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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 Leary[15], Michael P Gray[16], Rita A Popat[1], Roham T Zamanian[17,18]

On Behalf of the PHAR Study Group

[1]Department of Health Research and Policy, Stanford University School of Medicine, [2]Division of Pulmonary and Critical Care Medicine, University of Colorado, [3]Division of Pulmonary and Critical Care Medicine, Washington University at Barnes-Jewish, [4]Division of Cardiology, University of California San Francisco, [5]Arizona Pulmonary Specialists, [6]Division of Pulmonary and Critical Care Medicine, University of North Carolina at Chapel Hill, [7]Division of Pulmonary and Critical Care Medicine, Virginia Commonwealth University Medical Center, [8]Division of Pulmonary and Critical Care Medicine, Brown University, [9]Patient Representative, [10]Inova Fairfax Hospital, [11]Division of Cardiovascular Medicine, Mayo Clinic Rochester,[12]Cottage Pulmonary Hypertension Center, [13]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, [14]Division of Pulmonary and Critical Care Medicine, University of Pennsylvania, [15]Division of Pulmonary and Critical Care Medicine, University of Washington, [16]Pulmonary Hypertension Association, [17]Division of Pulmonary & Critical Care Medicine, Stanford University School of Medicine, and [18]Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University School of Medicine

The PHAR Study Group – Please refer to Author Appendix

Corresponding Author: Roham T Zamanian
300 Pasteur Dr, Room H3143
Stanford, CA 94305
Email: Zamanian@stanford.edu
Telephone: 650-521-4504

Take Home Message: Understanding quality of life is critical given the profound impact PAH has on patient lives. We show that emPHasis-10 score correlates with demographic and clinical characteristics at baseline and overtime, and potentially useful as a clinical trial endpoint.

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 PAH patients in the United States.

Methods: Using the Pulmonary Hypertension Association Registry, we evaluated relationships between the e10 score and demographic, functional, hemodynamics, 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 55.6±16.0 years of age. 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 six-minute walk distance and B-type natriuretic peptide/ N-terminal-pro BNP 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 to -7.6 points).

Conclusions: The e10 score was associated with demographic and clinical patient characteristics suggesting that HRQoL 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.

BACKGROUND:

Pulmonary arterial hypertension (PAH) is a rare and progressive cardiopulmonary disorder characterized 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 once realizing 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 U.S. Food and Drug Administration, 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 tradeoffs between gains in functional ability versus side effects with PAH therapies.

Most interestingly, HRQoL measures have potential as patient-centered clinical trial endpoints.

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, 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 questionnaires (13). The emPHasis-10 (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 dysponea and emotional distress (14), and mortality (15). However, these studies were limited to patients within the United Kingdom.

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 endpoint. 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 US-based PAH registry. We hypothesized that patients with sociodemographic and behavioral 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; NCT04071327), a large, multicentre registry of patients diagnosed with PAH and chronic thromboembolic pulmonary hypertension seen at any of thirty-three participating accredited pulmonary hypertension care centers (PHCC) in the United States (US) [Online Supplement]. We included adults with a PHCC-determined diagnosis of PAH recruited between 2015 and 2018. Patients with pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, chronic thromboembolic pulmonary hypertension, and persistent pulmonary hypertension of the newborn were excluded. The emPHasis-10 (e10) questionnaire consists of ten items formatted as a semantic six-point differential scale resulting in patient-reported scores ranging from 0 to 50.

Patients younger than 18 years of age 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 (Federalwide Assurance Number FWA00004028). Informed consent was obtained from each patient prior to enrollment.

Hemodynamic parameters were assessed via right heart catheterization 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 [Online Data Supplement]. Follow-up frequency was determined by each PHCC and typically occurred once every three to six months for clinically stable patients. The e10 score was calculated at each visit according to patient responses on the e10 questionnaire (**Figure S1** in Online Supplement).

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-pro BNP (NT-pro BNP) value, we created a BNP/NT-pro BNP z-score parameter which included scaled values centered around a mean BNP 246 pg/mL (SD, 386 pg/mL) and mean NT-pro BNP 1437 pg/mL (SD, 3292 pg/mL). REVEAL Registry risk scores (16) were calculated as described in the literature and risk strata represent the following ranges of predicted one-year survival: < 70% (very high risk), 70 to < 85% (high risk), 85 to < 90% (moderate high risk), 90 to < 95%

(average risk), and 95 to 100% (low risk). Please refer to the Online Supplement for a comprehensive list of and information about the variables collected.

Data analysis:

We summarized the study cohort demographic and clinical characteristics at baseline. Continuous parameters were expressed as mean ± standard deviation (SD). If data were not normally distributed, we reported the median (interquartile range [IQR]). Categorical parameters were expressed as counts (percentages). We evaluated data for completeness and applied standard multiple imputation methodology for those with greater than 10% missingness at baseline [Online Supplement].

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 utilized given their ability to handle both correlated and missing data. For continuous predictors of interest, we used a within-

subject centering 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 Core Team, 2018) 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 standard deviation, and effect size approaches. Data from the baseline and first follow-up visits were used in all calculations, the previously reported intraclass correlation 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 six months of their baseline visit and patients who were treatment naive 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 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 six months of PHAR enrollment (N=285) and the most common PAH etiologies 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 six-minute walk distance (6MWD) was 335±123 m, which was about half that expected in healthy subjects (20). A majority of the study cohort (N=281; 49.7%) were identified as having a 95 to 100% chance of one-year survival according to their REVEAL risk stratum. Furthermore, 14% of patients (N=81) were treatment naive and 38% used supplemental oxygen (N=214) at the time of their baseline visit (**Table S1** in Online Supplement).

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

The mean e10 score in our study cohort of 25.4±12.2 (**Table 2**) aligned with the center of the 0 to 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 ten-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**). Women had a 2.6-point higher e10 score (95% CI, 0.3-4.9; p=0.024) than men. 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 (beta coefficient [coef], -1.4; 95% CI, -2.2--0.6; p=0.001).

The e10 score was also significantly associated with several clinical parameters after adjustment for relevant confounders (**Table 4**; **Table S2**). Higher BMI values were associated with higher 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; 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; p<0.001) and 11.6-point (95% CI, 6.7-16.6; 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--1.0; p<0.001). Higher BNP/NT-pro BNP z-scores (coef, 1.7; 95% CI, 0.8-2.7; p<0.001) and supplemental oxygen use (coef, 3.4; 95% CI, 1.4-5.4; p=0.001) were both associated with higher e10 scores.

Worse hemodynamics as evidenced by higher right atrial pressures (per 3 mmHg; coef, 0.8; 95% CI, 0.3-1.4; p=0.001) and pulmonary vascular resistances (per 160 $dyn*s*cm^{-5}$; coef, 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. Patients who reported an emergency room visit (coef, 4.4; 95% CI, 2.4-6.4; p<0.001) or hospitalization (coef, 4.1; 95% CI, 2.1-6.1; p<0.001) in the six 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**).

Of all included variables, only baseline income level, 6MWD, heart rate, stroke volume, and pulmonary artery compliance had greater than 10% missing data. Imputation of missing data for these parameters did not alter our findings [Online Supplement].

Factors associated with emPHasis-10 over time: The median time between follow-up visits among active participants was 9.6 months (IQR, 6.0-14.5). 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 (**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 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**; **Table S3**). The within-subject coefficient for 6MWD was -0.6 (95% CI, -0.9--0.4; p<0.001), suggesting an expected 0.6-point decrease in e10 score for every 30 m increase in 6MWD relative to their personal average across PHCC visits. The coefficients for BNP/NT-pro BNP z-score (coef, 2.2; 95% CI, 1.0-3.4; p<0.001), frequency of emergency room visits (coef, 0.3; 95% CI, 0.0-0.6; p=0.034), and number of nights spent hospitalized (coef, 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**).

We also repeated our longitudinal analyses within the subgroup of incident patients (diagnosed within six months of their baseline visit) and demonstrated generally similar associations [Online Supplement].

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 standard deviation (-5.0 points), and effect size approaches (-6.1 points) for patients with e10 scores recorded at their baseline and first follow-up visits (**Table S4A**). The estimates generated for the subgroups of patients who were diagnosed within six 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 or more between PHCC visits was 35.0±88.5 m whereas the distance among patients whose e10 score decreased by less than 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 subtypes including iPAH, CTD-APAH, and D&T-APAH (**Table S4B)**.

DISCUSSION:

PHAR is the first US-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 one-year probability of survival of 90% or greater according to the REVEAL Registry Risk Score Calculator. At baseline, our study cohort had an average e10 score of approximately 25, which was normally distributed and represented full score 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, women reported significantly worse HRQoL than men, a finding consistent with data in the general population with chronic cardiopulmonary and infectious illnesses (22-25).While not well understood, gender 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-pro BNP z-score, and several hemodynamic 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 iPAH and CTD-APAH (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). Important but nonspecific indicators of poor health including emergency room visits and hospitalizations were similarly associated with poorer HRQoL. Association between the e10 score and patient-reported PHCC care rating may

perhaps 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-pro BNP 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 hospitalizations 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 endpoint.

We reported a MID estimate for the e10 score of -6.0 points (range -5.0 to -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 individualized 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 U.S. Food and Drug Administration 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 characterize the performance of e10 (and other modern HRQoL tools) may enable their use as formal clinical trial endpoints 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 likely contributed to the generalizability 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 six months of their baseline PHCC visit and very few patients were treatment naive 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 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, though 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.

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Figures Legends:

Figure 1 - Flowchart of patient selection. PHAR = Pulmonary Hypertension Association Registry.

Figure 2 - EmPHasis-10 versus 6MWD (A), WHO FC (B), and REVEAL risk stratum (C) at baseline. Mean and 95% CI are shown for (B, C); red 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. 6MWD = six-minute walk distance; WHO FC = World Health Organization functional class.

Figure 3 - EmPHasis-10, 6MWD (A), and WHO FC (B) across baseline and follow-up PHCC visits. EmPHasis-10 and 6MWD are shown as mean and 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. The mean emPHasis-10 score within our cohort also decreased as the proportion of participants in WHO FC III and IV decreased. FU = follow-up; 6MWD = six-minute walk distance; WHO FC = World Health Organization functional class.

Table 1. Baseline Patient Demographics

Parameters	Patients (N=565)
Age, yr	55.6 ± 16.0
Sex, female, n (%)	421 (74.5)
Race/ethnicity, n (%), (n=561)	
White, non-Hispanic	368 (65.1)
Asian/Pacific Islander	35 (6.2)
Hispanic	69 (12.2)
Black, non-Hispanic	67 (11.9)
Native American	7 (1.2)
Mixed race	15 (2.7)
Highest education level, n (%), (n=559)	
Less than high school	54 (9.7)
High school/GED	322 (57.6)
College or graduate degree	183 (32.7)
Employment status, n (%), (n=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, n (%), (n=456)	
Below poverty level	98 (21.5)
Above poverty, <$75k	225 (49.3)
≥$75k	133 (29.2)
Marital status, n (%), (n=556)	
Single	154 (27.7)
Married	288 (51.8)
Divorced	76 (13.7)
Widowed	38 (6.8)
Health insurance, n (%), (n=560)	
Uninsured	9 (1.6)
Medicare	247 (44.1)
Medicaid	58 (10.4)
Other government service	49 (8.7)
Private insurance	197 (35.2)

Values are expressed as mean ± SD; total number of observations is 565 unless otherwise noted.

Table 2. Baseline Patient Clinical Characteristics

Parameters	Patients (N=565)
EmPHasis-10 score, (n=554)	25.4 ± 12.2
BMI, kg/m^2, (n=553)	29.1 ± 7.3
PAH aetiology, n (%)	
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 functional class, n (%), (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, (n=331)	130 (50-370)
NT-pro BNP, pg/mL, (n=229)	531 (191-2242)
Creatinine, mg/dL, (n=546)	0.9 (0.8-1.1)
Hemodynamics*	
Heart rate, bpm, (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, (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, (n=357)	1.1 (0.8-1.6)
REVEAL risk stratum[‡], n (%), (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 (2.9)

Values are expressed as mean ± SD; total number of observations is 565 unless otherwise noted.
*Values are expressed as median (interquartile range)
[†]Of the 21 patients missing a value for mean pulmonary artery pressure, 15 were diagnosed with PAH more than six months prior to their baseline visit
[‡]Determined using the REVEAL Registry Risk Score Calculator (16)
BMI=body mass index; PAH=pulmonary arterial hypertension; CTD=connective tissue disease; PPHTN = portopulmonary hypertension; CHD=congenital heart disease; WHO=World Health Organization; 6MWD=six-minute walk distance; BNP=brain natriuretic peptide; NT-pro BNP=N-terminal pro B-type natriuretic peptide; mPAP=mean pulmonary artery pressure; PAWP/LVEDP=pulmonary artery wedge pressure or left ventricular end-diastolic pressure; PVR=pulmonary vascular resistance; PAC=pulmonary artery compliance.

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

	Unadjusted			Adjusted*		
Parameters	**Coefficient [95% CI]**	**R^2**	**p-value**	**Coefficient [95% CI]**	**R^2**	**p-value**
Age (per 10 yrs)	1.0 [0.4, 1.6]	0.02	0.002	0.9 [0.3, 1.5]	0.06	0.005
Sex (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 (Ref. group)						
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 (Ref. group)						
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 (Ref. group)						
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 (Ref. group)						
Above poverty, <$75k	-2.9 [-5.8, 0.0]			-3.5 [-6.5, -0.5]		
≥$75k	-6.6 [-9.8, -3.4]			-4.8 [-8.3, -1.4]		
Marital status		0	0.18		0.06	0.341
Single (Ref. group)						
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 (Ref. group)						
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]		
Pt. 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
Non-smoker (Ref. group)						
Past	3.3 [1.2, 5.4]			2.6 [0.5, 4.8]		

Current	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 (Ref. group)						
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]		

*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
Pt. = patient; PHCC = pulmonary hypertension care centre; PH = pulmonary hypertension.

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

	Unadjusted			Adjusted*		
Parameters	**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 last 6 mo.	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 (Ref. group)						
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 class		0.21	<0.001		0.21	<0.001
I (Ref. group)						
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-pro BNP 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 [-0.8, 3.1]	0	0.255	0.9 [-1.1, 3.0]	0.03	0.386
Hemodynamics						
Heart rate (per 10 bpm)	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)	-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)	-1.0 [-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 (Ref. group)						
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 last 6 mo.	4.0 [2.0, 6.0]	0.02	<0.001	4.4 [2.4, 6.4]	0.07	<0.001
Hospitalized in last 6 mo.	3.9 [1.9, 5.9]	0.02	<0.001	4.1 [2.1, 6.1]	0.06	<0.001

*Adjusted for age, sex, and body mass index with the exception of the model for body mass index, which was adjusted for age and sex

†Parameter reflects scaled values centered around a 246 pg/mL mean BNP (SD, 386 pg/mL) and 1437 pg/mL mean NT-pro BNP (SD, 3292 pg/mL)

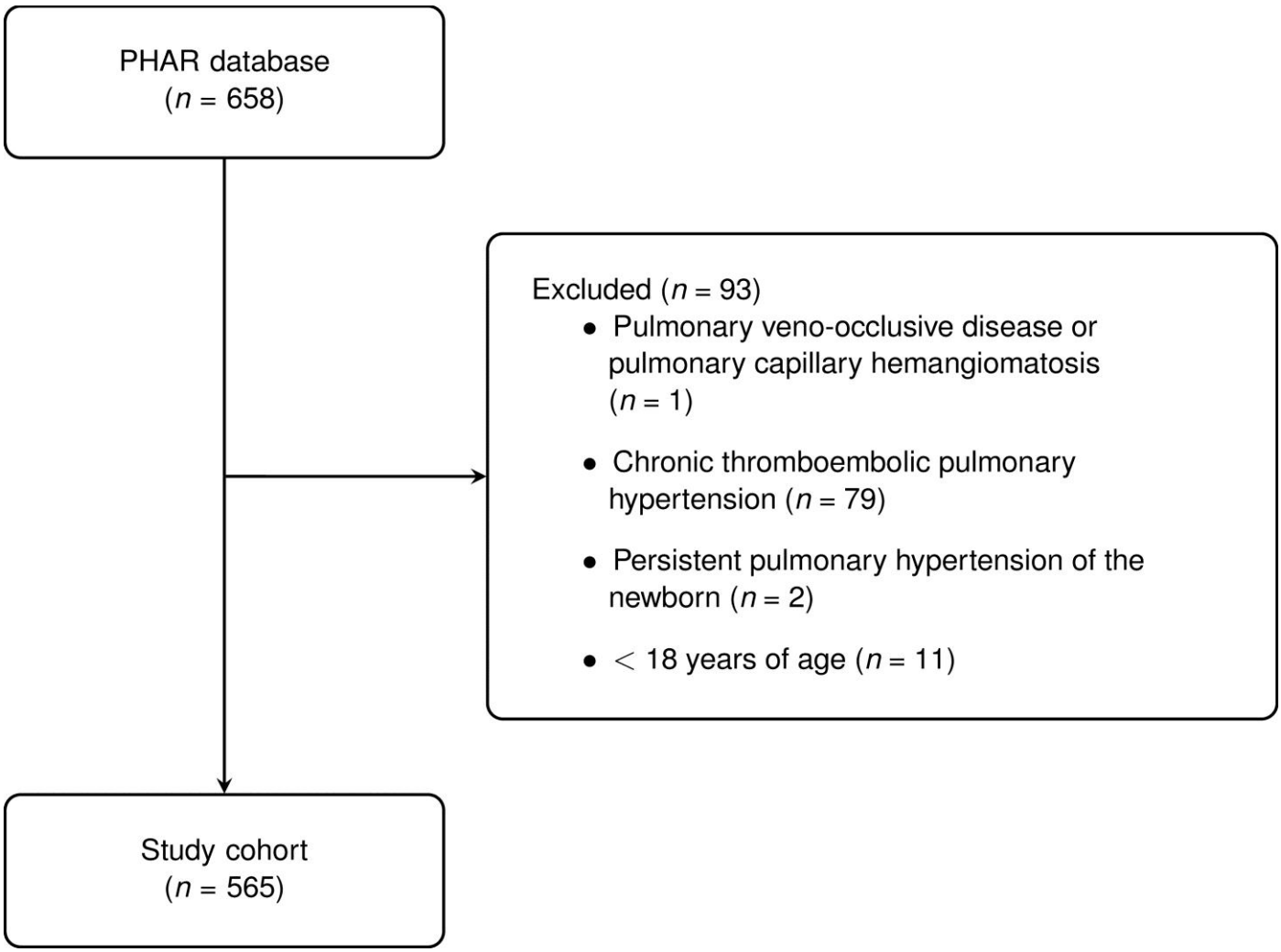
‡Determined using the REVEAL Registry Risk Score Calculator (16)

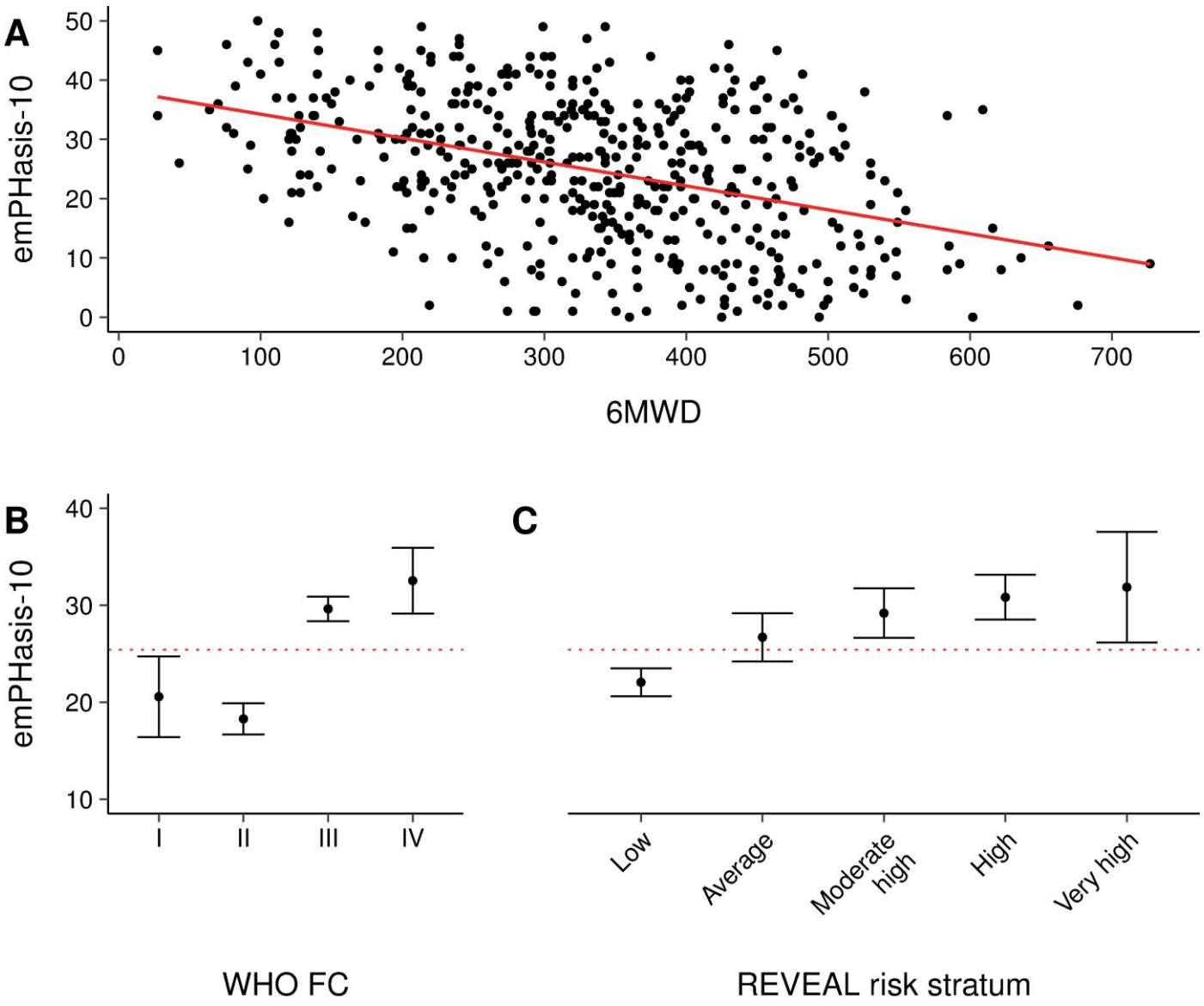
BMI = body mass index; PAH = pulmonary arterial hypertension; CTD = connective tissue disease; PPHTN = portopulmonary hypertension; CHD = congenital heart disease; WHO = World Health Organization; 6MWD = six-minute walk distance; BNP/NT-pro BNP = brain natriuretic peptide or N-terminal pro B-type natriuretic peptide; mPAP = mean pulmonary artery pressure; PAWP/LVEDP = pulmonary artery wedge pressure or left ventricular end-diastolic pressure; PVR = pulmonary vascular resistance; PAC = pulmonary artery compliance; ER = emergency room.

Table 5. Associations between within-patient changes and emPHasis-10 score

Parameters	Coefficient [95% CI]	R^2	p-value
Pt. 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 functional class (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-pro BNP z-score* (per SD)	2.2 [1.0, 3.4]	0.09	<0.001
Creatinine (per mg/dL)	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
No. ER visits (per visit)	0.3 [0.0, 0.6]	0.12	0.034
No. nights hospitalized (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.
*Parameter reflects scaled values centered around a 246 pg/mL mean BNP (SD, 386 pg/mL) and 1437 pg/mL mean NT-pro BNP (SD, 3292 pg/mL)
†Determined using the REVEAL Registry Risk Score Calculator (16)
Pt. = patient; PHCC = pulmonary hypertension care centre; BMI = body mass index; WHO = World Health Organization; 6MWD = six-minute walk distance; BNP/NT-pro BNP = brain natriuretic peptide or N-terminal pro B-type natriuretic peptide; ER = emergency room.


PHAR database
(n = 658)
Excluded (n = 93)
• Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis (n = 1)
• Chronic thromboembolic pulmonary hypertension (n = 79)
• Persistent pulmonary hypertension of the newborn (n = 2)
• < 18 years of age (n = 11)
Study cohort
(n = 565)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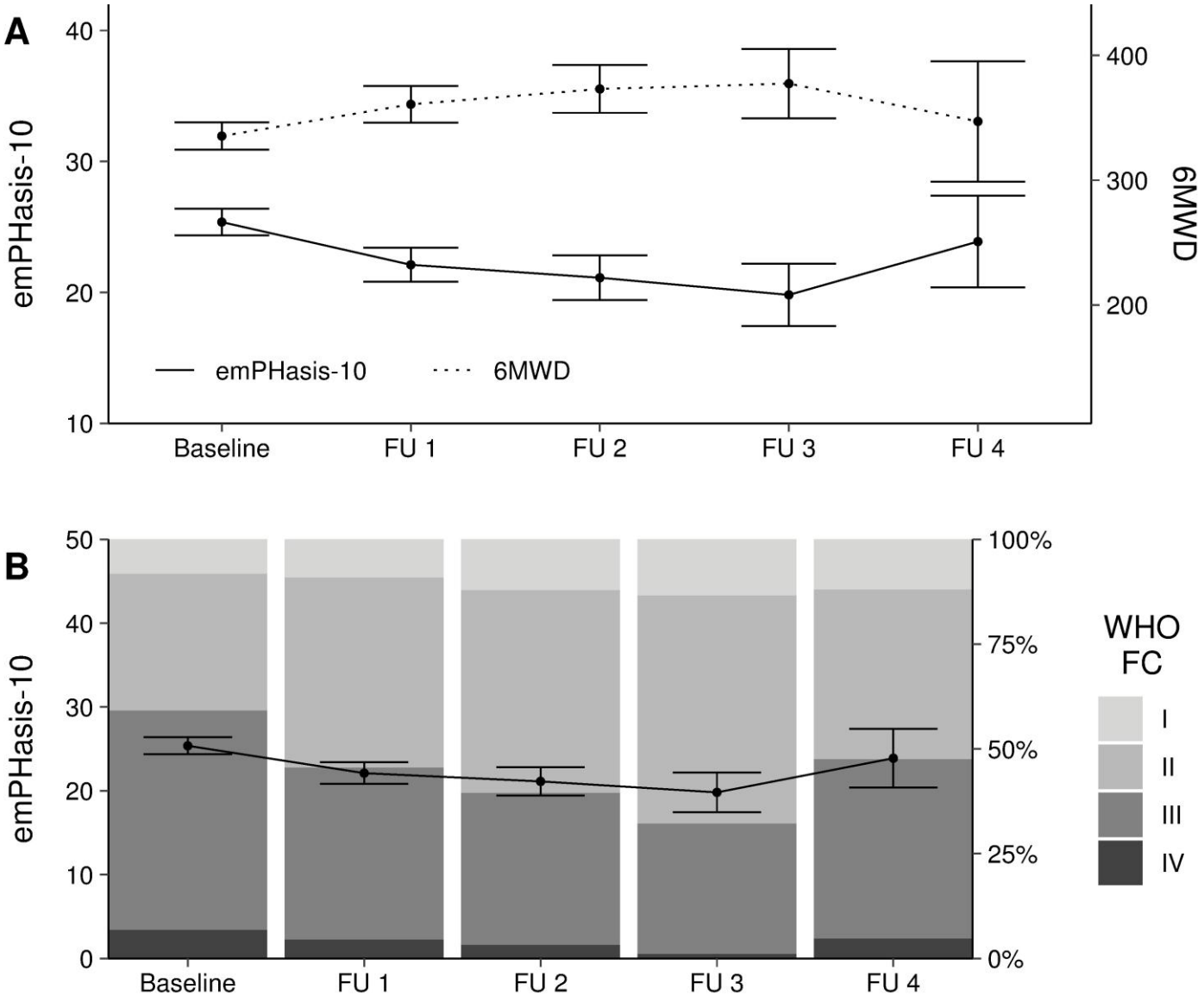
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10
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emPHasis-10
100%
75%
50%
25%
0%
WHO FC
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III
IV
Baseline
FU 1
FU 2
FU 3
FU 4

EmPHasis-10 as a Measure of Health-Related Quality of Life in Pulmonary Arterial Hypertension

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], Steven Mathai[13], Steven Kawut[14], Peter Leary[15], Michael P Gray[16], Rita A Popat[1], Roham T Zamanian[17,18]
On Behalf of the PHAR Study Group

[1]Department of Health Research and Policy, Stanford University School of Medicine, [2]Division of Pulmonary and Critical Care Medicine, University of Colorado, [3]Division of Pulmonary and Critical Care Medicine, Washington University at Barnes-Jewish, [4]Division of Cardiology, University of California San Francisco, [5]Arizona Pulmonary Specialists, [6]Division of Pulmonary and Critical Care Medicine, University of North Carolina at Chapel Hill, [7]Division of Pulmonary and Critical Care Medicine, Virginia Commonwealth University Medical Center, [8]Division of Pulmonary and Critical Care Medicine, Brown University, [9]Patient Representative, [10]Inova Fairfax Hospital, [11]Division of Cardiovascular Medicine, Mayo Clinic Rochester,[12]Cottage Pulmonary Hypertension Center, [13]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, [14]Division of Pulmonary and Critical Care Medicine, University of Pennsylvania, [15]Division of Pulmonary and Critical Care Medicine, University of Washington, [16]Pulmonary Hypertension Association, [17]Division of Pulmonary & Critical Care Medicine, Stanford University School of Medicine, and [18]Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University School of Medicine

The PHAR Study Group – Please refer to Author Appendix

ONLINE SUPPLEMENT

Pulmonary Hypertension Association Registry:

Beginning September 2015, patients have been consecutively approached for enrollment in the Pulmonary Hypertension Association Registry (PHAR) (S1) at the time of their first visit at a pulmonary hypertension care center (PHCC). Patients are considered active in the registry unless marked by their PHCC's clinical research coordinator as having refused, been lost to follow-up, transferred, received a lung transplant, or died. Data were collected using electronic study tablets. Demographic factors, height, pulmonary arterial hypertension (PAH) etiology, and hemodynamic data were recorded at baseline and lifestyle information, patient-assigned care ratings, weight, six-minute walk distance, World Health Organization (WHO) functional class, medication information, and lab values were recorded at baseline and follow-up PHCC visits.

Data Variables:

Demographic parameters recorded in PHAR include age, sex, race/ethnicity, highest education level, employment status, yearly income, marital status, health insurance information, patient-assigned PHCC quality-of-care rating, history of alcohol use, history of cocaine, crack cocaine, or methamphetamine use, smoking status, participation status in a pulmonary hypertension clinical trial, presence of an advance directive, and United States regional location of the PHCC. Clinical parameters include the emPHasis-10 (e10) score, 12-item Short Form Survey physical component summary and mental component summary scores, body mass index, whether a patient was diagnosed with PAH within six months of entry into PHAR, PAH etiology, WHO functional class, six-

minute walk distance, supplemental oxygen use, PAH therapy use, B-type natriuretic peptide (BNP), N-terminal-pro BNP (NT-pro BNP), creatinine, heart rate, right atrial pressure, mean pulmonary artery pressure, pulmonary artery wedge pressure, left ventricular end-diastolic pressure, cardiac output, pulmonary vascular resistance, stroke volume, pulmonary artery compliance, number of emergency room visits in the last six months or since the last PHCC visit, and number of hospitalizations in the last six months or since the last PHCC visit.

We used each patient's reported income range and number of individuals in household to assign a yearly income level according to the 2018 US Department of Health and Human Services guidelines (S2). PHCC care ratings were assigned by patients on a 0 to 10 scale, where 0 is the worst health care possible and 10 is the best health care possible. History of illicit stimulant use was defined as having ever used cocaine, crack cocaine, or methamphetamine prior to enrollment.

Medications were separated into four classes: prostacyclin analogs, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators. Pulmonary artery wedge pressure and left ventricular end-diastolic pressure data were combined into one variable and, if both values were available, the reported pulmonary artery wedge pressure was used. Values for cardiac output, stroke volume, and pulmonary artery compliance were computed for patients who were missing these values but had the hemodynamic parameters from which they could be derived. The REVEAL Registry Risk Score Calculator (S3) was used to determine the REVEAL risk

stratum for patients with a value available for at least seven of the following ten parameters: PAH etiology, creatinine, age and sex, WHO functional class, systolic blood pressure, heart rate, six-minute walk distance, brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT-pro BNP), right atrial pressure, and pulmonary vascular resistance.

Multiple imputation for missing data:

We identified variables with more than 10% missingness at baseline and used the R package 'mice' (S4) to impute missing data for these variables. The predictive mean matching method was used for continuous variables and the proportional odds model method was used for ordinal variables. Forty imputed data sets were generated, relevant baseline models were re-run using all imputed data sets, and model results were pooled for comparison against our initial model results. We reported on changes to the coefficient, standard error of the coefficient, or R^2 that differed from the initial results by more than 10% and changes to the p-value that affected our conclusions at the 0.05 significance level. We identified income level, six-minute walk distance, heart rate, stroke volume, and pulmonary artery compliance were as having over 10% missingness at baseline and repeated analyses as detailed below.

Income level: We found that 19% of income level values were missing at baseline. After imputing missing data, the R^2 value from the unadjusted model went from 0.03 to 0.04, indicating that income level explained a greater proportion of the variance in e10 score

with the imputed data. Still, the R^2 value remained small and our conclusions were not affected.

Six-minute walk distance: There were considerable amounts of data missing for the six-minute walk distance at baseline (14%). Imputation of missing baseline data had no or negligible effects on all baseline six-minute walk distance model outputs.

Heart rate: We found that 35% of heart rate values were missing at baseline. After imputing missing data, the heart rate parameter in the unadjusted model with heart rate as the independent variable and e10 score as the dependent variable reached statistical significance at a significance level of 0.05 ($p=0.032$). All other outputs from the unadjusted and adjusted models did not change or changes were negligible.

Stroke volume: We found that 36% of stroke volume values were missing at baseline. After imputing missing data, the R^2 for the adjusted stroke volume model decreased from 0.06 to 0.04. Still, the R^2 value from the initial model was small and our conclusions were not affected by the imputed data.

Pulmonary artery compliance: We found that 37% of pulmonary artery compliance values were missing at baseline. After imputing missing data, the coefficient from the unadjusted model went from -1.0 to -0.6, indicating a weakened correlation between pulmonary artery compliance and e10 score (although this relationship remained statistically insignificant). The coefficient from the adjusted pulmonary artery compliance

model went from -1.1 to -0.8, again suggesting a weakened correlation between pulmonary artery compliance and e10 score. The R^2 value from the adjusted model was also affected by the imputed data and went from 0.04 to 0.03, indicating that the adjusted pulmonary artery compliance model explained less of the variance in the e10 score after missing data were imputed. Still, the R^2 value from the initial model was small and our conclusions were not affected.

Factors Associated with Patient Attrition:

We identified patient demographic and clinical parameters associated with attrition via loss to follow-up and death or lung death (as indicated by lung transplant). We used the Wilcoxon rank-sum test to evaluate relationships between patient status in PHAR (active, lost to follow-up, and died/lung transplant) and continuous parameters and the Fisher's exact test to evaluate relationships between patient status and categorical parameters. Non-parametric tests were used due to small sample sizes in the lost to follow-up and died/lung transplant groups. We assessed differences between the active versus lost to follow-up and active versus died/lung transplant patients separately.

A total of 12 patients (2%) were lost to follow-up and 39 patients (7%) died or received a lung transplant signifying organ death during the data collection period. We found that patients lost to follow-up had significantly higher e10 scores, lower income, and reported higher PHCC care ratings than those who remained active (see table below). The majority of patients lost to follow-up also had marked medical leave/disability as their employment status, reported having a history of illicit stimulant use, were identified

as having drug/toxin-associated PAH, and reported having been hospitalized in the six months prior to their baseline PHCC visit. Further, compared to patients who remained active in PHAR during the study period, we found that deceased and lung transplant patients were significantly older, had higher e10 scores and BNP/NT-pro BNP z-scores, had shorter six-minute walk distances, were more frequently identified as belonging to WHO functional class IV and high-risk REVEAL risk strata, and had a greater proportion of individuals who indicated they were retired, insured through Medicare, had an advance directive, used supplemental oxygen, had visited the emergency room in the six months prior to their baseline PHCC visit, and were seen at a PHCC in the Northeast United States.

	Active	**Lost to follow-up**		**Died/lung transplant**	
Parameters	**(n = 498)**	**(n = 12)**	**p-value**	**(n = 39)**	**p-value**
Demographic					
Age, yr	55.5 (42.5-67.3)	51.6 (44.9-61.4)	0.788	67.5 (58.2-74.3)	<0.001
Sex, female, n (%)	377 (75.7)	7 (58.3)	0.181	25 (64.1)	0.125
Race/ethnicity, n (%)			0.574		0.725
White, non-Hispanic	320 (64.3)	6 (50.0)		28 (71.8)	
Asian/Pacific Islander	32 (6.4)	1 (8.3)		1 (2.6)	
Hispanic	62 (12.4)	2 (16.7)		4 (10.3)	
Black, non-Hispanic	62 (12.4)	3 (25.0)		2 (5.1)	
Native American	7 (1.4)	0 (0.0)		0 (0.0)	
Mixed race	7 (1.4)	0 (0.0)		0 (0.0)	
Highest education level, n (%)			0.273		0.324
Less than high school	44 (8.8)	2 (16.7)		6 (15.4)	
High school/GED	285 (57.2)	8 (66.7)		19 (48.7)	
College or graduate degree	165 (33.1)	2 (16.7)		12 (30.8)	
Employment status, n (%)			0.032		0.012
Unemployed	65 (13.1)	1 (8.3)		3 (7.7)	
Employed	146 (29.3)	0 (0.0)		5 (12.8)	
Medical leave/disability	132 (26.5)	8 (66.7)		9 (23.1)	
Student	8 (1.6)	0 (0.0)		1 (2.6)	

Retired	137 (27.5)	3 (25.0)		21 (53.8)	
Yearly income level, n (%)			0.047		0.91
Below poverty level	85 (17.1)	4 (33.3)		7 (17.9)	
Above poverty, <$75k	194 (39.0)	7 (58.3)		16 (41.0)	
≥$75k	120 (24.1)	0 (0.0)		8 (20.5)	
Marital status, n (%)			0.102		0.058
Single	138 (27.7)	5 (41.7)		6 (15.4)	
Married	254 (51.0)	3 (25.0)		24 (61.5)	
Divorced	68 (13.7)	4 (33.3)		2 (5.1)	
Widowed	31 (6.2)	0 (0.0)		5 (12.8)	
Health insurance, n (%)			0.481		0.003
Uninsured	9 (1.8)	0 (0.0)		0 (0.0)	
Medicare	205 (41.2)	5 (41.7)		28 (71.8)	
Medicaid	51 (10.2)	3 (25.0)		0 (0.0)	
Other government service	46 (9.2)	1 (8.3)		1 (2.6)	
Private insurance	183 (36.7)	3 (25.0)		9 (23.1)	
Pt. PHCC care rating	10 (9-10)	10 (10-10)	0.023	10 (9-10)	0.814
Drinks alcohol, n (%)	178 (35.7)	4 (33.3)	1	8 (20.5)	0.106
History of illicit stimulant use*, n (%)	71 (14.3)	7 (58.3)	0.001	2 (5.1)	0.145
Smoking status, n (%)			0.264		0.586
Non-smoker	272 (54.6)	5 (41.7)		20 (51.3)	
Past	185 (37.1)	5 (41.7)		17 (43.6)	
Current	33 (6.6)	2 (16.7)		1 (2.6)	
Participates in PH clinical trial, n (%)	71 (14.3)	0 (0.0)	0.388	10 (25.6)	0.064
Presence of an advance directive, n (%)	156 (31.3)	7 (58.3)	0.061	19 (48.7)	0.033
United States Region, n (%)			0.168		0.006
Northeast	91 (18.3)	1 (8.3)		16 (41.0)	
Midwest	81 (16.3)	0 (0.0)		2 (5.1)	
South	146 (29.3)	3 (25.0)		11 (28.2)	
West	180 (36.1)	8 (66.7)		10 (25.6)	
Clinical					
EmPHasis-10 score	26 (16-34)	39 (23-46)	0.006	31 (25-40)	0.005
PCS-12 score	34.8 (30.4-38.5)	35.2 (30.8-39.4)	0.955	34.1 (26.9-39.2)	0.674
MCS-12 score	48.3 (41.7-54.8)	48.0 (39.2-53.3)	0.555	49.8 (39.2-56.7)	0.657
BMI, kg/m^2	28.2 (24.1-32.6)	26.6 (23.1-33.1)	0.619	27.7 (22.9-32.7)	0.466
Diagnosed in last 6 mo., n (%)	250 (50.2)	6 (50.0)	1	22 (56.4)	0.508
PAH etiology, n (%)			0.003		0.174
Idiopathic	194 (39.0)	2 (16.7)		21 (53.8)	
Heritable	18 (3.6)	0 (0.0)		0 (0.0)	
Drug/toxin-associated	54 (10.8)	7 (58.3)		1 (2.6)	

CTD-associated	163 (32.7)	1 (8.3)		13 (33.3)	
HIV-associated	9 (1.8)	0 (0.0)		0 (0.0)	
PPHTN-associated	31 (6.2)	1 (8.3)		4 (10.3)	
CHD-associated	29 (5.8)	1 (8.3)		0 (0.0)	
WHO functional class, n (%)			0.43		0.008
I	40 (8.0)	0 (0.0)		3 (7.7)	
II	159 (31.9)	2 (16.7)		4 (10.3)	
III	241 (48.4)	8 (66.7)		19 (48.7)	
IV	28 (5.6)	1 (8.3)		6 (15.4)	
6MWD, m	341.0 (260.0-427.0)	303.9 (259.5-337.5)	0.197	249.0 (185.0-343.0)	0.002
Supplemental oxygen use, n (%)	178 (35.7)	5 (41.7)	0.764	23 (59.0)	0.006
No. PAH medications, n (%)			0.392		0.359
None	74 (14.9)	2 (16.7)		3 (7.7)	
One	151 (30.3)	6 (50.0)		13 (33.3)	
Two	207 (41.6)	2 (16.7)		17 (43.6)	
Three	61 (12.2)	2 (16.7)		6 (15.4)	
PAH medication classes, n (%)					
Prostacyclin analog	144 (28.9)	2 (16.7)	0.523	16 (41.0)	0.145
Endothelin receptor antagonist	257 (51.6)	3 (25.0)	0.082	19 (48.7)	0.741
Phosphodiesterase-5 inhibitor	338 (67.9)	10 (83.3)	0.356	29 (74.4)	0.478
sGC stimulator	11 (2.2)	1 (8.3)	0.252	1 (2.6)	0.601
Laboratory tests					
BNP/NT-pro BNP z-score[†]	-0.3 (-0.5-0.3)	-0.1 (-0.4-0.8)	0.49	0.1 (-0.3-1.2)	0.003
Creatinine, mg/dL	0.9 (0.8-1.1)	1.0 (0.7-1.2)	0.551	1.0 (0.8-1.2)	0.446
Hemodynamics					
Heart rate, bpm	79 (69-90)	80 (73-98)	0.54	76 (69-90)	0.954
Right atrial pressure, mmHg	9 (5-13)	13 (10-17)	0.084	10 (7-15)	0.179
mPAP, mmHg	48 (39-58)	44 (37-54)	0.256	52 (41-60)	0.394
PAWP/LVEDP, mmHg	10 (7-14)	11 (7-13)	0.902	10 (7-13)	0.538
Cardiac output, L/min	3.9 (3.3-5.2)	3.2 (2.1-5.6)	0.189	3.5 (3.0-4.9)	0.094
PVR, dyn*s*cm^{-5}	720 (480-1040)	680 (480-1105)	0.839	876 (640-1178)	0.071
Stroke volume, mL	50.6 (39.5-67.0)	40.0 (12.9-79.7)	0.141	49.5 (31.5-65.3)	0.434
PAC, mL/mmHg	1.1 (0.8-1.6)	1.0 (0.2-1.4)	0.229	1.0 (0.7-1.8)	0.407
REVEAL risk stratum[‡], n (%)			0.886		0.001
Low risk	257 (51.6)	5 (41.7)		11 (28.2)	
Average risk	77 (15.5)	2 (16.7)		3 (7.7)	
Moderate high risk	59 (11.8)	1 (8.3)		7 (17.9)	
High risk	63 (12.7)	2 (16.7)		10 (25.6)	
Very high risk	11 (2.2)	0 (0.0)		4 (10.3)	
Visited ER in last 6 mo., n (%)	268 (53.8)	10 (83.3)	0.074	30 (76.9)	0.007

Hospitalized in last 6 mo., n (%)	249 (50.0)	10 (83.3)	0.037	25 (64.1)	0.099

Values are expressed as median (interquartile range). The p-values correspond to comparisons between active versus lost to follow-up participants and active versus dead/lung transplant participants.
*Stimulants include cocaine, crack cocaine, and methamphetamine
†Parameter reflects scaled values centered around a 246 pg/mL mean BNP (SD, 386 pg/mL) and 1437 pg/mL mean NT-pro BNP (SD, 3292 pg/mL)
‡Determined using the REVEAL Registry Risk Score Calculator (S3)
Pt. = patient; PHCC = pulmonary hypertension care center; PH = pulmonary hypertension; PCS-12 = SF-12 physical component summary; MCS-12 = SF-12 mental component summary; BMI = body mass index; PAH = pulmonary arterial hypertension; CTD = connective tissue disease; PPHTN = portopulmonary hypertension; CHD = congenital heart disease; WHO = World Health Organization; 6MWD = six-minute walk distance; sGC = soluble guanylate cyclase; BNP/NT-pro BNP = brain natriuretic peptide or N-terminal pro B-type natriuretic peptide; mPAP = mean pulmonary artery pressure; PAWP/LVEDP = pulmonary artery wedge pressure or left ventricular end-diastolic pressure; PVR = pulmonary vascular resistance; PAC = pulmonary artery compliance; ER = emergency room.

Incident Patient Subgroup Analyses:

We sought to evaluate what effect restricting our study cohort to those who were marked as incident at baseline would have on our longitudinal analyses, where incident patients were defined as those who had been diagnosed with PAH within the six months prior to their baseline PHCC visit. To do this, we re-ran all longitudinal models using only data from incident patients and identified changes to the within-subject coefficients, standard errors of the coefficients, or R^2 that differed from the initial results by more than 10% and changes to p-values that affected our conclusions at the 0.05 significance level.

We found that the within-subject coefficients for smoking status (0.7; 95% CI, -2.5-3.8), body mass index (0.0; 95% CI, -0.3-0.4), REVEAL risk stratum (0.6; 95% CI, -1.1-2.2), supplemental oxygen use (0.5; 95% CI, -2.3-3.3), phosphodiesterase-5 inhibitor use (1.0; 95% CI, -1.9-3.9), and creatinine (0.1; 95% CI, -4.2-4.3) moved closer to zero,

meaning that the correlations between within-subjects changes in these parameters and the e10 score were weaker among incident patients. Conversely, the within-subject coefficients for alcohol consumption (-1.7; 95% CI, -4.3-0.8), prostacyclin analog use (2.2; 95% CI, -1.2-5.5), endothelin receptor antagonist use (-0.1; 95% CI, -2.7-2.6), soluble guanylate cyclase stimulator use (-6.5; 95% CI, -12.3--0.7), and BNP/NT-pro BNP z-score (2.8; 95% CI, 1.0-4.5) moved further from zero, meaning that the correlations between within-subjects changes in these parameters and the e10 score were stronger among incident patients. The standard errors of the within-subject coefficients from all models increased and this likely resulted from the small number of patients in the incident subgroup (n = 285) compared to the complete patient cohort (n = 565).

The marginal R^2 values for the WHO functional class (R^2, 0.17), REVEAL risk stratum (R^2, 0.10), supplemental oxygen use (R^2, 0.13), number of PAH medications (R^2, 0.11), prostacyclin analog use (R^2, 0.12), and endothelin receptor antagonist use (R^2, 0.12) models all decreased, indicating that the variance in the e10 score explained by each fixed effects model decreased among incident patients. We also found that the within-subject effect of the number of emergency room visits in the last six months/since last visit on the e10 score was no longer statistically significant (p=0.079) among the incident patient subgroup, while the within-subject effect of soluble guanylate cyclase stimulator use on the e10 score reached statistical significance (p=0.030) among the incident patient subgroup.

Through analyzing the relationships between within-subjects changes in patient characteristics and e10 score among the incident patient subgroup, we found that changes in PAH medication use appeared to have stronger relationships with the e10 score in incident patients as compared to a mixed cohort of both incident and prevalent patients. This might have been related to the large proportion of incident patients who were treatment naive at baseline (82%, compared to 14% in the whole study cohort). The number of incident patients on soluble guanylate cyclase stimulators also did not exceed ten across all PHCC visits.

SF-12 Relationship

We used Pearson correlation coefficients to evaluate relationships between the e10 score and the 12-item Short Form Survey (SF-12) (S4) physical component summary (PCS-12) and mental component summary (MCS-12) scores at baseline given that the SF-12 has been studied extensively as a measure of HRQoL in non-PAH cardiac and respiratory diseases. The mean e10 score in our study cohort (25.4 ± 12.2) aligned with the center of the 0 to 50-point range of possible scores. The mean PCS-12 (34.2 ± 6.7) and MCS-12 (48.1 ± 8.8) scores were lower than the United States population average of 50. Further, the entire e10 score range was represented in our study cohort (score range, 0 to 50; cohort range, 0 to 50) while the PCS-12 (score range, 0 to 100; cohort range, 15 to 56) and MCS-12 (score range, 0 to 100; cohort range, 20 to 80) score ranges were not.

We found that the correlations between baseline e10 and PCS-12 (Pearson correlation [r], -0.16; 95% confidence interval [CI], -0.24--0.07; $p < 0.001$) and baseline e10 and MCS-12 (r, -0.20; 95% CI,-0.28--0.12; $p < 0.001$) were both statistically significant. Still, the correlations were poor despite statistical significance and there was a greater degree of variability in the e10 score within our study cohort (25.4 ± 12.2) compared to the raw PCS-12 (34.2 ± 6.7) and MCS-12 (48.1 ± 8.8) scores.

Table S1. Patient demographic and clinical characteristics across baseline and follow-up PHCC visits

Parameters	Baseline (n = 565)	Follow-up 1 (n = 388)	Follow-up 2 (n = 214)	Follow-up 3 (n = 107)	Follow-up 4 (n = 47)
EmPHasis-10 score	25.4 ± 12.2	22.1 ± 12.3	21.1 ± 12.1	19.8 ± 11.9	23.9 ± 11.7
Pt. PHCC care rating*	10 (9-10)	10 (9-10)	10 (9-10)	10 (9-10)	10 (9-10)
Drinks alcohol, n (%)	197 (34.9)	119 (30.7)	65 (30.4)	29 (27.1)	14 (29.8)
Smoking status, n (%)					
Non-smoker	303 (53.6)	203 (52.3)	112 (52.3)	58 (54.2)	28 (59.6)
Past	217 (38.4)	127 (32.7)	78 (36.4)	40 (37.4)	13 (27.7)
Current	36 (6.4)	15 (3.9)	6 (2.8)	3 (2.8)	2 (4.3)
BMI, kg/m^2	29.1 ± 7.3	29.0 ± 7.1	29.3 ± 6.9	29.3 ± 7.0	28.7 ± 6.9
WHO functional class, n (%)					
I	43 (7.6)	30 (7.7)	22 (10.3)	12 (11.2)	5 (10.6)
II	172 (30.4)	150 (38.7)	88 (41.1)	49 (45.8)	17 (36.2)
III	276 (48.8)	136 (35.1)	66 (30.8)	28 (26.2)	18 (38.3)
IV	36 (6.4)	15 (3.9)	6 (2.8)	1 (0.9)	2 (4.3)
6MWD, m	335.4 ± 123.2	360.8 ± 128.9	373.1 ± 123.3	377.4 ± 127.9	347.1 ± 141.2
Supplemental oxygen use, n (%)	214 (37.9)	163 (42.0)	109 (50.9)	53 (49.5)	27 (57.4)
No. PAH medications, n (%)					
None	81 (14.3)	14 (3.6)	6 (2.8)	3 (2.8)	2 (4.3)
One	176 (31.2)	93 (24.0)	47 (22.0)	25 (23.4)	11 (23.4)
Two	231 (40.9)	183 (47.2)	113 (52.8)	58 (54.2)	21 (44.7)
Three	72 (12.7)	63 (16.2)	36 (16.8)	14 (13.1)	9 (19.1)
PAH medication classes, n (%)					
Prostacyclin analog	166 (29.4)	131 (33.8)	85 (39.7)	44 (41.1)	24 (51.1)
Endothelin receptor antagonist	288 (51.0)	227 (58.5)	129 (60.3)	60 (56.1)	22 (46.8)
Phosphodiesterase-5 inhibitor	389 (68.8)	268 (69.1)	154 (72.0)	76 (71.0)	33 (70.2)
sGC stimulator	13 (2.3)	25 (6.4)	15 (7.0)	5 (4.7)	2 (4.3)
Laboratory tests*					
BNP/NT-pro BNP z-score[†]	-0.3 (-0.5-0.3)	-0.4 (-0.5--0.1)	-0.5 (-0.5--0.2)	-0.4 (-0.5--0.3)	-0.4 (-0.5-0.0)
Creatinine, mg/dL	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.0)	0.9 (0.7-1.0)
REVEAL risk stratum[‡], n (%)					
Low risk	281 (49.7)	210 (54.1)	123 (57.5)	69 (64.5)	29 (61.7)
Average risk	84 (14.9)	56 (14.4)	24 (11.2)	12 (11.2)	5 (10.6)
Moderate high risk	69 (12.2)	42 (10.8)	25 (11.7)	6 (5.6)	4 (8.5)
High risk	78 (13.8)	47 (12.1)	25 (11.7)	12 (11.2)	4 (8.5)
Very high risk	15 (2.7)	10 (2.6)	8 (3.7)	3 (2.8)	2 (4.3)
No. ER visits*[‖]	1 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
No. nights hospitalized*[‖]	1 (0-10)	0 (0-0)	0 (0-2)	0 (0-2)	0 (0-3)

Values are expressed as mean ± SD.
*Values are expressed as median (interquartile range)
[†]Parameter reflects scaled values centered around a 246 pg/mL mean BNP (SD, 386 pg/mL) and 1437 pg/mL mean NT-pro BNP (SD, 3292 pg/mL)
[‡]Determined using the REVEAL Registry Risk Score Calculator (S3)
[‖]Over the last six months or since the patient's last PHCC visit

Pt. = patient; PHCC = pulmonary hypertension care center; BMI = body mass index; WHO = World Health Organization; 6MWD = six-minute walk distance; PAH = pulmonary arterial hypertension; sGC = soluble guanylate cyclase; BNP/NT-pro BNP = brain natriuretic peptide or N-terminal pro B-type natriuretic peptide; ER = emergency room.

Table S2. Associations between patient clinical parameters and emPHasis-10 score at baseline

	Unadjusted			Adjusted*		
Parameters	**Coefficient [95% CI]**	**R^2**	**p-value**	**Coefficient [95% CI]**	**R^2**	**p-value**
Supplemental oxygen use	5.6 [3.5, 7.6]	0.05	<0.001	3.4 [1.4, 5.4]	0.23	0.001
No. PAH medications (per medication)	-0.6 [-1.7, 0.6]	0	0.321	-0.2 [-1.3, 0.8]	0.21	0.652
PAH medication classes†						
Prostacyclin analog	1.3 [-0.9, 3.6]	0	0.243	0.9 [-1.3, 3.0]	0.21	0.425
Endothelin receptor antagonist	-1.2 [-3.3, 0.8]	0	0.23	-1.1 [-3.1, 0.8]	0.21	0.251
Phosphodiesterase-5 inhibitor	-2.1 [-4.3, 0.1]	0	0.063	-0.2 [-2.3, 2.0]	0.21	0.893
sGC stimulator	1.4 [-5.6, 8.3]	0	0.705	-0.8 [-7.3, 5.7]	0.21	0.805

*Adjusted for age, sex, body mass index, and WHO functional class
†All PAH medication classes also included in adjusted models
PAH = pulmonary arterial hypertension; sGC = soluble guanylate cyclase; WHO = World Health Organization.

Table S3. Associations between within-patient changes and emPHasis-10 score

Parameters	Coefficient [95% CI]	R^2	p-value
Supplemental oxygen use	1.6 [-0.5, 3.6]	0.15	0.133
No. PAH medications (per medication)	0.2 [-1.0, 1.3]	0.13	0.747
PAH medication classes, n (%)			
Prostacyclin analog	0.9 [-1.4, 3.3]	0.14	0.445
Endothelin receptor antagonist	0.0 [-2.0, 1.9]	0.14	0.989
Phosphodiesterase-5 inhibitor	1.7 [-0.7, 4.1]	0.14	0.161
sGC stimulator	-2.1 [-6.3, 2.1]	0.13	0.332

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.

PAH = pulmonary artery hypertension; sGC = soluble guanylate cyclase.

Table S4. Minimal important difference in emPHasis-10 for PAH patients

(A) Across total cohort and by treatment status at baseline

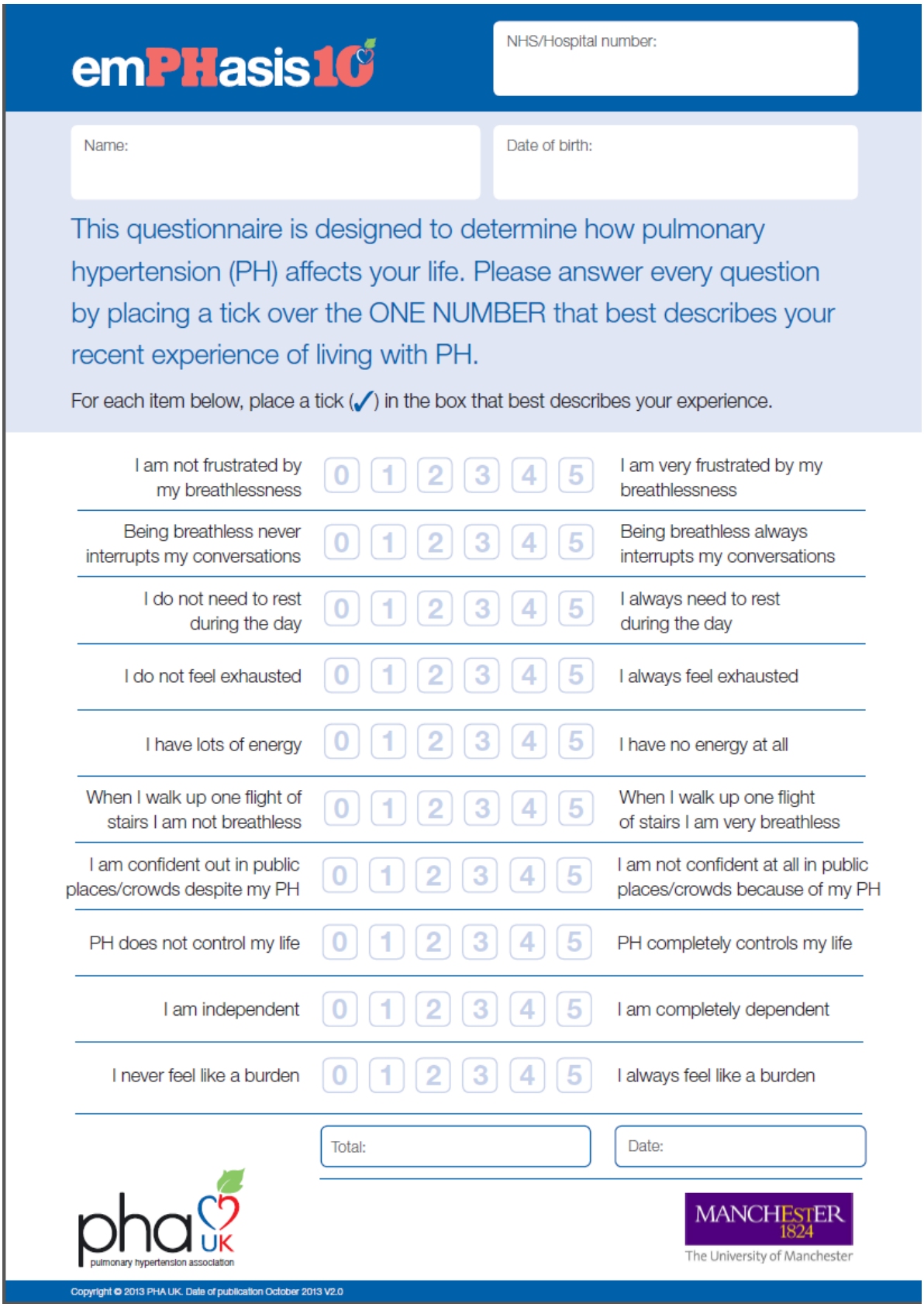
			Approach			
Patient group	**Baseline e10**	**e10**	**SEM**	**RCI**	**0.5 SD**	**ES**
All, (n=340)	25.4 ± 12.2	-2.3 ± 10.0	-5.3	-7.6	-5	-6.1
Incident, (n=180)	25.7 ± 12.1	-3.3 ± 10.1	-5.3	-7.5	-5.1	-6.1
Treatment naive, (n=49)	26.1 ± 12.3	-4.0 ± 11.4	-5.4	-7.7	-5.7	-6.2

(B) Across total and by PAH etiology

			Approach			
Patient group	**Baseline e10**	**e10**	**SEM**	**RCI**	**0.5**	**ES**
All, (n=340)	25.4 ± 12.2	-2.3 ± 10.0	-5.3	-7.6	-5	-6.1
Idiopathic PAH, (n=138)	24.2 ± 12.5	-2.4 ± 8.8	-5.5	-7.8	-4.4	-6.3
CTD-associated PAH, (n=119)	27.1 ± 11.0	-2.9 ± 9.8	-4.8	-6.8	-4.9	-5.5
D&T-associated PAH, (n=30)	29.0 ± 14.3	-3.0 ± 13.1	-6.3	-8.9	-6.6	-7.2

Baseline and change values are expressed as mean ± SD. Incident patients were those diagnosed within six months of their baseline visit and treatment naive patients were those on zero medications at their baseline visit. e10 = emPHasis-10; SEM = standard error of measurement; RCI = reliable change index; 0.5SD = 0.5 standard deviation; ES = effect size; CTD = Connective Tissue Disease, D&T = Drugs and Toxin.

Figure S1



emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

pha UK pulmonary hypertension association

MANCHESTER 1824 The University of Manchester

Figure S2 – Histogram of emPHasis-10 scores at baseline.

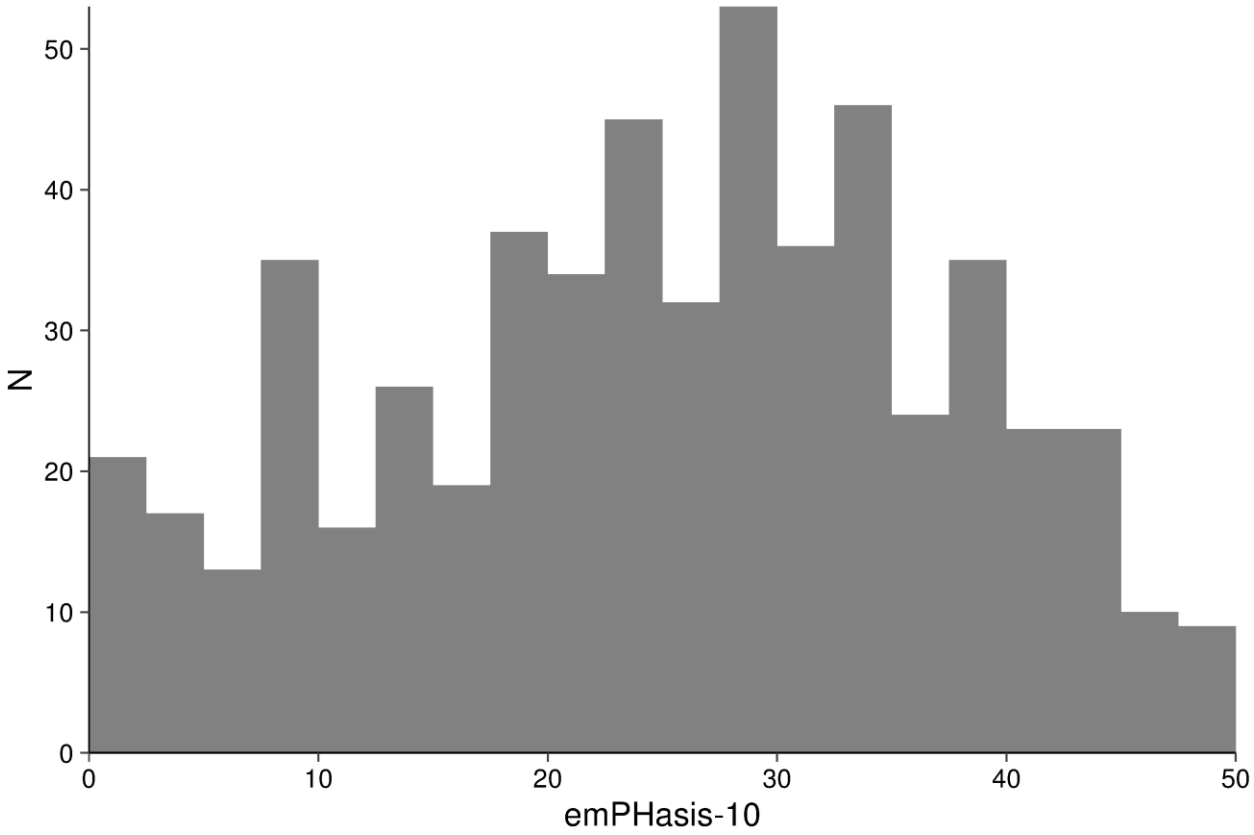
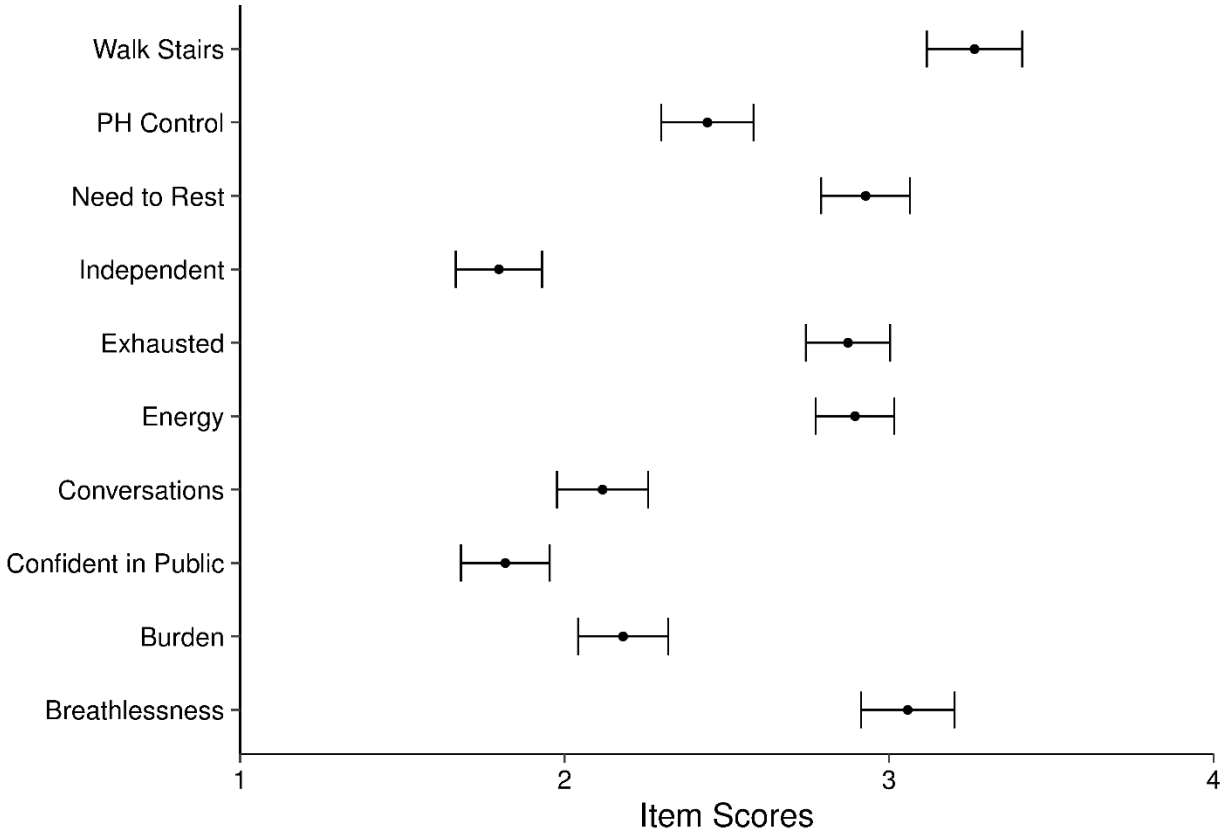


Figure S3 – Mean and 95% CI of emPHasis-10 item scores at baseline.



Author Appendix: Members of the PHAR Study Group (2 pages total)

Author	Institution	Contact Email
Raymond Benza	Allegheny General Hospital	Raymond.BENZA@ahn.org
Jeremy Feldman	Arizona Pulmonary Specialists, LTD	jpfeldman1@yahoo.com
Dianne Zwicke	Aurora St. Luke's Medical Center	dlzwicke1@yahoo.com
D. Dunbar Ivy	Children's Hospital Colorado	Dunbar.ivy@childrenscolorado.org
Russel Hirsch	Cincinnati Children's Hospital Medical Center	Russel.Hirsch@cchmc.org
Erika Berman-Rosenzweig	Columbia University	esb14@cumc.columbia.edu
Jeffrey Sager	Cottage PH Center	jsager@sblung.com
Kenneth Presberg	Froedtert Hospital/MCW	kpresber@mcw.edu
Oksana Shlobin	Inova Fairfax Medical Campus	Oksana.shlobin@inova.org
Stephen Mathai	Johns Hopkins University	smathai4@jhmi.edu
John Wesley McConnell	Kentuckiana Pulmonary Associates	mcco3526@bellsouth.net
Matthew Lammi	Louisiana State University	mlammi@lsuhsc.edu
Robert Frantz	Mayo Clinic (Rochester)	frantz.robert@mayo.edu
Charles Burger	Mayo Clinic Florida	Burger.charles@mayo.edu
Corey Ventetuolo	Rhode Island Hospital	corey_ventetuolo@brown.edu
James Klinger	Rhode Island Hospital	James_Klinger@Brown.edu
Michael Eggert	Sentara Hospital	msbe@aol.com
Roham Zamanian	Stanford University	zamanian@stanford.edu
Jeffrey Robinson	The Oregon Clinic	jerobinson@orclinic.com
Roblee Allen	UC Davis Health System	rpallen@ucdavis.edu
Jeff Fineman	University of California, San Francisco	Jeff.Fineman@ucsf.edu
Teresa De Marco	University of California, San Francisco	Teresa.DeMarco@ucsf.edu
Jean Elwing	University of Cincinnati	elwingj@ucmail.uc.edu
David Badesch	University of Colorado Denver	David.Badesch@CUAnschutz.edu
Todd Bull	University of Colorado Denver	Todd.bull@CUAnschutz.edu
Raymond Foley	University of Connecticut	r.foley@uchc.edu
Linda Cadaret	University of Iowa	Linda-cadaret@uiowa.edu
Timothy Williamson	University of Kansas	TWILLIA1@kumc.edu
Gautam Ramani	University of Maryland	gramani@som.umaryland.edu
Thenappan Thenappan	University of Minnesota	tthenapp@umn.edu
H. James Ford	University of North Carolina	hubert_ford@med.unc.edu
Steven Kawut	University of Pennsylvania	kawut@upenn.edu
Marc Simon	University of Pittsburgh	simoma@upmc.edu
R. James White	University of Rochester	Jim_white@urmc.rochester.edu

Author	Institution	Contact Email
John Ryan	University of Utah	john.ryan@hsc.utah.edu
Sula Mazimba	University of Virginia	SM8SD@virginia.edu
James Runo	University of Wisconsin	jrr@medicine.wisc.edu
Sonja Bartolome	UT Southwestern	Sonja.bartolome@utsouthwestern.edu
Anna Hemnes	Vanderbilt University	Anna.r.hemnes@vanderbilt.edu
Daniel Grinnan	Virginia Commonwealth University	Daniel.grinnan@vcuhealth.org
Murali Chakinala	Washington University at Barnes-Jewish Hospital	chakinalam@wustl.edu
Evelyn Horn	Weill Cornell Medicine	horneve@med.cornell.edu

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