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Symptom phenotypes in pulmonary arterial hypertension: The PAH “symptome”

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Abstract

Women with pulmonary arterial hypertension (PAH) experience multiple symptoms, including dyspnea, fatigue, and sleep disturbance, that impair their health-related quality of life (HRQOL). However, we know little about phenotypic subgroups of patients with PAH with similar, concurrent, multiple symptoms. The objectives of this study were to define the “symptome” by symptom cluster phenotypes and compare characteristics such as biomarkers, cardiac structure and function (echocardiography), functional capacity (6-min walk distance), and HRQOL between the groups. This cross-sectional study included 60 women with PAH. Subjects completed an assessment battery: Pulmonary Arterial Hypertension Symptom Scale, Pittsburgh Sleep Quality Index, Multidimensional Dyspnea Profile, Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function, PROMIS® Sleep-Related Impairment, and the emPHasis-10. Subjects also underwent transthoracic echocardiography, phlebotomy, 6-min walk distance, and actigraphy. The three symptoms of dyspnea, fatigue, and sleep disturbance were used to define the symptom clusters. Other PAH symptoms, plasma and serum biomarkers, cardiac structure and function (echocardiography), exercise capacity (6-min walk distance), sleep (actigraphy), and HRQOL were compared across phenotypes. The mean age was 50 ± 18 years, 51% were non-Hispanic white, 32% were non-Hispanic Black and 40% had idiopathic PAH. Cluster analysis identified Mild ($n = 28$, 47%), Moderate ($n = 20$, 33%), and Severe Symptom Cluster Phenotypes ($n = 12$, 20%). There were no differences for age, race, or PAH etiology between the phenotypes. WHO functional class ($p < 0.001$), norepinephrine levels ($p = 0.029$), right atrial pressure ($p = 0.001$), physical function ($p < 0.001$), sleep onset latency ($p = 0.040$), and HRQOL ($p < 0.001$) all differed significantly across phenotypes. We identified three

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distinctive symptom cluster phenotypes (Mild, Moderate, and Severe) for women with PAH that also differed by PAH-related symptoms, physical function, right atrial pressure, norepinephrine levels, and HRQOL. These phenotypes could suggest targeted interventions to improve symptoms and HRQOL in those most severely affected.

KEYWORDS

cluster analysis, symptom management, symptoms

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease that produces multiple symptoms such as dyspnea, fatigue, and sleep disturbance that are burdensome and impair health-related quality of life (HRQOL).^{1,2} PAH affects mostly women for reasons which are still unknown. The pathobiology of PAH involves endothelial dysfunction characterized by inflammation, vasoconstriction, platelet activation and thrombosis, and vascular remodeling of the small muscular pulmonary arterioles.^{3,4} Increasing right ventricular afterload with disease progression leads to right ventricular dysfunction, exercise limitation, and increased mortality.⁵

Patients experience multiple symptoms in PAH.⁶ Previous research in various diseases demonstrates that symptoms can occur in clusters,^{7–11} that is the appearance of two or more co-occurring symptoms that are related to each other.^{7–11} Symptoms in PAH tend to cluster together (the “symptome”) but the relationship between symptom cluster phenotypes is not well known and the utility of such clusters has not been investigated in PAH. Identifying the PAH “symptome” could provide a way to stratify or enrich interventional studies. Interventions often have a greater impact in patients who are more severely affected, leading to treatment heterogeneity. For example, a sleep intervention of interest might be best studied in those patients with the most severe sleep disturbance, since they would likely have the most room for improvement. Therefore, early-stage clinical trials of interventions for these symptoms could be designed to target those most significantly affected.

Using phenomapping techniques, we aimed to describe the symptom cluster of dyspnea, fatigue, and sleep disturbance in women with PAH. We assessed the relationship between phenotypes defined by these three parameters and traditional indicators of PAH severity including hemodynamics, echocardiography, and plasma and serum biomarkers.

METHODS

Study design and subjects

This was a cross-sectional study approved by the Institutional Review Board. Subjects were recruited from the Pulmonary Hypertension/Pulmonary Vascular Disease Program. We included women ≥ 18 years of age with a diagnosis of PAH (idiopathic, heritable, drug or toxin-induced, or associated with connective tissue disease, congenital heart disease, portal hypertension, or HIV). Subjects were receiving targeted PAH therapy at stable doses for at least 3 months at enrollment. Exclusion criteria included a diagnosis of chronic fatigue syndrome, obstructive sleep apnea, restless leg syndrome, narcolepsy, major depression, current hospitalization, acute illness, or having received a lung transplant.

Procedures

All women with PAH at our center were screened for eligibility. Eligible patients were approached by the research coordinator at their routine clinic visit or by telephone and informed consent was obtained. The subject attended a formal study visit which included a battery of questionnaires (see below), which were completed in approximately 20–30 min. Subjects also underwent 6-min walk testing, transthoracic echocardiogram, 7 days of wrist actigraphy, and phlebotomy for plasma and serum biomarkers (norepinephrine [NE], N-terminal pro b-type Natriuretic Peptide [NT-pro BNP]) using a standardized research protocol.

Measures

Subjects completed the following questionnaires including a sociodemographic and medical history interview (see Supporting Information for details). The Multi-dimensional Dyspnea Profile (MDP)¹² measures overall

breathing discomfort, the quality and intensity of sensory dimensions of dyspnea and emotional responses.¹² Items are measured 0–10 scale, with higher scores indicating greater intensity. The Pittsburgh Sleep Quality Index (PSQI)¹³ measures sleep disturbance and quality.¹³ Scores range from 0 to 21; higher scores indicated worse sleep quality. Scores greater than 5 indicate worse sleep disturbance and poor sleep quality. The Pulmonary Arterial Hypertension Symptom Scale (PAHSS)¹⁴ is self-administered and contains 17 symptoms such as shortness of breath with exertion and fatigue.¹⁴ Symptoms were rated on a 0–10 scale, higher scores indicate higher symptom intensity.

The Patient-Reported Outcomes Measurement Information System (PROMIS®) Sleep-Related Impairment Short Form 8a¹⁵ measures self-reported perceptions of alertness, sleepiness, and tiredness during waking hours and perceived functional impairments during waking associated with sleep problems.¹⁶ Higher scores indicate increased sleep-related impairment. The PROMIS® Physical Function Short Form 8a¹⁷ is a self-administered questionnaire that measures physical capability rather than actual physical activity performance.¹⁷ Higher scores indicated better physical function. The Patient Health Questionnaire (PHQ-8)¹⁸ is a self-administered questionnaire that measures depression. Scores range from 0 to 24. Scores 4–9 indicate mild-to-moderate depressive symptoms; scores ≥ 10 are considered major depression, and scores ≥ 20 indicate severe major depression.^{18–20}

The Epworth Sleepiness Scale (ESS)²¹ measures how likely an individual will fall asleep during routine daily activities.²¹ The higher the score the higher the daytime sleepiness. Scores greater than 10 indicate excessive daytime sleepiness. The emPHasis-10 measures HRQOL.²² Scores range from 0 to 50 and higher scores indicate greater HRQOL impairment.²³ The WHO functional class categorizes patients based on their physical limitations in relation to dyspnea. WHO functional classes range from I–IV, the higher the functional class the more symptomatic.^{24,25}

Echocardiograms were analyzed at the Center for Quantitative Echocardiography. All measurements were performed using the American Society of Echocardiography guidelines.²⁶ Right atrial pressures were estimated by the inferior vena cava diameter and the presence of inspiratory collapse. The 6 min walk test was performed according to the American Thoracic Society's guidelines.²⁷ All readers and technicians were blinded to other results from the subjects.

The actigraph is a highly sensitive wristwatch-like accelerometer worn on the dominant wrist to provide objective data regarding sleep.^{28,29} These data were

analyzed as counts per minute by computer software using the Cole-Kripke algorithm.³⁰ Sleep onset latency was defined as the first minute the algorithm scores asleep. Sleep efficiency was the ratio of total sleep time compared to the total amount of time in bed. Wake after sleep onset (WASO) was the total number of minutes the subject was awake after sleep onset. Total sleep time was the total number of minutes scored as asleep. The number of awakenings was the number of different awakenings scored by the algorithm and the average time awake during awakenings is the average length of all awakening episodes.

Serum NT-pro BNP was measured using an Electrochemiluminescence immunoassay by Roche (catalog number 276345). Plasma NE, epinephrine, and dopamine were measured using reversed-phase high-performance liquid chromatography with electrochemical detection after extraction with activated alumina.

Data analysis

Symptom clusters are generally created either a priori or de novo.³¹ We chose the former since these symptoms are all clinically impactful on patients, are quite common in patients and suggest potentially different interventions to address them. These three symptoms (dyspnea, fatigue, and sleep disturbance) were specifically selected since they are so highly prevalent in PAH.^{6,32} We conducted bivariate Spearman's ρ correlations among measures of dyspnea (MDP breathing a lot subscale scores), fatigue (PAHSS fatigue subscale scores), and sleep disturbance (PSQI global scores) to test the associations between symptoms. We performed a cluster analysis using dyspnea (MDP breathing a lot subscale), fatigue (PAHSS fatigue subscale), and sleep disturbance (PSQI global score). We used a TwoStep cluster analysis, which is an exploratory tool designed to reveal natural groupings or clusters. This approach identifies groupings by running pre-clustering first and then by running hierarchical methods that automatically select the number of clusters. This method has been shown to perform better than traditional hierarchical procedures.^{33,34} Because we had no way of knowing how many subgroups would be formed, we ran models with two, three, four, and five latent symptom cluster groups and compared them to determine which model provided the best fit to the data. The best model fit was determined using the Akaike information criterion.³⁵

We then compared the following variables by symptom cluster phenotype: other PAH symptoms and patient-reported outcomes (PAHSS, MDP, PSQI, PHQ-8, PROMIS® Physical Function, and Sleep-Related

Impairment and ESS), and plasma and serum biomarkers (NT-pro BNP, NE, epinephrine, dopamine), cardiac structure and function (echocardiography), functional exercise capacity (6MWD), sleep variables (actigraphy), and HRQOL (emPHasis-10). One-way analysis of variance was used to compare symptom cluster phenotypes for normally distributed continuous variables and the Kruskal–Wallis test for those variables that were either not normality distributed or ordinal. χ^2 and Fisher's exact tests were used to compare categorical variables. Omnibus statistical significance ($p < 0.05$) was used to compare the phenotypes on all variables. If omnibus statistical results were $p < 0.05$ then Bonferroni correction was used ($p < 0.02$) for pairwise comparisons. Analyses were conducted using Statistical Package for the Social Sciences (SPSS®) version 26.³²

RESULTS

Demographic and clinical variables are displayed in Table 1. Overall, the sample had a mean age of 51 years. Fifty-one percent of the sample was non-Hispanic White and 32% non-Hispanic Black. Forty-six percent had idiopathic/heritable PAH. Forty-five percent were classified as WHO functional class II and 47% were class III.

The clustering variables dyspnea (MDP breathing a lot subscale), fatigue (PAHSS fatigue subscale score) and sleep disturbance (PSQI global score) were all significantly correlated (dyspnea and fatigue $\rho = 0.638$, $p < 0.001$; dyspnea and sleep disturbance $\rho = 0.531$, $p < 0.001$; sleep disturbance and fatigue $\rho = 0.655$, $p < 0.001$). We then performed cluster analysis using the dyspnea, fatigue, and sleep disturbance variables noted above which showed that three symptom clusters fit the data best: Mild Symptoms ($n = 28$, 46%), Moderate Symptoms ($n = 20$, 33%), and Severe Symptoms ($n = 12$, 20%), Figure 1. Table 2 showed that these groups were similar in terms of age, race/ethnicity, and type of PAH. Right atrial pressures were associated with the severity of symptom cluster, but other echocardiographic variables were not. While 6 min walk distances were higher in patients with more mild symptoms, the differences were not statistically significant.

By design, there were several differences in symptoms between the groups shown in Tables 3 and 4. Notably, patients in more symptomatic phenotypes had significantly worse PAH-specific health-related quality of life, measured by the emPHasis-10. On average patients with elevated depression levels were in the severe symptom cluster phenotype group. Self-reported physical function levels measured by the PROMIS® physical function were

TABLE 1 Demographic and clinical characteristics of pulmonary arterial hypertension sample

Characteristics (N = 60)	Mean ± SD or counts (%)
Age (years)	50.6 ± 17.8
Female	60 (100%)
Race/ethnicity	
White (non-Hispanic)	31 (51%)
White (Hispanic)	6 (10%)
Black	19 (32%)
Asian	4 (7%)
WHO Group 1 PAH etiology	
Idiopathic	23 (38%)
Heritable	5 (8%)
Connective tissue disease	21 (35%)
Congenital heart disease	7 (12%)
HIV	2 (3%)
Portopulmonary	2 (3%)
Echocardiography	
Right atrial pressure (mmHg)	4.6 ± 3.4
Right Atrium 4-chamber Area—diastole (cm ²)	21.0 ± 29.7
Right Atrium 4-chamber Area—systole (cm ²)	27.5 ± 36.2
Pulmonary artery systolic pressure (mmHg)	61.3 ± 28.1
Tricuspid annular plane systolic excursion (TAPSE) (cm)	2.0 ± 0.3
RV size (basal diameter)—systole (cm)	3.5 ± 0.7
RV size (basal diameter)—diastole (cm)	4.3 ± 0.9
Left ventricular ejection fraction (%)	55.5 ± 7.5
Tricuspid regurgitation (n = 51)	
None	12 (24%)
Mild	11 (22%)
Moderate	23 (45%)
Severe	5 (10%)
Medications	
Intravenous prostacyclin analog	16 (27%)
Inhaled prostacyclin analog	5 (8%)
Subcutaneous prostacyclin analog	5 (8%)

TABLE 1 (Continued)

Characteristics (N = 60)	Mean ± SD or counts (%)
Oral prostacyclin analog	11 (18%)
Endothelin receptor antagonists	17 (28%)
PDE-5 inhibitors	24 (40%)
Riociguat	1 (2%)
Selexipag	1 (2%)
Combination therapy	22 (37%)
Diuretics	43 (72%)
Anticoagulants	19 (31%)
WHO functional class	
I	5 (8%)
II	27 (45%)
III	28 (47%)
Body mass index (kg/m ²)	28.2 ± 6.5
6 min walk distance (m)	392.1 ± 135.9

Abbreviations: PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; RV, right ventricle; WHO, World Health Organization.

also worse for those in the more symptomatic phenotypes. NT-pro BNP levels were significantly higher in the more symptomatic phenotypes as was NE levels (Table 4). Similarly, sleep onset latency measured by actigraphy was significantly prolonged in the severe symptom cluster phenotype group.

DISCUSSION

Using phenomapping techniques, we identified three symptom cluster phenotypes (from mild to severe) in a sample of women with PAH. Forty-seven percent of the sample were categorized in the Mild Symptom Cluster Phenotype, 33% Moderate Symptom Cluster Phenotype, and 20% Severe Symptom Cluster Phenotype. Right atrial pressures (assessed by echocardiography), NE levels, sleep (actigraphy), and WHO functional class differed among the phenotypes. There were of course many differences in symptoms (some related to the clustering variables, and some not), sleep onset latency, and PH-specific health-related quality of life.

To our knowledge, this is the first study to identify higher right atrial pressures in those with more severe

symptoms. A reduction in right atrial pressures measured by right heart catheterization has been shown to decrease levels of dyspnea in heart failure.³⁶ Other disorders with potential for volume overload such as end-stage renal disease have found self-reported fatigue to be associated with an extracellular water excess.³⁷ Similarly, increased volume status was associated with fewer hours of sleep and more frequent nighttime awakenings in dialysis patients.³⁸ Elevated right atrial pressures appear to coincide with an increase in dyspnea, fatigue, and sleep disturbance in PAH, which could be explained by cardiorenal or cardiohepatic syndromes.

We found that the Severe Symptom Cluster Phenotype had significantly higher NE levels than the Moderate Symptom Cluster Phenotype. The pathobiology and PAH disease severity may be related to circulating neurohormonal mediators (e.g., sympathetic nervous system) that act as disease modifiers.³⁹ Activation of the sympathetic nervous system has been demonstrated in PAH and is thought to contribute to the pulmonary vascular remodeling process and right ventricular dysfunction.⁴⁰ Higher NE is associated with clinical deterioration⁴¹ in PAH.⁴² With regard to symptoms, dyspnea is associated with increased levels of NE in idiopathic pulmonary fibrosis compared to healthy individuals.⁴³ NE levels are elevated in people with short sleep⁴⁴ and in a sample of sleep-deprived men (N = 30) over a 4-week period there was a significant increase in NE.⁴⁵ NE was found to be elevated in women with breast cancer (N = 109) who reported fatigue.⁴⁶ Moderating the effects of the sympathetic nervous system could have an effect on symptoms and play a role in pulmonary vascular remodeling in PAH.⁴⁷ Other biomarkers were not significantly different among the groups (e.g., epinephrine). Perhaps different measures such as cortisol to measure stress may correlate with PAH symptoms.⁴⁸ There were trends in the hypothesized direction; for example, NT-pro BNP levels were higher in the more symptomatic group, but not statistically significant.

There can be discordance between symptoms and physiological variables as they measure different constructs.⁴⁹ The actigraph measures of latency of sleep onset were significantly different between the Moderate and Severe Symptom Cluster phenotypes with the severe group experiencing more time to fall asleep. The actigraph measures showed all the subgroups had difficulty maintaining sleep where the WASO was greater than 30 min for all the groups. While actigraphy is valid to measure sleep objectively, polysomnography may be warranted to further define sleep problems in patients with PAH.

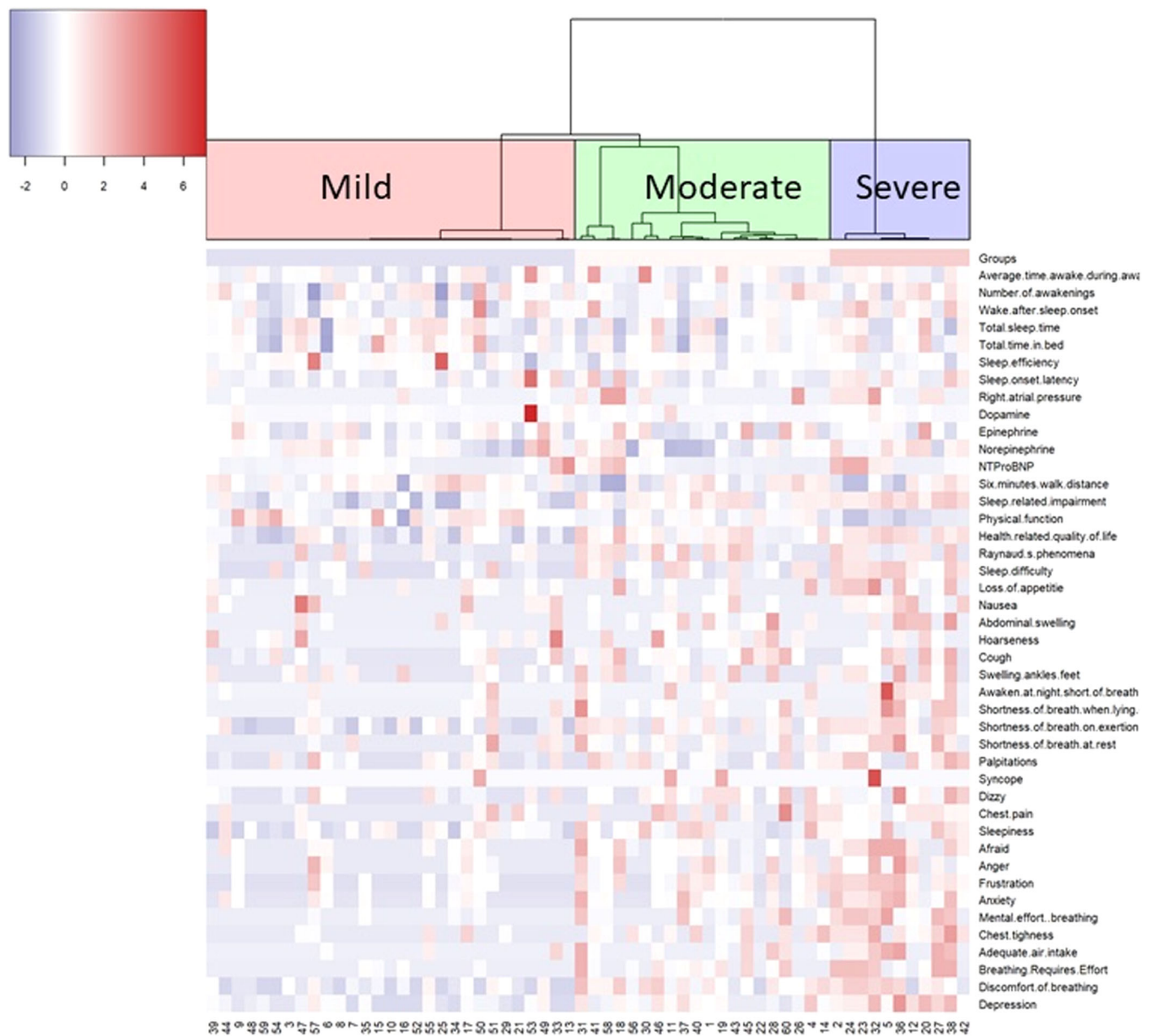


FIGURE 1 Heatmap of symptom cluster subgroups

Given the importance of symptoms to sufferers of PAH, this could provide a useful framework for diagnostic, prognostic, clinical trials, and treatment paradigms for the future, even if our data require confirmation in larger cohorts. Patients could be screened to identify their symptom cluster phenotype membership to best match symptom management interventions, taking a “precision medicine” approach to symptom management. For example, physical activity, cognitive behavioral therapy, or palliative care could be studied specifically in those in the Moderate and Severe Symptom Cluster Phenotypes. Clinically, symptoms can be readily assessed and integrated into a patient visit or

remote assessment. Ultimately assessing and treating symptom clusters may improve quality of life and outcomes in PAH.

Our study has several strengths. We used rigorous standardized blood collections, echocardiography, and 6-min walk tests to decrease the potential for measurement error and blinding to other subject information for those performing testing to minimize bias. We recruited a racially/ethnically diverse sample. Our study was limited by several factors. We a priori decided to focus on women since there would be limited power to draw inferences for men who much more rarely develop PAH. Future multicenter studies should focus on men with

TABLE 2 Symptom Cluster Phenotype comparisons for demographics and clinical characteristics

Characteristics (N = 60)	Mild Symptom Cluster Phenotype (n = 28) Mean ± SD or counts (%)	Moderate Symptom Cluster Phenotype (n = 20) Mean ± SD or counts (%)	Severe Symptom Cluster Phenotype (n = 12) Mean ± SD or counts (%)	χ ²	P Value
Age (years)	49.4 ± 21.2	52.7 ± 15.8	50.0 ± 11.9	0.3	0.823
Race/ethnicity					
White (non-Hispanic)	14 (50%)	11 (55%)	6 (50%)	0.44	0.889
White (Hispanic)	3 (11%)	1 (5%)	2 (17%)		
Black	10 (36%)	6 (30%)	3 (25%)		
Asian	1 (4%)	2 (10%)	1 (8%)		
WHO Group 1 PAH etiology					
Idiopathic	11 (39%)	7 (35%)	5 (42%)	0.02	0.989
Heritable	1 (4%)	2 (10%)	2 (17%)		
Connective tissue disease	9 (32%)	9 (45%)	3 (25%)		
Congenital heart disease	3 (11%)	2 (10%)	2 (17%)		
HIV	1 (4%)	0	1 (8%)		
Portopulmonary	2 (7%)	0	0		
Echocardiography					
Right atrial pressure (mmHg) ^{b,c}	3.2 ± 1.0	5.2 ± 4.5	6.8 ± 3.7	14.26	0.001
Right Atrium 4-chamber Area—diastole (cm ²)	15.2 ± 6.3	19.2 ± 10.5	38.2 ± 64.8	0.06	0.064
Right Atrium 4-chamber Area—systole (cm ²)	20.9 ± 6.7	25.0 ± 13.7	47.7 ± 79.4	3.63	0.163
Pulmonary artery systolic pressure (mmHg)	59.2 ± 27.8	56.1 ± 27.8	73.8 ± 30.1	2.36	0.308
Tricuspid annular plane systolic excursion (TAPSE) (cm)	2.1 ± 0.3	1.9 ± 0.4	2.0 ± 0.3	0.37	0.368
RV size (basal diameter)-systole (cm)	3.6 ± 0.7	3.3 ± 0.8	3.5 ± 0.8	0.65	0.647
RV size (basal diameter)-diastole (cm)	4.3 ± 0.9	4.2 ± 1.0	4.3 ± 1.0	0.19	0.909
Left ventricular ejection fraction (%)	56.7 ± 7.6	54.0 ± 8.2	55.0 ± 5.7	1.97	0.373

(Continues)

TABLE 2 (Continued)

Characteristics (N = 60)	Mild Symptom Cluster	Moderate Symptom Cluster	Severe Symptom Cluster	χ^2	P Value
	Phenotype (n = 28) Mean \pm SD or counts (%)	Phenotype (n = 20) Mean \pm SD or counts (%)	Phenotype (n = 12) Mean \pm SD or counts (%)		
Tricuspid regurgitation (n = 51)					
None	7 (25%)	4 (20%)	1 (8%)	1.42	0.565
Mild	4 (14%)	4 (20%)	3 (25%)		
Moderate	10 (36%)	9 (45%)	4 (33%)		
Severe	2 (7%)	1 (5%)	2 (17%)		
Medications					
Intravenous prostacyclin analog	5 (18%)	6 (30%)	5 (42%)	2.56	0.307
Inhaled prostacyclin analog	4 (14%)	0	1 (8%)	3.07	0.204
Subcutaneous prostacyclin analog	1 (4%)	1 (5%)	3 (25%)	5.39	0.106
Oral prostacyclin	4 (14%)	5 (25%)	2 (17%)	0.91	0.69
Endothelin receptor antagonists	7 (25%)	5 (25%)	5 (42%)	1.29	0.531
PDE-5 inhibitors	13 (46%)	6 (30%)	5 (42%)	1.31	0.58
Riociguat	1 (4%)	0	0	1.14	1
Selexipag	0	1 (5%)	0	2	0.533
Combination therapy	10 (36%)	5 (25%)	7 (58%)	3.55	0.181
Diuretics	18 (64%)	15 (75%)	10 (83%)	1.64	0.458
Anticoagulants	7 (25%)	8 (40%)	4 (33%)	1.21	0.585
WHO functional class					
I	4 (14%)	1 (5%)	0	17.92	<0.001
II	17 (61%)	10 (50%)	0		
III ^{a,b}	7 (25%)	9 (45%)	12 (100%)		
Body mass index (kg/m ²)	28.2 \pm 6.5	27.4 \pm 3.6	29.3 \pm 9.8	0.01	0.994
6 min walk distance (m)	416.7 \pm 117.3	395.3 \pm 147.5	331.4 \pm 147.5	2.7	0.259

Abbreviations: PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; RV, right ventricle; WHO, World Health Organization.

^aPost hoc pairwise difference $p \leq 0.02$ between Phenotype Mild and Phenotype Moderate.

^bPost hoc pairwise difference $p \leq 0.02$ between Phenotype Mild and Phenotype Severe.

^cPost hoc pairwise difference $p \leq 0.02$ between Phenotype Moderate and Phenotype Severe.

TABLE 3 Symptom Cluster Phenotype comparisons for selected pulmonary arterial hypertension symptoms and health-related quality of life

	Total (N = 60) Mean ± SD	Mild Symptom Cluster Phenotype (n = 28, 47%) Mean ± SD	Moderate Symptom Cluster Phenotype (n = 20, 33%) Mean ± SD	Severe Symptom Cluster Phenotype (n = 12, 20%) Mean ± SD	χ^2	p Value
Pulmonary Arterial Hypertension Symptom Scale (PAHSS)						
Chest pain/discomfort ^{b,c}	1.2 ± 1.8	0.4 ± 1.1	2.2 ± 2.3	1.8 ± 1.1	16.16	<0.001
Dizzy ^{b,c}	1.8 ± 2.0	0.9 ± 1.4	2.3 ± 1.8	2.8 ± 2.8	11.12	0.004
Shortness of breath with exertion ^{a,b}	4.9 ± 3.2	3.1 ± 2.7	5.6 ± 2.7	7.7 ± 2.4	20.00	<0.001
Swelling ankles/feet ^b	2.3 ± 2.9	1.5 ± 2.1	2.4 ± 2.9	4.1 ± 3.7	6.02	0.049
Cough ^b	2.1 ± 2.6	1.2 ± 1.9	2.5 ± 2.8	3.4 ± 3.1	7.25	0.027
Loss of appetite ^b	1.4 ± 2.4	0.7 ± 1.2	1.2 ± 2.4	3.6 ± 3.6	6.72	0.035
Numb, painful hands or feet with cold and stress (Raynaud's phenomena) ^{b,c}	2.9 ± 3.6	1.4 ± 2.7	4.2 ± 3.9	4.4 ± 3.8	11.15	0.004
Multidimensional dyspnea profile (MDP)						
Discomfort of breathing ^{a,b}	2.9 ± 2.4	1.4 ± 1.5	3.7 ± 2.0	4.9 ± 2.5	20.96	<0.001
Anxiety ^{a,b,c}	2.4 ± 2.9	0.8 ± 1.5	2.5 ± 2.3	6.0 ± 3.2	24.64	<0.001
Frustration ^{a,b,c}	2.9 ± 3.1	1.1 ± 2.1	3.3 ± 2.6	6.4 ± 2.6	25.13	<0.001
Afraid ^{b,c}	2.1 ± 2.9	0.6 ± 1.2	1.8 ± 1.9	5.7 ± 3.8	21.02	<0.001
Patient Health Questionnaire (PHQ 8) ^{b,c}	4.8 ± 4.4	2.4 ± 2.3	4.6 ± 3.2	10.8 ± 4.6	26.85	<0.001
Epworth Sleepiness Scale (ESS) ^b	7.07 ± 4.6	5.1 ± 3.6	8.3 ± 4.8	9.6 ± 4.8	8.73	0.013
emPHasis-10 ^{b,c}	19.8 ± 11.7	12.8 ± 9.3	23.8 ± 10.1	31.5 ± 7.8	23.64	<0.001

Note: PAHSS: Scores range 0–10; 0 = none; 10 = “the most I can imagine.” MDP: Scores range 0–10; 0 = none; 10 = “the most I can imagine.” PHQ: Scores range 0–24; scores 0–3 are no-to-minimal depressive symptoms; scores 4–9 mild-to-moderate depressive symptoms; score ≥10 is considered major depression, ≥20 is severe major depression. ESS: Scores range 0–24; 0–10 normal; 11–14 mild sleepiness; 15–17 moderate sleepiness; 18–24 severe sleepiness. emPHasis-10: Scores range 0–50; higher scores indicate greater impairment.

^aPost hoc pairwise difference $p \leq 0.02$ between Phenotype Mild and Phenotype Moderate.

^bPost hoc pairwise difference $p \leq 0.02$ between Phenotype Mild and Phenotype Severe.

^cPost hoc pairwise difference $p \leq 0.02$ between Phenotype Moderate and Phenotype Severe.

PAH. While much rarer than females, males with PAH have worse outcomes than females.^{50,51} Response bias, tendencies for subjects to respond inaccurately, may have occurred, although we used psychometrically valid patient-reported outcomes including the PROMIS® measures. We did not have any WHO functional class IV patients in our study, which may have influenced our results. Additionally, Type 1 error is possible. To minimize this, we performed the Bonferroni correction.

The sample size resulted in a relatively small number of patients in each phenotype. However, there

is no consensus on sample size when using cluster analysis.⁵² As an exploratory technique, clustering does not rely on linear assumptions, and variables do not need to be removed for collinearity. This study begins to demonstrate subgroups of patients with similar phenotypic characteristics but should be considered hypothesis-generating. We need to validate these results in larger more diverse samples from other centers. Additionally, this was a cross-sectional study, a longitudinal study to determine if and/or how patients change over time with regard to phenotypes is needed.

TABLE 4 Symptom Cluster Phenotype comparisons for selected patient-reported physical function, and sleep-related impairment, plasma, and serum biomarkers, and actigraphy

	Total (N = 60)		Mild Symptom Cluster Phenotype (n = 28, 47%)		Moderate Symptom Cluster Phenotype (n = 20, 33%)		Severe Symptom Cluster Phenotype (n = 12, 20%)		χ ²	p Value
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD			
PROMIS® Physical Function 8a ^{a,b}	41.1 ± 7.2		44.8 ± 7.6		40.1 ± 4.9		34.2 ± 3.2		24.63	<0.001
PROMIS® Sleep-related Impairment ^{a,b}	50.2 ± 10.1		41.9 ± 6.7		54.6 ± 5.7		62.0 ± 4.6		41.1	<0.001
Plasma and serum biomarkers										
NT-pro BNP	661.7 ± 1059.0		503.0 ± 997.6		508.1 ± 856.1		1248.3 ± 1340.2		4.98	0.083
Norepinephrine ^b	609.3 ± 184.2		638.1 ± 164.2		519.0 ± 192.4		697.7 ± 158.6		7.05	0.029
Epinephrine	34.7 ± 23.7		33.0 ± 21.1		36.5 ± 27.9		35.3 ± 23.6		0.03	0.987
Dopamine	28.2 ± 58.7		35.3 ± 88.7		19.5 ± 22.5		27.1 ± 16.8		4.85	0.088
Actigraphy										
Sleep onset latency (minutes) ^a	11.1 ± 12.1		9.5 ± 13.5		10.4 ± 10.9		16.2 ± 9.8		6.46	0.04
Sleep efficiency (%)	85.7 ± 16.0		89.2 ± 21.9		83.8 ± 6.9		80.5 ± 6.5		4.52	0.105
Wake after sleep onset (minutes)	77.4 ± 40.2		72.2 ± 43.9		71.4 ± 31.8		99.3 ± 38.8		5.3	0.071
Total sleep time (minutes)	431.2 ± 74.0		440.8 ± 72.4		422.9 ± 72.4		422.8 ± 72.4		1.38	0.501

Note: PROMIS® Sleep-related impairment: Scores range 30.0–80.1; higher scores indicate worse impairment. PROMIS® Physical Function 8a: Scores range 30.0–80.1; higher scores indicate better physical function. Actigraphy: Sleep onset latency normal <20 min; Wake after sleep onset normal <30 min; Total sleep time normal 7–9 h.

Abbreviations: NT-pro BNP, N-terminal pro b-type Natriuretic Peptide; PROMIS, Patient-Reported Outcomes Measurement Information System.

^aPost hoc pairwise difference $p \leq 0.02$ between Phenotype Mild and Phenotype Severe.

^bPost hoc pairwise difference $p \leq 0.02$ between Phenotype Moderate and Phenotype Severe.

CONCLUSIONS

In conclusion, this study shows the symptoms of distinct symptom cluster phenotypes in women with PAH. Over 50% of the sample were categorized in the Moderate and Severe Symptom Cluster Phenotypes. The Symptom Cluster Phenotypes differed in important patient-reported outcomes (e.g. symptoms, physical function), NE levels, and sleep onset latency (actigraphy). Identifying the distinct symptom cluster phenotypes can allow clinicians to know which patients are at risk for worse symptoms and outcomes to intervene.

AUTHOR CONTRIBUTIONS

Lea Ann Matura takes responsibility for the integrity of the data and the accuracy of the data analysis, contributed to the study design and conception, and data analysis and interpretation. She drafted the first version of the manuscript and approved the final manuscript. Jamison D. Fargo contributed to the study design, data analysis and interpretation, and manuscript preparation. Kathleen Boyle contributed to the study design, data acquisition, and manuscript preparation. Jason S. Fritz contributed to the study design, data acquisition, data analysis interpretation, and manuscript preparation. Kerri A. Smith contributed to the study design, data acquisition, and manuscript preparation. Jeremy A. Mazurek contributed to the study design, data acquisition, data analysis interpretation, and manuscript preparation. Diane Pinder contributed to the study design, data acquisition, and manuscript preparation. Christine L. Archer-Chicko contributed to the study design, data acquisition, and manuscript preparation. Harold I. Palevsky contributed to the study design, data acquisition, data analysis interpretation, and manuscript preparation. Allan I. Pack contributed to the study design, data analysis interpretation, and manuscript preparation. Marilyn S. Sommers contributed to the study design, data analysis interpretation, and manuscript preparation. Steven M. Kawut contributed to the study design, data acquisition, data analysis interpretation and manuscript preparation.

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CONFLICTS OF INTEREST

L. A. M. is a member of the American Journal of Hospice and Palliative Medicine editorial board. J. S. F. is a site PI for United Therapeutics and speaker for Simply Speaking PAH CME program and Pulmonary Hypertension Association on Demand CME program. K. A. S. has grants from United Therapeutics and Janssen. J. A. M. is a speaker for Abbott and a member of a data safety monitoring board for United Therapeutics. H. I. P. is a member of the safety advisor boards for Acceleron, Actelion, Janssen, United Therapeutics, and a member of a data safety monitoring board for United Therapeutics. S. M. K has provided consulting for Janssen and has been a member (Chair) of the Data Safety Monitoring Boards of United Therapeutics and the Advisory Boards of Acceleron and Vivus. He was a member of a United Therapeutics study section; a member of the European Respiratory Journal editorial board; and he received in-kind monitoring equipment from PhysiQ. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

This study was approved by the University of Pennsylvania Institutional Review Board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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