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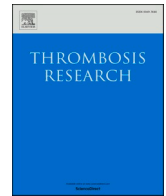
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## Review Article

# Comparison of important factors to patients recovering from pulmonary embolism and items covered in patient-reported outcome measures: A mixed-methods systematic review

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## ABSTRACT

**Objective:** Up to 50 % of patients recovering from pulmonary embolism (PE) experience negative long-term outcomes. Patient-reported outcome measures (PROMs) are important in identifying what matters to patients. We aimed to identify PROMs used in clinical studies and recommended by the International Consortium of Health Outcomes (ICHOM) and compare individual items with factors considered important by patients recovering from PE.

**Methods:** This was a convergent mixed-methods systematic review, including quantitative studies, using PROMs and qualitative studies with non-cancer-related PE patients. Items from each PROM and qualitative findings were categorised using an International Classification of Function linking process to allow for integrated synthesis.

**Results:** A total of 68 studies using 34 different PROMs with 657 items and 13 qualitative studies with 408 findings were included. A total of 104 individual ICF codes were used, and subsequently sorted into 20 distinct categories representing patient concerns. Identified PROMs were found to adequately cover 17/20 categories, including anxiety, fear of bleeding, stress, depression, dizziness/nausea, sleep disturbance, pain, dyspnea, fatigue, activity levels, family and friends, socializing, outlook on life, and medical treatment. PROMs from the ICHOM core set covered the same categories, except for dizziness/nausea.

**Conclusions:** No single PROM covered all aspects assessed as important by the PE population. PROMs recommended in the ICHOM core set cover 16/20 aspects. However, worrisome thoughts, hypervigilance around symptoms, and uncertainty of illness were experienced by patients with PE but were not covered by PROMS.

## 1. Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease globally and is a frequent cause of cardiovascular mortality [1]. It affects 1–2 per 1000 persons annually [1], and up to 50

% of patients recovering from PE experience negative long-term outcomes, often termed ‘post-PE syndrome’ [2,3]. These negative outcomes continue beyond three months after the PE event and may impact the quality of life for several years [4–8]. On a physical level, patients report dyspnea, deconditioning and exercise intolerance; psychologically, they feel hypervigilant about symptoms, are anxious and distressed [3,9–11];

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and on a social level they feel limited in their ability to participate in meaningful everyday life with leisure activities, family and work life [12,13]. Equally important, reduced physical capacity may be associated with increased cardiovascular morbidity and mortality, as well as recurrence of PE [10]. Patient Reported Outcome Measures (PROMs) are used to ascertain patients' views of their symptoms, functional status and health-related quality of life [14]. The systematic use of PROMs may promote individualized care from a bio-psycho-social perspective, as PROMs focus on what outcomes matter to patients in all aspects of life. The International Consortium for Health Outcomes Measurement (ICHOM) established a working group of expert healthcare providers and researchers to define a core set of outcome measures for VTE, the results of which were published in 2022 [14]. This included five core PROMs on global health, quality of life, and functional status: two single questions on treatment satisfaction and changes in life views; and four PROMs on pain, dyspnea, anxiety, and depression, opted in via a cascade system [15]. The majority of the 22 patient representatives invited to validate the ICHOM recommended core set of outcomes, considered it to broadly capture the important aspects that matter most to patients with VTE [15]. However, considering the heterogeneity of this patient group in terms of age, comorbidities, and health status [16], and the range of consequences reported by qualitative studies in the field, the ICHOM outcome core set may not cover the individual variation in patients' needs. Thus, a more in-depth analysis of patients' experiences, comparing them to the content of PROMs recommended by the ICHOM group and PROMs used for PE populations in clinical studies, could help clinicians and researchers select PROMs that measure what is important to the individual patient, thus facilitating patient-centered care. Therefore, this review aimed to identify whether PROMs used in clinical studies cover all aspects of patients' experiences and needs, and to what extent PROMs recommended by ICHOM cover the same aspects. The results of this review will identify possible gaps in PROMs used in research and clinical practice, thus facilitating further development, and understanding of important patient factors that should be addressed in future research and clinical practice.

The aim of this mixed-methods systematic review was to assess to what extent PROMs, used in clinical research in PE, cover aspects reported to be important for patients during their recovery, and to what extent these PROMs as recommended by ICHOM cover the same aspects.

## 2. Material and methods

A convergent mixed-methods review design was applied [17], collecting qualitative and quantitative data simultaneously, followed by an integrated synthesis of the data. Prior to data extraction, the review was registered online in PROSPERO (CRD42022353938), it is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Guidelines (PRISMA) [18].

### 2.1. Study selection

This review included studies performed in a primary-, secondary-, or tertiary health care setting, published in English, Danish, Swedish, Norwegian, or Dutch. We included articles fulfilling the following criteria: studies including adult patients (>18 years) who had experienced at least one PE, reporting either quantitative outcome using at least one PROM related to PE or qualitative outcomes related to patients' experiences following PE. Studies including a VTE patient cohort without reporting the distribution of PE ± DVT or DVT patients and studies primarily focused on cancer-associated PE, where cancer was the focus, were excluded.

### 2.2. Literature search strategy

A systematic search using a three-step search strategy, was performed. An initial search was performed in PubMed to identify relevant

text words and subject headings. Based on the identified keywords: 'pulmonary embolism', 'patient-reported outcome measures' or 'qualitative interviews' a search strategy was developed in collaboration with a research librarian, and performed in PubMed, Cinahl, Embase, PEDRO, Cochrane and PsychInfo.

All databases were searched from inception to final search date, and the search was re-run prior to final analysis. Reference lists of eligible studies and review articles, trial registers (i.e. [clinicaltrials.gov](https://www.clinicaltrials.gov)) and conference abstracts were consulted to identify further eligible studies for inclusion. After removing duplicates, titles and abstracts were independently screened by two authors (SIM and CKC) using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Discrepancies in studies identified for inclusion were settled by convening the research group to reach a consensus. Full text article review and data extraction were undertaken by SIM and CKC.

### 2.3. ICHOM recommended outcome measures

All nine PROMs recommended in the ICHOM core set of outcome measures were included in the review and compared with the findings from the qualitative studies using the ICF-linking rules described below. The ICHOM recommended PROMs are as follows: Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form Global Health [19], Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire [20], Venous Insufficiency Epidemiological and Economic Study on Quality Of Life (VEINES-QOL) questionnaire [21], Post-Venous Thromboembolism Functional Status (PVFS) scale [22], PROMIS short form v2.0 Pain intensity 3a [23], PROMIS Short Form v1.0 Dyspnea Severity 10a [24], Patient Health-Care Questionnaire-9 (PHQ-9) [25], Generalized Anxiety Disorder-7 (GAD-7) [26] and the Anti-Clot Treatment Scale (ACTS) [27].

### 2.4. Data extraction and quality assessment

Data was charted on PROM characteristics (PROM name, purpose and articles cited), presented in Table 1, and for qualitative studies (article, sample size, percentage of PE in cohort, age of informants and time since VTE diagnosis), presented in Table 2. For data charted on article (title, year, country and first author) and participants (sample size and age) for all identified articles, please refer to Appendix 1. Each specific item/question from unique PROMs and findings from qualitative studies as well as items from the PROMs and the two questions recommended by ICHOM [15] were extracted and entered in an excel spreadsheet (Appendix 2) in preparation for data synthesis.

One change was made to the protocol after registration. As the aim of this review was to evaluate the intrinsic properties of the PROMs, not the effect of interventions, the review team did not consider that the intended quality assessment of articles reporting the use of PROMs would provide any added value to the review process. The Joanna Briggs Institute checklist for Qualitative studies [28] was used to assess the quality of included qualitative studies.

### 2.5. Data synthesis

This mixed-method review employed an integrated design. The first step was to categorise the findings from qualitative studies and items from PROMs according to the International Classification of Functioning, Disability and Health (ICF) classification browser [29] by the primary investigator (SIM). The ICF classification browser [29] is structured in categories; bodily functions (b), body structure (s), activity, and participation (d), environmental factors (e) and personal factors (pf). Each category, except for personal factors, is subdivided into chapters covering specific topics within each category, and each topic is further subdivided into specific codes and subcodes. The most specific code or subcode available that best described each item and finding was selected. For example, there is no subcode for anxiety, so it was classified

**Table 1**  
Included PROMs and measurement properties.

PROM	Measurement properties	Studies used
Anti-Clot Treatment Scale (ACTS)	Disease-specific (VTE) measure satisfaction with anticoagulant treatment [27]	[15,36]
Beck's Depression Inventory (BDI)	Disease-generic measure of depression [37]	[38]
Brief Fatigue Inventory (BFI)	Disease-specific (cancer) assessment of fatigue severity in cancer patients [39]	[40]
Medical Outcomes Study 6-Item Cognitive Functioning Scale (CFS)	Disease-generic assessment of cognitive function [41]	[42]
Checklist Individual Strength-Fatigue (CIS)	Disease-generic assessment of fatigue, and its impact on daily activities and quality of life [43]	[44]
Chronic Respiratory Questionnaire - CRQ	Disease-generic assessment of health-related quality of life in chronic respiratory disease [45]	[46]
Depression, Anxiety and Stress Scale (DASS21)	Disease-generic assessment of stress, anxiety and depression [47]	[40]
EuroQoL 5 Dimension Health-related quality of life (EQ. 5D-5 L)	Disease-generic assessment of health-related quality of life at five levels of severity, in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety & depression) [48]	[49–60]
EuroQoL 3 Dimension Health-related quality of life (EQ-5D-3L)	Disease-generic assessment of health-related quality of life at three levels of severity, in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety & depression) [61]	[62–65]
Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)	Disease-generic assessment of fatigue [66]	[36]
Generalized Anxiety Disorder-7 (GAD-7)	Disease-generic assessment of generalized anxiety disorder [26]	[15,67]
Hospital Anxiety and Depression Scale (HADS)	Disease-generic assessment of depression and anxiety in the setting of medical practices [68]	[42,44,46,56,59,67,69–73]
Health Anxiety Inventory (HAI)	Disease-generic assessment of health anxiety and hypochondriasis [74]	[72]
Lawton-Brody Instrumental activities of daily living (IADL)	Disease-generic assessment of independent living skills [75]	[70]
Impact of Event Scale (IES)	Disease-generic assessment of the level of subjective stress, related to a specific event [76]	[70,72]
Internal health locus of control (IHLC)	Disease-generic assessment of global control over health [77]	[78]
Brief illness perception questionnaire (IPQ)	Disease-generic assessment of cognitive and emotional representation of illness [79]	[72]
Multidimensional Fatigue Symptom Inventory (MFSI-SF)	Disease-specific (cancer) assessment of fatigue and its impact on quality of life [80]	[73]
Multidimensional Health Locus of Control - Form C (MHCL)	Disease-generic assessment of subjective control of health [81]	[42,71]
Modified MRC Dyspnea Scale (mMRC)	Disease-specific (chronic obstructive pulmonary disorder) assessment of dyspnea and its impact on physical function [82]	[56,67]
Perception of Anti-Coagulant Treatment Questionnaire (PACT-Q)	Disease-generic assessment of patients expectations of, and satisfaction with anticoagulant treatment [83]	[55]
Pulmonary Embolism Quality of Life (PEmb-QoL)	A disease-specific (PE) assessment of quality of life [20]	[2,3,10,15,32,35,44,46,49,50,53,56,58–60,63,64,84–98]
Patient Health Questionnaire (PHQ-9)	Disease-generic assessment of depression [25]	[15]
Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form v 1.0 Dyspnea Severity 10 a	Disease-generic assessment of dyspnea severity and related functional limitation [24]	[15,67]
Patient-Reported Outcomes Measurement Information System General Health (PROMIS-GH)	Disease-generic assessment of general perception of health [19]	[15]
Patient-Reported Outcomes Measurement Information System - Short Form v2.0 Pain Intensity 3a	Disease-generic assessment of pain intensity [23]	[15,67,99]
Pittsburg sleep quality index (PSQI)	Disease-generic assessment of sleep quality [100]	[101]
Penn State Worry Questionnaire (PSWQ)	Disease-generic assessment of worry [102]	[69]
Post-Venous Thromboembolism Functional Status (PVSF)	Disease-specific (VTE) assessment of functional limitations [22]	[15,67,90,103]
Rosenberg self-esteem scale (RSES)	Disease-generic assessment of self-esteem [104]	[105]
The Optum Health Survey Short Form Health Survey 12 items (SF-12)	Disease-generic assessment of general health [106]	[58,71,73]
The Optum Health Survey Short Form Health Survey 36 items (SF-36)	Disease-generic assessment of general health [107]	[2,32,58,70,84,85,89,93,97,98,103,105,108–118]
Shortness of Breath Questionnaire (SOBQ)	Disease-generic assessment of dyspnea [119]	[2,56,84,120]
State-Trait Anxiety Inventory (STAI)	Disease-generic assessment of anxiety [121]	[38]
The Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms (VEINES-QoL)	Disease-specific (VTE) assessment of quality of life [21]	[15,35,49,52,53,58,64,99,111,112,117,122]

under the category bodily functions with the specific code b1522: 'Range of emotion'. For personal factors, all items and findings were coded as 'pf'. In the instances where one item or finding covered more than one aspect of the patients' experience, a conservative approach was taken to avoid dismissing any categories prematurely, categorising it to all relevant ICF codes. The second step employed an ICF linking process

[17,30], where each individual ICF code selected for the PROM items was compared with each individual ICF code selected based on the qualitative findings to determine if the PROM items adequately covered the patients' concerns. For example patients in the study by Danielsbacka et al. [31], reported dyspnea as an ongoing symptom following PE and was coded b460 'Sensations associated with cardiovascular and

**Table 2**  
Included qualitative studies.

Study	# informants	%PE	Age	Time since VTE diagnosis
Danielsbacha, 2021 [31]	14	100 %	60 (47–70)	3–34 months
Etchegary, 2008 [130]	13	38.5 %	60 (45–71)	6 months to 4 years
Feehan, 2017 [123]	17	58.8 %	n.a.	4 months to >2 years
Hernandez-Nino, 2022 [133]	21	100 %	18–70	6 months to >2 years
Højen, 2016 [134]	12	75 %	24.8 ± 4.9	6 months to 13 years
Hunter, 2017 [124]	12	75 %	18–68	6 months
Hunter, 2019 [125]	11	75 %	18–69	9 months
Kirchberger, 2020 [126]	18	100 %	26–82	≤3 months to ≥4 years
Noble, 2014 [127]	9	100 %	26–72	9–60 months
Rolving, 2019 [4]	16	100 %	34–78	6–12 months
Rolving, 2020 [128]	16	100 %	34–78	6–12 months
Tran, 2021 [132]	37	100 %	28–85	n.a.
Ven De Brug, 2022 [129]	18	44 %	32–83	1–15 months

n.a. not described in the study.

Age median (range) or ± SD.

%PE: where the cohort is a mix of PE and DVT patients.

respiratory functions' matching the item 'Difficulty in breathing or breathlessness?' from the PEmb-QoL [32] also coded b460. The items were considered to be general (i.e. pain) or specific to PE (i.e. respiratory pain) and if there was no PROM item matching a specific finding in a qualitative study, that aspect of patients' experience was considered inadequately covered by the identified PROMs. The ICF linking rules has previously been used successfully to compare the content of PROMs used for heart diseases [33].

To increase the validity of the ICF linking process, a close collaboration between the main author and the author group was maintained throughout. Initial quality assurance was performed on the PEmb-QoL [32] to clarify any uncertainty in the coding process by three of the authors (SIM, JA and NR) and discussed by the author group. The main author (SIM) then performed the linking process comparing items for five PROMs and findings from five qualitative studies and presented the findings to the author group. Any disagreements on linked items and findings were discussed and a consensus was reached before the linking process was performed for the remaining PROMs and qualitative studies. A synthesis of the results of the ICF linking process and data analysis is presented under each of the five ICF domains: body function, activity, participation, environmental- and personal factors [34] and the codes for all PROM items and qualitative findings can be found in appendix to provide transparency of the process.

### 3. Results

The systematic literature search produced a total of 6.217 articles and an additional 22 articles were identified by screening reference lists of included studies. Following removal of duplicates, a total of 4.813 abstracts and titles were screened, and 4.663 articles were excluded with the most common reasons for exclusion being DVT cohort, studies with epidemiologic or diagnostic outcome, VTE prophylaxis, and patient satisfaction surveys after surgery where PE was mentioned as an adverse event. The remaining 129 quantitative studies using PROMs and 22 qualitative full text articles were scrutinized and reasons for exclusion are provided in Fig. 1. In total 68 articles using PROMs and 13 qualitative studies were included in the review.

(PRISMA) flow diagram illustrating study selection process. PROM: Patient-reported outcome measure, PE: Pulmonary Embolism, HCP: Health care professional, DVT: Deep Vein Thrombosis.

#### 3.1. Identified PROMs through data extraction

Individual PROMs that were singularly focused on DVT (i.e. leg symptoms) were excluded, including the DVTQOL, VTQOL, SQOR-V [35]. A total of 34 PROMs were identified and are presented in Table 1.

#### 3.2. Qualitative studies

Thirteen qualitative studies were identified from the systematic search and one additional study [123] was identified reviewing reference lists (Table 2). The studies were primarily conducted in Europe [4,5,31,124–129] and the North Americas [123,130–132].

#### 3.3. Quality of included studies

The quality of the included qualitative studies was generally considered good (Table 3). The most common downgrades were explained by a failure to describe the interviewers cultural or theoretical position [4,31,123–125,130,133,134] or their influence on the research [4,31,123–125,130,134]. Only one study [134] reported their philosophical perspective and two studies [128,133] were rated not to show an adequate representation of their patients views.

#### 3.4. Integrated synthesis

A total of 104 individual ICF codes were used to code 657 items from 34 individual PROMs and 408 findings from 13 qualitative studies (Appendix 2). During data synthesis, 20 distinct categories representing patients' concerns were identified, divided over four ICF categories as presented in Table 4. No ICF codes were identified addressing environmental factors; these are therefore not described. Each individual patient concern and which PROMs covers that specific concern will now be presented for each of the four ICF categories (Fig. 2).

##### 3.4.1. Body functions

The emotional impact of recovering from PE were the most common findings for the category 'bodily function', cited in all 13 qualitative studies [4,29,121–123,125–130,133,134]. Anxiety, usually caused by uncertainty in the risk of another PE event [4,29,121–123,125,126,130,133–135] is only specifically covered in the PEmb-QoL, while questions about general feelings of anxiety are covered in 13 of the PROMs: BDI, DASS-21, EQ5D-5 L/3 L, GAD-7, HADS, HAI, IES, IPQ, MFSI, PROMIS-GH, PVSF, SF-36, and STAI. The feeling of anxiety was often spurred on by a hypervigilance around bodily sensations [4,121–124,133], which is only covered in HAI. Fear of bleeding in relation to anticoagulation treatment has been mentioned [121,124] and is covered specifically in ACTS. Feelings of stress [4,122,124,127,130] were not directly covered in any of the identified PROMs, but indirect items covering irritability and anger were found in five of the PROMs: BDI, DASS-21, GAD-7, PEmb-QoL, and PROMIS-GH. Feelings of depression, mentioned in two qualitative studies [121,124], were covered in 12 PROMs: BDI, BFI, DASS-21, EQ5D-3 L/5 L, FACIT-F, IPQ, MFSI, PEmb-QoL, PHQ-9, SF-12 and SF-36. Worrying thoughts, described as ruminations about having another PE and the potential lethal outcome [4,122,123,133], were considered intrusive by some patients and could trigger flashbacks for others, reminiscent of post-traumatic stress disorder (PTSD) [125]. The IES PROM was developed particularly to identify symptoms of PTSD [74] and specifically asks about this type of content of mind, while the PSWQ is focused on worrying behaviour in general [100], while the HADS has one question about worrying thoughts. Other patients experience trouble sleeping due to the emotional distress they experience [4,124]. Here, PSQI

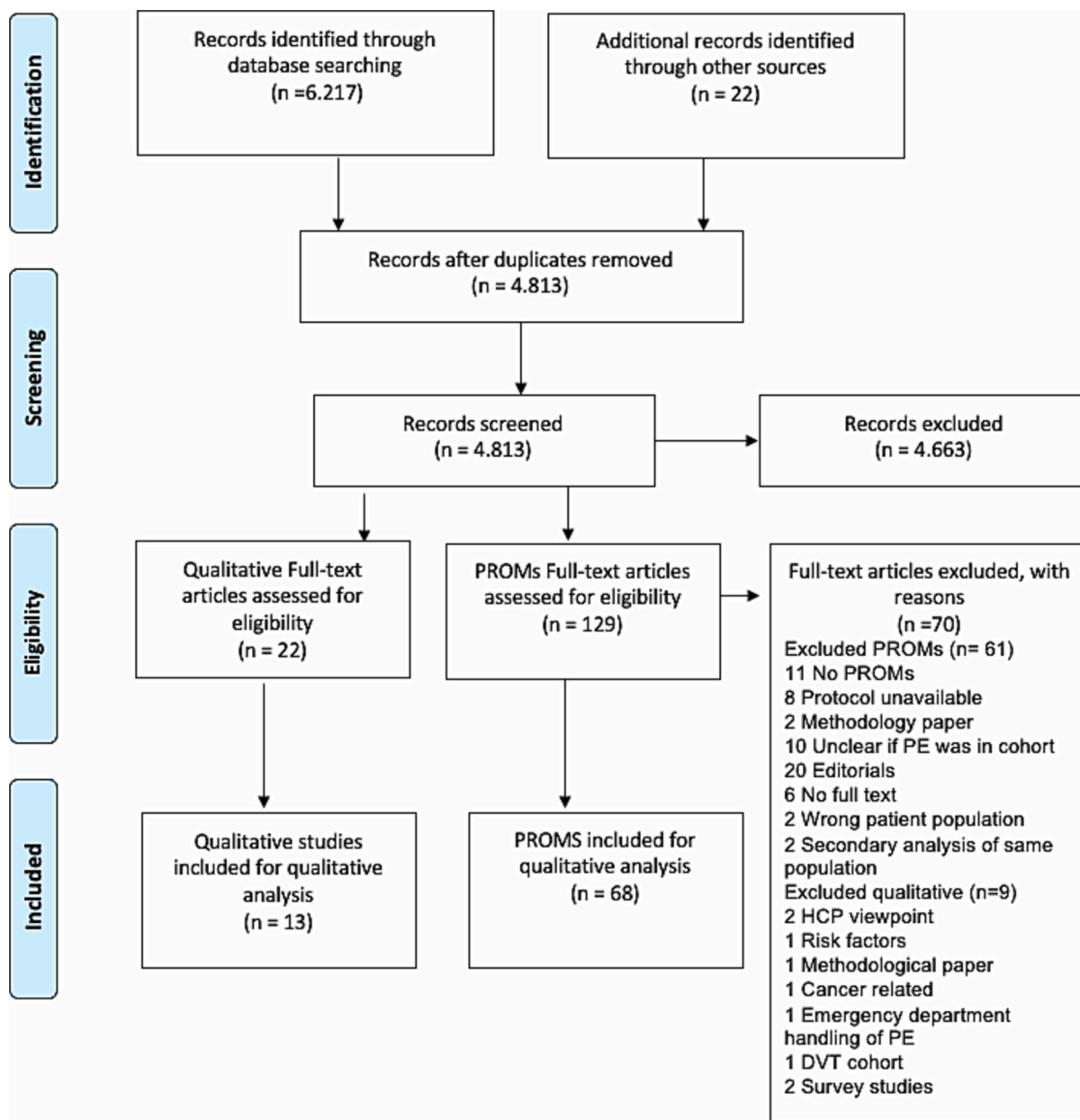


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses.

Table 3

Critical appraisal of methodological quality according to the JBI Critical Appraisal checklist for Qualitative studies.

Study (first author, year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Danielsbacha, 2021 [31]	N	Y	Y	Y	Y	N	N	Y	Y	Y
Etchegary, 2008 [130]	N	N	Y	Y	Y	N	N	Y	Y	Y
Feehan, 2017 [123]	N	Y	Y	Y	Y	N	N	U	Y	Y
Hernandez-Nino, 2022 [133]	N	Y	Y	Y	Y	N	Y	N	Y	Y
Hojen, 2016 [134]	Y	Y	Y	Y	Y	N	N	U	Y	Y
Hunter, 2017 [124]	N	Y	Y	Y	Y	N	N	Y	Y	Y
Hunter, 2019 [125]	N	Y	Y	Y	Y	N	N	Y	Y	Y
Kirchberger, 2020 [126]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Noble, 2014 [127]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Rolving, 2019 [4]	N	Y	Y	Y	Y	N	N	Y	Y	Y
Rolving, 2020 [128]	N	Y	Y	Y	Y	Y	Y	N	Y	Y
Tran, 2021 [132]	N	Y	Y	N	N	Y	Y	Y	Y	Y
Ven De Brug, 2022 [129]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y

(Y)es, (N)o, (U)nclear, N/A Not applicable.

**Table 4**  
ICF Categories, definitions and categories identified during data synthesis.

ICF category	ICF category definition [29]	Integrated synthesis category
Bodily functions	The physiological functions of body systems (including psychological functions)	Anxiety Fear of bleeding Hypervigilance around symptoms Stress Depression Worrisome thoughts Sleep disturbance Pain Dizziness/nausea Dyspnea Fatigue
Activity	The execution of a task or action by an individual.	Activity levels
Participation	An individual's involvement in a life situation.	Family and friends Work Leisure activities Socializing
Personal factors	An individual's knowledge and education, personality and self-construal, sense of control, values, political and world views and goals	Outlook on life Self-image Uncertainty (about information) Medical treatment
Environmental factors	The physical, social and attitudinal environment in which people live and conduct their lives.	

thoroughly explores the subject of sleep quality and an additional five PROMs, namely BDI, FACIT-F, IES, MFSI and PHQ-9, all of which have single questions related to sleep.

Ongoing pain was a common bodily sensation with respiratory pain [29], pain in the chest, upper back, neck, and shoulders [124,128,130]. The PEmb-QoL has a wide range of questions covering pain both in specific body parts as well as respiratory pain. General questions about pain was found in 6 of the PROMs: EQ5D-3 L/5 L, FACIT-F, HAI, MFSI, and SF-12. The PVSF has a single question about the interference of pain on everyday life, while four of the PROMs, PEmb-QoL, SF-36, PROMIS-GH and PROMIS-Pain Severity, allows patients to rate their level of pain. Other bodily sensations included dizziness [126,130], covered with a single question in MFSI, and nausea [130], likewise covered with a single question in FACIT-F. Persisting dyspnea was pervasive for many patients [29,123,126,127,130,136], sometimes even progressing and being present both during exercise as well as at rest [124]. The three PROMs MRC, SOBQ and PROMIS-Dyspnea scale have been specifically developed to address different aspects of dyspnea. Another four PROMs, DASS-21, IES, MFSI, and MRC, all have a general question about breathlessness while the PEmb-QoL allows the patient to score how much breathlessness has been experienced during the past four weeks.

The ongoing symptoms resulted in fatigue, lack of energy to take part in everyday activities [4,124] or work [29]. Here, the BFI and CIS questionnaires are purposefully developed to explore the impact of fatigue, while the MFSI has a fatigue subscale for this purpose. The FACIT-F has several questions dedicated to energy levels, while PROMIS-GH lets patients rate their level of fatigue.

In summary, the impact of PE on bodily functions included both affective and physical consequences for patients. Emotional distress, hypervigilance around symptoms and worrisome thoughts were the most prominent affective consequences, while pain and dyspnea were the most common physical consequences described by patients. Several aspects of emotional status, pain and dyspnea are covered in a wide range of disease-specific and disease-generic PROMs, while hypervigilance around symptoms and worrisome thoughts were only covered by a few disease-generic PROMs.

### 3.4.2. Activity

Uncertainty about, or fear of symptoms led some patients to decrease their physical activity levels [4,126,127,129] by for example taking a bus instead of walking or avoiding stairs [31]. Others would avoid recreational activities and daily duties [135] or in general do less than they used to do before their PE [4]. Activity levels are covered by 17 PROMs where the six PROMs FACIT-F, GAD-7, PACT-Q, PROMIS-GH, PVSF, SF-12 include questions on a more general level. Seven PROMs - EQ5D 3 L/5 L, MRC, SF-36, PROMIS-Dyspnea, SOBQ, and VEINES-QoL - have more detailed activities like kneeling, lifting/carrying, walking/running, washing/dressing. The last category of PROMs has both general level and specific activities (BFI, IADL, MFSI, PEmb-QoL).

Activity levels was found to be the focus of the majority of the PROMs identified from the level of general activity to more specific tasks and activities.

### 3.4.3. Participation

The impact of PE on family relationships was complex and had both positive and negative impact on patients' lives. Some patients felt that the seriousness of the illness presented a burden to their families and tried to protect them from it [4,31,125,126]. Other patients shared their concerns with their relatives and experienced support [4,132]. In some cases, sharing their concerns with family members, could lead to increased worry and overprotective behaviour towards the patient [126,130]. Relationships with family and friends are covered in nine PROMs: BDI, BFI, FACIT-F, HAI, PHQ-9, PROMIS-GH, MFSI, SF-36 and VEINES-QoL. The negative impact of ongoing symptoms after PE on work, was highlighted by some patients [4,31,126,128], and general questions about work ability can be found in the nine PROMs BDI, BFI, FACIT-F, PEmb-QoL, PVFS, PROMIS-GH, SF-12, SF-36 and VEINES-QoL.

Leisure activities such as travelling [4,130,133,136] and sports [4,126] felt unsafe due to the risk of recurrence and bleeding [127] and was subsequently curtailed by some patients. General questions about the ability to participate in usual activities can be found in the five PROMs EQ5D-3 L/5 L, PVFS, SF-36 and VEINES-QoL. The PEmb-QoL has specific questions about sports and travel, while ACTS has questions about limiting participation due to risk of bleeding.

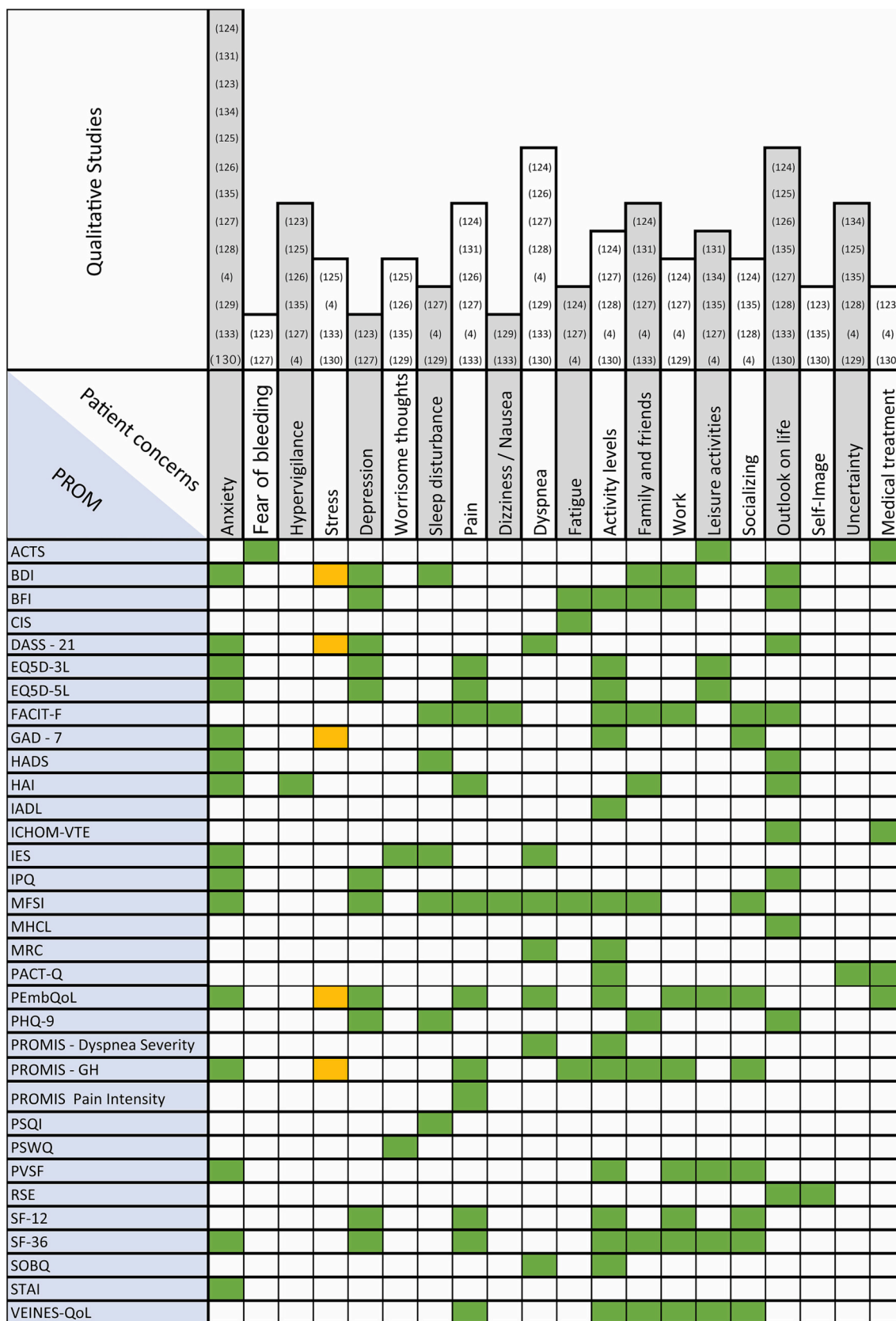
Social activities were increasingly more difficult to attend for some patients [4,31,127,137] leaving them feeling isolated and in need of a social support network [31]. Questions about patients' ability to partake in general social activities are covered in the nine PROMs FACIT-F, GAD-7, MFSI, PEmb-QoL, PROMIS-GH, PVFS, SF-12, SF-36 and VEINES-QoL.

In summary, ongoing symptoms and fear of further negative outcomes limited patients from partaking in work, travel, sports- and leisure activities. Furthermore, the seriousness of PE put a strain on family relations and could lead to social isolation. Participation was covered by a subset of the identified PROMs.

### 3.4.4. Personal factors

Realising the seriousness of PE led patients to change their outlook on life [132,138]. Some would see it as a second chance and would make positive lifestyle changes like changing career or leading a more healthy life [31,124–127]. For others, it was a source of concern [125], reminding them about their own mortality [124,136] and frequent medical follow-ups reinforced these concerns [124]. General questions about patients' outlook on life can be found in ten of the PROMs: BDI, BFI, DASS-21, FACIT-F, HADS, HAI, IPQ, MHCL, PHQ-9, RSE and the ICHOM group recommends asking a single question regarding patients' expectations, aspirations, values, or perspectives on life since the diagnosis of VTE. Some patients experienced a feeling of loss of trust in their own bodies [138] and a changed self-image [4,123,136]. While these outcomes were not covered directly in any PROMs, the RSE covers the patients' confidence in themselves which could be considered a proxy.

Lack of information caused uncertainty about the risk of recurrence versus the risk of antithrombotic treatment leading to anxiety and frustration [124]. The need for more information both during the initial



**Fig. 2.** Displaying the results of the ICF linking process showing to what extent the 34 PROMs (vertical rows) cover 20 categories of what is important to patients recovering from pulmonary embolism (PE) (horizontal columns) as expressed by patients in 13 qualitative studies (bars). Green markings indicate the category is covered adequately in the specific PROM and orange markings a partial match. A white marking indicates no match between the PROM and the specific category. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



consultation [4,124,127,128] and following discharge [123] was considered a way to reduce this uncertainty. Likewise, having peer support [125,127,128,136], the ability to self-monitor for risk of recurrence [123], and the possibility to speak to a health care professional following discharge [128] could help reduce the feeling of uncertainty. PACT-Q has some specific questions about the satisfaction of treatment but otherwise none of the identified PROMs touched uncertainty or if the patients felt sufficiently informed about their condition.

Medical treatment was another aspect of post-PE management that occupied patients. In particular, not understanding or accepting the balance between the higher risk of bleeding, versus the lower risk of VTE recurrence could cause concern [138]. Once patients were told to stop taking medication, fear and anxiety of recurrence would resurface [4,123,126]. ACTS and PACT-Q were specifically tailored to cover the experience of antithrombotic treatment, while the PEmb-QoL has a single question about worry associated with stopping anticoagulant medicine. The ICHOM recommends a similar single question and if the patient reports dissatisfaction with medical treatment, ICHOM further recommends administering ACTS to allow patients to supply further information if they have any dissatisfaction with medical treatment.

In summary, several personal factors were identified including a change in outlook on life and self-identity while lack of information and uncertainty around medical treatment led to further anxiety. Apart from anticoagulant therapies, these aspects were not adequately represented in the PROMs identified.

### 3.4.5. ICHOM

Fig. 3 displays the items from the international standard set of outcome measures for VTE as, compared with the findings from the qualitative studies. The cumulative items from the eight PROMs ACTS, GAD-7, PEmb-QoL, PHQ-9, PROMIS-GH/Pain severity/Dyspnea severity and VEINES-QoL as well as two specific questions, recommended by ICHOM [15] covers most of the findings from the qualitative studies. However, hypervigilance, worrisome thoughts, dizziness/nausea and uncertainty about medical information are not covered in the recommended outcome measures.

## 4. Discussion

The aim of this mixed-methods review was to explore the extent to which items from PROMs currently used in clinical research and PROMs recommended by the ICHOM group cover what is important to patients recovering from PE, viewed through the bio-psycho-social lens of the ICF framework. Twenty categories were identified from the data analysis, showing how PE impacts patients at the ICF-levels bodily functions, activity, participation, and personal factors. No single PROM was found to cover all categories of what was considered important by patients, but the PEmb-QoL and MFSI each covered ten categories. If the eight PROMs recommended by the ICHOM are used, 16 categories are covered. Based on the pooled findings, the issues experienced by patients seemed to be tightly connected. A tentative line can be drawn from the initial shock of diagnosis through how affective and physical symptoms impact all areas of patients' lives, leading to social isolation and poor mental health. These issues are further compounded by patients struggling to make sense of their situation. It may therefore be important that clinicians do not compartmentalise patients' experiences into categories based on the PROMs used but consider what aspects of patient disease is most important to them and measure progress in line with their needs.

The fact that this review identified 36 different PROMs used in 68 clinical studies shows a lack of consistency in selecting outcome measures, making it difficult to evaluate the effect of interventions between studies and gather pooled knowledge about PE patients through PROMs. The work of the ICHOM group is an important step in the right direction in defining an outcome set, including PROMs that cover most aspects considered important to patients following PE. Clinicians might be concerned that using eight PROMs to evaluate a patient's health condition is a burden to patients [139]. However, patients show little concern regarding the number of, or length of PROMs as long as they are relevant to their condition [140]. Therefore, it is crucial that the content validity of PROMs is established to ensure relevance to a PE population. If, due to time constraints [139], clinicians do not find it feasible to use all eight PROMs recommended by the ICHOM, a minimalized set of

Patient concerns PROM	Anxiety	Fear of bleeding	Hypervigilance	Stress	Depression	Worrisome thoughts	Sleep disturbance	Pain	Dizziness / Nausea	Dyspnea	Fatigue	Activity levels	Family and friends	Work	Leisure activities	Socializing	Outlook on life	Self-image	Uncertainty	Medical treatment
	ICHOM PROMs Combined	Green	Green	Green	Orange	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
ACTS	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
GAD - 7	Green	Green	Green	Orange	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
ICHOM-VTE	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
PEmbQoL	Green	Green	Green	Orange	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
PHQ-9	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
PROMIS - Dyspnea Severity	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
PROMIS - GH	Green	Green	Green	Orange	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
PROMIS Pain Intensity	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
PVSF	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
VEINES-QoL	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green

Fig. 3. Displaying the results of the ICF linking process showing to what extent the nine PROMs and two specific questions recommended by ICHOM as part of the international standard set of outcome measures for VTE cover 20 categories of what is important to patients recovering from pulmonary embolism (PE) (horizontal columns) as expressed by patients in 13 qualitative studies (bars). Green markings indicate the category is covered adequately in the specific PROM and orange markings a partial match. A white marking indicates no match between the PROM and the specific category. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

outcomes using the four PROMs PEmb-QoL, ACTS, PhQ9, and PROMIS GH, cover the same number of categories as the full set. When considering single PROMs, the PEmb-QoL and MFSI were both found to cover ten of the 20 identified categories. The latter, however, is a disease-generic PROM developed for fatigue with 83 items [80] and was only used in a single PE study [73]. PEmb-QoL on the other hand is a disease-specific PROM developed specifically for PE [20] making it more relevant to patients. Furthermore, disease-specific PROMs appear to be more sensitive to changes over time than disease-generic PROMs [141], making them a better tool for measuring progress. It should be noted that PEmb-QoL might underestimate fear of recurrence and self-imposed social restrictions [133]. Finally, if the goal is simply to measure functional limitations after PE, the PVSF is considered clear and relevant by experts [22]; however, its psychometric properties have not yet been established in a PE cohort. Another important point to consider is the distinction between PROMs that measure outcomes and PROMs that measure the symptom burden. PEmb-QoL, for example, has questions concerning anxiety [20] but is insufficient to evaluate the severity of anxiety. Therefore, if a clinician suspects anxiety as playing a role in a patient's condition, either based on the PEmb-QoL or clinical suspicion, a more specific PROM like GAD-7 can be employed to quantify the amount of anxiety and diagnose anxiety disorder [26].

The findings concerning the qualitative studies are supported by a recent scoping review where VTE was shown to impact patients' daily lives, cause continued psychological distress, challenge medical management, and frustrate patients due to lack of information [7]. The mental health impacts of anxiety, depression, and PTSD were also highlighted specifically in PE in another review [142], further emphasizing the importance of identifying mental health issues and targeting treatment accordingly [123]. Although PROMs were found to cover most of the categories identified, there are still a few blind spots, which may cause concern in terms of treatment plans and stimulate new areas of research.

Uncertainty was a recurring theme in qualitative studies. Some patients felt uncertain about the risk of recurrence [134], the underlying cause of PE [126], safety of physical activity [126], treatment duration, and risk factors for bleeding [124]. For these patients, uncertainty led to emotional distress, particularly anxiety and stress [127], reinforcing fears of recurrence and causing patients to become socially isolated [124]. At the same time, other patients used the PE as a springboard prompting positive lifestyle changes [124,127]. Another cause of uncertainty in some patients was the perceived lack of information [4,126], leading to poorer self-management [123,124]. Although not explicitly explored in any of the studies, a possible explanation for the difference in how patients manage their symptoms could be the tolerance of uncertainty. Intolerance of uncertainty is a measure of how people deal with emotional, cognitive, and behavioural reactions to ambiguous situations [143], and a previous study has shown a clear correlation between uncertainty and anxiety [144]. This may partly explain why some patients experience anxiety following PE, while others who might be more tolerant to uncertainty do not.

Hypervigilance around symptoms caused anxiety in several patients [4,123–126,136] and was not adequately covered by the identified PROMs. To the knowledge of the review team, there are no PROM specific to hypervigilance around symptoms or worrisome thoughts. Dizziness and nausea were not covered by any PROMs; however, considering that only two patients [4,132] mentioned these symptoms, it is possible that it is not a generic ongoing symptom after PE. Surprisingly, sexual health was not covered in any of the identified PROMs, although poor sexual health has been linked to poor quality of life in pulmonary arterial hypertension, a serious complication experienced by many patients following PE [145]. Indeed, a European consensus document on follow-up of PE survivors stressed the need for routine assessment of sexual problems [146].

The main strength of this mixed-methods review is the rigorous systematic literature search, identifying additional PROMs compared to

previous work [15] using two reviewers for all steps, from the literature search to data extraction and quality assessment. One of the main limitations of this mixed-methods review is that the data from the qualitative interviews are not based on raw data but on the content, quotes, and themes in the published articles. However, considering that findings in all 20 categories were identified by at least two independent qualitative studies, this supports the validity of the findings presented. The decision to exclude PROMs focusing on leg symptoms related to DVT was made due to the aim of this study is on PE. It is however not known if concomitant symptomatic DVT is a relevant determinant on long-term outcomes for PE, in which case including PROMs covering leg symptoms will be relevant. Another limitation is that the qualitative studies were mainly conducted in a Caucasian population set in a Western context, and it is therefore not clear if these results can be applied to other contexts. The review did not assess the psychometric properties (i. e., reliability, validity, and responsiveness) of the PROMs, as the aim was a content comparison of items in PROMS and patients' perspectives in using a bio-psycho-social framework. However, the psychometric properties of PROMs should always be established in the population of interest [147].

## 5. Conclusions

In conclusion, no PROMS covered all aspects being assessed as important by a PE population. PEmb-QoL is the single PROM covering most items. If feasible, the full set of PROMs as recommended by ICHOM should be implemented in clinical practice to cover most aspects reported by patients. However, worrisome thoughts, hypervigilance around symptoms and uncertainty of illness were experienced by patients with PE but was not covered in any PROMS. Future research should focus on these issues to better address what is deemed important by patients with PE.

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## Declaration of competing interest

None related to this manuscript. The authors report the following general conflicts:

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## Appendices. Supplementary data

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