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Pulmonary hypertension due to interstitial lung disease or chronic obstructive pulmonary disease: a patient experience study of symptoms and their impact on quality of life

Hilary M. DuBrock[1], Steven D. Nathan[2], Bryce B. Reeve[3], Nicholas A. Kolaitis[4], Stephen C. Mathai[5], Peter M. Classi[6], Andrew C. Nelsen[6], Bimpe Olayinka-Amao[7], Lindsey N. Norcross[7] and Susan A. Martin[8]

[1]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA; [2]Inova Heart and Vascular Institute, Falls Church, VA, USA; [3]Department of Population Health Sciences, Duke University School of Medicine, Durham, NC, USA; [4]Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, San Francisco Medical Center, University of California, San Francisco, CA, USA; [5]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [6]Global Medical Affairs, United Therapeutics, Durham, NC, USA; [7]Patient-Centered Outcomes Assessment, RTI Health Solutions, Durham, NC, USA; [8]Patient-Centered Outcomes Assessment, RTI Health Solutions, Ann Arbor, MI, USA

Abstract

Pulmonary hypertension resulting from chronic lung disease such as chronic obstructive pulmonary disease and interstitial lung disease is categorized by the World Health Organization as Group 3 pulmonary hypertension. To identify the symptoms and impacts of World Health Organization Group 3 pulmonary hypertension and to capture data related to the patient experience of this disease, qualitative research interviews were undertaken with 3 clinical experts and 14 individuals with pulmonary hypertension secondary to chronic obstructive pulmonary disease or interstitial lung disease. Shortness of breath, fatigue, cough, and swelling were the most frequently reported symptoms of pulmonary hypertension due to chronic obstructive pulmonary disease or interstitial lung disease, and shortness of breath was further identified as the single most bothersome symptom for most patients (71.4%). Interview participants also described experiencing a number of impacts related to pulmonary hypertension and pulmonary hypertension symptoms, including limitations in the ability to perform activities of daily living and impacts on physical functioning, family life, and social life as well as emotional impacts, which included frustration, depression, anxiety, isolation, and sadness. Results of these qualitative interviews offer an understanding of the patient experience of pulmonary hypertension due to chronic obstructive pulmonary disease or interstitial lung disease, including insight into the symptoms and impacts that are most important to patients in this population. As such, these results may help guide priorities in clinical treatment and assist researchers in their selection of patient-reported outcome measures for clinical trials in patients with pulmonary hypertension due to chronic obstructive pulmonary disease or interstitial lung disease.

Keywords

pulmonary hypertension, symptoms, impacts, qualitative research, patient-reported outcomes, patient-centered outcome assessment, patient experience data, clinical trials, patient-focused drug development

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Introduction

Pulmonary hypertension (PH), defined by elevated pressures in the pulmonary arteries that can be attributable to a number of distinct etiologies, has been gaining prevalence in recent years.[1,2] There are a number of possible causes of PH, and PH resulting from chronic lung disease such as interstitial lung disease (ILD) or chronic obstructive

Corresponding author:
Susan A. Martin, MSPH 3005 Boardwalk Drive, Suite 105, Ann Arbor, MI 48108, USA.
Email: smartin@rti.org

pulmonary disease (COPD) is categorized by the World Health Organization (WHO) as Group 3 PH.[3] Chronic lung disease is the second leading cause of PH,[4] and mortality rates for patients with WHO Group 3 PH are among the highest reported for any of the diagnostic groups, with one study finding a standardized mortality ratio of 8.9 for patients diagnosed in 2011 (compared to an age- and sex-matched general population).[2,5] Because there are no US Food and Drug Administration (FDA)-approved treatments for WHO Group 3 PH, treatment of the condition in clinical practice is based on management of the underlying lung disease[6] as well as off-label use of certain treatments approved for WHO Group 1 PH.[7] Despite the clear importance of research addressing the many unmet needs in this population—including treatment options—literature documenting the symptom experience and quality of life burden of WHO Group 3 PH is limited.

In recent years, the FDA has underscored the importance of patient-focused drug development, with guidance documents encouraging the thoughtful incorporation of patient experience data in both the development of clinical trial designs and the assessment of clinical outcomes.[8–10] The importance of patient input in PH management has been recognized, with clinical experts at the 6th World Symposium on Pulmonary Hypertension stressing the need for improved strategies for gathering patient experience data in order to develop treatment approaches that reflect patients' values and priorities.[11] Studies of health-related quality of life (HRQOL) in other populations with PH (e.g. those with pulmonary arterial hypertension (PAH)) have shown that the symptoms that patients experience cause significant disease-related impairments in HRQOL[12–16] and further support the need for research that explores HRQOL and treatment goals in patients with PH secondary to ILD or COPD.

While clinical considerations regarding the best way to identify and treat patients with Group 3 PH are being continually refined, the lack of knowledge about patients' experience of PH and the impact of therapies remains pronounced. To address this gap and move toward a more complete understanding of the patient experience, in-depth interviews with patients with Group 3 PH are essential. The goals of this qualitative study were to gather insight into the patient experience of PH due to ILD or COPD in a manner consistent with the FDA draft guidance on patient-focused drug development and to identify areas of unmet need in this patient population, with a particular focus on disease symptoms and impacts on daily living.

Methods

Study design

This qualitative research study was designed to identify the symptoms and impacts of PH secondary to ILD or COPD and to capture data related to the patient experience of this disease. Specifically, qualitative research interviews were undertaken in alignment with the methods outlined by the FDA[9] and by the International Society for Pharmacoeconomics and Outcomes Research.[17] In accordance with these guidelines, the design of the study included interviews with clinicians with experience treating patients with WHO Group 3 PH in order to collect information on significant signs, symptoms, and impacts from a clinical perspective prior to the conduct of the patient interviews that represent the major research focus. The study protocol and all materials were reviewed and approved by our institutional review board, and all participants provided informed consent prior to participating in the interviews.

Participants

Clinical expert participants. To support the development of a patient-focused interview guide, input was sought from clinical experts with experience treating patients with WHO Group 3 PH. Interviews were conducted with three clinicians (including two coauthors of the current manuscript, S.D.N. and S.C.M.) to gather information on the symptoms and impacts associated with WHO Group 3 PH and to determine whether differences were observed between patients with PH resulting from ILD and those with PH resulting from COPD. The clinicians were all practicing pulmonologists who are recognized experts in the treatment of patients with PH and who reported treating between 8 and 25 patients with WHO Group 3 PH per month.

Patient participants. Patient participants were identified through collaboration with clinical sites, patient advocacy groups, and a patient panel organization in the United States. For clinical sites, potential participants were identified by investigators. For the patient advocacy group and patient panel, recruitment materials describing the study were circulated and interested individuals were invited to contact the research staff for screening. To be eligible for participation in the interviews, patients were required to be 18 years or older and have a diagnosis of PH secondary to ILD or COPD (a subset of WHO Group 3 PH). Patients with a diagnosis of PAH (i.e. WHO Group 1 PH) were not eligible for participation in the study. Diagnoses were self-reported, except those for participants identified through clinical sites ($n = 3$).

Interview process and analysis

Each semi-structured concept elicitation interview was audio recorded and began with general questions intended to get participants talking about their experiences with symptoms associated with their PH due to ILD or COPD and the impacts of these symptoms. Open-ended questions were designed to observe the ways in which participants talked about their experiences with PH, including the terminology

that patients used in discussing their condition. These general questions were followed by more targeted questions designed to assess key symptoms and impacts identified by clinical experts and to evaluate the relative importance of symptoms and impacts. Participants were then asked to rank their most bothersome symptoms. Interviews concluded with participants describing the impact of PH on daily life and the most difficult aspect of living with PH.

Thematic analysis of the qualitative data (transcripts and field notes) was conducted in a standard, systematic manner by two members of the research team (B.O.A. and S.A.M.). Identified discrepancies were reviewed across researchers and resolved through examination of the source data and discussion. Tables were developed to display the symptoms and impacts described during each interview in order to document results across all interviews, with the aim of documenting concept saturation (i.e. the point at which no new key concepts emerged).[18,19] In addition, quotations representing participants' feedback were documented to illustrate the reported symptoms and impacts.

Results

Clinician interview results

Findings from the clinician interviews indicated that while the symptoms of PH were consistent regardless of whether ILD or COPD was the underlying cause, treatment approaches were individualized based on clinical presentation and the severity of disease. Clinicians noted that understanding the contribution of the underlying lung disease to symptomology in PH is important in the management of patients but that this can be difficult to determine, as both PH and the underlying ILD or COPD commonly present with similar symptoms (e.g. shortness of breath). Clinicians further reported that based on their experience treating patients, shortness of breath was the most bothersome symptom, primarily due to the significant impact of shortness of breath on patients' ability to be fully engaged in physical activities and activities of daily living.

Patient interview results

Fourteen individuals with PH due to ILD or COPD participated in interviews. Participants' mean age was 59.2 years (range: 38–73), and 64.3% of the participants were female. Of the 14 participants, 5 (35.7%) were diagnosed with PH secondary to ILD and 9 (64.3%) were diagnosed with PH secondary to COPD. The mean time since receiving their PH diagnosis was 4.8 years, and 8 participants (57.1%) reported that they were on treatment for PH at the time of the interview (Table 1).

Table 1. Characteristics of interview participants.

Patient characteristics	Total ($N = 14$)
Sex, *n* (%)	
Male	5 (35.7)
Female	9 (64.3)
Age (years)	
Mean (SD)	59.2
Range	38–73
Race, *n* (%)	
White	12 (85.7)
Black or African American	2 (14.3)
Education, *n* (%)	
High school diploma or equivalent	2 (14.3)
Some college	8 (57.1)
College degree	3 (21.4)
Professional or advanced degree	1 (7.1)
Employment status, *n* (%)	
Full-time	2 (14.3)
Part-time	1 (7.1)
Not employed/retired	11 (78.6)
Geographic region, *n* (%)	
Northeast	1 (7.1)
South	7 (50.0)
Midwest	3 (21.4)
West	2 (14.3)
Pacific	1 (7.1)
Recruitment source, *n* (%)	
Patient panel	4 (28.6)
Patient advocacy group	7 (50.0)
Clinic[a]	3 (21.4)
Underlying cause of PH, *n* (%)	
ILD	5 (35.7)
COPD	9 (64.3)
Time since PH diagnosis (years)	
Mean	4.8
Median	2.5
Range	0.5–14
Currently on treatment for PH, *n* (%)	
Yes	8 (57.1)
No	6 (42.9)

COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; PH: pulmonary hypertension; SD: standard deviation.
[a]Two pulmonology clinics (in NC and VA) participated, providing a total of three physician-confirmed participants.

Patient-reported symptoms of PH due to ILD or COPD. Participants identified shortness of breath ($n = 14$; 100.0%), fatigue ($n = 12$; 85.7%), cough ($n = 12$; 85.7%), and swelling or weight gain ($n = 11$; 78.6%) as being the symptoms that they experienced most frequently (Table 2).

The only symptom experienced by all participants was shortness of breath, which nine participants reported experiencing on a daily basis. Most participants ($n = 9$; 64.3%) noted that shortness of breath occurred only during activity or exertion, although three individuals (21.4%) described occasionally experiencing shortness of breath even at rest. Ten patients (71.4%) further reported shortness of breath to be the single most bothersome symptom, explaining that this was due to both the discomfort of

Table 2. Signs and symptoms of PH secondary to ILD or COPD reported by interview participants.

	Interviews														ILD total ($n=5$)	COPD total ($n=9$)	Overall total ($N=14$)
	Participants with PH Secondary to ILD					Participants with PH Secondary to COPD											
Shortness of breath	S	S	S	S	S	S	S	P	S	S	S	S	P	S	S = 5	S = 7	**S = 12**
															P = 0	P = 2	**P = 2**
Fatigue/tiredness	S	S	P	S	P	S	P	S	–	–	P	P	S	P	S = 3	S = 3	**S = 6**
															P = 2	P = 4	**P = 6**
Cough	P	P	S	–	S	–	P	P	P	P	P	P	P	P	S = 2	S = 0	**S = 2**
															P = 2	P = 8	**P = 10**
Swelling	P	P	P	–	–	S	S	–	P	P[a]	S	P	S	P	S = 0	S = 4	**S = 4**
															P = 3	P = 4	**P = 7**
Chest pain	S	S	S	–	–	S	S	–	–	–	–	–	–	–	S = 3	S = 2	**S = 5**
															P = 0	P = 0	**P = 0**
Dizziness	–	–	S	–	S	S	–	–	–	–	–	–	–	–	S = 2	S = 1	**S = 3**
															P = 0	P = 0	**P = 0**
Heart palpitations/ heart racing	S	S	–	–	–	–	–	–	–	–	S	–	–	–	S = 2	S = 1	**S = 3**
															P = 0	P = 0	**P = 0**
Brain fog/memory problems	–	S	–	S	–	–	–	–	–	–	–	–	–	–	S = 2	S = 0	**S = 2**
															P = 0	P = 0	**P = 0**
Difficulty speaking for long periods/hoarseness	–	–	–	–	–	–	–	–	–	S	–	–	–	S	S = 0	S = 2	**S = 2**
															P = 0	P = 0	**P = 0**
Weakness/low endurance/low stamina	–	–	–	–	–	–	–	–	–	S	–	–	–	–	S = 0	S = 1	**S = 1**
															P = 0	P = 0	**P = 0**
Muscle spasms	–	S	–	–	–	–	–	–	–	–	–	–	–	–	S = 1	S = 0	**S = 1**
															P = 0	P = 0	**P = 0**
Tremors	–	S	–	–	–	–	–	–	–	–	–	–	–	–	S = 1	S = 0	**S = 1**
															P = 0	P = 0	**P = 0**
Sleep disturbance	–	–	–	–	S	–	–	–	–	–	–	–	–	–	S = 1	S = 0	**S = 1**
															P = 0	P = 0	**P = 0**

COPD: chronic obstructive pulmonary disorder; ILD: interstitial lung disease; PH: pulmonary hypertension.
Note: "S" indicates a concept that was spontaneously reported; "P" indicates a concept that was endorsed upon probing. A dash (–) indicates that the concept was not reported.
[a]Participant reported weight gain associated with swelling.

the experience and the way that the symptom impacted their ability to perform daily activities.

- *The shortness of breath [. . .] feels like I literally can't catch my breath. It feels like sometimes I have an elephant sitting on my chest because it's like I can't get any air.*
- *Oh, the shortness of breath [is most bothersome], for sure. Because it limits me and so much of what I can do.*

Fatigue or tiredness was reported by 12 participants (85.7%), many of whom described the experience as feeling "exhausted," "sluggish," or "lethargic." Four participants (28.6%) observed that physical activity could trigger the symptom, which seven participants (50.0%) reported experiencing every day.

- *It's maybe about 12 feet from my bed to the actual restroom. When I get there, I'm so worn out, it makes me sluggish.*
- *Just running out of oomph or just being too exhausted or worn out to really be able to do much of anything.*

Twelve participants (85.7%) indicated that they experienced coughing, although this sign was more often endorsed upon probing ($n=10$; 71.4%) than spontaneously reported by patients ($n=2$; 14.3%). When asked to describe the cough, participants reported a "hacking" cough that could be either dry or productive and noted that coughing caused soreness in the throat and made participants feel that there was fluid in the chest or lungs.

- *I have a dry, unproductive cough. I'll get like a dry tickle sometimes in the back of my throat. Sometimes when I'm doing way too much and I'm running my oxygen a lot more I'll get like a sore throat.*
- *Like a more productive cough that you have than when it's with a cold. It seems like the mucus is getting into your lungs causing the cough. If I cough hard enough, I get that phlegm up and that'll clear up the breathing for me some.*
- *It's a dry, hacking cough.*

Swelling or weight gain associated with fluid retention was reported by 11 participants (78.6%). Specifically,

participants with PH due to ILD or COPD described their experience of swelling as feeling like the skin is being stretched, feeling uncomfortable and tight, or a feeling of heaviness and noted that the experience could occur in different parts of the body.

- *When I was working, I had problems all the time with fluid retention.*
- *I feel like it's [swelling] in my chest or belly area almost, right in the diaphragm area where I could feel fluid.*
- *In my legs and ankles. I've always had that problem with my legs and ankles swelling.*

When asked how their symptoms have changed since diagnosis, five participants (35.7%) said some or all of their symptoms had gotten worse and five (35.7%) reported improvement in at least one symptom. Among the participants who reported improvement in specific symptoms, two said their chest pain had improved, five said their shortness of breath had improved, and two reported improvement in swelling or weight.

Given that participants' PH was secondary to ILD or COPD, participants and clinicians were also asked whether it was possible for them to differentiate between reported symptoms caused by PH and those caused by the underlying lung disease. Although there was some variability in reports by symptom, both participants and clinicians acknowledged having difficulty determining the underlying cause of some symptoms. Specifically, participants were generally evenly split in their ability to attribute a symptom specifically to PH or in being uncertain whether the symptom was due to PH or the underlying lung disease, ILD or COPD.

Patient-reported impacts of PH due to ILD or COPD. Participants elaborated on the impacts they experienced related to PH and their reported symptoms, describing limitations in their ability to perform activities of daily living ($n = 14$; 100.0%) and impacts on their physical functioning ($n = 13$; 92.9%), family life ($n = 12$; 85.7%), and social life ($n = 11$; 78.6%). In addition, participants reported impacts on emotions, including frustration ($n = 12$; 85.7%), depression ($n = 11$; 78.6%), anxiety ($n = 10$; 71.4%), isolation ($n = 8$; 57.1%), and sadness ($n = 8$; 57.1%) (Table 3).

- *Not being able to do a lot of things I used to do.*
- *Having my life taken away from me. I'm not working, I love working.*
- *Actually, the hardest part about having pulmonary hypertension is the fear. And the reason being because I don't know if I'll go to sleep and not wake up or if I'll be walking and my chest pain will get so bad that I'll have a heart attack.*

All 14 participants (100.0%) reported that their PH impacted their ability to perform daily activities, including washing dishes, cooking, cleaning, grocery shopping, and making the bed. Patients indicated that both their shortness of breath and their fatigue affected their ability to complete these activities.

- *I can't wash dishes. I don't cook at all. I can't even do basic things like if I make a sandwich, I'm wiped out.*
- *It'd be nice to be able to breathe and tie my shoes simultaneously.*
- *I don't go grocery shopping. I haven't been to a store to shop for anything because I know that I just can't get around in a store.*
- *I can't walk through the mall anymore. Anything that involves a lot of walking, I can't do. I can take sheets off the bed but I can't put sheets back on the bed. I can't do any floor scrubbing.*

Thirteen participants (92.9%) reported experiencing physical functioning impacts related to their PH, with shortness of breath being the symptom that participants most frequently reported as the cause of these limitations.

- *I can't pick up anything over 5 pounds.*
- *I used to dance and I used to love hiking. Stairs is just a really bad one. I mean two stairs I'm fine but when it's a set of stairs I truly think that I might die going up them.*
- *I used to go for long walks or go out to swim. I'm afraid to be in the pool alone now and I won't go far for a walk because I won't make it.*
- *We also used to ride bikes. I can't do that anymore.*

Impacts on relationships with family and friends were reported by 12 and 11 participants (85.7% and 78.6%), respectively. Specifically, participants described how they were not able to spend as much time with family and friends and the need to limit the amount of time they spent in public.

- *My husband and I used to love to go to yard sales and flea markets. I can't do that anymore because I get worn out way too fast.*
- *I used to go out and meet up with friends every week. It could've been to go shopping or out to lunch or we went to Weight Watcher meetings. I just can't do it anymore.*

The emotional impacts of having PH due to ILD or COPD were also described by many participants who described struggling with feelings of frustration, depression, anxiety, isolation, and sadness.

- *Depression, anxiety, sadness. Jealousy in seeing everybody else doing things that I wish I could do. And then I get angry a lot.*
- *Dealing with the day-to-day symptoms, especially the shortness of breath. That's probably the most difficult and most frustrating part of it.*

Table 3. Impacts of PH secondary to ILD or COPD reported by interview participants.

	Interviews														ILD total ($n=5$)	COPD total ($n=9$)	Overall total ($N=14$)
	Participants with PH Secondary to ILD					Participants with PH Secondary to COPD											
Activities of daily living	S	S	P	S	S	S	S	P	S	S	P	P	P	P	S = 4 P = 1	S = 4 P = 5	**S = 8** **P = 6**
Physical functioning	S	S	P	S	P	S	S	S	S	P	S	–	S	P	S = 3 P = 2	S = 6 P = 2	**S = 9** **P = 4**
Family life	S	S	P	P	P	P	S	–	P	P	P	–	P	P	S = 2 P = 3	S = 1 P = 6	**S = 3** **P = 9**
Emotional impacts, including:																	
Frustration	*P*	*P*	*P*	*S*	*P*	*P*	*P*	*P*	*P*	*P*	*P*	–	–	*P*	S = 1 P = 4	S = 0 P = 7	**S = 1** **P = 11**
Depression	*P*	*P*	–	*P*	*P*	*P*	*P*	*S*	*P*	*S*	*S*	–	–	*P*	S = 0 P = 4	S = 3 P = 4	**S = 3** **P = 8**
Anxiety	*P*	*P*	*P*	–	*P*	*P*	*P*	–	*P*	*S*	*P*	–	–	*P*	S = 0 P = 4	S = 1 P = 5	**S = 1** **P = 9**
Isolation	*P*	*P*	*P*	–	*P*	*P*	*P*	–	–	*P*	*S*	–	–	–	S = 0 P = 4	S = 1 P = 3	**S = 1** **P = 7**
Sadness	*P*	*P*	–	*P*	–	*P*	*P*	–	–	*P*	*S*	–	–	*S*	S = 0 P = 3	S = 2 P = 3	**S = 2** **P = 6**
Fear	*P*	*P*	–	–	–	*P*	*P*	–	–	*P*	*P*	–	–	–	S = 0 P = 2	S = 0 P = 4	**S = 0** **P = 6**
Social impacts	P	S	S	P	P	P	P	–	–	P	P	–	P	P	S = 2 P = 3	S = 0 P = 6	**S = 2** **P = 9**
Impacts on work/ productivity	S	S	S	S	S	P	P	–	–	–	S	–	S	P	S = 5 P = 0	S = 2 P = 3	**S = 7** **P = 3**
Cognitive impacts	P	S	–	S	–	P	–	–	P	P	P	P	–	–	S = 2 P = 1	S = 0 P = 5	**S = 2** **P = 6**
Intimate relationships	P	P	P	P	–	P	–	S		S	P	–	–	–	S = 0 P = 4	S = 2 P = 2	**S = 2** **P = 6**
Hobbies	P	P	S	P	P	S	–	–	–	P	P	–	–	–	S = 1 P = 4	S = 1 P = 2	**S = 2** **P = 6**
Impacts on sleep	–	–	P	P	S	P	–	–	–	P	P	–	–	P	S = 1 P = 2	S = 0 P = 4	**S = 1** **P = 6**

COPD: chronic obstructive pulmonary disorder; IDI: in-depth interview number; ILD: interstitial lung disease; PH: pulmonary hypertension.
Note: "S" indicates a concept that was spontaneously reported; "P" indicates a concept that was endorsed upon probing. A dash (–) indicates that the concept was not reported.

- *[PH] makes you depressed. It makes you sad. It makes you unsure. It makes you feel isolated.*
- *[PH] has affected me a lot. It pisses me off. Frustration. Not knowing what the future brings. There's a lot of emotions.*

Discussion

In this study, we identified shortness of breath, fatigue, and swelling as the most common symptoms in patients with PH related to underlying lung disease. We also found that cough is a prominent symptom in these participants and may be more common in PH related to lung disease (i.e. WHO Group 3 PH) than in other PH populations. Importantly, most participants were unable to distinguish whether these symptoms were related to PH or to the underlying lung disease, highlighting a difficulty in understanding and treating their disease. Furthermore, participants uniformly reported significant impact of disease on physical, social, and emotional well-being. Taken together, these data reveal a pattern of symptoms that reflect the intersection of pulmonary vascular and airways or parenchymal disease, emphasize the significant impact of the disease on patients, and highlight the need for patient education and therapeutic interventions to address both the symptoms and their impact on HRQOL.

Although in recent years a number of clinical trials and qualitative studies have focused on other types of PH (e.g. PAH), Wijeratne and colleagues[2] have argued that greater emphasis should be placed on policies and practices designed to prevent and treat patients with WHO Groups 2 and 3 PH due to the rapid increase in these patient populations and the high mortality rates observed in these groups. Such efforts may be supported, in part, by increased

recognition of the disease among clinicians and in the community; one qualitative study of patients with PH found that a "lack of awareness" about the disease—on the part of both patients and their health care providers—was an issue of concern for patients and a factor partly attributed for delays in diagnosis.[15] Recognizing and managing PH early can be key for long-term success, and heightened vigilance on the part of clinical experts regarding indicators of risk can be seen in recommendations from the 6th World Symposium on Pulmonary Hypertension which sought to refine the clinical definition of PH as a mean pulmonary arterial pressure of >20 mm Hg, a recommendation that lowered the previous diagnostic standard of ≥25 mm Hg.[3] By lowering the diagnostic standard, experts hope to increase the sensitivity of criteria for identifying patients with PH and, as a result, to be able to pursue critical therapeutic interventions earlier.

In the absence of an approved treatment for PH secondary to ILD or COPD, the clinical approach for these patients revolves around the management of symptoms and treatment of the underlying lung disorder. Treatment of patients with WHO Group 3 PH can be challenging since particularly bothersome symptoms, such as dyspnea, are often multifactorial and may not consistently improve with disease-specific therapies. Recent studies examining the effect of using PAH-targeted therapy on patients with PH due to ILD have shown positive results.[20] However, studies including patients with PH secondary to COPD have shown mixed results in terms of improvement in exercise tolerance, symptom burden, and HRQOL, and the need for further trials in a patient population with WHO Group 3 PH has been noted.[21] Significantly, to demonstrate the benefit of therapeutic interventions designed for patients with WHO Group 3, clinical trials must assess the specific symptoms and impacts that these patients experience and consider to be important.

The inclusion of patient-reported outcome (PRO) instruments in clinical trials provides an essential avenue for capturing the benefit of treatment on symptom burden and other aspects of HRQOL. Disease-specific PRO instruments that assess HRQOL have been developed and validated in WHO Group 1 PAH (e.g. PAH-Symptoms and Impact Questionnaire[22]), but the relevance of such measures has not been evaluated in WHO Group 3 PH. There is a need for the development of PRO measurement strategies specific to WHO Group 3 PH, and an understanding of the specific experiences of patients in this population is therefore a necessary first step. Thus, this study contributes to the understanding of the relevance of concepts that should be included in the evaluation of the content validity of a PRO measure of symptoms or HRQOL in individuals with WHO Group 3 PH.

Although development of PH complicates the disease course and treatment approach for patients with lung disease and is associated with worse survival, no previous qualitative studies have specifically examined the experiences of patients with PH secondary to ILD or COPD. The findings presented here describe the specific symptom and impact burden of PH secondary to ILD or COPD, a major subset of WHO Group 3 PH, and provide a foundation for future studies to develop treatment options that address these patient-centered outcomes. Through the qualitative interviews conducted in this study, participants described the experience of living with PH secondary to ILD or COPD. Prior qualitative research studies in patients with COPD and ILD without known PH similarly highlighted shortness of breath, fatigue, and cough as prominent symptoms, although symptoms such as swelling were not commonly reported.[23,24] In PAH, symptoms of shortness of breath, fatigue, and swelling were reported as well as other cardiovascular symptoms, such as chest pain and palpitations.[22] Our study suggests that patients with PH due to ILD or COPD experience a distinctive set of symptoms compared with patients with PH or with COPD or ILD alone. Consequently, PH, ILD, and COPD disease-specific PRO measures may not accurately reflect symptom burden and quality of life impact in patients with Group 3 PH.

Although PRO measures specific to PH due to ILD or COPD have not been determined, recent commentary has suggested that—once content validity has been established in the patient population—use of existing measures may represent an optimal measurement strategy.[25] In light of this, existing PRO measures focused on the relevant symptoms, such as the University of California San Diego Shortness of Breath Questionnaire and the PROMIS Fatigue measures could be assessed for content validity in a population of patients with WHO Group 3 PH and, if content validity is confirmed, used to capture the symptoms that patients have identified as important. Other existing measures may be used to assess both key symptoms and impacts; the Saint George Respiratory Questionnaire, for example, assesses several symptom and impact domains and has been used extensively in clinical studies evaluating treatments for lung diseases. Given the significant impact that study participants reported on daily activities and physical functioning, an instrument that evaluates potential changes on functioning, such as the PROMIS Physical Functioning measures, may also provide insight. While these general considerations are recommended based on the results of the qualitative research, the PRO measurement strategy in a clinical trial must be developed to reflect the anticipated treatment effects for the intervention being evaluated and, to avoid excessive burden to participants, refrain from assessing symptoms or impacts that are not expected to change with treatment.

Limitations of this study include the fact that participants were limited to individuals with PH secondary to ILD or COPD and, as such, did not incorporate perspectives from patients with WHO Group 3 PH resulting from other underlying conditions (e.g. obstructive sleep apnea).

The authors acknowledge a need for further research in additional etiologies. In addition, participants in these interviews had a mean time since diagnosis of PH of 4.8 years; while this provides a rich length of time for these patients to draw from in describing their symptom and impact experiences, future qualitative work in patients with newly diagnosed with PH secondary to ILD or COPD might be of particular value in identifying the symptoms that are present at the time of diagnosis. Possible selection bias may exist in the convenience sample of patients who volunteered to participate and whose experiences may not be reflective of the entire population of patients with PH due to ILD or COPD. This sample included a majority of white participants with high levels of education. Finally, while the results were generally consistent across participants, the lack of physician-confirmed diagnoses across participants, relatively small sample size, and no comparison group may limit the identification of differences (if any) between participants based on the underlying cause of PH (i.e. ILD or COPD) as may the limited additional clinical characteristics, such as specific treatments and comorbidities, that were included in the analysis. Further research that includes clinic-based recruitment in this population is therefore warranted. Despite these limitations, this is the first study to explore the experience of PH due to ILD or COPD directly from the patient's perspective. In both the conduct of the interviews and the analysis of the data, researchers followed a rigorous and systematic approach that was grounded in established best practices for qualitative research and in alignment with FDA guidance;[9,17–19] all of these considerations further support the trustworthiness of the study and these results. To expand upon the findings of this study and to further confirm these results, further qualitative research to establish the content validity of existing measures in this population is recommended. In addition, a particular focus on ensuring the robust assessment of shortness of breath and fatigue in future clinical trials to reflect the patient input collected in this research is warranted.

Contributorship

B.B.R., B.O.-A., S.A.M., P.M.C., and A.C.N. contributed to the study design. S.D.N. and S.C.M. participated in the clinical interviews. B.O.-A. and S.A.M. conducted all qualitative interviews. B. O.-A., L.N.N., and S.A.M. performed the analyses. H.M.D., S.D. N., B.B.R., N.A.K., S.C.M., P.M.C., A.C.N., B.O.-A., L.N.N., and S.A.M. contributed to the development of the manuscript.

Ethical approval

Clinician interviews were deemed exempt by the RTI IRB. The patient interviews were reviewed and approved by the RTI IRB.

Conflict of interest

H.M.D. is a consultant for Actelion. S.D.N. is a consultant for Bellerophon, United Therapeutics, Roche-Genentech, and Boehringer Ingelheim and is on the speakers' bureau for Roche–Genentech and Boehringer Ingelheim. B.B.R. is a consultant for United Therapeutics, Higgs Boson, and Takeda. N.A.K. has received advisory board fees from United Therapeutics and Bayer. S.C.M. has served as a consultant for Actelion, Liquidia, and United Therapeutics and serves on the Rare Disease Advisory Panel for the Patient-Centered Outcomes Research Institute. P.M. C. and A.C.N. are employees of and minor shareholders in United Therapeutics. B.O.-A., L.N.N., and S.A.M. are employees of RTI Health Solutions.

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ORCID iDs

Hilary M. DuBrock https://orcid.org/0000-0001-8410-4429
Susan A. Martin https://orcid.org/0000-0002-9594-5036

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