CHEST

Considerations When Selecting Patient-Reported Outcome Measures for Assessment of Health-Related Quality of Life in Patients With Pulmonary Hypertension

A Narrative Review

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It is well established that pulmonary hypertension (PH) places a substantial burden on patients' health-related quality of life (HRQoL). As more effective treatments have been developed for this condition, evaluating treatment benefit based on experiences reported by patients regarding their well-being and physical, social, and emotional functioning has increased. A review of the published literature and clinical trials in PH was conducted to identify and evaluate patient-reported outcome measures (PROMs) that assess PH-specific HRQoL for use in clinical studies. The Cambridge Pulmonary Hypertension Outcome Review, emPHasis-10, Living with Pulmonary Hypertension Questionnaire, and Pulmonary Arterial Hypertension—Symptoms and Impact were selected for in-depth evaluation with respect to their content validity, psychometric properties, interpretation guidelines, conceptual coverage, and administrative feasibility. Recommendations for clinical study end point strategies are provided. The review identified many strengths for each of the PROMs. Content development for all PROMs followed best practices, and any weaknesses in assessment of measurement properties were from a scarcity of available data. Although conceptual coverage and patient burden varied greatly across the PROMs, each provided a unique strength relative to the others, and no one PROM was recommended as most appropriate across all contexts of use. Optimal end point selection for assessing PH-specific HRQoL thus requires consideration of the purpose and situation in which the assessment will be conducted. These recommendations should be considered as a snapshot of a quickly evolving landscape that should be updated as new information emerges.

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ABBREVIATIONS: ADL = activity of daily living; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; C/E = cognition/emotional; CTEPH = chronic thromboembolic pulmonary hypertension; HRQoL = health-related quality of life; LPHQ = Living With Pulmonary Hypertension Questionnaire; mPAP = mean pulmonary arterial pressure; MWPC = meaningful within-patient change; NA = not applicable; PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension—Symptoms and Impact; PH = pulmonary hypertension; PROM = patient-reported outcome measure; WSPH = Sixth World Symposium on Pulmonary Hypertension

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Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) of > 20 mm Hg at rest as assessed by right heart catheterization.[1] The Sixth World Symposium on Pulmonary Hypertension (WSPH) classified PH into five clinical subtypes based on cause: group 1, pulmonary arterial hypertension (PAH); group 2, PH resulting from left-heart disease; group 3, PH resulting from chronic lung disease; group 4, chronic thromboembolic PH (CTEPH); and group 5, PH with unclear or multifactorial mechanisms, or both.[2] PAH is a particular type of PH; although PH generally refers to high BP in the pulmonary arteries resulting from any cause, PAH occurs when this increase is caused by stiffening or narrowing of the pulmonary arteries. Although PH is present in approximately 1% of all individuals, including 10% of individuals older than 65 years, and in at least half of patients with a diagnosis heart failure, PAH and CTEPH are rare diseases, affecting a few persons per 1 million.[3]

The clinical manifestations of PH vary across causes; however, the primary symptoms ubiquitous to all groups include dyspnea, fatigue, and weakness. As a result, PH places a substantial burden on patients' health-related quality of life (HRQoL). Generic patient-reported outcome measures (PROMs), such as the 12- and 36-item Short-Form Health Surveys, the EuroQol 5-Dimensions, and the Nottingham Health Profile, consistently have shown deficits in patients' functioning and well-being, with the largest impacts typically on physical functioning and activities of daily living (ADLs).[4-10]

Historically, clinical studies of patients with PH have demonstrated treatment benefits on objective outcomes, such as hemodynamic parameters, delaying time to clinical events (eg, hospitalization or mortality), or exercise capacity (eg, increased 6-min walking distance), that may not directly reflect changes in patients' well-being and functioning. As more effective treatments have been developed, the past 2 decades have seen increased evaluation of treatment benefit on patient-reported experiences, including ability to engage in ADLs, social activities and relationships, employment and work productivity, and emotional health.[10-14] Before 2000, HRQoL end points in clinical studies were captured using generic PROMs or PROMs developed for similar cardiopulmonary diseases, such as the Minnesota Living with Heart Failure Questionnaire for patients with heart failure or the St. George's Respiratory Questionnaire for patients with chronic lung disease. However, the early 2000s saw the development of PH or PAH-specific PROMs, including the Pulmonary Arterial Hypertension Quality of Life Questionnaire in 2003[15] and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) in 2006.[16] The last decade has seen the development of several new PH-specific PROMs, including the Living with Pulmonary Hypertension Questionnaire (LPHQ) in 2013,[17] emPHasis-10 in 2014,[18] and the Pulmonary Arterial Hypertension—Symptoms and Impact (PAH-SYMPACT) questionnaire in 2016.[19] These latter three measures, along with CAMPHOR, increasingly are being included as end points in studies evaluating PH treatments and in clinical practice.

In current and future studies of patients with PH, the question is no longer whether to capture PH-specific impacts on HRQoL, but rather how best to capture these outcomes. Given the increased number of available PH-specific PROMs, which is the best measure to use? A narrative review aimed to answer this question by (1) identifying PH-specific PROMs that have been used in clinical studies or practice; (2) evaluating selected PROMs with respect to history of use, content validity and psychometric properties, interpretation guidelines, conceptual coverage, and administrative feasibility; and (3) providing recommendations regarding the appropriateness of each PROM across different contexts of use.

Literature Search

Identification of PH-Specific PROMs

We performed literature searches of four electronic databases in accordance with an a priori search strategy protocol (available on request). The PubMed database was searched to identify published studies of patients with PH. The ClinicalTrials.gov database was searched to identify PROMs included as end points in interventional and observational studies of patients with PH. Search terms used for these searches are provided in e-Appendix 1.

Mapi Research Trust's Patient-Reported Outcome and Quality of Life Instruments Database and PROLABELS databases were searched to identify PH-specific PROMs and PROMs included on regulatory label claims of PH treatments, respectively. Because these searches did not yield any additional PROMs, these searches are not described further.

For the PubMed search, abstracts from all retrieved records were screened, followed by a screening of selected full-text articles, with reasons for exclusion recorded.

Prespecified selection criteria for articles included the following: publication in English in a peer-reviewed journal, the study sample included adult patients with PH, and mention of a specific PRO instrument(s). For the ClinicalTrials.gov search, all retrieved records were screened to identify studies of adults with PH that included any PROM(s) as an end point. All PROMs not captured in the PubMed search were added to the list, and the number of interventional and observational studies in which each PROM was included was tallied.

Selection of PH-Specific PROMs to Be Evaluated and Additional Literature Search

PH-specific PROMs identified from initial searches were selected for in-depth evaluation. Selected PROMs were those that had been included as an end point in one or more registered study and demonstrated face validity. A second round of literature searches of the PubMed database identified additional articles that included any PH-specific PROM that was selected for in-depth evaluation. After abstract and full-text screenings, all information related to a PROM's content validity, psychometric properties, or interpretation guidelines was extracted from selected articles.

Criteria for Evaluation of Selected PH-Specific PROMs

History of Use in Clinical Studies: This evaluation was based on the number and type of studies identified from the ClinicalTrials.gov search that included the PROM, as well as its end point positioning.

Content Validity: Content validity is the extent to which the items, response options, and scoring of a PROM capture concepts of interest in a manner that is comprehensible to the intended patient population. United States Food and Drug Administration guidelines strongly recommend the use of patient input when developing and refining the content of a PROM.[20] Specifically, item generation and selection should include patient input on concepts most relevant and important to their experience, and cognitive debriefing interviews should be conducted to ensure that the PROM's content is clear and comprehensible to patients.

Psychometric Properties: Evidence addressing relevant psychometric properties for each PROM was extracted from articles. For each PROM, the following psychometric properties were evaluated: fit of data to factor structure; evidence of floor or ceiling effects; item-level convergent or discriminant validity (ie, stronger correlations between items with their parent domain than with other domains); internal consistency; test-retest reliability or reproducibility, scale-level convergent or divergent validity, known-groups validity; predictive or criterion validity; and responsiveness, including sensitivity to treatment. For each PROM, the evidence supporting each property was rated as weak, moderate, strong, negative, or missing, based on findings from individual studies and synthesized findings across studies.

Guidelines for Score Interpretation: Evidence supporting interpretability included normative-based scoring, score-based severity staging, and evidence supporting score thresholds indicating minimally important differences between patient groups or meaningful within-patient change (MWPC) over time. Strength of evidence for recommended score interpretations was evaluated using the same approach as described for psychometric properties.

Conceptual Coverage: The degree to which the content of each PROM maps onto concepts that are important and relevant to patients with PH was evaluated. The content assessed by each item of a PROM was mapped to individual concepts on a thematic list. The depth and breadth of content coverage for each PROM then was evaluated based on the number and type of concepts captured by that PROM, and the degree to which the concepts captured are considered to be important or relevant to patients. For this purpose, an additional review of the literature was used to identify concepts for content mapping. The PubMed database was searched to identify qualitative concept elicitation studies of patients with PH.

Data extracted from articles meeting inclusion criteria were coded using an inductive approach to content analysis using NVivo version 12 software (QSR International Pty Ltd.). From these data, the thematic list of concepts, organized hierarchically, was constructed to include all concepts reported by patients across studies. The number of studies in which each concept was reported was included as a proxy of concept's importance and relevance. Content for each PROM item then was mapped to these concepts.

Administrative Feasibility: The feasibility of each PROM was evaluated with respect to patient burden, with the number of items and time for completion used as a proxy, as well as the number of available translations.

Initial Literature Searches for PH-Specific PROMs

All literature searches were conducted in June and July 2021.

PubMed Search: The PubMed search of PH studies that included PROMs yielded a total of 283 articles (see e-Fig 1 for a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram). Abstract and full-text screening led to the exclusion of 197 and 31 articles, respectively; reasons for exclusions are reported in e-Table 1. Data were extracted from the remaining 55 articles, yielding 37 unique PROMs.

ClinicalTrials.gov Search: The search yielded a total of 163 registered studies (107 interventional, 56 observational). Forty-eight studies were excluded from data extraction for not including any PROM as a study end point (n = 39) or for not including adult patients with PH (n = 9). From the remaining 115 studies (86 interventional, 29 observational), a total of 45 PROMs were extracted, including 24 not identified from the PubMed search.

Selection of PH-Specific PROMs for In-Depth Evaluation

The initial literature searches yielded a total of 61 unique PROMs. (In some cases, variations of PROMs were combined, such as the 12-item Short Form and 36-item Short Form health outcomes surveys, or original and modified versions of the Borg Dyspnea Index.) Of these, six PH-specific PROMs were identified as having sufficient face validity: CAMPHOR, emPHasis-10, LPHQ, Minnesota Living with Heart Failure Questionnaire for Pulmonary Hypertension, Pulmonary Arterial Hypertension Quality of Life Questionnaire, and PAH-SYMPACT. (Although the Minnesota Living with Heart Failure Questionnaire has been included as a PROM end point in clinical studies of patients with PH, such as INSPIRE [ClinicalTrials.gov Identifier: NCT03399604], it is not considered to be a PH-specific instrument.) As shown in Table 1, four of these PROMs—CAMPHOR, emPHasis-10, LPHQ, and PAH-SYMPACT—were included in at least one PH study. These four PROMs were selected for in-depth evaluation. Key characteristics of these PROMs are presented in Table 2,[16-21] and brief descriptions are provided in e-Appendix 2.

Literature Searches for Selected PH-Specific PROMs

Results from PubMed searches targeting the selected PROMs are summarized in e-Table 2. The search retrieved 95 articles, with an additional three articles identified from references of review articles. Abstract screening excluded 20 articles that did not report relevant evidence for evaluating the selected PROMs. Given the large number of articles describing psychometric properties of CAMPHOR, 17 articles describing cross-sectional studies and 13 articles describing studies validating adapted translations of CAMPHOR were excluded from data extraction. Also excluded were three articles each from emPHasis-10 and LPHQ searches and two articles from the PAH-SYMPACT search that did not report relevant information. Data thus were extracted from 40 articles.

TABLE 1] PH-Specific PROMs Identified From Literature Search and Frequency of Inclusion as End Points in Clinical Studies of Patients With PH

PROM	ClinicalTrials.gov Studies	
	Interventional (n = 86)	Observational (n = 29)
CAMPHOR	16	3
emPHasis-10	8	7
LPHQ	4	3
MLHFQ-PH	0	0
PAH-QoL	0	0
PAH-SYMPACT	6	1

CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; LPHQ = Living With Pulmonary Hypertension Questionnaire; MLHFQ-PH = Minnesota Living With Heart Failure Questionnaire for Pulmonary Hypertension; PAH-QoL = Pulmonary Arterial Hypertension—Quality of Life Questionnaire; PAH-SYMPACT = Pulmonary Arterial Hypertension—Symptoms and Impact Questionnaire; PH = pulmonary hypertension; PROM = patient-reported outcome measure.

Evidence Review

History of Use in Clinical Studies

The numbers of interventional and observational studies for which each evaluated PROM was included as an end point, as well as their end point positioning in studies, are presented in e-Table 3. CAMPHOR was the PH-specific PROM most frequently used in interventional studies, whereas the emPHasis-10 was the PROM most frequently included in observational studies. These PROMs were positioned most frequently as secondary end points, although CAMPHOR, LPHQ, and PAH-SYMPACT each were a primary end point in one interventional study, whereas CAMPHOR, PAH-SYMPACT, and emPHasis-10 were primary outcomes in 1 to 2 observational studies.

Content Validity

Findings related to the evaluation of content validity of selected PROMs are summarized in Table 3.[16-19,22,23]

TABLE 2] Key Characteristics of PROMs Selected for In-Depth Evaluation

PROM	Year Developed	Development Reference	Recall Period	No. of Items	Conceptual Framework	Item Response Scale	Scoring[a]
CAMPHOR	2006	McKenna et al. *Qual Life Res*. 2006;15:103-115	Today	65	3 domains: symptoms (25 items), activities (15 items), QoL (25 items) No global score Health utility index	Symptoms: yes/no (1/0) Activities: 3-point (0-2) Likert scale QoL: true/false (1/0)	Symptoms: 0-25 Activities: 0-30 QoL: 0-25
emPHasis-10	2013	Yorke et al. *Eur Respir J*. 2014;43: 1106-1113	Recent experience	10	Global score only	6-point (0-5) semantic differential scale	0-50
LPHQ	2013	Bonner et al. *Health Qual Life Outcomes*. 2013; 11:161	7 d	21	2 domains: physical (8 items), emotional (5 items) Global score	6-point (0-5) Likert scale	Global: 0-105 Physical: 0-40 Emotional: 0-25
PAH-SYMPACT	2016	McCollister et al. *Respir Res*. 2016;17:72	Symptoms: 24 h Impacts: 7 d	23	4 domains: symptoms (cardiopulmonary [6 items], cardiovascular [5 items]), impacts (physical [7 items], C/E [4 items]), oxygen use (1 item) No global score	5-point (0-4) Likert scale	Cardiopulmonary: 0-24 Cardiovascular: 0-20 Physical: 0-28 C/E: 0-16 Oxygen use:0-4

CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; C/E = cognition/emotional; CP = cardiopulmonary; CV = cardiovascular; LPHQ = Living With Pulmonary Hypertension Questionnaire; PAH-SYMPACT = Pulmonary Arterial Hypertension—Symptoms and Impact; PROM = patient-reported outcome measure; QoL = quality of life.

[a]For all scales, higher scores indicate worse health outcomes (eg, worse symptoms, lower QoL).

TABLE 3] Evaluation of Evidence Supporting Content Validity of Selected PROMs

PROM	PH Type(s) in Validation Sample	Initial Source for Item Generation		Concept Elicitation			Cognitive Debriefing		
		Instrument/ Literature Review	Expert Review	Patients	Clinicians	Caregivers	Patients	Clinicians	Caregivers
CAMPHOR	PAH,[16,22] CTEPH[16]	No	No	Yes[16]	No	No	Yes[16,22]	No	No
emPHasis-10	PAH,[18] CLD,[18] CTEPH[18]	No	Yes[18]	Yes[18]	No	No	Yes[18]	No	Yes[18]
LPHQ	PAH[17]	Yes[17]	No	Yes[17]	No	No	Yes[17]	No	No
PAH-SYMPACT	PAH,[19] CTEPH[23]	Yes[19]	Yes[19]	Yes[19,23]	Yes[19]	No	Yes[19,23]	No	No

CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CLD = chronic lung disease; CTEPH = chronic thromboembolic pulmonary hypertension; LPHQ = Living With Pulmonary Hypertension Questionnaire; PAH = pulmonary arterial hypertension; PAH-SYMPACT = Pulmonary Arterial Hypertension—Symptoms and Impact; PH = pulmonary hypertension; PROM = patient-reported outcome measure.

Evidence supporting content validity was strong for all four PH-specific PROMs. In concordance with Food and Drug Administration guidelines for development of PROMs,[20] the content assessed by each PROM was developed and refined based on patient input from concept elicitation interviews to ensure that the content is considered relevant and important to patients, as well as cognitive debriefing interviews to ensure that the instructions, items, and response options are comprehensible. All four PROMs were content validated in samples of patients with PAH,[16-19,22] whereas validation samples for CAMPHOR, PAH-SYMPACT, and emPHasis-10 also included patients with CTEPH.[16,18,23]

Psychometric Properties

Table 4[16-18,22,24-55] summarizes findings related to the evaluation of psychometric properties for PH-specific PROMs. Detailed descriptions of findings for each PROM are provided in e-Appendix 3. In summary, available evidence generally was supportive of adequate psychometric properties of each instrument, but the amount of available evidence varied substantially across the instruments. Specifically, a great deal of evidence evaluated reliability and validity of CAMPHOR and emPHasis-10, whereas very few studies examined these properties for LPHQ and PAH-SYMPACT. Few studies evaluated responsiveness for any of the instruments. Data from several interventional studies evaluated sensitivity to treatment for CAMPHOR and LPHQ, but data were available only from one such study for emPHasis-10 and from no such studies for PAH-SYMPACT.

Guidelines for Interpretation of Scores

Detailed descriptions of findings for each PROM are provided in e-Appendix 4. In summary, MWPC thresholds have been established across multiple studies and multiple methods (including anchor-based) for CAMPHOR[30,31,41] and emPHasis-10,[31,34,38] one study using a distribution-based method provided preliminary estimates of MWPC thresholds for LPHQ,[17] and no MWPC thresholds have been estimated for PAH-SYMPACT.

Conceptual Coverage

The search of qualitative concept elicitation studies conducted in June 2021 yielded 120 articles. Abstract and full-text screening led to the exclusion of 88 and 16 articles, respectively; reasons for exclusions are reported in e-Table 4. Data were extracted from the remaining 16 articles.[17,19,56-69]

Table 5 depicts a concept map showing links between content captured by the four PH-specific PROMs and concepts reported by patients with PH in qualitative studies. Detailed descriptions of mappings for each PROM are provided in e-Appendix 5. In summary, CAMPHOR and PAH-SYMPACT capture more symptoms than the others, with PAH-SYMPACT uniquely capturing symptoms related to respiratory and cardiac problems. CAMPHOR captured the most impacts of symptoms on physical functioning and ADLs, whereas emPHasis-10 captured no ADL impacts. CAMPHOR was the only measure to capture some key emotional impacts, but it also captured several emotional impacts not reported by patients. LPHQ and PAH-SYMPACT capture impact on cognitive

TABLE 4] Evaluation of Evidence Supporting Psychometric Properties of Selected PH-Specific PROMs in PH Studies

Category	Property	PH-Specific PROM			
		CAMPHOR	emPHasis-10	LPHQ	PAH-SYMPACT
Item-level psychometric performance	Factor structure	Strong[16]	NA[a]	Moderate[17]	Moderate[24]
	Lack of floor/ceiling effects	Strong[16,22,25]	Moderate[26]	—	Moderate[24]
	Convergent/discriminant validity	—	NA[a]	Strong[17]	—
	Internal consistency reliability	Strong[16,22,25]	Strong[18,26-28]	Moderate[17]	Moderate[24]
Scale-level psychometric performance	Test-retest reliability	Strong[16,22,25,29]	Strong[18,26,27]	—	Moderate[24]
	Convergent/divergent validity	Strong[16,22,30,31]	Strong[18,26-28,31-34]	Weak[17]	Moderate[35]
	Known-groups validity	Strong[16,22,25]	Strong[18,26-28,34,36-38]	Moderate[17]	Moderate[24,35]
	Predictive/criterion validity	Moderate[29,30,39]	Strong[34,40]	—	—
	Responsiveness	Strong[29,31,39,41]	Weak[31]	Weak[17]	Weak[24]
	Sensitivity to treatment	Strong[41-50]	Weak[51]	Strong[52-55]	—

CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; — = no evidence available; LPHQ = Living With Pulmonary Hypertension Questionnaire; NA = not applicable; PAH-SYMPACT = Pulmonary Arterial Hypertension—Symptoms and Impact; PH = pulmonary hypertension; PROM = patient-reported outcome measure.
[a]This propery is not applicable because no subscales are scored for the emPHasis-10.

functioning, whereas LPHQ uniquely captures impacts on work and productivity, finances, and treatment side effects.

Administrative Feasibility

Administrative characteristics of the four PH-specific PROMs are presented in Table 6. Patient burden, based on survey completion time, varies greatly across the PROMs, ranging from 10 min for CAMPHOR to 2 to 3 min for emPHasis-10, with LPHQ and PAH-SYMPACT falling in between. CAMPHOR has been translated into 22 languages, whereas LPHQ currently is available only in English.

Recommendations Based on Evidence Review

Content for all four PROMs was developed following best practices by incorporating patient input to ensure capture of appropriate concepts and that instructions, items, and response choices were comprehendible. Further, almost all extant evidence supported the reliability and validity of each PROM. For the three multidomain PROMs (ie, CAMPHOR, LPHQ, and PAH-SYMPACT), evidence supported good fit of data to their proposed conceptual framework. Although currently a great amount of evidence for measurement properties of CAMPHOR exists, fewer data were available to evaluate several of the other more recently developed PROMs. As these newer PROMs are included in future studies, additional evidence will emerge, allowing for better comparisons of these properties.

Among these PROMs, CAMPHOR has been used most frequently in interventional studies. Evidence strongly supports CAMPHOR as responsive and sensitive to treatment. MWPC thresholds are established for all subscales, affording interpretation of change at the individual patient level. Comprising many more items than the other PROMs, CAMPHOR captures a much broader set of disease impacts, particularly on ADLs and physical social, as well as emotional functioning. However, it also captures several emotional impacts not reported by patients with PH, which may dilute the responsiveness of its quality-of-life subscale. CAMPHOR's 1-day recall period limits recall bias, although it also limits the clinical usefulness of the measure, requiring frequent assessments to capture change. CAMPHOR also includes a utility index that enables comparisons of cost-effectiveness across treatments. A limitation of CAMPHOR is its binary response choices for items on symptoms (yes or no) and quality-of-life domains (true or false), capturing only the presence or absence

TABLE 5] Evaluation of Conceptual Coverage of PH-Specific PROMs

Variable	No. of Qualitative Studies in That Mentioned Concept (N = 16)	CAMPHOR	emPHasis-10	LPHQ	PAH-SYMPACT
No. of items	. . .	65	10	21	23
Symptoms	. . .	. . .	. . .	. . .	. . .
SoB	7	X		X	X
Fatigue/tiredness	7	X	X	X	X
Cough	2	. . .	. . .	. . .	X
Swelling	3	. . .	. . .	X	X
Chest pain	2	. . .	. . .	. . .	X
Chest tightness	0	. . .	. . .	. . .	X
Lightheadedness/dizziness	3	. . .	. . .	. . .	X
Heart palpitations/heart racing	5	. . .	. . .	. . .	X
Difficulty speaking because of SoB	1	X	. . .	. . .	. . .
Low endurance/stamina	2	X	. . .	. . .	. . .
Loss of appetite	1	X	. . .	X	. . .
Lack of energy	1	X	X	X	X
Impacts	. . .	. . .	. . .	. . .	. . .
Physical functioning	4	. . .	. . .	. . .	. . .
Standing	0	X	. . .	. . .	. . .
Bending over	0	X	. . .	. . .	. . .
Stairs	4	X	X	X	. . .
Lifting/carrying	3	X	. . .	. . .	X
Need for rest	1	X	X	X	. . .
Slow or difficult walking	2	X	. . .	X	. . .
Walking	. . .	. . .	. . .	. . .	. . .
Flat	0	X	. . .	. . .	X
Hill	0	X	. . .	. . .	X
Interrupts conversation (SoB)	0	. . .	X	. . .	. . .
Standing up from chair	0	X	. . .	. . .	. . .
Activities of daily living	4	. . .	. . .	. . .	. . .
Personal care/dressing	3	X	. . .	. . .	X
Household chores	4	X	. . .	X	X
Gardening	1	. . .	. . .	X	. . .
Moderate activities	0	X	. . .	. . .	. . .
Vigorous activities	0	X	. . .	. . .	. . .
Leave house	0	X	. . .	X	. . .
Hobbies	1		. . .	X	. . .
Travel	3	X	. . .	. . .	. . .
Emotional functioning	16	. . .	. . .	. . .	. . .
Frustration	4	. . .	X	. . .	X
Feeling depressed	9	X	. . .	X	. . .
Anxiety	9	X	. . .	. . .	. . .
Isolation	7	X	. . .	. . .	. . .
Sadness	4	X	. . .	. . .	X
Embarrassed	3	X	. . .	. . .	. . .

(Continued)

TABLE 5] *(Continued)*

Variable	No. of Qualitative Studies in That Mentioned Concept (N = 16)	CAMPHOR	emPHasis-10	LPHQ	PAH-SYMPACT
Worry/concern	7	. . .	. . .	X	X
Loss of independence	5	X	X	X	. . .
Guilt	1	X	. . .	. . .	. . .
Disappointment	0	X	. . .	. . .	. . .
Mood swings	0	X	. . .	. . .	. . .
Hopeless	0	X	. . .	. . .	. . .
Lack of enjoyment	0	X	. . .	. . .	. . .
Lack of confidence	0	. . .	X	. . .	. . .
Lack of spontaneity	0	X	. . .	. . .	. . .
Loss of purpose	0	X	. . .	. . .	. . .
Vulnerable	0	X	. . .	. . .	. . .
Social functioning	8	. . .	. . .	. . .	. . .
Reduced time with family/friends	1	X	. . .	. . .	. . .
Sex	3	. . .	. . .	X	. . .
Feeling like a burden	3	X	X	X	. . .
Needing assistance from others	5	X	. . .	. . .	X
Maintaining relationships	3	X	. . .	X	. . .
Other impacts	. . .	. . .	. . .	. . .	. . .
Work and productivity	9	. . .	. . .	X	. . .
Financial	5	. . .	. . .	X	. . .
Cognitive functioning	5	. . .	. . .	X	X
Sleep problems	2	. . .	. . .	X	. . .
Treatment side effects	4	. . .	. . .	X	. . .
Oxygen use	0	. . .	. . .	. . .	X

CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; LPHQ = Living With Pulmonary Hypertension Questionnaire; PAH-SYMPACT = Pulmonary Arterial Hypertension—Symptoms and Impact; PH = pulmonary hypertension; PROM = patient reported-outcome measure; SoB = shortness of breath.

of a symptom or impact, and not frequency or severity. In contrast, the other PROMs use Likert or semantic differential scales that capture gradations of symptom or impact frequency or severity, producing greater variability among patients that could increase responsiveness. Because of the high patient burden, CAMPHOR likely is not optimal for use in clinical practice or patient registries where multiple PROMs are administered at many time points.

TABLE 6] Administrative Properties of Selected PH-Specific PROMs

PROM	Estimated Completion Time (min)	Translations[a]
CAMPHOR	10	22
emPHasis-10	2-3[b]	7
LPHQ	5-10[b]	1
PAH-SYMPACT	5-7[b]	11

CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; LPHQ = Living With Pulmonary Hypertension Questionnaire; PAH-SYMPACT = Pulmonary Arterial Hypertension—Symptoms and Impact; PH = pulmonary hypertension; PROM = patient-reported outcome measure.
[a]Not provided; estimate based on no. of items.
[b]Information supplied by Patient-Reported Outcome and Quality of Life Instruments Database or other website; information may be outdated.

EmPHasis-10 is very brief and has limited conceptual coverage, yielding only a global HRQoL score. It does not capture many symptoms, including dyspnea (although it does capture dyspnea impact), nor impacts on walking, ADLs, social activities, or emotions. The recall period—"recent experiences"—is ambiguous and could be interpreted differently across patients. Although evidence supports emPHasis-10 as reliable and valid, little evidence evaluates its responsiveness or sensitivity to treatment is available. Despite these limitations, emPHasis-10 was the most frequently used among these PROMs in observational studies and has

been included as an end point in several ongoing clinical studies, from which more evidence should be forthcoming. An MWPC threshold for emPHasis-10 score has been established across several studies enhancing interpretability of scores. Given the short completion time and low burden, emPHasis-10 likely would be appropriate for use in clinical practice and in observational studies, or even possibly as an add-on measure in combination with another PROM in interventional studies.

LPHQ is efficient in its conceptual capture: with 44 fewer items than CAMPHOR, and only 11 more than emPHasis-10, it covers numerous key concepts, particularly disease impacts. In addition to major symptoms (dyspnea, fatigue, swelling, and lack of energy), the LPHQ captures many impacts on physical functioning, ADL, social functioning, and emotional functioning reported by patients. Further, it alone among these PROMs captures impacts of disease on work productivity, finances, sleep problems, and treatment side effects. The 1-week recall period is fairly short, but does introduce potential recall bias. Unlike CAMPHOR and emPHasis-10, weak support exists for the reliability, construct validity, and responsiveness of the LPHQ because of the scarcity of available data. Thus, further examination is needed to evaluate its measurement properties adequately. However, findings from several interventional studies do show the LPHQ as sensitive to effective treatments. MWPC thresholds were estimated in only a single study using only distribution-based methods. The LPHQ currently is available only in English, limiting its current usefulness in global studies or in practice with non-English-speaking patients. The moderate response burden, as well as coverage of key PH symptoms and myriad impacts, indicate that the LPHQ may be appropriate for use in clinical practice or as an end point in interventional and observational studies.

Although all four PROMs evaluated herein capture cardiopulmonary symptoms, only the PAH-SYMPACT captures cardiovascular symptoms. However, although it does capture key impacts on physical and emotional functioning, it has fairly restricted assessment of impacts on ADLs and social functioning. The use of a 1-day interval for the symptoms domain, which is captured daily and averaged over 7 days, allows for capturing experiences that occur over a longer period while minimizing recall bias. Given that the PAH-SYMPACT is the most recently developed PROM among those evaluated, it is not surprising that data addressing its psychometric properties are limited. Further, the PAH-SYMPACT is the only one of these PROMs with no published data from interventional studies for assessing its sensitivity to effective treatment. Similar to emPHasis-10, the PAH-SYMPACT has been included as an end point in ongoing studies, and so more data should be available for evaluation in the near future. As it stands, the PAH-SYMPACT would seem most appropriate for use in practice and studies for which capturing cardiovascular symptoms of patients with PH is a key objective, or as an exploratory variable in interventional and observational studies that could provide data needed to evaluate its measurement properties fully.

Although we evaluated PROMs with respect to feasibility, we did not formally assess other factors that are used to inform selection of end points in clinical studies and selection of assessments in clinical practice, such as licensing acquisition and costs. Licensing fees for each PROM differ across settings (eg, industry-funded trials, clinical practice) and, even within a setting, may differ across factors such as number of administrations. Licensing fees exist for all four PROMs when used in industry-funded research, whereas none charge licensing fees when used in unfunded academic or student research. The CAMPHOR, emPHasis-10, and PAH-SYMPACT have no licensing fees when used in clinical practice, nor do CAMPHOR or emPHasis-10 in non-industry-funded academic research (although in all circumstances, regardless of funding or costs, permission is required from the Galen Institute for the use of the CAMPHOR questionnaire, including approval of the study proposal by the Galen Institute and signing of a contract).

One general limitation across all four PROMs is that their development and use mostly or solely have been restricted to some WSPH groups. Most input into the content development and evaluation of measurement properties of these PROMs was from patients with PAH, with patients with CTE and PH in a smaller number of studies and patients with other WSPH groups of PH almost completely missing. Although this reflects the current treatment landscape, with more treatments being developed and approved for patients with PAH than other groups, it also limits the generalizability of our recommendations because it is not clear whether they are appropriate for use with these other patient groups. For example, because these PROMs do not capture respiratory symptoms and impacts relevant to

patients in WSPH group 3,[58] interventional studies have attempted to capture these outcomes using respiratory-specific PROMs, such as the St. George's Respiratory Questionnaire. Yet these respiratory-specific PROMs may not be appropriate for use in studies of patients whose respiratory conditions are complicated by PH. As an example, a recent phase 3 study of inhaled treprostinil for patients with PH with interstitial lung disease found significant treatment benefit on all clinical and performance end points, yet not with the St. George's Respiratory Questionnaire.[70] This gap in measurement of PH-specific HRQoL for patients in WSPH groups 2, 3, and 5 requires potential modifications of existing PROMs, development of new PROMs that target these groups, or both.

Although this review focused on measures of PH-specific HRQoL, the importance of assessing generic HRQoL in studies of patients with PH should not be overlooked. Although disease-specific PROMs typically are more responsive, generic PROMs offer several benefits, including the ability to compare the burden of patients with PH with patients with other conditions or general population norms. This feature of generic PROMs is vital to identifying unmet clinical needs of patients with PH and to facilitate an understanding of the impact of comorbid conditions. Further, such benchmarks increase interpretability of treatment benefit by allowing assessment of not just whether patients become better, but additionally if patients become well, such that HRQoL in patients can be contextualized to the general population. Finally, generic HRQoL PROMs have a long history of use in studies of PH in which they repeatedly have been shown to concord with signs and symptoms of PH. This enables a more complete picture on how specific attributes of a disease impact everyday functional status and well-being and provide additional assessment of treatment benefit.

The current review should be considered preliminary. Several PROMs evaluated herein only recently have been developed, and more data are needed for full evaluation. Also PH-specific PROMs currently are in development that soon will merit in-depth evaluation. For example, the Pulmonary Hypertension Functional Classification Self-Report[71] is a recently developed single-item self-reported version of the World Health Organization Functional Classification that lends itself well to remote use. The recommendations proffered here should be treated as tentative rather than final. It is anticipated that an update to this review will be required within a few years.

Summary

This review identified many strengths for each of the four evaluated PROMs capturing PH-specific HRQoL. Content for all four PROMs was developed using best practices. Available evidence supports each scale as reliable and valid, but evaluation of psychometric properties for more recently developed PROMs should be considered preliminary. Although conceptual coverage and patient burden vary greatly, each PROM provided a unique strength relative to the others, and no one PROM is superior to others across all contexts of use. As a result, selection of a PROM to assess PH-specific HRQoL requires consideration of situational factors and objectives. These recommendations should be considered as a snapshot of a quickly evolving landscape that should be updated as new information emerges.

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References

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913.
2. Galiè N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J*. 2019;53(1):1802148.
3. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. *Lancet Respir Med*. 2016;4(4):306-322.
4. Mathai SC, Suber T, Khair RM, Kolb TM, Damico RL, Hassoun PM. Health-related quality of life and survival in pulmonary arterial hypertension. *Ann Am Thorac Soc*. 2016;13(1):31-39.

5. Ivarsson B, Hesselstrand R, Rådegran G, Kjellström B. Health-related quality of life, treatment adherence and psychosocial support in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. *Chron Respir Dis*. 2019;16:1479972318787906.
6. Reis A, Santos M, Vicente M, et al. Health-related quality of life in pulmonary hypertension and its clinical correlates: a cross-sectional study. *Biomed Res Int*. 2018;2018:3924517.
7. Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. *Arch Bronconeumol*. 2013;49(5):181-188.
8. Sarzyńska K, Świątoniowska-Lonc N, Dudek K, et al. Quality of life of patients with pulmonary arterial hypertension: a meta-analysis. *Eur Rev Med Pharmacol Sci*. 2021;25(15):4983-4998.
9. Shafazand S, Goldstein MK, Doyle RL, Hlatky MA, Gould MK. Health-related quality of life in patients with pulmonary arterial hypertension. *Chest*. 2004;126(5):1452-1459.
10. Taichman DB, Shin J, Hud L, et al. Health-related quality of life in patients with pulmonary arterial hypertension. *Respir Res*. 2005;6:92.
11. Cenedese E, Speich R, Dorschner L, et al. Measurement of quality of life in pulmonary hypertension and its significance. *Eur Respir J*. 2006;28(4):808-815.
12. Chen H, Taichman DB, Doyle RL. Health-related quality of life and patient-reported outcomes in pulmonary arterial hypertension. *Proc Am Thorac Soc*. 2008;5(5):623-630.
13. Delcroix M, Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. *Eur Respir Rev*. 2015;24(138):621-629.
14. Parikh KS, Rajagopal S, Arges K, et al. Use of outcome measures in pulmonary hypertension clinical trials. *Am Heart J*. 2015;170(3):419-429.e3.
15. McKenna SP, Doughty N, Pepke-Zaba J, Meads D, Doward LC. Development of patient-reported outcome measures for pulmonary arterial hypertension. *Value Health*. 2003;6(6):671.
16. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res*. 2006;15(1):103-115.
17. Bonner N, Abetz L, Meunier J, Sikirica M, Mathai SC. Development and validation of the living with pulmonary hypertension questionnaire in pulmonary arterial hypertension patients. *Health Qual Life Outcomes*. 2013;11:161.
18. Yorke J, Corris P, Gaine S, et al. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *Eur Respir J*. 2014;43(4):1106-1113.
19. McCollister D, Shaffer S, Badesch DB, et al. Development of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) questionnaire: a new patient-reported outcome instrument for PAH. *Respir Res*. 2016;17(1):72.
20. United States Food and Drug Administration. Department of Health and Human Services. Patient-reported outcome measures: use in medical product development to support labeling claims. Food and Drug Administration website. 2009. https://www.fda.gov/media/77832/download. Updated.
21. Yorke J, Armstrong I, Harries C. EmPHasis-10 is associated with clinical outcome measures in pulmonary hypertension. *Eur Respir J*. 2013;42(suppl 57):P4089.
22. Gomberg-Maitland M, Thenappan T, Rizvi K, Chandra S, Meads DM, McKenna SP. United States validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). *J Heart Lung Transplant*. 2008;27(1):124-130.
23. Currie B, Davies E, Beaudet A, Stassek L, Kleinman L. Symptoms, impacts, and suitability of the Pulmonary Arterial Hypertension—Symptoms and Impact (PAH-SYMPACT™) questionnaire in patients with chronic thromboembolic pulmonary hypertension (CTEPH): a qualitative interview study. *J Patient Rep Outcomes*. 2021;5(1):51.
24. Chin KM, Gomberg-Maitland M, Channick RN, et al. Psychometric validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) questionnaire: results of the SYMPHONY Trial. *Chest*. 2018;154(4):848-861.
25. Twiss J, McKenna S, Ganderton L, et al. Psychometric performance of the CAMPHOR and SF-36 in pulmonary hypertension. *BMC Pulm Med*. 2013;13:45.
26. Takeyasu R, Tamura Y, Abe K, et al. Psychometric validation of a Japanese version of the emPHasis-10 questionnaire, a patient-reported outcome measure for Pulmonary Hypertension—Multicenter Study in Japan. *Circ Rep*. 2020;2(4):255-259.
27. Odevoglu P, Demir R, Okumus G, Kucukoglu MS, Kuran Aslan G. Validity and reliability of the Turkish version of the emPHasis-10 questionnaire in patients with pulmonary hypertension. *J Eval Clin Pract*. 2019;25(5):896-902.
28. Banerjee D, Vargas SE, Guthrie KM, et al. Sexual health and health-related quality of life among women with pulmonary arterial hypertension. *Pulm Circ*. 2018;8(4):2045894018788277.
29. Matura LA, McDonough A, Carroll DL. Symptom interference severity and health-related quality of life in pulmonary arterial hypertension. *J Pain Symptom Manage*. 2016;51(1):25-32.
30. Bunclark K, Doughty N, Michael A, et al. A minimal clinically important difference measured by the Cambridge Pulmonary Hypertension Outcome Review for patients with idiopathic pulmonary arterial hypertension. *Pulm Circ*. 2021;11(2):2045894021995055.
31. Hendriks PM, van Thor MCJ, Wapenaar M, et al. The longitudinal use of emPHasis-10 and CAMPHOR questionnaire health-related quality of life scores in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Respir Med*. 2021;186:106525.
32. Arvanitaki A, Mouratoglou SA, Evangeliou A, et al. Quality of life is related to haemodynamics in precapillary pulmonary hypertension. *Heart Lung Circ*. 2020;29(1):142-148.
33. Kocakaya D, ; Keniş-Coşkun Ö, Şentürk-Saraç B, Yıldızeli B, Mutlu B, Karakurt S. Caregiver burden in patients with pulmonary hypertension. *Clin Nurs Res*. 20201054773820977316.
34. Lewis RA, Armstrong I, Bergbaum C, et al. EmPHasis-10 health-related quality of life score predicts outcomes in patients with idiopathic and connective tissue disease-associated pulmonary arterial hypertension: results from a UK multicentre study. *Eur Respir J*. 2021;57(2):2000124.
35. Hrustanovic-Kadic M, Ziegler C, El-Kersh K. Palliative care perception in pulmonary arterial hypertension: evaluating the interaction of PPCI, PAH-SYMPACT questionnaire, and the REVEAL 2.0 risk score. *Ann Am Thorac Soc*. 2021;18(2):361-364.
36. Tamura Y, Takeyasu R, Furukawa A, et al. How COVID-19 affected the introduction of telemedicine and patient reported outcomes among patients with pulmonary hypertension - a report from a referral center in Japan. *Circ Rep*. 2020;2(9):526-530.
37. Yorke J, Deaton C, Campbell M, et al. Symptom severity and its effect on health-related quality of life over time in patients with pulmonary hypertension: a multisite longitudinal cohort study. *BMJ Open Respir Res*. 2018;5(1):e000263.
38. Borgese M, Badesch D, Bull T, et al. EmPHasis-10 as a measure of health-related quality of life in pulmonary arterial hypertension: data from PHAR. *Eur Respir J*. 2021;57(2):2000414.
39. McCabe C, Bennett M, Doughty N, MacKenzie Ross R, Sharples L, Pepke-Zaba J. Patient-reported outcomes assessed by the CAMPHOR questionnaire predict clinical deterioration in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest*. 2013;144(2):522-530.
40. Favoccia C, Kempny A, Yorke J, et al. EmPHasis-10 score for the assessment of quality of life in various types of pulmonary hypertension and its relation to outcome. *Eur J Prev Cardiol*. 2019;26(12):1338-1340.
41. Newnham M, Bunclark K, Abraham N, et al. CAMPHOR score: patient-reported outcomes are improved by pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2020;56(4):1902096.

42. Wilkins MR, Ali O, Bradlow W, et al. Simvastatin as a treatment for pulmonary hypertension trial. *Am J Respir Crit Care Med*. 2010;181(10):1106-1113.
43. Koudstaal T, Wapenaar M, van Ranst D, et al. The effects of a 10-wk outpatient pulmonary rehabilitation program on exercise performance, muscle strength, soluble biomarkers, and quality of life in patients with pulmonary hypertension. *J Cardiopulm Rehabil Prev*. 2019;39(6):397-402.
44. Lee W-TN, Brown A, Peacock AJ, Johnson MK. Use of non-invasive haemodynamic measurements to detect treatment response in precapillary pulmonary hypertension. *Thorax*. 2011;66(9):810-814.
45. Hoole SP, Coghlan JG, Cannon JE, et al. Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: the UK experience. *Open Heart*. 2020;7(1):e001144.
46. Howard LSGE, He J, Watson GMJ, et al. Supplementation with iron in pulmonary arterial hypertension. Two randomized crossover trials. *Ann Am Thorac Soc*. 2021;18(6):981-988.
47. Humbert M, McLaughlin V, Gibbs JSR, et al. Sotatercept for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2021;384(13):1204-1215.
48. Chan L, Chin LMK, Kennedy M, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. *Chest*. 2013;143(2):333-343.
49. Bourge RC, Tapson VF, Safdar Z, et al. Rapid transition from inhaled iloprost to inhaled treprostinil in patients with pulmonary arterial hypertension. *Cardiovasc Ther*. 2013;31(1):38-44.
50. Berlier C, Schwarz EI, Saxer S, Lichtblau M, Ulrich S. Real-life experience with selexipag as an add-on therapy to oral combination therapy in patients with pulmonary arterial or distal chronic thromboembolic pulmonary hypertension: a retrospective analysis. *Lung*. 2019;197(3):353-360.
51. Hemnes AR, Silverman-Loyd L, Huang S, et al. A mobile health intervention to increase physical activity in pulmonary arterial hypertension. *Chest*. 2021;160(3):1042-1052.
52. Ying M, Song J, Gu S, Zhao R, Li M. Efficacy and safety of riociguat in the treatment of chronic thromboembolic pulmonary arterial hypertension: a meta-analysis. *Medicine (Baltimore)*. 2021;100(22):e26211.
53. Zhao R, Jiang Y. Influence of riociguat treatment on pulmonary arterial hypertension: a meta-analysis of randomized controlled trials. *Herz*. 2019;44(7):637-643.
54. Gerhardt F, Dumitrescu D, Gärtner C, et al. Oscillatory whole-body vibration improves exercise capacity and physical performance in pulmonary arterial hypertension: a randomised clinical study. *Heart*. 2017;103(8):592-598.
55. Sood N, Aranda A, Platt D, LaRose A, Kleinjung F, O'Brien G. Riociguat improves health-related quality of life for patients with pulmonary arterial hypertension: results from the phase 4 MOTION study. *Pulm Circ*. 2019;9(1):2045894018823715.
56. Armstrong I, Billings C, Kiely DG, et al. The patient experience of pulmonary hypertension: a large cross-sectional study of UK patients. *BMC Pulm Med*. 2019;19(1):67.
57. Chiang Y-C, Hu L-Y, Couper J, et al. Exploring the experiences and psychosocial stresses of Taiwanese patients with pulmonary hypertension: a qualitative interview study. *Pulm Circ*. 2018;8(3):2045894018787479.
58. DuBrock HM, Nathan SD, Reeve BB, et al. 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. *Pulm Circ*. 2021;11(2):20458940211005641.
59. Ferrari P, Armstrong I, Aldrighetti R, et al. Impact of pulmonary arterial hypertension (PAH) on the lives of patients and carers. *Eur Respir J*. 2013;42(suppl 57):P2631.
60. Flattery MP, Pinson JM, Savage L, Salyer J. Living with pulmonary artery hypertension: patients' experiences. *Heart Lung*. 2005;34(2):99-107.
61. Goddard JC, Armstrong IJ, Kiely DG, et al. Combining creative writing and narrative analysis to deliver new insights into the impact of pulmonary hypertension. *BMJ Open Respir Res*. 2017;4(1):e000184.
62. Hall H, Côté J, McBean A, Purden M. The experiences of patients with pulmonary arterial hypertension receiving continuous intravenous infusion of epoprostenol (Flolan) and their support persons. *Heart Lung*. 2012;41(1):35-43.
63. Hidayati F, Gharini PPR, Hartopo AB, Anggrahini DW, Dinarti LK. The effect of oral sildenafil therapy on health-related quality of life in adults with pulmonary arterial hypertension related to uncorrected secundum atrial septal defect: a quasi experimental study. *Health Qual Life Outcomes*. 2020;18(1):278.
64. Kingman M, Hinzmann B, Sweet O, Vachiéry J-L. Living with pulmonary hypertension: unique insights from an international ethnographic study. *BMJ Open*. 2014;4(5):e004735.
65. Matura LA, McDonough A, Aglietti LM, Herzog JL, Gallant KA. A virtual community: concerns of patients with pulmonary hypertension. *Clin Nurs Res*. 2013;22(2):155-171.
66. Rawlings GH, Beail N, Armstrong I, et al. Adults' experiences of living with pulmonary hypertension: a thematic synthesis of qualitative studies. *BMJ Open*. 2020;10(12):e041428.
67. Takita Y, Takeda Y, Fujisawa D, Kataoka M, Kawakami T, Doorenbos AZ. Depression, anxiety and psychological distress in patients with pulmonary hypertension: a mixed-methods study. *BMJ Open Respir Res*. 2021;8(1):e000876.
68. Uhlenbusch N, Löwe B, Depping MK. Perceived burden in dealing with different rare diseases: a qualitative focus group study. *BMJ Open*. 2019;9(12):e033353.
69. Yorke J, Armstrong I, Bundock S. Impact of living with pulmonary hypertension: a qualitative exploration. *Nurs Health Sci*. 2014;16(4):454-460.
70. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med*. 2021;384(4):325-334.
71. Highland KB, Crawford R, Classi P, et al. Development of the pulmonary hypertension functional classification self-report: a patient version adapted from the World Health Organization Functional Classification measure. *Health Qual Life Outcomes*. 2021;19(1):202.