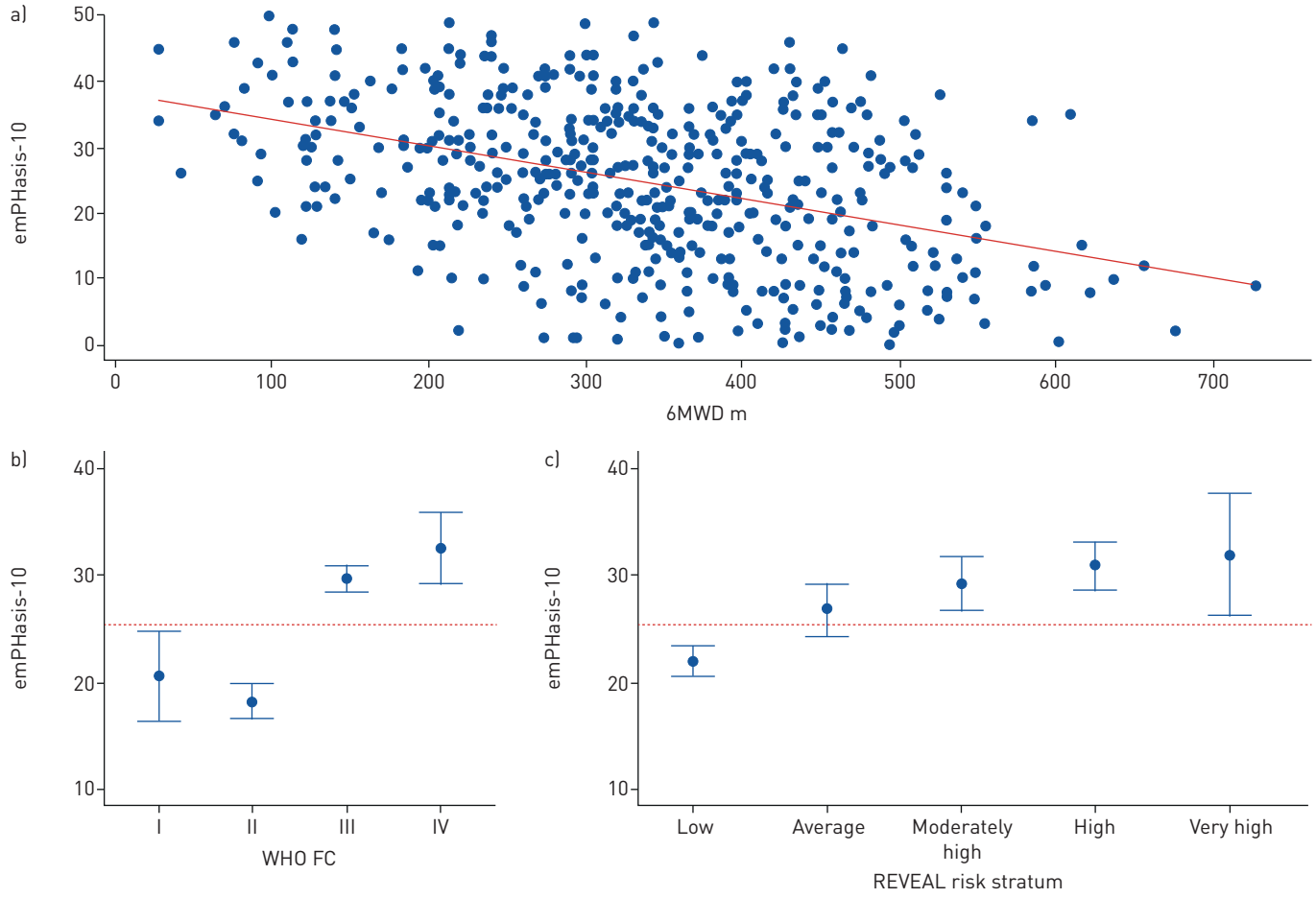

FIGURE 2 EmPHasis-10 *versus* a) 6-min walk distance (6MWD), b) World Health Organization functional class (WHO FC) and c) REVEAL risk stratum at baseline. Mean (95% CI) are shown for b and c; dotted line represents the mean baseline emPHasis-10 score (25.4). Within our baseline cohort, 6MWD was negatively associated with emPHasis-10 score, more advanced WHO FCs were associated with greater emPHasis-10 scores, and higher-risk REVEAL risk strata were associated with greater emPHasis-10 scores.

TABLE 5 Associations between within-patient changes and emPHasis-10 score

	Coefficient (95% CI)	R^2	p-value
Patient PHCC care rating per point	−0.4 (−0.9–0.1)	0.09	0.086
Drinks alcohol	−0.9 (−2.7–1.0)	0.08	0.354
Smoking status	1.4 (−0.8–3.7)	0.09	0.22
BMI per kg·m^{-2}	0.2 (0.0–0.5)	0.05	0.083
WHO FC per class	3.0 (1.9–4.0)	0.21	<0.001
6MWD per 30 m	−0.6 (−0.9–−0.4)	0.19	<0.001
Laboratory tests			
BNP/NT-proBNP z-score[#] per SD	2.2 (1.0–3.4)	0.09	<0.001
Creatinine per mg·dL^{-1}	0.8 (−2.4–4.0)	0.05	0.622
REVEAL risk stratum[¶] per stratum	1.1 (−0.2–2.4)	0.12	0.089
Number of ER visits per visit	0.3 (0.0–0.6)	0.12	0.034
Number of nights hospitalised per night	0.1 (0.0–0.1)	0.06	0.019

Coefficients and p-values correspond to the within-subject effects in each model. Marginal R^2 values are given and represent the variance in emPHasis-10 explained by each fixed effects model. PHCC: pulmonary hypertension care centre; BMI: body mass index; WHO FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; ER: emergency room. [#]: parameter reflects scaled values centred around a 246±386 pg·mL^{-1} mean BNP and 1437±3292 pg·mL^{-1} mean NT-proBNP; [¶]: determined using the REVEAL Registry Risk Score Calculator [16].

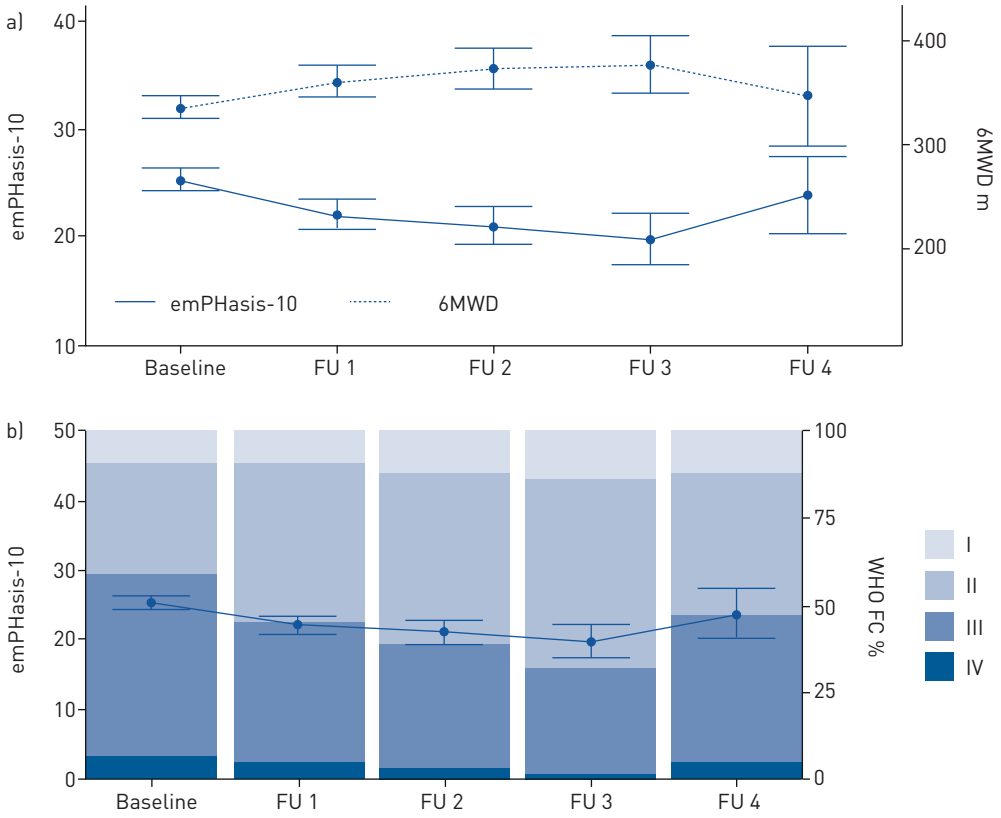

FIGURE 3 EmPHasis-10 and a) 6-min walk distance (6MWD) and b) World Health Organization functional class (WHO FC) across baseline and follow-up (FU) pulmonary hypertension care centre visits. EmPHasis-10 and 6MWD are shown as mean (95% CI); proportion of patients in each WHO FC are shown. Over time, the mean emPHasis-10 score within our cohort decreased as the mean 6MWD increased and *vice versa*. In addition, the mean emPHasis-10 score within our cohort decreased as the proportion of participants in WHO FC III and IV decreased.

subtypes including idiopathic PAH, connective tissue disease-associated PAH and drug and toxin-associated PAH (supplementary table S4B).

Discussion

PHAR is the first United States-based multicentre, prospective, observational PAH registry with HRQoL data. This study is among the first to report on characteristics of the patients in PHAR and to explore the relationships between these characteristics and HRQoL measured using a PAH-specific quality-of-life questionnaire in the United States. We demonstrate that worse clinical symptoms, worse exercise tolerance and higher-risk clinical characteristics are associated with higher e10 scores (poorer HRQoL). Moreover, we show that changes over time in the e10 score are associated with changes in well-established, clinically important metrics used to quantify symptom and PAH disease severity. Finally, through averaging results from several analytic approaches we report a MID estimate for the e10 score of −6.0 points.

Similar to other PAH registry studies, our cohort has a mean age of 56 years, is predominantly female and has idiopathic PAH as the dominant PAH aetiology [5]. Most of the patients were symptomatic at baseline according to their WHO functional class, though the majority had a predicted 1-year probability of survival ⩾90% according to the REVEAL Registry Risk Score Calculator. At baseline, our study cohort had an average e10 score of ∼25, which was normally distributed and represented full range from 0 to 50 points. The high prevalence of functionally limiting symptoms among patients with relatively good prognoses supports the need for a disease-specific quality-of-life questionnaire for PAH patients.

We identified several patient characteristics associated with HRQoL in PAH as measured by the e10 score. At baseline, patients' reported HRQoL had notable relationships with factors that might be expected to impact quality of life outside the context of PAH, including age, education level, employment status, income, history of illicit stimulant use, smoking status [21] and BMI. Interestingly, females reported significantly worse HRQoL than males, a finding consistent with data in the general population with

chronic cardiopulmonary and infectious illnesses [22–25]. While not well understood, sex differences in HRQoL may be due to differences in perception of disease impact or higher prevalence of disabilities and comorbities [26]. Drug and toxin-associated PAH also tended to be associated with poorer HRQoL, potentially suggesting an added negative effect on quality of life by the PAH causative factor. In the case of connective tissue disease-associated PAH (the second most common PAH aetiology in our study), comorbidities and knowledge of a poor disease prognosis relative to other PAH groups might have further contributed to poor HRQoL [27]. Parameters indicative of symptom and disease severity, including 6MWD, WHO functional class, REVEAL risk stratum, supplemental oxygen use, BNP/NT-proBNP z-score and several haemodynamic parameters, were also identified as having significant associations with the e10 score. Our findings are consistent with recent data from the UK referral centres demonstrating that e10 is an independent prognostic marker and tracks with improvement in exercise capacity in idiopathic PAH and connective tissue disease-associated PAH [28]. These associations are in agreement with concerns expressed by PAH patients about how worsening clinical symptoms interfere with their ability to engage in personally meaningful activities [3]. Similarly, important but nonspecific indicators of poor health, including emergency room visits and hospitalisations were associated with poorer HRQoL. Association between the e10 score and patient-reported PHCC care rating may suggest that patients' perceptions of quality of life and the quality of care received were influenced by their overall attitudes towards their health status.

The results from our longitudinal analyses further elucidated the nature of the relationships between patient characteristics and HRQoL in PAH. Focusing on within-subject effects allowed us to better identify factors which might influence a PAH patient's HRQoL over the course of their care. We found that changes in WHO functional class and exercise tolerance were strongly associated with the e10 score. Increased 6MWD was associated with improved e10 scores and progression to more a severe WHO functional class was associated with worsened e10 scores [24]. It is possible that the association is linked to the nature of the questions included in the e10 questionnaire since functional class, 6MWD and e10 score are all metrics that reflect the degree to which PAH symptoms interfere with a patient's ability to complete physical tasks. We found that within-participant changes in BNP/NT-proBNP z-score were associated with changes in e10 score over time, possibly suggesting that disease progression towards heart failure was associated with a decline in HRQoL. Finally, increases in the number of visits to the emergency room and hospitalisations between PHCC visits were also associated with worsened HRQoL over time, which might reflect the impact of declining health. When taken together, the strong association of e10 with clinically meaningful disease parameters both at baseline and over time suggests that e10 may be useful as a clinical surrogate or clinical trial end-point.

We reported a MID estimate for the e10 score of −6.0 points (range −5.0–−7.6 points). The MID of a metric is an important benchmark against which within-patient changes can be deemed relevant to clinical decision-making without relying on the idea of statistical significance (which is sensitive to sample size and is often not applicable in the context of individualised care). Identification of a MID for the e10 score is especially important given that medical management of PAH is focused on alleviating symptoms and promoting patient comfort, both of which are best quantified using a patient-reported HRQoL metric. During a public meeting hosted by the US FDA, in which PAH patients shared their experiences with PAH therapies, a few common themes arose: many patients recounted being treated through trial and error; they often found it difficult to isolate which therapies helped the most; and they frequently noted that the downsides of some medications were considerable [3]. The net benefit resulting from the balance between functional improvements and therapy-related burdens is critically important to patients who suffer with PAH and the e10 score may be a promising quantitative measure of HRQoL in this respect. Ultimately, efforts to characterise the performance of e10 (and other modern HRQoL tools) may enable their use as formal clinical trial end-points and help guide medical management from a patient's perspective.

Our study has several limitations. The group of patients included in our study were individuals with access to an accredited PHCC in the United States, and those who agreed to participate in PHAR at baseline and follow up. Thus, there are a variety of sources for potential selection bias. Still, our study cohort was similar to other registry-based PAH study cohorts with regards to several key variables [5] and our use of data from multiple study sites located throughout the United States probably contributed to the generalisability of our study. Performance of procedures and clinical decision-making followed institution-specific standards rather than study protocols. Each enrolling centre was directed to mark patients as active or lost to follow-up at their own discretion. Only half of our study cohort was diagnosed within 6 months of their baseline PHCC visit and very few patients were treatment naïve at baseline; such heterogeneity in disease status at baseline made it difficult to isolate treatment effects of PAH medications. An analysis of treatment effect on e10 could not be reliability performed in this observational registry. The use of registry data precluded us from answering questions or using methods that would have required data that weren't collected. While we were

able to compare the performance of e10 with short form (SF)-12, unfortunately a more comprehensive SF-36 was not collected. Given that SF-12 is a general health questionnaire, it is difficult to compare and contrast its utility to that of the PAH-specific e10 tool. Future studies should evaluate the performance of PAH-specific surveys such as CAMPHOR [10], SYMPACT [12] and e10 together in the same study population. Moreover, it would have been ideal to include anchor-based MID estimation approaches focused on patients' perceptions of their illness relative to themselves or others in our analyses, but the necessary data were not available. Finally, the ability to make causal inferences may also be limited by measured and unmeasured confounders.

In conclusion, we showed that the e10 score is associated with important demographic and clinical patient characteristics in patients in the United States, suggesting that HRQoL in PAH is influenced by both social factors and indicators of disease severity. We further demonstrated that considerable amounts of variability in the e10 score both between patients at baseline and within patients over time could be explained by the 6MWD and WHO functional class. The strong associations of these two well established, clinically important metrics with the e10 score are evidence that the e10 score can potentially aid in clinical practice by serving as a quantitative measure of a patient's functional ability that implicitly takes into account their overall perception of the impact PAH has on their life. We also established an estimate of the MID e10 score of −6.0 points, although future research using anchor-based methods that take into account patients' opinions regarding changes in their HRQoL is needed to validate this estimate. Future studies are needed to demonstrate the impact of the e10 score on clinical decision-making and to evaluate its utility for assessing clinically important interventions.

Acknowledgements: The Pulmonary Hypertension Association Registry (PHAR) is supported by Pulmonary Hypertension Care Centers, Inc., a supporting organisation of the Pulmonary Hypertension Association. The authors thank the other investigators, the staff, and particularly participants of the PHAR for their valuable contributions. A full list of participating PHAR sites and institutions can be found at www.PHAssociation.org/PHAR

Conflict of interest: M. Borgese has nothing to disclose. D. Badesch reports grants, personal fees and other (long-term stockholder in Johnson & Johnson) from Actelion/Janssen/Johnson & Johnson, grants and personal fees from Arena/United Therapeutics/Lung LLC, Acceleron, Complexa, Liquidia and Belleraphon, personal fees from Pfizer, grants from Altavant, outside the submitted work. T. Bull reports grants from Bayer, personal fees from Liquidia, outside the submitted work; and is a member of a clinical trial steering committee for Liquidia. M. Chakinala reports grants and consultancy fees from Actelion, Reata Pharmaceuticals, United Therapeutics, Phase Bio and Acceleron, grants from Medtronic, Eiger Bio Pharmaceuticals, GeNO LLC, GSK, Liquidia, Complexa, Altavant and Trio Health Analytics, consultancy and lecture fees from WedMD LLC (Medscape), consultancy fees from SteadyMed Therapeutics Inc. and Express Scripts Holding Company, grants, personal fees for lectures and consultancy fees from Bayer and Gilead Sciences, outside the submitted work. T. DeMarco serves as a consultant to Actelion, United Therapeutics, Arena and SCOPE/BIAL, and as PI on a multicenter trial sponsored by Acceleron. J. Feldman reports personal fees for consultancy and lectures from United Therapeutics and Actelion, personal fees for consultancy from Acceleron, Bayer and Altavant, outside the submitted work. H.J. Ford reports grants and personal for consultancy fees from United Therapeutics and Actelion/Jannsen, personal fees for consultancy from Bayer, grants from Liquidia, outside the submitted work. D. Grinnan reports grants from Johnson & Johnson, Bayer and United Therapeutics, outside the submitted work. J.R. Klinger has nothing to disclose. L. Bolivar has nothing to disclose. O.A. Shlobin has nothing to disclose. R.P. Frantz has nothing to disclose. J.S. Sager reports personal fees for consultancy, lectures and research from Actelion and United Therapeutics, personal fees for consultancy from Bayer, personal fees for research from Reata and PhaseBio, outside the submitted work. S.C. Mathai reports personal fees for consultancy from Actelion, Arena, Liquidia and United Therapeutics, outside the submitted work; and is a member of the Rare Disease Advisory Panel for the Patient Centered Outcomes Research Institute. S. Kawut reports grants from NIH, non-financial support from ATS, and grants from Actelion, United Therapeutics, Gilead, Lung Biotech, Bayer and Mallinkrodt to the Perelman School of Medicine for CME courses; reports grants and non-financial support from Cardiovascular Medical Research and Education Fund and non-financial support from Pulmonary Hypertension Association; and has served in an advisory capacity (for grant review and other purposes) for United Therapeutics, Akros Pharmaceuticals, GlaxoSmithKline and Complexa, Inc. without financial support or in-kind benefits. P.J. Leary has nothing to disclose. M.P. Gray has nothing to disclose. R.A. Popat has nothing to disclose. R.T. Zamanian reports grants from Actelion, Tenax, PHaware and United Therapeutics, personal fees for consultancy from Morphogen-IX and Vivus, outside the submitted work; and has a patent FK506 for PH issued.

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