PERSISTENT DYSPNEA, EXERCISE LIMITATION AND IMPAIRED HEALTH-RELATED QUALITY OF LIFE IN PATIENTS SURVIVING PULMONARY EMBOLISM

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Summary

Background: Apart from recurrence and bleeding from anticoagulative treatment, chronic thromboembolic pulmonary hypertension (CTEPH) has long been considered the main long-term complication affecting patients surviving pulmonary embolism (PE). The incidence of CTEPH is, however, low, reportedly not exceeding more than 2-4%. Consequently, it has been thought that long-term PE sequalae affect only a minority of patients with a history of PE. Recent studies have revealed that persistent dyspnoea, exercise limitation and impaired health-related quality of life (HRQoL) are frequently present in PE survivors. However, these outcomes have not been studied extensively in patients with a history of PE.

Aims: 1) To translate and validate the Norwegian version of the Pulmonary Embolism-Quality of Life (PEmb-QoL) questionnaire. 2) To assess generic HRQoL in PE survivors compared to the general population and to explore possible determinants of generic HRQoL in PE patients. 3) To describe the main differences between patients with and without dyspnea as well as to assess the predictors of dyspnea, exercise capacity and disease-specific HRQoL. 4) To assess whether echocardiographic parameters could explain the presence of dyspnea or exercise limitation.

Materials and Methods: Patients diagnosed with PE between 2002 and 2011 were identified from hospital databases and the Østfold registry for venous thromboembolism (TROLL). The registry includes consecutive patients diagnosed and/or treated for deep vein thrombosis and/or PE at Østfold Hospital, Norway. Patients with an objectively verified diagnosis, i.e., by computed tomography pulmonary angiogram or by ventilation/perfusion scintigraphy were eligible for inclusion in a follow-up study, which included a scheduled visit with a clinical examination, blood sampling, 6-minute walk test and echocardiography. Generic and disease-specific HRQoL questionnaires were sent to the patients prior to the study visit.

Results: In total, 213 patients were included, of whom 117 (55%) were males. The mean age was 61 years (SD 15), and the median time from diagnosis was 3.8 years (range 0.9-9.5). The exploratory factor analysis of the Norwegian version of the PEmb-QoL yielded six factors

explaining 71% of the variance, with a Cronbach's alpha of 0.94, indicating good internal consistency.

Criterion validity revealed good correlation with the EQ-5D dimensions. The intra-class correlation coefficient (ICC) ranged from 0.75 to 0.86, indicating that the Norwegian version of the PEmb-QoL has good repeatability. The observed HRQoL, as assessed by EQ-5D-3L index values, was lower in PE patients than in the general population, 0.80 vs 0.86. Dyspnea, unemployment and the 6-minute walk test results were found to be independently associated with impaired HRQoL. Forty-seven percent of the patients complained of persistent dyspnea. Patients reporting dyspnea had shorter walking distances on the 6-minute walk test, 413 metres vs 488 metres, $p<0.005$. This was also found in the subset of patients with no comorbidities (Charlson Comorbidity Index=0), $p=0.03$. Dyspnea was independently correlated with both impaired disease-specific HRQoL and exercise limitation. Right ventricular dysfunction, indicated by tricuspid annular plane systolic excursion (TAPSE) <1.7 cm, was predictive of the 6-minute walk test results at follow-up (unstandardized beta -88 metres SE 36, $p=0.014$).

Conclusion: PE survivors appear to have higher prevalences of persistent dyspnea, exercise limitation and impaired HRQoL than previously recognized. These measures are inter-related, indicating a global impairment. Future studies need to establish the causal relationship between the PE event and these outcomes.

Abbreviations

ADL	Activities of daily living
ATS	American Thoracic Society
BMI	Body mass index
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRF	Case record form
CTEPH	Chronic thromboembolic pulmonary hypertension
CTED	Chronic thromboembolic disease
CTPA	Computed tomography pulmonary angiography
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
EQ-5D (3L)	EuroQol 5 dimensional (3 level) questionnaire
estPASP	Estimated pulmonary artery systolic pressure
INR	International normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
HRQoL	Health-related quality of life
LAVI	Left atrial volume index
LMWH	Low-molecular weight heparin
LVEF	Left ventricular ejection fraction
LVGLS	Global longitudinal strain of the left ventricular free wall
mPAP	Mean pulmonary artery pressure
NYHA	New York Heart Association
PE	Pulmonary embolism
PEA	Pulmonary endarterectomy
PEmb-QoL	Pulmonary embolism quality of life questionnaire

Post-PE syndrome	Post-pulmonary embolism syndrome
pTRV	Peak tricuspid regurgitation velocity
PTS	Post-thrombotic syndrome
QoL	Quality of life
RVD	Right ventricular dysfunction
RVGLS	Global longitudinal strain of the right ventricular free wall
RV/LV-ratio	Right-to-left ventricular ratio
SF-36	Short form 36 questionnaire
SpO2	Peripheral oxygen saturation
TAPSE	Tricuspid annular plane systolic excursion
TROLL	Østfold registry for venous thromboembolism
TTE	Transthoracic echocardiography
UCSD SOBQ	University of California and San Diego shortness of breath questionnaire
US	United States
VEINES/QoL-Sym	Venous insufficiency epidemiological and economical study quality of life and symptom questionnaire
VKA	Vitamin K antagonist
V/Q-scan(ning)	Ventilation perfusion scintigraphy
VTE	Venous thromboembolism
WSPH	World symposium on pulmonary hypertension
6MWT	6-minute walk test

List of papers

The thesis is based on the following papers:

Paper I

Tavoly M, Jelsness-Jørgensen L-P, Wik HS, Roaldsnes C, Sandset PM, Ghanima W. Quality of life after pulmonary embolism: first cross-cultural evaluation of the pulmonary embolism quality-of-life (PEmb-QoL) questionnaire in a Norwegian cohort. Qual Life Res. 2014;24(2):417–25.

Paper II

Tavoly M, Utne KK, Jelsness-Jørgensen L-P, Wik HS, Klok FA, Sandset PM, Ghanima W. Health-related quality of life after pulmonary embolism: a cross-sectional study. BMJ Open. 2016;6(11):e013086–11.

Paper III

Tavoly M, Wik HS, Sirnes P-A, Jelsness-Jørgensen L-P, Ghanima JP, Klok FA, Sandset PM, Ghanima W. The impact of post-pulmonary embolism syndrome and its possible determinants. Thrombosis Research. 2018;171:84–91.

1 Introduction

In the acute setting, pulmonary embolism (PE) is a potentially fatal disease. The long-term complications of PE mainly include recurrence and/or haemorrhagic events associated with anti-coagulative treatment. However, apart from these complications, PE has historically been considered a disease with infrequent long-term sequalae, such as persistent dyspnea and functional limitations. A plausible explanation for this perception may be that for a long time, the only recognized long-term sequalae of PE has been chronic thromboembolic pulmonary hypertension (CTEPH). Although devastating for patients suffering from it, the incidence of CTEPH has generally been estimated to be approximately 0.5-4% [1,2]. However, several reports have recently highlighted the existence of a considerable number of patients, far exceeding the incidence and prevalence of CTEPH, who struggle with long-term consequences of PE [3-8]. These studies have mainly reported persistent dyspnea, limited exercise capacity and impaired health-related quality of life (HRQoL). However, as this is a fairly novel research field, there is an ongoing debate regarding not only whether these findings are substantiated but also the pathophysiological basis and the possible determinants of these observations.

The main scope of this thesis has therefore been to participate in this new field by evaluating patients with a history of PE with regard to persistent dyspnea, exercise capacity and HRQoL.

1.1 The history of venous thromboembolism

Although the first described case of venous thromboembolism (VTE) dates back to the 13th century [9], it was not until the second half of the 19th century that the current understanding of the pathophysiological mechanisms of VTE was proposed, consisting of a triad including damage to the vessel wall, slowing of the venous flow and hypercoagulability [10,11]. At this very early stage of VTE research, it became evident to scientists, and in particular to Virchow (Figure 1), that VTE is caused by clots in the lower extremities, and that these clots have the potential to travel to the pulmonary arteries via the right side of the heart, leading to various local reactions and ultimately to death (Figure 2a and 2b) [12].

Figure 1. Rudolf Virchow during his period in Würzburg (1849-1856).

(Adapted from **http://commons.wikimedia.org/wiki/Image:Rudolf_Virchow.jpg**)

Figure 2a and 2b. Descriptions by Virchow of thrombosis in the leg veins and the pulmonary arteries.

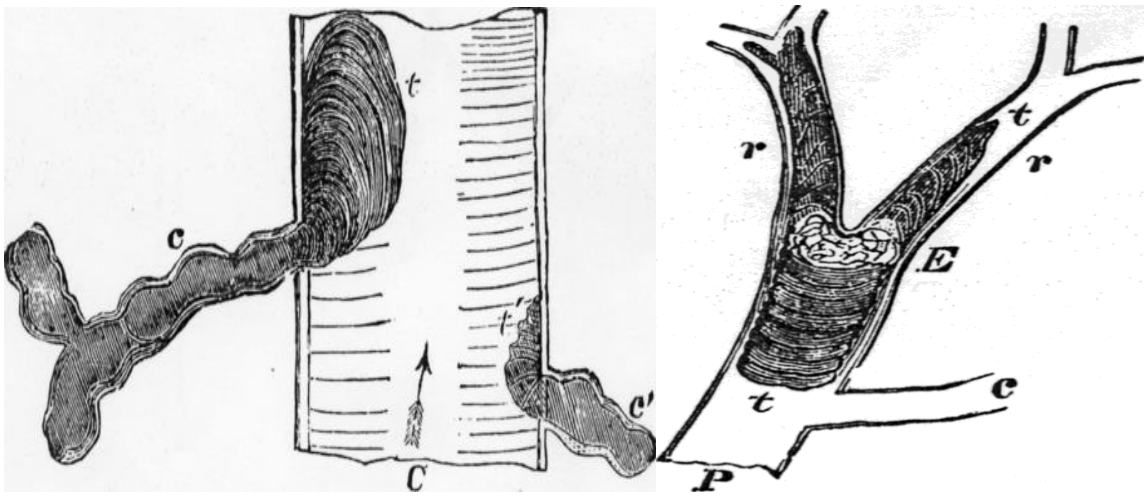


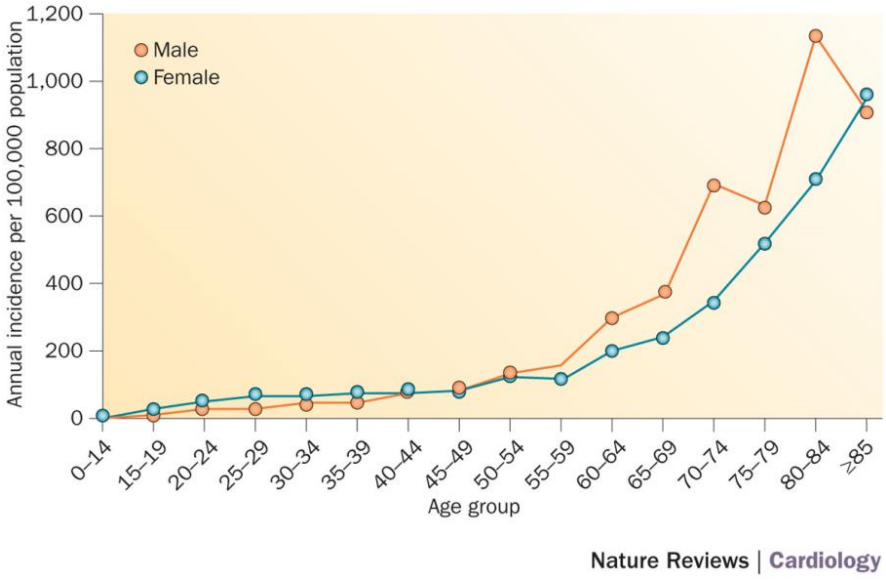
Figure a: Autochthonous and prolonged thrombi *c, c'*. Smallish, varicose, lateral branches (circumflex veins of the thigh), filled with autochthonous thrombi that project beyond the orifices into the trunk of the femoral vein
Figure b: Emboli of the pulmonary artery. Adapted with permission from British Journal of Haematology [12,13].

1.2 Epidemiology and risk factors of venous thromboembolism

The estimated annual incidence of VTE among Europeans ranges from 104 to 183 per 100 000 persons/year [14], of which two thirds consist of deep vein thrombosis (DVT) and one third PE [15]. The incidence of VTE is age-dependent, with increasing number of VTE incidents with more advanced age (Figure 3). Although VTE collectively is associated with reduced survival, PE is believed to be the main driver of this association. In a cohort study by Heit et al., it was shown that the observed reduced survival in a VTE population was attributable to PE, as these patients had an 18-fold increase in death compared to patients with DVT alone [16].

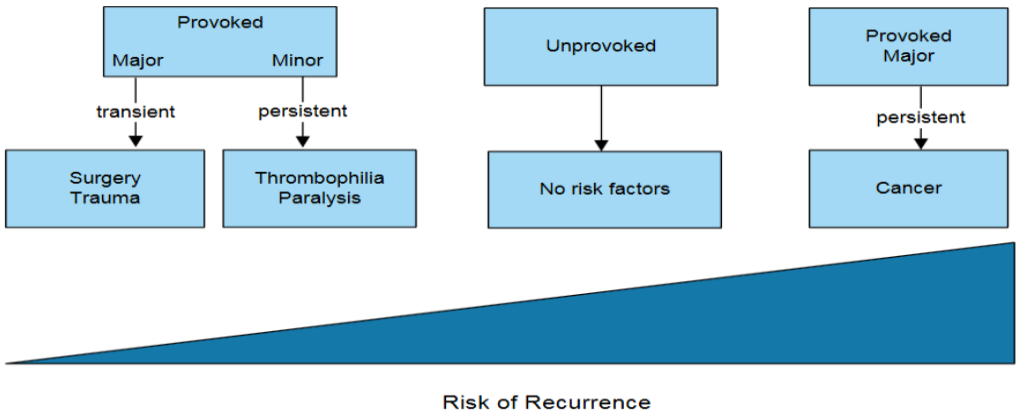
According to the International Society of Thrombosis and Haemostasis (ISTH), a VTE episode can be categorized as unprovoked (no environmental risk factors identified) or provoked by transient or persistent risk factors [17]. Risk factors such as male sex or inherited thrombophilia that evidently increase the risk of VTE are classified as non-environmental. Transient risk factors for provoked VTE can be further classified as strong or weak risk factors. For example, major abdominal surgery and trauma are factors that are considered to increase the risk of a VTE episode by more than 10-fold [18]. Obesity and oestrogen therapy are, on the other hand, considered weak risk factors [18]. Cancer-associated thrombosis is usually considered a persistent environmental risk factor until it is cured [17]. The categorization of an episode of VTE is fundamental for the risk assessment of possible recurrence if the withdrawal of anticoagulation is contemplated (Figure 4).

Figure 3. Annual incidence of venous thromboembolism among residents of Olmsted County, MN, USA, from 1966 to 1990, by age and sex.



Adapted with permission from the American Medical Association© [19]

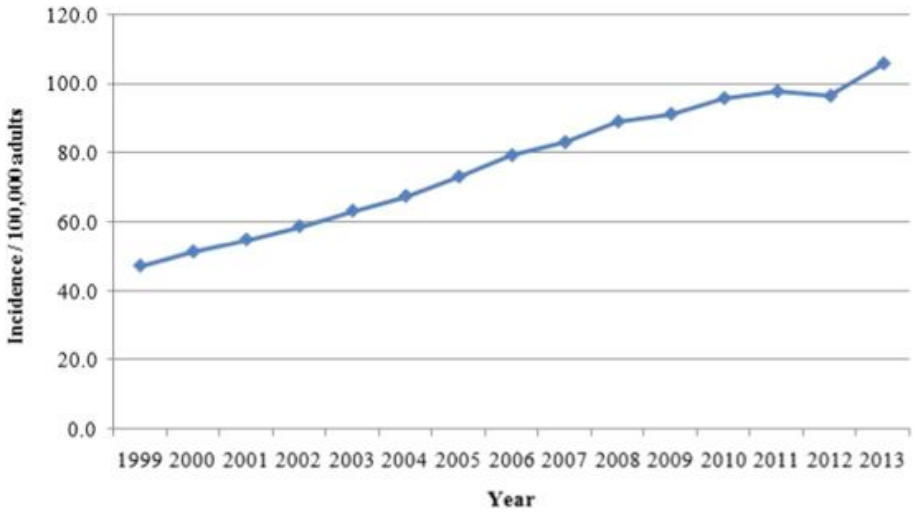
Figure 4. A schematic figure regarding the categorization and assessment of the risk of recurrence in a patient with VTE.



1.3 Economic burden and societal impact of venous thromboembolism

Tremendous efforts have been made by clinicians, researchers and health-care authorities to globally disseminate information about VTE to reduce its incidence. However, existing evidence suggests the contrary. The incidence rates of VTE appear to have remained unchanged throughout the recent decades [20], and some studies report increasing rates (Figure 5) [21,22]. Financial modelling studies in the United States (US) and Europe have highlighted the magnitude of the economic burden that VTE imposes on society. In the US, the annual VTE costs (direct and indirect) are estimated to be 7-10 billion dollars [23]. In Europe, based on the same modelling algorithm as in the US, the annual VTE costs are estimated to be 1.5-13.2 billion dollars [24]. Furthermore, the incidence of VTE increases with increasing age, with an almost six times higher incidence rate in the 8th decade of life compared to the 5th decade of life [25]. Concomitantly, life expectancy has doubled in the last century. Together, these facts indicate that health care resource utilization related to VTE is not only substantial but will increase in the future and impose an even larger burden on global health care systems.

Figure 5. Incidence of acute pulmonary embolism in New York State, 1999 to 2013.



Adapted with permission from Journal of Thoracic and Cardiovascular Surgery. [21]

1.4 Diagnosis and treatment of venous thromboembolism

The diagnosis of DVT and PE is based on an integrated approach including clinical probability assessment and biochemical and radiological tests. Several clinical algorithms, e.g., that given in Table 1, have been developed to optimize the management of VTE patients [26-28]. These algorithms aid physicians in categorizing patients into groups with low, intermediate and high clinical probabilities for VTE. Incorporating a D-dimer test into the work-up for patients with low or intermediate probabilities can safely rule out VTE if the D-dimer results are normal. Patients with a high pre-test probability, however, need imaging tests to rule out the diagnosis.

Table 1. Clinical prediction rule for PE according to Wells [29].

Items	**Clinical decision rule points**
Previous PE or DVT	1.5
Heart rate >100 beats per minute	1.5
Surgery or immobilization within the past four weeks	1.5
Haemoptysis	1
Active cancer	1
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3
Clinical probability	
Low	0-1
Intermediate	2-6
High	≥7

1.4.1 Imaging tests to diagnose pulmonary embolism

The gold standard method to diagnose an obstruction of the pulmonary arteries was conventional pulmonary angiogram. This method has, however, been primarily replaced by computed

tomography pulmonary angiogram (CTPA) and, in some circumstances, ventilation/perfusion scintigraphy (V/Q-scan).

CTPA has several advantages over the other diagnostic modalities. Apart from being universally available and rapid, it also enables an assessment of how severe the PE might be. Quantification of the embolic burden and estimation of the most proximal extension of the clot [30], the right to left ventricular diameter ratio (RV/LV-ratio) [31], septal bulging [32] and contrast reflux into the inferior vena cava [33] are additional parameters that can be provided by CTPA and aid physicians in more accurate risk stratification of patients. Finally, CTPA has the potential to reveal other causative or concomitant diseases, such as pneumothorax, pneumonia and pleural effusion.

1.4.2 Treatment of venous thromboembolism

The treatment of VTE is based on inhibiting the activation of the coagulation system with anticoagulants. In 1933, Charles and Scott succeeded in producing pure heparin, enabling its use in humans [34]. Low molecular weight heparin (LMWH) was, however, not introduced into clinical practice until the mid-1990s [35-37]. Treatment with LMWH combined with vitamin K antagonists (VKA) is administered until the international normalized ratio (INR) is in the therapeutic range (2.0-3.0), and thereafter, VKA therapy alone has been administered as the standard treatment since the middle of the 20th century [38]. In recent years, we have witnessed a paradigm shift in the treatment of VTE. Several large-scale randomized trials have demonstrated the non-inferiority of direct oral anticoagulants (DOAC) compared to VKA therapy [39-42]. The benefits of reduced bleeding tendencies, fast onset and few drug interactions that come with treatment with DOACs [43,44] have outweighed the possible disadvantages of not being able to control compliance and the absence of an antidote (dabigatran excluded). Subsequently, the endorsement of DOACs as a first-line treatment has been made by major international guidelines [45,46].

For PE patients presenting with hemodynamic instability, i.e., signs of massive or high-risk PE, the guidelines recommend systemic intravenous thrombolytic treatment [45,46]. If the patient has contraindications for thrombolytic treatment, surgical embolectomy or catheter-directed treatment should be considered. Of note, several studies have evaluated the role of systemic

thrombolytic treatment or catheter-directed treatment for sub-massive/intermediate risk PE [47-49]. However, to date, there are no convincing data indicating a favourable risk-benefit ratio of these treatment options regarding short- and long-term outcomes in patients with sub-massive/intermediate risk PE [50,51].

1.5 Follow-up after venous thromboembolism

The main objectives to be pursued during follow-up of VTE patients are to determine the duration of anticoagulation based on the risk of recurrence vs. the risk of bleeding, assess the indication for screening of occult cancer, and identify patients with CTEPH and post-thrombotic syndrome (PTS). Although current guidelines provide rather specific recommendations regarding patients at the far ends of each spectrum, they fail to address the standard follow-up procedure in a large subset of VTE patients who fall in between, e.g., those with a first episode of unprovoked PE and a moderate bleeding risk or those with manifest PTS. As such, the optimal duration and intensity of medical follow-up for VTE is not fully established, and local practice tends to dictate the follow-up course [52].

The duration of anticoagulation treatment is usually based on several factors. The main factor that determines the duration is often the risk of recurrence if anticoagulants are stopped versus the risk of bleeding if anticoagulants are continued. Several algorithms have been developed to aid this decision-making process [53-55]. However, none of the currently available algorithms has had a global implementation in clinical practice. Additionally, patient and doctor preferences as well as persistent symptoms such dyspnoea or signs of PTS are also important factors affecting the suspension or continuation of treatment.

Generally, patients having a provoked episode of VTE are treated for 3 months, especially if the provoking factor is considered “strong”. Patients with unprovoked VTE or recurrent VTE may undergo life-long treatment [56].

1.6 Complications after venous thromboembolism

1.6.1 General complications

The most prevalent short- and long-term complications of an episode of VTE are treatment-related complications, i.e., bleeding, or disease-related complications, i.e., recurrence, PTS and CTEPH.

The estimated case-fatality rate of a recurrent VTE event is 11.3% (during the initial 3 months of treatment) [57]. Conversely, with the entrance of DOACs as the first-line treatment option for VTE, the case-fatality rate of bleeding from anticoagulant therapy during the initial 6-12 months was reduced from 11% [57] to 5% [58]. Nevertheless, bleeding, particularly major haemorrhage, from anticoagulative treatment is a serious complication that is associated with substantial mortality, morbidity and health-care costs [59,60].

Apart from the obvious devastating consequences of the abovementioned complications, VTE and, notably, recurrent VTE episodes are associated with an increased risk of developing PTS (in the case of DVT) and CTEPH (in the case of PE).

1.6.2 Long-term complications after DVT

Patients suffering from DVT are at risk of developing PTS. Several scoring systems for grading PTS have been developed, e.g., the Villalta score [61] and the CEAP score [62]. An assessment of the extent of PTS is possible based on grading the severity of the following symptoms: pain, paraesthesia, itching, heaviness, swelling, skin discoloration and ulceration. PTS affects 30-50% of patients suffering from DVT [63,64]. Studies have shown that PTS has major societal implications and is associated with markedly reduced HRQoL and work-related disability [65]. As such, research has been extensive in attempts to understand the underlying pathophysiology of PTS and, more importantly, how to prevent PTS. In addition to standard anticoagulant therapy, the potential benefits of invasive treatment modalities such as catheter-directed thrombolysis have been evaluated. However, the published results are conflicting [66-68]. Consequently, in addition to

anticoagulative treatment, the only available prophylactic treatment option is unfortunately merely compression stockings [69], the true efficacy of which has also been debated [70].

1.6.3 Long-term complications after PE

In contrast to DVT, with the exception of CTEPH, PE has not received the same attention from the scientific community regarding its long-term complications.

1.6.3.1 Chronic thromboembolic pulmonary hypertension

CTEPH is classified as a pulmonary hypertension type IV disorder, which is defined by a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg as assessed by right heart catheterization in the presence of signs of chronic residual pulmonary thrombosis [71]. However, this criterion was challenged in 2018 at the 6th World Symposium on Pulmonary Hypertension (WSPH). The new upper limit of normal of mPAP was proposed to be >20 mmHg [72]. However, the WSPH task force has emphasized that a single diagnostic parameter does not characterize the whole condition per se [72]. In this sense, the diagnosis of pre-capillary pulmonary hypertension, which CTEPH is an important cause of, should be based on an mPAP level >20 mmHg in tandem with pulmonary vascular resistance of 3 or more Wood Units [72].

The pathophysiological basis of CTEPH has not been fully clarified, and the common predisposing factors for VTE do not seem to increase the risk of CTEPH [73]. However, it is evident that residual thrombosis contributes to vascular remodelling and scarring, which in turn leads to progressive pulmonary arterial hypertension [74]. Although the pathogenesis seems to be triggered by PE, it is important to clarify that antecedent PE diagnosis is not present in up to 25% of patients diagnosed with CTEPH [75].

In 2004, a landmark study by Pengo et al. reported that the previous incidence rate of 0.5% for CTEPH was underestimated [1]. In their study, CTEPH occurred in up to 4% of the patients during a 2-year follow-up period. Although this study sparked the debate regarding CTEPH being

underdiagnosed, determining the precise incidence of CTEPH has been difficult. The reported incidence rates range from 0.1 to 11%, with most studies reporting rates between 2-4% [2,75].

The guideline-supported diagnostic work-up for CTEPH includes echocardiography and V/Q-scanning in patients with clinical signs of pulmonary hypertension such as persistent dyspnea and/or limited functional capacity 6-12 months after PE diagnosis [46]. If signs of residual thrombosis and right ventricular dysfunction (RVD) are found, a "gold standard" right heart catheterization should be performed to confirm the diagnosis of CTEPH [46]. However, the optimal timing of initiating this work-up is debated. Studies have revealed a remarkable latency in CTEPH diagnosis, with the majority of patients diagnosed more than 1 year after clinical presentation [75]. From this perspective, it would be natural to conclude that a more aggressive approach should be undertaken in the diagnosis of CTEPH. On the other hand, due to the low incidence rate of CTEPH and the fact that 25% percent of patients eventually diagnosed with CTEPH have no previous VTE diagnosis, an aggressive diagnostic approach would lead to increased health care costs with no obvious morbidity or mortality benefits. In an attempt to facilitate this process, studies have evaluated possible clinical scoring and/or screening algorithms for CTEPH [76]. However, to date, no such validated algorithm is available.

In line with other pulmonary hypertension diseases, the prognosis of CTEPH is poor if no treatment is provided. Currently, patients with CTEPH may be offered three different treatment modalities. For patients with accessible disease who are considered suitable surgical candidates, surgical thrombendarteriectomy (PEA) should be recommended according to international guidelines because it is potentially curative [71]. This treatment modality has repeatedly been shown to significantly improve survival, functional capacity and HRQoL [77-79]. For patients not suited for PEA or those with residual/recurrent CTEPH, pharmacotherapy with a soluble guanylate cyclase stimulator (Riociguat; Adempas©) is indicated [80]. In recent years, a third treatment modality, balloon pulmonary angioplasty, has shown promising results. However, it is currently only recommended for patients with inoperable or persistent/recurrent CTEPH [71]. Finally, all patients in whom CTEPH has been confirmed, regardless of the provided treatment options mentioned above, should be treated with anticoagulant therapy indefinitely.

1.6.3.2 Chronic thromboembolic disease

Chronic thromboembolic disease (CTED) is a condition that has gained attention in recent years. Although formal diagnostic criteria have yet to be established, current studies have identified CTED as a state of persistent symptoms with chronic perfusion defects that does not fulfil the diagnostic criteria for CTEPH, i.e., resting mPAP >25 mmHg or >20 mmHg according to recent recommendations. A recent study comparing a CTED population to both healthy controls and CTEPH patients showed that the magnitude of cardiorespiratory pathology is not observable unless testing occurs during exercise [81]. Another study showed that echocardiography may not be a sensitive method for detecting RVD in these patients because many patients with normal echocardiographic evaluations had pathological cardiopulmonary exercise tests (CPETs) [82]. Furthermore, the same authors reported in a second study that the CPET results in CTED patients are comparable to those in patients with a firm diagnosis of CTEPH [83]. To this end, recent consensus reports have proposed that an integration of exercise testing and assessment of HRQoL should be performed in CTED patients [84,85]. As such, this approach may ameliorate the vexing clinical problem of making an accurate diagnosis of CTED in these patients.

The optimal treatment modality and its timing in patients with CTED is unknown. Reports from CTEPH-specialized centres suggest that PEA could be indicated in carefully selected patients with extensive CTED [86,87]. Previous studies have shown that the functional status in patients eventually diagnosed with CTEPH is an important prognostic predictor [78]. At the same time, there is a considerable delay in diagnosis, which ultimately contributes to diagnosed patients being in worse functional condition, as CTEPH is a progressive disease. As such, it could be argued that perhaps the treatment of patients with CTED could prevent the progression to CTEPH and because CTED patients have limited disease, the postoperative morbidity and mortality rates would decrease. However, this statement suggests that CTED is a precursor to CTEPH and to date, there is no scientific evidence supporting this assumption. Although not formally outlined in guidelines, similar to patients with CTEPH, patients diagnosed with CTED should be recommended for indefinite anticoagulant therapy.

In summary, CTED is being increasingly recognized as a specific condition, and patient selection is ultimately the most challenging task at hand with regard to providing optimal

treatment. However, in this subset of patients with no signs of pulmonary hypertension at rest, perhaps more functional diagnostic work-up, e.g., CPET, the 6-minute walk test (6MWT) and/or stress-echocardiography, could very well be the most sensitive means of diagnosis. Hopefully, future studies will address these questions.

1.7 Right ventricular dysfunction in pulmonary embolism

The presence of RVDis the hallmark of the severity of an acute PE [46]. However, once the acute setting is survived by the patients, it is unclear how a present RVD at diagnosis impacts the long-term prognosis of the patients, when CTED and/or CTEPH is excluded. In one study present RVD at diagnosis did not predict 6-months follow-up outcomes of functional limitation in a cohort of 109 patients [88]. Furthermore, there is limited data in how well functional limitations correlate with RVD in the follow-up setting. One study revealed that the presence of dyspnea was significantly higher in patients with RVD at follow-up compared to those not having RVD [89]. The recently published post-hoc analysis of the PEITHO trial reinforced these findings by observing a significantly increased risk of functional limitations in those having signs of RVD at 6-months echocardiography [90]. However, as evidence is scarce the current guidelines lack to provide distinct recommendations regarding how a present RVD in the acute setting should be addressed in the follow-up setting.

1.8 Dyspnea

Dyspnea is defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” [91]. The pathophysiology of dyspnoea is, however, multimodal and complex. It has been suggested that the experience of dyspnea derives from interactions among multiple physiological, psychological, social and environmental factors [91].

Dyspnea is one of the most common complaints in both emergency and chronic states of various diseases. It has been shown that dyspnea in itself has the potential to predict all-cause

mortality regardless of any underlying condition [92,93], and from a socioeconomic perspective, dyspnea accompanies extreme morbidity with reduced HRQoL [94].

Dyspnea is the most common symptom of acute PE, affecting more than 70% of the patients [95]. In the follow-up setting of PE, dyspnea is the core symptom that mandates further evaluation to rule out residual thrombosis, RVD and ultimately CTEPH [46].

However, it has been difficult to find objective correlates to persistent dyspnea in the majority of the patients complaining of this symptom following their PE. Therefore, the overall perception in both the academic and clinical settings has been that persistent dyspnea is perhaps more due to physical deconditioning, comorbidities or psychosomatic causes.

In 2008, a study by Klok et al reported that more than 50% of PE patients complain of persistent dyspnea long after their PE diagnosis [96]. Subsequent studies reinforced these findings, establishing that dyspnea is a relatively common symptom in PE survivors [3,50,97]. Although lacking a clear indication of what the underlying cause of the unexplained dyspnea may be, these publications highlighted that there might be a large body of patients still suffering from their disease. This finding reinforces the need for further research in this area.

1.8.1 The pathophysiology and the descriptors of dyspnea

In most cases, dyspnea starts with a physical impairment that sends signals via the stimulation of pulmonary and extrapulmonary afferent receptors to the respiratory centre in the brainstem and further to the cortex, which then interprets the sensation as unpleasant or uncomfortable [98]. In addition, neuroimaging studies have shown that dyspnea activates, in the same manner as pain perception, the cortico-limbic system [99]. The reaction to the perception of dyspnea is highly individual. Depending on the circumstances in which dyspnea occurs, it could be perceived as a threat, causing fear and anxiety. If so, patients tend to avoid situations that precipitate dyspnea, e.g., exercise, thus entering a downward spiral with a sedentary lifestyle and progressive deconditioning [100].

Understanding the possible descriptors (the language the patients typically use to describe their shortness of breath) of dyspnea could be valuable because it may provide insight into the

underlying mechanism [101]. However, to explore the descriptors of dyspnea, it is imperative to understand that the general term dyspnea subsumes several sensations. These could be the sense of respiratory work or effort, tightness in the chest or air hunger [102]. For example, asthmatic patients tend to describe their dyspnea as a sensation of chest tightness, whereas patients with congestive heart failure often use the terms air hunger or urge to breath [103]. Although the descriptors of dyspnea in PE patients have not been studied, efforts have been made to explore the possible determinants. However, the results are conflicting, with some studies arguing that persistent dyspnea is mostly related to comorbidities [3] and deconditioning [7], while others have found associations with residual vascular obstruction [104].

1.8.2 Measuring dyspnea

The American Thoracic Society (ATS) guidelines on dyspnea strongly recommend that, with regard to pain management, dyspnea ought to be measured [91]. However, in line with the evaluation of pain, careful attention should be directed to what dimensions the instrument at hand is measuring. Preferably, multidimensional tools should be used as they reveal phenomena not captured by unidimensional scales (Table 2) [91]. From this perspective, only two of the available general dyspnea questionnaires include all the dimensions presented in Table 2, i.e., the University of California, San Diego (UCSD) Shortness of Breath Questionnaire (SOBQ) [105] and the Dyspnea-12 questionnaire [106]. Given the non-disease-specific nature of these questionnaires, it would be logical to assume adequate sensitivity to measure dyspnea in PE patients. However, none of these studies included PE patients in their development or validation processes [105,106].

Studies evaluating dyspnea in PE survivors have predominantly used the New York Heart Association (NYHA) classification [96,107]. Of note, NYHA is predominantly a measure of physical performance and does not include the patients' view of dyspnea. In clinical practice, on the other hand, dyspnea is rarely measured, instead merely descriptively outlined in the medical charts of the PE patients.

To conclude, dyspnea is a common symptom in PE patients, not only in the acute phase but also in the follow-up phase. Little is known regarding dyspnea, especially during the follow-up

phase, in PE patients; therefore, further research and perhaps guideline-supported recommendations are needed to assist physicians in evaluating shortness of breath in patients with a history of PE.

Table 2. Domains of dyspnea

Domain	Definition	Examples
Sensory-perceptual experience	Measures of what breathing feels like to the patient or research subject.	Single-item ratings of intensity (e.g., Borg scale, VAS)
Affective distress	Measures of how distressing breathing feels. Focus can be either immediate (e.g., unpleasantness) or evaluative (e.g., judgements of meaning or consequences).	Single-item ratings of severity of distress or unpleasantness and multi-item scales of emotional responses such as anxiety
Symptom impact or burden	Measures of how dyspnea/breathlessness affects functional ability, employment (disability), quality of life, or health status.	Unidimensional rating of disability or activity limitation (e.g., MRC scale, NYHA)

VAS; Visual analogue scale.
MRC; Medical research council dyspnea scale.
NYHA; New York Heart Association.

Adapted with permission from the American Journal of Respiratory and Critical Care Medicine. [91]

1.9 Functional capacity

From the patient's perspective, it could be argued that the ability to remain active is the most important outcome of medical care. It is important to mention that the functional status that the health provider is interested in is often physiological. However, functional status also encompasses patients' abilities to function normally in psychological and sociological aspects.

Although functional capacity, exercise capacity and functional exercise capacity are used interchangeably in the literature, there are some fundamental differences between these entities [108]. Functional capacity is a term used to describe the patients' ability to perform activities of daily living (ADL). Functional exercise capacity is a measure of the patients' ability to perform exercises that resemble those that are required to function in a normal life. Exercise capacity, however, also encompasses tests such as CPET that do not necessarily mirror patient function in normal life.

Exercise capacity has been studied extensively in cardiorespiratory disorders [108,109]. Apart from being an objective and highly reproducibility evaluation tool, unsurprisingly, it has also been shown that exercise intolerance provides additional prognostic information [110,111] and has the ability to predict all-cause mortality [112]. Traditionally, questions such as "how many flight of stairs can you climb?" have been used as a substitute for an approximation of the patients' exercise capacity. However, patients may overestimate or underestimate their functional capacity [113]. Hence, a more precise manner of evaluating exercise capacity is to physically test the patient [114]. To this end, the advantages of exercise testing have their basis in the theory of the cardiorespiratory reserve. The cardiorespiratory reserve capacity is in excess of that needed to sustain normal functioning. As such, physiological variables deemed normal in a resting state may be pathological when the cardiorespiratory system is under stress [115].

1.9.1 Exercise capacity tests

Several exercise capacity tests have been developed and used in research and in the clinical setting. To date, the gold standard test is considered to be CPET [116]. CPET enables a thorough assessment of the cardiorespiratory system under stress, with the availability of gas-exchange and peak $V0_2$ -max calculations. As such, unlike other exercise tests, including functional tests, CPET has the potential to differentiate whether the observed exercise limitation is predominantly related to cardiac, pulmonary or muscular dysfunction [117]. However, this method of exercise

testing is cumbersome, expensive and not available in all settings. Furthermore, the results of CPET may not reflect the patients' functional exercise capacity in normal life [115].

The time-distance walk was first introduced by Cooper and co-workers in the 1960s as a straightforward and objective measure of functional capacity [118]. The test simply required a patient to walk as far as they possibly could in a fixed period of time, with the primary outcome measure being the total distance walked in the time allotted. Since then, a variety of walk tests have been developed. The fixed-time tests include 2-, 6- and 12-minute walk tests [119]. The fixed-distance tests consist of 100 metre, half mile and 2 km walk tests [120-122]. Finally, there are velocity-dependent walk tests that are paced externally (e.g., self- or controlled-paced shuttle walk tests) [123,124].

As opposed to the exercise capacity test, walk tests possess the advantages of being feasible and inexpensive and reflecting more accurately the ADL. The most commonly used walk test in the literature is the 6MWT, which has several benefits [125]. It is better tolerated by the patients and more responsive and reliable compared to the 12- and the 2-minute walk tests, respectively [119]. The paced walk tests have the disadvantage of requiring more equipment and may not mirror the activities of daily life [125]. Strengthening the position of the 6MWT further is the fact that it is the only walk test with published standardized protocol guidelines that outline how the test ought to be performed [114]. However, even with a standardized protocol available, the outcome of the 6MWT is unsurprisingly affected by age, sex, height and weight. However, these anthropometric variables have been incorporated into reference equations for so-called predictive distances [126].

1.9.2 Exercise and exercise capacity tests in pulmonary embolism

It is logical to assume that any modality of exercise will enhance the performance of the cardiorespiratory system and ultimately lead to improved morbidity and mortality [127]. Regarding other major cardiorespiratory diseases than PE, e.g., chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF), this assumption have been studied extensively and the effect of exercise and how to test exercise intolerance are subjects that are specifically addressed by international guidelines concerning COPD and CHF [128,129].

Moreover, attempts have been made to establish minimally clinically important difference thresholds for exercise tests in these conditions [130,131]. Although studies evaluating the long-term course of PE have reported outcomes pertaining to exercise capacity [97,107], CTEPH excluded, the benefits of exercise and exercise capacity testing have not been studied specifically in PE survivors. Consequentially, available guidelines do not address the role of pulmonary rehabilitation and exercise capacity testing in PE survivor with persistent symptoms. Future studies will hopefully clarify whether widening the indication for (functional) exercise tests to all PE survivors with dyspnea will have additional value.

1.10 Health-related quality of life

The roots of the term ”Quality of Life” (QoL) can be traced back to the definition of health by the World Health Organization in 1947 [132]. Health is defined as “a state of complete, physical and mental and social well-being and not merely the absence of disease and infirmity.”

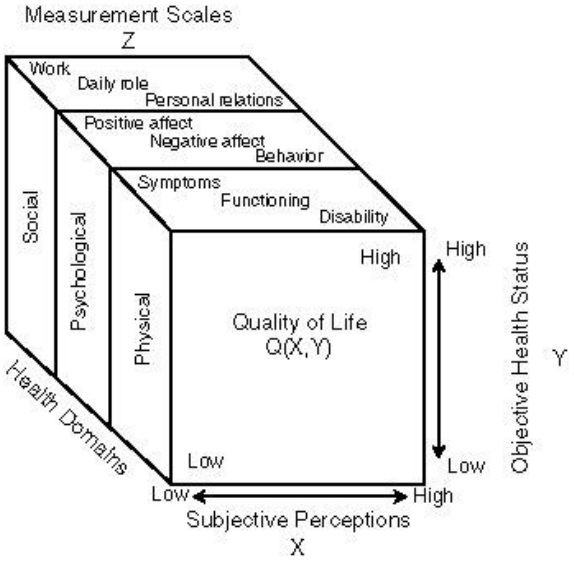
Since its introduction into the medical sciences, the concept of QoL has become increasingly popular [133]. Searching for the term quality of life as a MeSH term in PubMed between 1964 and 1977 rendered 40 articles [134]. Expanding the search to include recent decades renders thousands of articles. This fact shows the increased awareness regarding the importance of incorporating the patient’s view as an outcome in clinical trials. To this end, an increasing number of physicians agree that the clinical assessment in a follow-up setting should be accompanied by the assessment of the patient’s QoL and that this information should be complementary, aiding the clinician in efforts to help the patient.

Although the terms QoL and HRQoL are used interchangeably in the literature, there is a fundamental conceptual difference. Whereas QoL represents an individual’s global QoL, HRQoL is supposed to focus on the aspects of QoL related to the patient’s health status [135,136].

HRQoL has three domains, namely, the patient’s physical, mental and societal statuses (Figure 4) [137]. As such, instruments developed to measure HRQoL usually include items that represent these three domains.

HRQoL can be assessed either by generic or disease-specific instruments [138]. The main difference between these two types of questionnaires lies in the questions being asked. Disease-specific questionnaires measure aspects of QoL related specifically to the condition being evaluated. Consequentially, disease-specific questionnaires are not suitable for patients not experiencing a specific disease. It has been debated which of these measures assess HRQoL more accurately. The beneficial aspects of disease-specific questionnaires are their ability to detect subtle changes in HRQoL, whereas generic questionnaires would more often miss these changes. However, a generic questionnaire is more versatile due to its indiscriminatory nature and has the enormous benefit of being comparable across populations and with population norms [138]. However, most agree that in order to perform a comprehensive evaluation of HRQoL, it is advised to use both generic and disease-specific instruments [139].

Figure 4. Conceptual scheme of the domains involved in a HRQoL assessment.



Adapted with permission from New England Journal of Medicine. [137]

1.10.1 Impaired Health-Related Quality of Life after an episode of venous thromboembolism

The huge burdens that PTS imposes on both the affected patient and the health-care system have been recognized for many years [140,141]. These burdens have contributed to the development of tools to standardize both the diagnosis of PTS, e.g., Villalta score [61], and the evaluation of its impact on the patients, e.g., , VEINES-QoL/Sym questionnaire [142]. With this in mind, one would think that the same attention has been given to the long-term consequences of PE. However, this is not the case.

It was not until 2010 that a focused HRQoL study involving PE patients was published [6]. In this landmark study, Klok et al demonstrated that PE patients had worse HRQoL compared to age- and sex-matched population norms [6]. The same group also developed the first disease-specific quality of life questionnaire, i.e., the Pulmonary Embolism Quality of Life questionnaire (PEmb-QoL) [143].

Although current evidence emphasizes that PE also leads to impaired HRQoL [4,6,8], unlike in DVT patients in whom there is a clear causality between PTS and impaired HRQoL [65], the factors that contribute to this impairment in PE patients have not yet been fully explored [144].

The present work will shed some light on HRQoL in PE patients and resolve some of the outstanding issues. However, more importantly, it will generate hypotheses and serve as a guide for future studies that intend to evaluate HRQoL in PE patients.

1.10.1.1 Pulmonary embolism quality of life questionnaire

The PEmb-QoL questionnaire is the only disease-specific HRQoL questionnaire available for PE. The original development of this questionnaire was enabled by a qualitative semi-structured interview of 10 outpatients with a history of PE with no other comorbidities [145]. Based on the findings of these interviews, the structure of the questionnaire was modelled in line with the generic Short Form 36 (SF-36) and the disease-specific VEINES-QoL/Sym questionnaires. The questionnaire was subsequently shown to be a valid measure for studying HRQoL in PE patients

because it had adequate performance regarding internal reliability (Cronbach's alpha >90%), reproducibility (interclass correlation coefficient > 80%) and criterion validity [143]. In recent years, not only has the PEmb-QoL been translated into several other languages[146-148] but it has also had a minimal clinically important change threshold established [149].

1.10.1.2 EuroQol - 5 dimensions – 3 levels

In 1987, several experts in the field of QoL met with the aim of developing a standardized general purpose instrument for describing and valuating HRQoL. The important objective that the group had was to emphasize simplicity and international applicability when constructing an instrument that could facilitate collection of data and had the capacity for cross-national comparisons of health state valuations. This collaboration led to the development of the EuroQol-5D questionnaire (EQ-5D) [150,151]. Since its development, the EQ-5D has gained much attention and has been validated and used widely worldwide. It has currently been translated into more than 170 languages, via international cross-cultural adaptation procedures [152], and has population norm value sets for 24 countries [153].

1.11 The "post-pulmonary embolism syndrome"

The negative impact that VTE collectively has on the patients' well-being and health care systems is well established. A paper by the ISTH steering committee in 2014 outlined the magnitude of the socioeconomic burden that VTE imposes worldwide [154]. However, the main driving force behind this negative impact has mostly been attributed to PTS and CTEPH. Consequently, extensive research has been performed with regard to these post-VTE complications but not regarding patients with impaired post-PE recovery in whom the criteria for the abovementioned conditions are not fulfilled.

By 2014, several reports had shown that dyspnea, reduced functional exercise capacity and impaired HRQoL are common in PE survivors [3,5,6,96,97,107]. Additionally, available evidence during that period suggested that 20-30% of the patients have persistent RVD long after their PE diagnosis [88,155]. More importantly, however, it raised the question of whether there might be an association between these outcomes. To this end, a published review article acknowledged these findings as possible impairments of post-PE recovery and proposed a new syndrome, which the authors named the post-pulmonary embolism syndrome (post-PE syndrome) [156]. The authors emphasized that the growing body of evidence indicates, as opposed to the traditional view, that there might be objective correlates to persistent dyspnea, exercise limitation and impaired HRQoL in PE patients. An important perspective provided in that review article was that CTEPH should be regarded as the most extreme presentation of a given long-term complication in PE survivors. Thus, the general assumption that persistent dyspnea is merely subjective and psychosomatic in patients in whom CTEPH is excluded should be questioned, and further research is needed in this specific area [156]. Although an effort was made to define post-PE syndrome as a combination of dyspnea with reduced functional exercise capacity and/or impaired HRQoL, formal diagnostic criteria were not outlined.

Since 2014, several studies have evaluated impaired post-PE recovery [7,8,157,158]. The majority of the studies acknowledge its presence. The results concerning its pathophysiology are, however, conflicting [144]. The only prospectively designed study evaluating post-PE recovery concluded that this impairment is mainly caused by physical deconditioning [7]. However, although retrospectively designed, other studies suggest remodelling of the pulmonary vasculature with persistent subnormal right ventricular function as a possible cause of post-PE syndrome [107]. The definition of this novel condition is evolving and further clarification is needed. The task at hand is perhaps reaching an international consensus on how to define this condition. An important question which need to be addressed by future studies is whether the definition of the post-PE syndrome should rest on objectively verified findings, e.g., residual pulmonary vasculature obstruction, echocardiographic verified RVD, and firm diagnosis of CTEPH or patient-reported outcomes such as dyspnea, functional limitation and HRQoL, or both. The benefit of a broad definition which encompasses the whole spectra of impaired post-PE recovery (from dyspnea to CTEPH) is possibly

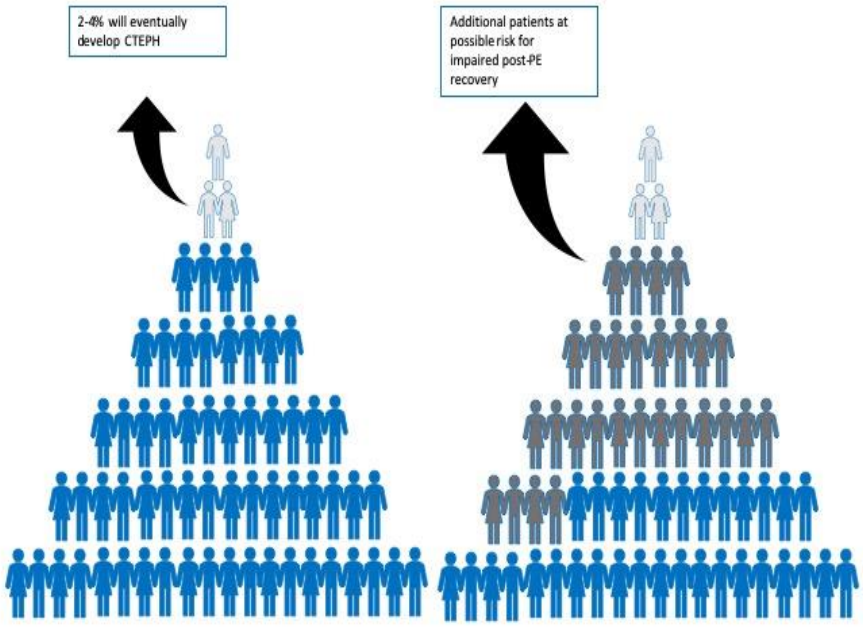
that it enables the concept of post-PE syndrome acting as an umbrella. Furthermore, this approach may allow staging and grading of the post-PE syndrome in the future. However, the disadvantage of a broad criteria is that studies exploring the post-PE syndrome use various definitions of the condition, leading to difficulties in interpretation of outcomes and cross-study comparisons.

Regardless of its pathophysiology however, in parallel to PTS, impaired post-PE recovery has been recognized as an important sequelae of PE that merits further attention. A review article attempted to elucidate the possible magnitude of post-PE syndrome and hypothesized that if the assumed prevalence of post-PE syndrome is accurate, it would mean that 50% of surviving PE patients have dyspnea with reduced functional capacity and/or impaired HRQoL (Figure 6). If true, according to the authors' postulation, this would mean that of the approximately 300 000 patients receiving the diagnosis of PE annually in Europe [159], 150 000 would experience persistent symptoms [157]. To further reinforce the possible socioeconomic burden that impaired post-PE recovery can impose, recent studies have revealed that 30% of PE patients are still on sick leave or report reduced working hours one year after their diagnosis [52,160].

In summary, VTE has an enormous impact on the global disease burden, and there is consistent evidence that the global incidence of VTE increases with increasing age. Because life expectancy continues to improve, it is not illogical to hypothesize that the prevalence of long-term sequelae of VTE will increase accordingly and will have major implications for global public health. As such, there is an urgent need for research in this specific field of PE.

To clarify, impaired post-PE recovery and post-PE syndrome will be used interchangeably throughout this thesis. Additionally, it is recommended that these two are regarded as a condition encompassing any combination of persistent dyspnea and/or reduced physical capacity and/or impaired HRQoL regardless of the presence or absence of an underlying cardiopulmonary impairment secondary to PE. However, from a clinical point of view, persistent dyspnea is obviously the core symptom of post-PE syndrome.

Figure 6. Tentative schematic illustration of the impact of impaired post-PE recovery



2 Aims

Evaluating patients after an episode of PE with regard to patient-reported outcomes such as shortness of breath, functional capacity and HRQoL has received little attention from the academic world. Emerging studies have reported that up to 50% of PE patients may suffer from a combination of the abovementioned outcomes. However, there is still a need to explore these outcomes in more detail in PE survivors to identify their possible pathophysiological mechanisms, determinants and impacts. Hence, the overall objective of the present work was to evaluate possible post-PE complications from the patient's perspective.

The specific aims were as follows:

- To translate and validate the first disease-specific questionnaire for PE (PEmb-QoL) into the Norwegian language (Paper I). This was an essential step to enable a comprehensive evaluation of HRQoL in PE patients.
- To evaluate HRQoL in patients with PE compared to the general population and to study possible predictors of impaired generic HRQoL in PE patients (Paper II).
- To describe the differences in PE survivors with and without dyspnea with regard to general patient characteristics, exercise capacity and disease-specific HRQoL. Furthermore, we explored possible predictors of dyspnea, exercise capacity and disease-specific HRQoL in patients with a history of PE (Paper III).
- To evaluate whether underlying right or left ventricular dysfunction as assessed by echocardiography can explain the presence of dyspnea and/or exercise limitation in long-term PE survivors (Paper III).

3 Materials and methods

3.1 Study design

The present work was designed as an observational cross-sectional study. When this work started, the literature provided rather little information regarding long-term outcomes other than CTEPH in PE patients. As such, although a formal specific hypothesis was not considered for this thesis, the overall objective was to investigate the long-term complications in an unselected cohort with a history of PE.

3.2 Study participants

3.2.1 Identification of cases

The Østfold Thrombosis (TROLL) registry is a VTE registry that includes all patients treated for DVT and/or PE at Østfold Hospital. Østfold Hospital covers Østfold County, Norway, and serves a population of approximately 300,000 inhabitants. The TROLL registry was established in 2005. The inclusion of patients is still ongoing, and the registry is continuously updated. Patients diagnosed, treated and/or followed for any VTE are registered in the TROLL registry. Objective validation procedures for VTE include ultrasound, venography, CTPA, ventilation-perfusion scan (V/Q-scan), magnetic resonance imaging (MRI) and autopsy.

Currently, the TROLL registry includes 5000 patients and is considered to be one of Scandinavia's most comprehensive VTE-specific registries.

All patients with the International Classification of Diseases-10 codes I26.0 and I26.9 were eligible for study inclusion. In the first step, patients diagnosed with PE between 2002 and December 2004 were identified from hospital databases. For the period from 2005 to 2011, patients were identified from the TROLL registry. Then, the electronic medical charts for each patient were reviewed to assure that the diagnosis of PE had been established objectively, i.e., via CTPA or ventilation/perfusion scintigraphy, and that the patient was alive. If the diagnosis of

PE was confirmed, patients were considered eligible if the remaining exclusion criteria were not met (Table 3).

In the next step, patients were sent a written invitation and consent form. After 1-2 weeks, patients who had been sent the initial letter were contacted by study personnel. Further information was given, and if they agreed to participate, they were scheduled for an appointment. The HRQoL questionnaires were sent to the patients either by post or e-mail. Patients were asked to return the questionnaires at the study visit.

3.2.1.1 Inclusion and exclusion criteria

Patients who were alive and between 18 and 90 years old were eligible for study inclusion. A detailed list of exclusion criteria is given in Table 3. We hypothesized that conditions that could possibly interfere with the assessments of dyspnea, functional capacity and HRQoL should be regarded as exclusion criteria. Consequently, patients with psychiatric diagnoses, such as major depression and any psychotic disorder, were excluded. Furthermore, patients living in nursing homes or receiving major help from social services, representing those essentially unable to participate in the activities of daily life, were also excluded. Moreover, patients diagnosed with any degree of dementia or cognitive impairment were also excluded (Table 3).

Although aware of the significant impact of cardiorespiratory diseases other than PE, e.g., COPD and CHF, on HRQoL and functional capacity, we chose not to exclude patients with these conditions. The reason for this approach was that PE is not exclusive to healthy subjects and including patients diagnosed with these common comorbidities would ensure that the study sample better resembles the real-world affected population.

Table 3. Detailed list of exclusion criteria

Major psychiatric disorders • Psychotic disorder, e.g., schizophrenia, schizoaffective diagnosis or any diagnosis of delusional syndrome • Major depression
Cognitive impairment • Diagnosis of dementia of any degree
Major functional limitations hindering administration of the walk test • Having major help from social services • Living in nursing homes • Paralyzed or amputated limb(s)
Geographically unavailable • Living outside Østfold county or unable to attend the study visit
Age • Under 18 or above 90 years
Not having objectively verified the PE diagnosis
Language barrier hindering the ability to read/answer the HRQoL questionnaire in Norwegian
Unable to provide informed consent

3.2.2 Study population for paper I

Figure 6 displays the overall flow chart for this thesis and a detailed list of the number of patients excluded according to the predefined exclusion criteria. Patients who had complete PEmb-QoL questionnaires were eligible for Paper I. Cases with more than 50% of items missing within a dimension (n=5) were excluded from analyses, leading to a final study population of 213 patients.

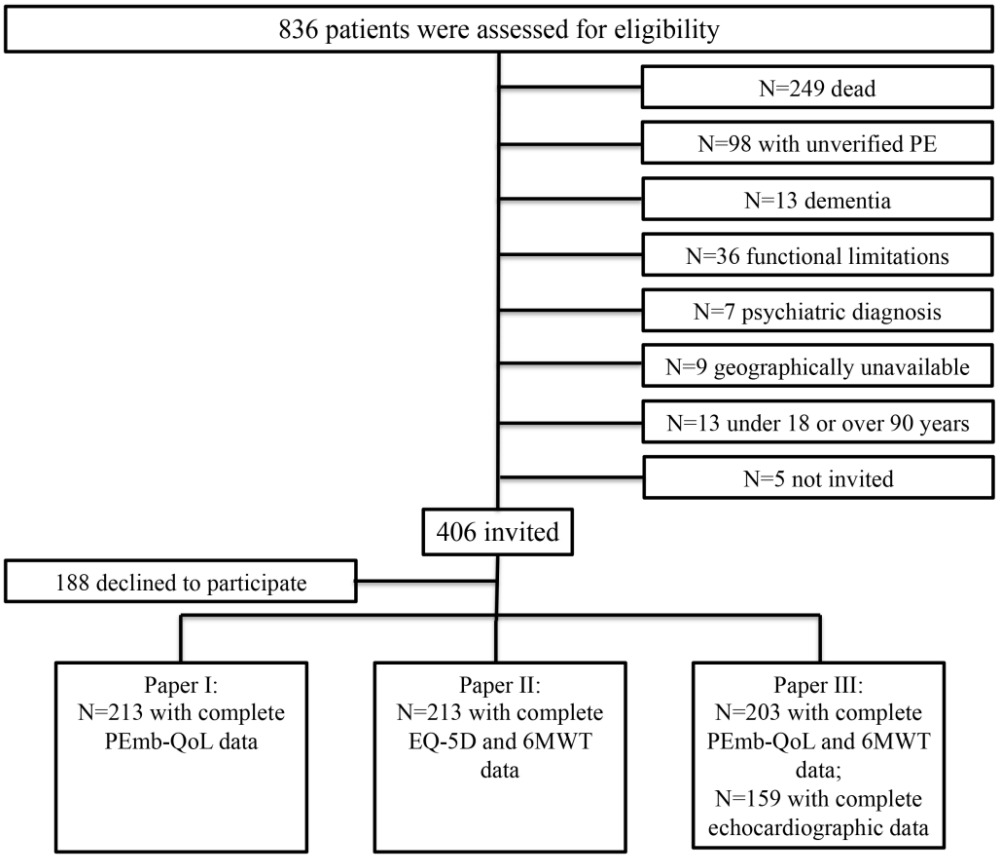
3.2.3 Study population for Paper II

Because the objective of Paper II was to evaluate possible predictors of the generic HRQoL, as assessed by EQ-5D-3L, and the fact that 6MWT results were a potentially important predictor, the data regarding both the EQ-5D-3L and 6MWT needed to be complete. In total, 189 patients declined to participate after one additional patient withdrew consent. Of the remaining 217 participants, four patients had either an incomplete HRQoL questionnaire (missing EQ VAS) or were unable to perform the 6MWT. Thus, the final study population comprised 213 patients.

3.2.4 Study population for Paper III

Paper III required complete data for the PEmb-QoL questionnaire and 6MWT. As such, 14 patients were excluded due to not fulfilling these criteria. One additional patient withdrew consent, leading to a final study population of 203 patients. In this paper, we also included data from transthoracic echocardiography. Although all patients were referred to echocardiography, only 170 underwent the examination. Of these patients, 159 had complete data for both the PEmb-QoL and 6MWT (Figure 6).

Figure 6. Thesis flow chart.



3.2.5 Identification of controls

To more accurately evaluate the HRQoL of our patients, we intended to compare their HRQoL score as assessed by EQ-5D with the normative values of the general population. However, EQ-5D population norm data are not available for Norway. Based on the assumption that the Scandinavian countries are rather similar from a cultural and socioeconomic point of view, we compared our results to the Danish population norms [161]. Possible issues with normative population data are the potential presence of incidental VTE cases and the fact that the controls might be in a different socioeconomical class. The latter in particular may impact HRQoL.

Consequently, we included a second control group from which we could be sure that cases of VTE were absent and in which the controls were more likely to be in the same socioeconomic class. To do so, we asked every patient to give the EQ-5D questionnaire to two acquaintances or relatives who were age- (+/- 5 years) and sex-matched with no previous VTE diagnosis. These controls were then referred to as “buddy controls”. Unfortunately, we did not ask for consent from the buddy controls, which mandated anonymity, restricting the registration of further data pertaining to them.

3.3 Data collection and outcome measures

A specific case record form (CRF) was developed for the present work, which was used to register all data except for the 6MWT and echocardiographic results. The latter two sets of data were recorded manually in separate Excel databases. Data were collected in a stepwise fashion. Prior to the study visit, all the variables that could be retrieved from the electronic medical charts were recorded in the CRF. In the next step, the CRF was further completed at the study visit with comprehensive information from the patients’ medical history and present symptoms, as well as results from the HRQoL questionnaire and 6MWT. If there was any disagreement between the medical chart and the patients’ medical history, the medical charts were reviewed a second time.

3.3.1 Dyspnea

To mirror daily clinical practice, dyspnea was simply registered as present or absent by asking the patients whether they had persistent dyspnea, which was perceived as initiating after their PE diagnosis. Although the NYHA classification system is not validated as a dyspnea grading tool in PE patients, it has been used in the majority of studies evaluating dyspnea in patients with a history of PE. Moreover, the NYHA classification system is feasible and rapid to assess and provides an estimate of the impact of dyspnea on daily life in patients. As such, we used the NYHA classification system to grade persistent dyspnea.

3.3.2 Functional exercise capacity

Functional exercise capacity was assessed by the 6-minute walk test according to published guidelines [114]. In addition, peripheral oxygen saturation (SpO2) was measured before, during and after the walk test. This enabled calculation of the mean decrease in SpO2 by subtracting the resting SpO2 with the lowest value during the walk test. To more comprehensively assess the physical performance of our study population, reference walking distances were calculated for every participant according to the literature [126].

3.3.3 Health-related quality of life questionnaires

HRQoL was assessed by both disease-specific, i.e., PE-mb QoL and generic, i.e., EQ-5D, questionnaires. For all papers, the questionnaires were sent to the patients prior to the scheduled study visit. Incomplete forms were completed at the study visit.

The translation procedure for the PE-mb QoL was performed according to international guidelines with forward-backward translation from English into Norwegian [162]. Two bilingual translators, one with a medical background and both with Norwegian as their mother tongue, translated the questionnaire in a first step to Norwegian. Hereafter, one translation was synthesized by merging the two versions. Subsequently, a backward translation to English was performed by a translator with English as her mother tongue. Finally, three independent individuals evaluated the questionnaire by comparing the English and Norwegian versions with regard to semantic, idiomatic, experiential, and conceptual equivalence.

For test-retest validity, the questionnaire was sent to the patients a second time two weeks after their study visit. The external validity was analysed by comparing the PEmb-QoL and EQ-5D-3L results.

The PEmb-QoL questionnaire includes six domains that consist of nine questions with a total of 38 single items. A hypothesized dimensional structure was created based on the contents of the items consisting of the following: *frequency of complaints* (PEmb question one, consisting of eight items), *ADL limitations* (PEmb question four, consisting of 13 items), *work-related problems* (PEmb question five, consisting of four items), *social limitations* (PEmb question six, consisting of

one item), *intensity of complaints* (PEmb question seven and eight, consisting of two items) and *emotional complaints* (PEmb question nine, consisting of ten items). Two items (i.e., items two and three) are descriptive. In the dimensions, the frequency of complaints (question one), ADL limitations (question four), work-related problems (question five) and emotional complaints (question nine) items are reverse scored. The mean dimensional scores are calculated by dividing the respondent's score in that particular dimension by the number of items in the dimension. Consequently, the minimum and maximum score of, for example, the frequency of complaints dimension will range from one (lowest possible score) to five (highest possible score) [143]. Although a summary score is not provided by the original article, a sum score, ranging from 6-27, was calculated by summing each patient's dimensional crude score and dividing by the number of dimensions.

As we used a control group, a generic questionnaire was used, i.e., the EQ-5D-3L. The EQ-5D-3L contains one descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive questions encompass five domains of HRQoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question is answered based on three response options (1= "no problems", 2= "moderate problems", 3= "severe problems"). The 243 (3^5) potential patterns of responses each indicate a unique health state ranging from 11111 for perfect health to 33333 for the worst possible state. The health states can then be converted into a single summary index value, which ranges from 1 (state of full health) to values lower than 0 (states regarded as worse than being dead). These index values are derived from normative values of the general population (EQ-5D population norms). The questionnaire has been found to be valid and reliable in several languages, including Norwegian[151].

3.3.4 Possible predictors of the main outcome measures

Particularly in Papers II and III, in addition to exploring the prevalences of dyspnoea, limited exercise capacity and impaired HRQoL, we attempted to study whether these three outcomes could be attributed to patient- or PE-related factors. Accordingly, based on clinical experience

and previous studies, the following parameters were recorded for every patient: age, sex, body mass index (BMI; kg/m^2), occupation, smoking, comorbidities (any degree of diagnosed CHF or non-asthmatic COPD) at follow-up, active malignancy (treatment within the past six months), disease duration (time from diagnosis to study inclusion), recurrence (the first PE during the inclusion period of 2002-2011 was classified as the index event), ongoing anticoagulation and the proximal extension of the clot at diagnosis according to the scoring system by Ghanima et al. [163].

Of note, in papers I and II, comorbidities were reported separately as different disease entities, e.g., CHF, COPD or cancer. However, in Paper III, in an effort to make the interpretation of the results easier, we reported the comorbidities also in a more standardized fashion with a single score, i.e., the Charlson Comorbidity Index score [164].

3.3.5 Laboratory tests

Based on the hypothesis that biochemical parameters could be associated with or explain the symptoms of dyspnea and reduced functional exercise capacity, the following blood tests were evaluated in all patients directly after the scheduled study visit: the levels of haemoglobin (g/dl) and brain natriuretic peptide (P-BNP, ng/L). The rationale was that low levels of haemoglobin could contribute to dyspnea and reduced exercise capacity. Furthermore, as brain natriuretic peptides are considered signs of strain on the cardiac muscle, we hypothesized that a possible association of levels of P-BNP with dyspnea and/or functional exercise capacity could indicate the presence of a cardiac correlate to these outcomes.

3.3.6 Transthoracic echocardiography

Transthoracic echocardiography (TTE) was one of the outcome measures in Paper III. All patients were informed about the TTE examination and the referral procedure at the scheduled study visit. The TTE examination was performed by a board-certified cardiologist according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging

recommendations [165,166], using a Vivid E9 machine (GE Vingmed Ultrasound, Horten, Norway). The examination was scheduled at the study participants' convenience and was performed between 2012 and 2013. Right ventricular function was assessed by the following four measurements: 1) tricuspid annular plane systolic excursion (TAPSE; cm), a value < 1.7 cm was considered abnormal; 2) estimated pulmonary artery systolic pressure (estPASP; mmHg), a value > 36 mmHg was considered abnormal; 3) peak tricuspid regurgitation velocity (pTRV; m/s), a value > 2.9 m/s was considered abnormal and 4) the global longitudinal strain of the right ventricular free wall (RVGLS; %), a value > -20% (i.e., <20% in absolute value) was considered abnormal. RVD was considered present if any of these four parameters were abnormal. The left ventricular systolic function was assessed by measuring the left ventricular ejection fraction (LVEF; %) by 3D echo and global longitudinal strain (LVGLS; %). Values below 53% and -20% (i.e., <20% in absolute value) were considered abnormal. Diastolic function of the left ventricle was assessed by analysis of the left atrial volume index (LAVI; mL/body surface area), and a value >34 mL/m^2 was considered abnormal. Left ventricular dysfunction was considered present if any of these three measurements were abnormal.

3.4 Ethics approval and consent

The present work was approved by the Southeastern Regional Ethics committee (REK 2011/2557), and written informed consent was obtained from all patients. The patients were informed that they could withdraw from the study at any point.

3.5 Statistical analyses

All analyses were performed using SPSS v.22-25 (SPSS Inc., Chicago, IL, USA). Findings with P-values less than 0.05 were considered significant.

An overview of the statistical methodology used in this thesis is presented in Table 4. Descriptive statistics are used to present the characteristics of the study population in all three papers. Categorical data are displayed as frequencies, n (%), whereas means with standard deviations (SDs) and medians with interquartile ranges (IQR) are used for continuous data based on the normality of the distributions of the variables. A two-sample *t*-test was used to compare two continuous variables if their distribution was close to normal; otherwise, a non-parametric test (Mann-Whitney) was used. A two-sided chi-square test was used to compare dichotomous variables. For the analysis of possible predictors of dyspnea, 6MWT or HRQoL regression analysis was used. For continuous dependent variables, linear regression was used and for dichotomous variable, binary logistic regression was used. To test the robustness of our models, r^2 was used for linear regression models to estimate the percentage of the effect explained by the model, and for logistic regression models, the Hosmer Lemeshow test was used to estimate the goodness of fit of the model.

Table 4. Overview of the statistical methods used in this thesis.

Statistical Method	Paper I	Paper II	Paper III
Factor analysis (PCA† with varimax rotation)	X		
Spearman's rho	X	X	
Cronbach's alpha	X		
Intra-class correlation	X		
Multiple imputation		X	
Variance inflation factor and tolerance	X		X
Student's t-test		X	
Mann-U-Whitney		X	
Chi-square		X	
Linear regression		X	X
Binary logistic regression		X	X
Bonferroni adjustment			X

†: Principal component analysis

Paper I: Construct validity of the PEmb-QoL was tested by factor analysis using principal component analysis with varimax rotation. A criterion cut-off at eigenvalues >1 was used, and factorial loadings >0.40 were considered high. Criterion validity was determined by correlating the dimensions of the PEmb-QoL with those of the generic EQ-5D-3L. Inter-dimension correlations and criterion validity were calculated using Spearman's rho correlation coefficient. Internal consistency reliability was calculated with Cronbach's alpha [167] and was considered adequate at the 0.7 level or above [168]. Test–retest reliability was analysed using intra-class correlation coefficients (ICC) between the two different measurements at different time points. Missing values were treated in accordance with the recommendations in the literature; if data for half of the items or fewer within a dimension were missing, they were replaced by the mean value

of the respondent's completed items in the same dimension. Cases with more than 50% of the items missing within a dimension were excluded from the analyses [138].

Variance inflation factor (VIF) and tolerance were used to check for multicollinearity between PEmb-QoL dimensions. A VIF value above > 5 or a tolerance <0.20 was considered suggestive of multicollinearity [169].

Paper II: In this paper, the primary aim was to determine the HRQoL, measured by the EQ-5D-3L, of the PE patients compared to the buddy controls and population norms. For the latter, age and sex adjustment was performed by weighing the population norm EQ-5D index values and EQ VAS according to the distribution of our sample, as recommended by Hjermstad et al. [170].

To analyse possible predictors of HRQoL, variables deemed predictive of HRQoL were first identified using univariate analysis (Spearman's rho). Correlations below the significance level of α=0.1 were retained in the multivariate regression analysis. Of note, the EQ-5D-3L index values deviated from normality. In an attempt to surpass this obstacle, logarithmic transformation was performed. However, analysis of the regression model residual plots revealed that the issue remained. As such, a binary logistic multiple regression analysis was performed instead with the possible predictors tested against each of the five EQ-5D-3L dimensions (mobility, self-care, usual activities, pain and discomfort and anxiety/depression) that were dichotomized, i.e., problems versus no problems. As the EQ VAS scores were normally distributed, multiple linear regression was performed.

The multiple imputation model was used to address missing values in the EQ-5D questionnaires of the buddy controls who did not have the possibility to complete the questionnaires during a study visit. Cases with missing EQ VAS values were omitted.

Paper III: To explore possible determinants of the outcomes of dyspnea, the 6MWT and PEmb-QoL sum score (dependent variables), three regression models were generated (one logistic and two linear, respectively). Independent variables with a significance level below alpha = 0.1 in the univariate regression models were retained in the multivariate regression analysis using the enter

model. Of note, in our study, the objectives were to evaluate whether there were independent associations among dyspnea, 6MWT and PEmb-QoL sum score. As such, dyspnea was included in the models with the 6MWT and PEmb-QoL sum score as dependent variables and the 6MWT in the model with the PEmb-QoL sum score as dependent variable.

Because the PEmb-QoL sum score was not normally distributed, log-transformation was performed. Subsequently, variables were tested for independency in a multivariate linear regression analysis (enter model). Because three different multiple regression analyses were performed, the p-value was adjusted in the final multivariate model according to the Bonferroni correction, and a two-sided alpha < 0.017 ($0.05/3$) was considered significant. The echocardiographic parameters were evaluated as possible determinants of dyspnea and the 6MWT in a similar fashion as mentioned above. The parameters were dichotomized based on the abnormality thresholds, i.e., normal versus non-normal. All models were adjusted for age, sex and BMI as well as Charlson Comorbidity Index scores. Because we used two dependent variables in these analyses, the p-value was adjusted according to the Bonferroni correction, and a two-tailed alpha < 0.025 was considered significant.

4 Summary of results

4.1 Paper I

Quality of life after pulmonary embolism: First cross-cultural evaluation of the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire in a Norwegian cohort.

A total of 218 patients completed the PEmb-QoL questionnaire. Five patients were omitted due to missing more than 50% of the values. Thus, the final cohort consisted of 213 patients with a median time (IQR) from PE diagnosis of 3.6 years (1.8-6.5). Ninety-five patients (45%) were female, and the mean age at inclusion was 60 years (SD 15). Eighty-five of the 131 patients (65%) who reported not working were retired.

The internal consistency tests revealed that 71% of the cumulative variance was explained by the six factors produced from the principal component analysis with a Cronbach's alpha of 0.94. These findings indicate that the items in the questionnaire scales/subscales were adequately homogenous, thus representing good internal consistency.

We analysed the criterion validity by assessing to what extent the Norwegian version of the PEmb-QoL related to an external criterion, i.e., the EQ-5D-3L. The correlation analysis (Spearman's rho) displayed factors related to ADL and work/regular activities associated with the dimension of "usual activities" in the EQ-5D. Factors pertaining to pain and emotional complaints were correlated to the domains of pain and anxiety in the EQ-5D. Hence, the Norwegian version of the PEmb-QoL had good criterion validity.

A total of 145 patients (68%) completed the questionnaire a second time. There was a significant difference in age and time from diagnosis between non-responders and responders (non-responders were younger and had shorter disease durations). The ICC ranged from 0.75 to 0.86, with all factors being significant, indicating good test-retest reliability.

In conclusion, the Norwegian version of the PEmb-QoL was found to have overall good internal and external validity and repeatability.

4.2 Paper II

Health-related quality of life after pulmonary embolism: a cross sectional study

In total, 213 patients with a mean age of 61 years (SD 15) were included in this study. One hundred seventeen (55%) were males, and the median time since diagnosis was 3.8 years (range 0.3-9.5). The majority of the patients (89%) had been diagnosed with PE more than 1 year prior to study inclusion.

PE patients reported more problems in all five EQ-5D dimensions compared to both the general population and the "buddy controls", $p<0.05$. This impairment in HRQoL was also observed on the EQ VAS, on which patients with PE had a mean score of 67 (SD 21) compared to 81 and 80 (SD 19), in the general population and "buddy controls", respectively ($p<0.005$).

Factors that were independently associated with reduced HRQoL were the 6-minute walking distance, persistent dyspnea and unemployment. For every metre increase in the 6-minute walking distance, patients had, on average, a 0.09 increase in their EQ VAS scores (unstandardized beta 0.09, SE 0.01, $p<0.005$). Persistent dyspnea was associated with a mean reduction of 11 in the EQ VAS score (unstandardized beta -11.27, SE 2.56, $p<0.005$). Finally, being unemployed was associated with a mean decrease of 9 points in the EQ VAS score (unstandardized beta -8.98, SE 2.97, $p<0.005$).

In addition, the 6MWT results were independently associated with all of the EQ-5D dimensions, except for "pain and discomfort" (OR 0.99, 95%CI 0.98-0.99).

4.3 Paper III

The impact of post-pulmonary embolism syndrome and its possible determinants

Of the 203 participants, 96 patients reported dyspnea (47%). Dyspneic patients had a higher BMI (29.5 vs 27.7, p=0.009), a higher frequency of unemployment (32 vs 18, p=0.009) and a higher average Charlson Comorbidity Index score (1.05 vs 0.53, p<0.005).

Dyspneic patients walked shorter distances on the 6MWT compared to non-dyspneic patients (413 metres vs 488 metres, p<0.005). However, even in the subgroup of patients (n=113) with no known comorbidities (Charlson comorbidity index=0), dyspneic patients were observed to have reduced 6-minute walking distances compared to patients without dyspnea (452 metres vs 503 metres, p=0.03).

Impaired HRQoL was observed in patients reporting dyspnea, as they had worse scores in all of the PEmb-QoL dimensions compared to non-dyspneic patients. This significant impairment was also observed in the subgroup of patients with no known comorbidities (n=113).

All of the predefined variables deemed possible determinants of persistent dyspnea failed to show any significant association with dyspnea in the multiple regression analysis. In addition to sex, age and BMI, higher PESI-score and higher RV/LV-ratio at the time of diagnosis of PE were independently associated with the 6MWT results at follow-up (B=-1.2, SE 0.5 and B=-63.7, SE 23.3, respectively). HRQoL was determined by unemployment and ongoing anticoagulation treatment, which were found to be associated with a higher PEmb-QoL sum score (worse HRQoL), p<0.05.

There was an independent inter-related association among dyspnea, the 6MWT results and the PEmb-QoL sum score in all three multiple regression analyses.

One hundred fifty-nine participants had available echocardiographic data, of whom 87 patients (54%) reported dyspnea. There were no significant differences observed between patients with and without dyspnea concerning left ventricular dysfunction. None of the echocardiographic variables were independently associated with dyspnea. However, patients with an abnormal TAPSE (TAPSE <1.7 cm) performed significantly worse on the 6MWT (unstandardized beta -88 metres SE 36, p=0.014).

5 Discussion

5.1 Methodological aspects

Many methodological limitations may influence the reliability of study results in medical research. These may be encountered during study design, data collection, data analyses, and data presentation.

Major methodological aspects in observational studies include selection bias, recall bias, imprecision of measurements and confounding. The degree to which the findings of this thesis may have been influenced by these issues are discussed below.

5.1.1 Study design

The three papers presented in this thesis were all designed as cross-sectional studies. Cross-sectional studies have several advantages. One is feasibility, enabling the inclusion of large numbers of patients within a short time. Furthermore, because the participants are only evaluated once, there is no loss to follow-up [171]. However, the disadvantages include the inability to investigate temporal relations between associative variables and the absence of a firm conclusion regarding causality. To this end, there are issues with establishing whether the observed associations are a consequence or a cause of the disease. As such, our results cannot exclude potential reverse associations between our dependent (e.g., persistent dyspnea) and independent (impaired HRQoL) variables (Paper II). Furthermore, it is also important to mention that due to the cross-sectional design, we cannot exclude that the outcomes of interest in this thesis (dyspnea, exercise limitation, impaired HRQoL and presence of RVD) were present prior to the exposure (diagnosis of PE). Perhaps these obstacles would have been overcome if we had performed the study prospectively. However, the ELOPE study is an example of the difficulties with a prospectively designed study intended to explore outcomes such as dyspnea, exercise limitation and HRQoL in PE patients. Although the study period was three years with five university-affiliated inclusion sites, the study included no more than 80 patients (after loss to follow-up) [7]. However,

the subject being explored by this thesis was novel when this project started. As such, we never aimed to establish a cause-and-effect relationship but rather to descriptively outline these outcomes in a PE population and generate hypotheses for future studies.

5.1.2 Patients selection and potential bias

The primary patient selection objective for this thesis was to include all patients with a history of PE. However, only 25% of the original population was included in the final study cohort. One of the major limitations of this thesis is the absence of data regarding non-participants. To this end, we cannot assess our cohorts' external validity, limiting the generalizability of our results. Of note, however, this was due to the lack of consent from the non-participating patients, which is required by law in Norway. Consequently, although the selection of the participants was consecutive with broad inclusion criteria, we cannot rule out the possibility of selecting sicker patients. It is plausible that patients with persistent symptoms and/or lower HRQoL were more likely to participate, whereas patients who lacked symptoms completely and/or were healthy otherwise chose not to participate. If this bias occurred, it would have more heavily weighted our results towards an overestimation of the prevalence and impact of impaired post-PE recovery. However, it is important to mention that the results in our cohort regarding the frequency of persistent dyspnea, 6-minute walking distances and HRQoL outcome are comparable to those in other similar studies [5,97,107].

Additional issues that are noteworthy are the inclusion of patients with the time from their PE diagnoses to study inclusion ranging from 3 months to 10 years, with the majority of the patients being diagnosed more than 1 year prior to study inclusion. It could be argued that including patients long after their diagnosis favours the assessment of the outcomes of dyspnea, exercise capacity and HRQoL, as the obtained results will be less likely to improve with time. This theory is supported by the prospectively designed ELOPE study, which showed that although PE survivors had reduced HRQoL and exercise capacity shortly after their PE diagnosis, by 1 year, the

majority of the patients had normalized their HRQoL results [8]. However, when exploring patient-reported outcomes, the factor of time is a variable that needs special consideration. By including patients who have been diagnosed with PE up to 10 years prior to study inclusion, it becomes difficult to assess if the observed results regarding the outcomes are indeed related to the exposure of interest (PE). In contrast, selecting a lower arbitrary cut-off threshold for the time since PE diagnosis may lead to selection bias. Finally, we did not formally exclude patients with CTEPH. However, only one patient was found to have an established CTEPH diagnosis in the final study cohort.

5.1.3 Control groups

In Paper II, we included two control groups. EQ-5D valuation sets for the general Norwegian population are lacking. We therefore compared our cohorts' HRQoL results to those of the Danish population. The conceptual framework of a given health state may, however, be influenced by cultural differences. As such, it cannot be excluded that a comparison to the Norwegian population would have contributed to a lesser degree of difference in HRQoL. However, the Scandinavian countries are considered rather similar from both socioeconomical and cultural standpoints.

The use of "buddy controls" was an attempt to control for incident cases of VTE, which was not possible in the general population. Furthermore, because "buddy controls" were acquaintances, friends, relatives and/or family members, it would be more likely that they were in the same socioeconomic status as the participants, consequentially enabling a better comparison regarding HRQoL. Unfortunately, as we did not obtain consent from the "buddy controls", we were unable to collect anthropometric data on this control group, leading to the possible inclusion of "very healthy" controls, which may have overemphasized the observed differences between patients and "buddy controls". Furthermore, although it is most likely that the buddy controls were age- and sex-matched, we could not objectively control this. Additionally, as mentioned above, because we did not have demographic data on the non-participants, we also cannot rule out that inclusion of "buddies" among non-participants would have affected the observed difference in HRQoL between subjects and controls. However, the test scores of "buddy

controls" were comparable to those of the general population, implying that the effects of these issues were minor.

Choosing matched random control subjects without a VTE event from the national registry would perhaps have been a better option as a control group. However, this approach is cumbersome and would have contributed to an extended study period, reduced cost-efficiency and lower response rates on the questionnaires.

5.1.4 Measurement issues

The three fundamental outcome measurements in the present work were persistent dyspnea, reduced functional exercise capacity and HRQoL. Below, the imprecision(s) of each measurement is discussed.

5.1.4.1 Dyspnea

Dyspnea is a complex symptom that is difficult to assess. Although dyspnea could be measured objectively, e.g., tachypnoea and/or hypoxemia, it is often registered as a patient-reported outcome, making dyspnea a measurement prone to recall bias. Because the majority of the patients in the present work had been diagnosed with PE more than a year prior to study inclusion, their perception of whether their dyspnea was due to their PE, i.e., emerged after the PE or was present before, could be questioned. It is possible that patients who experienced additional diseases or complications after their PE that were unrelated to their PE believed their dyspnea was caused by the PE. However, identifying the appropriate inclusion period presented a paradox in this matter. Including newly diagnosed patients with PE would, on the other hand, raise the argument that the reported persistent dyspnea will eventually subside, which has been observed in a recent study [8].

Although not validated in PE patients and not a dyspnea grading score per se, the NYHA classification system is a rapid, feasible grading tool that is widely used for the evaluation of dyspnea. The majority of studies evaluating dyspnea after PE have used the NYHA classification

system [3,88,107]. Therefore, to make comparisons between study populations, the NYHA classification system was used. However, it is plausible that NYHA could have been insensitive to subtle changes. To this end, it cannot be excluded that if a more comprehensive dyspnea scoring questionnaire such as the SOBQ had been used, the results of this thesis could have been interpreted more accurately. In addition, registering dyspnea simply in a dichotomous fashion may also have resulted in overestimation of the presence of this symptom. However, available scoring instruments for dyspnea have been studied scarcely in PE patients. As such, little is known concerning their abnormal vs normal thresholds or prognostic performance in patients with a history of PE. Consequentially, from a clinical point of view it is debatable if the results from a dyspnea questionnaire will aid the treating physician in its evaluation and assessment of the patient. To this end, at least currently, while a specific score on a dyspnea questionnaire will not impact the management of the patients a simple question of does the patient have dyspnea will.

5.1.4.2 Functional exercise capacity

The benefits of the 6MWT over the other submaximal functional exercise capacity tests have been outlined previously in this thesis. Apart from being the walking test most frequently used in studies evaluating exercise capacity after PE [107,155], it is also the only "walking test" with published practical guidelines [114]. However, the 6MWT has some potential measurement imprecision that merits further mention. The ATS guidelines provide a list of possible factors that may contribute to the variability of the 6-minute walking distance [114]. Although several of these were accounted for in the statistical analyses, e.g., sex, BMI, and comorbidities, other variables were not. By performing the test once we could not rule out temporary factors unrelated to the PE diagnosis affecting the performance of the participants, such as respiratory infections, pain, weight gain, general deconditioning and/or lack of motivation. Furthermore, an additional issue is what the measurement actually represents. In contrast to other common cardiorespiratory diseases, e.g., heart failure and COPD, the 6MWT has not been extensively evaluated in PE patients. Accordingly, there are no available data regarding abnormal thresholds and minimal clinically important differences. Consequently, it could be difficult to interpret the 6MWT results in our study population.

Furthermore, although the calculation of predictive 6-minute walking distances for every patient perhaps added some benefits to the interpretation of the results, it is important to mention that these prediction models were based on healthy subjects in the state of Arizona in the US from 1972 to 1973 [126]. As such, both from a geographical and a point-in-time perspective, it could be argued that the reference values are not valid for a Norwegian population in the 21st century.

Finally, a walking test lacks the ability to provide information regarding the cause of dyspnea during exertion and the mechanism underlying exercise limitations. Given that exercise limitation was one the main outcomes in this thesis, it could be argued that CPET would have been far more informative. CPET has the ability to distinguish between dyspnea caused by deconditioning and dyspnea caused by cardiorespiratory pathology [116]. It is also, an exercise test that has been increasingly advocated for unexplained dyspnea in PE survivors [84,172]. However, it is expensive, not readily available and requires adequate knowledge in its interpretation.

5.1.4.3 HRQoL

HRQoL is an outcome measure that is evaluated through self-report. Due to its subjectivity and dynamic nature, it is difficult to assess. HRQoL can lead to measurement bias from two general sources. First, HRQoL is dependent on the respondents' frame of reference [173]. Their frames of reference are in turn influenced by their experiences in life. As such, the items on a questionnaire may be interpreted differently by various respondents, although the attribute being measured is the same [173]. Second, an individual's concept of health is susceptible to change. This change could be time- or condition-dependent, a phenomenon that is defined as "response shift" [174]. For example, during the course of a disease, a patient may experience recalibration, reprioritization and reconceptualization [173]. Although response-shift is a concern, particularly in longitudinal studies, the abovementioned general measurement bias issues in HRQoL are applicable to all study designs and instruments that intend to measure HRQoL as an outcome.

There are further considerations to address regarding the specific instruments used in this thesis. The EQ-5D questionnaire is simple and brief, which are substantial benefits. However, as opposed to, for example, the SF-36 questionnaire, it does not produce an automatic score in its

dimensional structure. Instead, it produces a health state that is then weighted against the health states generated in the general population, thus generating a single index value [151]. These index values were originally developed by economists to facilitate statistical inferences in health economics studies [175]. These facts suggest two possible considerations. First, index values may not be applicable to the assessment of HRQoL in clinical studies. Thus, the dimensional structure should only be subject to descriptive statistics and, at most, contingency table inferences. Second, if more advanced statistical methods, i.e., multiple regression analyses, are performed, then the EQ VAS score should be used as the dependent variable [175]. These arguments are also reinforced by the developers of the EQ-5D, i.e., the EuroQoL group [176,177]. The results of Paper II, in which the index values and multiple regression analysis were used for comparisons between groups and the identification of possible predictors of HRQoL, respectively, may be affected by the abovementioned considerations. However, the descriptive statistics, contingency tables and regression analysis with EQ VAS as the dependent variable rendered similar results, indicating that the measurement bias in this instance was minor. It could be argued that by using the SF-36, this imprecision could have been avoided. However, the SF-36 is a more comprehensive questionnaire with far more questions that could potentially lead to lower response rates and more missing values.

The development of the PEmb-QoL questionnaire was based on semi-structured interviews with 10 patients with a history of PE [145]. Although it has been shown to be valid, it is not implausible that the population from which it was derived was too small [178]. This might have led to overemphasizing or missing relevant items capturing all aspects of HRQoL in PE patients. Furthermore, the item regarding whether respondents would be worried if they stopped anticoagulation therapy is not applicable to patients in whom anticoagulation has already been withdrawn. The authors do not provide an explanation on how to score this question in such cases. Additionally, the PEmb-QoL does not provide a summary score. Published studies, including this thesis, have used ad hoc solutions to overcome this issue, generating the question of whether this approach accurately represents the global disease-specific HRQoL in PE patients as assessed by the PEmb-QoL. Although these aspects of the PEmb-QoL questionnaire are potential measurement biases that need to be considered when interpreting the results presented in this

work, the PEmb-QoL questionnaire is to date the only available disease-specific questionnaire for PE patients.

5.1.5 Confounding factors

Apart from selection and measurement bias, confounding factors are a major methodological issue in cross-sectional studies. The specific criterion for a confounding factor is a variable acting as a risk factor for both the exposure and the outcome that is not a result of the exposure or outcome. Due to the nature of a cross-sectional study in which the exposure has already occurred, usually the only solution at hand is to adjust for possible confounders via different statistical methods, e.g., stratification, regression or propensity scores. In such cases, one of the most essential steps is to identify possible variables that could act as confounders.

Patient-reported outcomes such as dyspnea and HRQoL are particularly susceptible to the effects of numerous confounding elements. Education, employment status and income are factors closely related to public health and, by extension, to HRQoL [179,180]. Moreover, factors such as self-reported mental illness, chronic conditions and chronic pain are also important possible confounding factors to consider when evaluating patient-reported outcomes [179,181]. Although an attempt was made to minimize this issue by excluding, for example, patients with major psychiatric disorders or by controlling for unemployment and Charlson Comorbidity Index scores in the regression models, possible confounding variables such as chronic pain and the use of antidepressants and/or anxiolytic drugs were not registered. Additionally, it would also have been useful to record if the comorbidities were present prior to the PE diagnosis. Moreover, information regarding any "major changes and/or happenings", e.g., the loss of a family member, in the participants' lives during the past three months prior to study inclusion would perhaps have had identified further possible confounders. Not accounting for these possible confounders was due to the lack of sufficient knowledge in the field of patient-reported outcomes on the part of the authors combined with limited existing literature regarding this aspect of PE. Consequently, we cannot rule out that the high prevalence of dyspnea and impaired HRQoL in our cohort could partially be confounded by unmeasured variables, thus leading to residual confounding bias.

Several further aspects need to be mentioned: In Papers II and III, the multiple regression analyses were adjusted for a wide range of covariates. Although a priori defined and conceived of as being important to account for from a clinical point of view, adjusting for numerous covariates and non-confounders may introduce bias. Additionally, when dichotomizing important covariates (such as unemployment), which have a significant impact on the point estimate, may also introduce bias. However, these formal statistical criteria are usually applied when the intention is causal inference. Again, however, this was not the primary aim of this thesis, and in addition, our results are comparable to those of other studies.

5.1.6 Methodological aspects of the statistical analyses

In Papers II and III, multiple regression analysis was performed to find predictors of the outcomes of dyspnea, exercise limitation and HRQoL. From a statistical point of view, several obstacles were encountered during this process. In Paper II, the EQ-5D index values did not meet the assumption of normality, which could not be circumvented by a logarithmic transformation. As such, the dimensional structure was dichotomized to “problems” vs “no problems”, allowing the application of logistic regression with the dimensions as the dependent variable. However, although this method has been used in other studies [182], it is not fully endorsed by the EuroQoL group. Furthermore, this method also raises the issue of multiple testing. Perhaps a more convenient approach to this statistical dilemma would have been to a priori define, in addition to the EQ VAS score, one of the EQ-5D dimensions as a dependent variable or to use statistical methods to adjust the significance level, e.g., the Bonferroni correction. Of note, our main results would not have differed based on a hypothesized post hoc Bonferroni adjustment ($\frac{\alpha}{\kappa} = \frac{0.05}{5} = 0.01$). Moreover, the independent variables significantly correlated with the EQ-5D dimensions were also significantly associated with the EQ VAS score in the linear regression model, reinforcing the findings based on the dimensional structure.

In Paper III, a transformation of the PEmb-QoL sum score was performed due to the non-normal distribution of this outcome. Transforming dependent variables representing HRQoL outcomes may distort the scale and make the interpretation of the effect size difficult [138]. However, logarithmical transformation is suggested by some to be the most appropriate method in such cases [183].

5.1.7 Missing data

The concern regarding missing data is based on the potential of introducing bias, resulting from the available data not accurately representing the true study population. Several statistical methods may be used to address missing data. A popular option is to impute the missing values based on the data that have been observed. This approach is considered to be one of the most robust methods when dealing with missing data [184]. In Paper I, we excluded patients if more than 50% of the PEmb-QoL items (five patients) were missing and substituted missing data with imputed values if <50% were missing (seven patients). Although that approach is advocated for by some [138], others recommend omitting cases with more than 25% missing values for any item [185]. Nevertheless, only 5% of the study population had issues with missing data, and both the number of missing values and the method used to address them were provided to the reader.

Missing data on HRQoL questionnaires may also contribute to an observer effect. The definition of the observer effect is conditional based on the type of research. In studies pertaining to HRQoL, the presence of an investigator when forms are filled out may influence HRQoL results [186]. In our studies, incomplete questionnaires were completed during the study visit, albeit without encouragement. This may have affected our HRQoL results for two reasons. First, the patients may have reported improved responses due to the presence of the investigator. Second, the questionnaires were completed in two separate settings and at different points in time.

In Paper II, a second control group, i.e., buddy controls, was included. The response rate of the buddy controls was 42% (177 out of potential 426 buddy controls if every patient forwarded the questionnaire to two buddies). Because we did not have the possibility to request completion of the EQ-5D questionnaires from the “buddy controls”, multiple imputation was used.

Consequently, due to the anonymity and the low response rate, we cannot rule out the possibility of the imputed values having over- or underestimating the HRQoL results of the buddy controls. However, their test scores were comparable to those of the general population.

5.2 Discussion of main findings

The state of knowledge regarding patient-reported outcomes and functional exercise capacity in PE survivors was limited when this work was initiated. Moreover, the majority of the handful studies published at that time were from a single centre in the Netherlands. Since then, patient-reported outcomes in PE survivors have gained attention, and impaired post-PE recovery has been increasingly recognized as an important research field in PE survivors.

5.2.1 Paper I

To enable a more comprehensive evaluation of HRQoL in our study subjects, we translated and validated the PEmb-QoL questionnaire in Paper I. The principal component factor analysis yielded six factors. Table 5 displays a comparison between our factorial loadings and those in the original article by Klok et al [143]. Our factorial loadings clustered adequately in relation to the items, indicating good construct validity. Furthermore, the comparison to the original study reveals a n approximately similar loading pattern. Recent studies validating the PEmb-QoL in other languages have reported similar clustering of factorial loadings, although their factor analyses only produced three to four factors [146-148]. Discrepancies in the number of factors and their relation to the various items is, however, described as an existing phenomenon in the cross-cultural validation of questionnaires [187]. The observed discrepancies between our study and other validation studies may be attributed to slightly different study populations. For example, patients included in the French validation study had a median time from PE diagnosis of 15 months [147]. Our participants were diagnosed with PE a median of 3.6 years prior to study inclusion.

Table 5. Summarized factorial loadings in the original validation article compared to our study. Only the range of highest loading factors and the predominantly related items are presented.

PEmb-QoL	**Klok et al** [143]		**Tavoly et al** [188]	
Domain and related items	Item(s)	Factorial loadings	Item(s)	Factorial loadings
Frequency of complaints (1a-1 h)	1(a-g)	0.608-0.772	1 (a-d)	0.46-0.79
Limitations of ADL (4a-4 m)	4(b-m)	0.568-0.860	4 (b-m)	0.50-0.84
Work-related problems (5a-5d)	5 (a-d)	0.603-0.672	5 (a-d)	0.6-0.75
Social limitations (6)	6,7	-	6,7	-
Intensity of complaints (7,8)	8	0.507	8	-
Emotional complaints (9a-9j)	9 (a-h, j)	0.439-0.834	9 (a-b, d-j)	0.52-0.88

Internal consistency and reproducibility tests revealed good performance of the Norwegian version of the PEmb-QoL questionnaire. However, the external validity showed only modest correlation to the EQ-5D dimensions ($0.29 \leq r \leq 0.64$), as opposed to other studies that have reported stronger correlations between their factors and the dimensions of the criteria [146,147]. One plausible explanation may be that all other validation studies have used the SF-36 as a criterion, which is a far more comprehensive questionnaire.

Finally, all four European validation studies have reported an issue with the flooring effect (better HRQoL) in the majority of the PEmb-QoL dimensions [143,146,147,188]. Conversely, the recent Chinese validation study reported issues with ceiling effects [148]. A possible explanation may again be the inclusion of participants long after their diagnosis or recruiting patients with fewer comorbidities.

5.2.2 Paper II

Long-term PE survivors reported worse HRQoL in all EQ-5D dimensions compared to the age- and sex-matched population and “buddy controls”. Additionally, the global self-assessment scores, i.e., EQ VAS and EQ-5D index values, were also reduced in PE survivors in comparison to the two

control groups. These findings are supported by both past and recent studies. In the study by Klok et al, PE survivors had worse HRQoL in all of the SF-36 dimensions [6]. Of note, however, compared to our population, that study included a significantly higher proportion of patients with cardiopulmonary comorbidities and cancer [6]. A subsequent study with far fewer patients with cardiopulmonary diseases observed results similar to ours when comparing the HRQoL of PE patients to that of the general Dutch population [5].

Patients with impaired HRQoL tended to more frequently struggle with persistent dyspnea and being unemployed. Although neither of these covariates were included in the two abovementioned studies, a recent study has observed similar findings regarding the association of dyspnea and reduced HRQoL [8]. This is, however, not surprising. Correlations between these covariates and the outcome of HRQoL have previously been established in studies evaluating other cardiopulmonary diseases [189,190]. Moreover, contrary to the study by Klok et al, we did not find the anticipated associations between HRQoL and BMI or cardiorespiratory comorbidities. Apart from the high number of included patients with comorbidities in their study (63% vs 15%) as a possible explanation, this discrepancy could also be due to the goodness of fit of their regression model (r^2), which was rather low (r^2 range 0.01-0.12), indicating that their model was not precise [6]. Furthermore, a prospectively designed study did not find asthma and COPD to be significant determinants of HRQoL [8]. However, at one year the HRQoL of the study population was comparable to that of the general population, contrasting other studies by indicating normalisation of HRQoL within one year [8]. A recently published study based on the data from the prospectively designed PREFER registry [191] reported a reduced HRQoL, as assessed by the EQ-5D, in 1399 PE patients compared to that of the general population [192]. In this study, improvement of HRQoL overtime was also observed. Although, this improvement was mainly driven by the surviving patient population. In addition, they reported several comorbidities as being significant determinants of HRQoL [192]. Nevertheless, this particular topic has been a major subject of debate in which some suggest the impaired HRQoL is caused by comorbidities and/or deconditioning [7], whereas others argue that possible associations with the PE event itself cannot be ruled out [157]. To this end, it is important to mention that although coexisting comorbidities probably play a

central role in impaired HRQoL in PE patients, we cannot rule out that the diagnosis of PE in addition to other comorbidities could very well be the factor that tips the patients over the edge.

5.2.3 Paper III

5.2.3.1 Dyspnea

Forty-seven percent of the study population reported persistent dyspnea which they perceived to be newly onset after their PE diagnosis. The majority of the patients (86.5%) reported mild dyspnea, i.e. NYHA II. These observations are in in line with previous studies evaluating dyspnea in PE survivors [3,50]. The multiple regression analysis failed to find any of the variables predictive of dyspnea. These findings contradict the results from the largest study evaluating dyspnea in PE patients [3]. In that study, persistent dyspnea was shown to be determined by cardiopulmonary comorbidities rather than the PE event. A possible explanation could be that one-third of their population had cardiopulmonary diseases. Another possible cause could be the classification of comorbidities according to the Charlson Comorbidity Index in our study. The Charlson Comorbidity Index includes conditions such as hypertension, diabetes mellitus and peptic ulcer [164], which do not necessarily contribute to dyspnea. Consequently, this approach may have diluted the real effect of cardiopulmonary diseases as a possible significant determinant of dyspnea. Although the ELOPE study concluded that deconditioning is the main driver of reduced exercise capacity and in extension dyspnea their results failed to find pulmonary diseases significantly associated with these outcomes [7].

Dyspnea is a common, albeit complex, symptom in PE survivors. The mechanisms contributing to persistent dyspnea in PE-patients require further clarification. Although deconditioning and comorbidities could reveal itself to be the main drivers of this symptom, the effect of the PE-event itself is not adequately studied. Traditionally, once CTED, CTEPH and other cardiopulmonary disorders have been excluded the presence of dyspnea in PE survivors has been referred to “unexplained” dyspnea. Furthermore, international guidelines lack any guidance regarding the evaluation and management of these patients. Future studies ought to evaluate

whether an expansion of the diagnostic approach to these patients with CPET, stress echocardiography and functional exercise capacity tests adds any value.

5.2.3.2 Functional exercise capacity

The 6MWT results were independently associated with both dyspnea and the PEmb-QoL sum scores, implying that there is an underlying exercise limitation that may attenuate shortness of breath and impaired HRQoL in PE survivors. This finding is in line with the results of a study evaluating residual thrombosis, showing that patients with dyspnea also had reduced 6-minute walking distances [97]. However, whether the exercise limitation is indeed due to the PE event is unclear. As previously mentioned, because the symptom of dyspnea tends to be exacerbated by exertion, patients may choose a more sedentary lifestyle, ultimately leading to frailty and deconditioning. This claim is supported by the findings of the ELOPE study, which concluded that the observed exercise limitation and increased prevalence of dyspnea were probably due to physical deconditioning [7]. Further substantiating this speculation is a qualitative study reporting that a significant number of PE patients modify their exercise behaviour for fear of either exacerbating the thrombus or causing a haemorrhage [193].

Furthermore, we found that the PESI score and RV/LV-ratio at baseline were associated with worse performance on the 6MWT at follow up. This is supported to some extent by the ELOPE study, which reported that the baseline variables related to the RVD were associated with the 6-minute walking distance at follow-up [8]. As PESI-score and RV/LV-ratio are related to the PE event, this association may indicate, as opposed to deconditioning being the core factor resulting in exercise limitation, that the PE event affects long-term exercise capacity. However, this association should be regarded with caution due to the single measurement of exercise capacity, unavailable data regarding residual thrombosis and a time from PE diagnosis longer than three years.

Although the available body of evidence suggests deconditioning as the main driver of impaired post-PE recovery, it cannot be excluded that a considerable number of patients with post-PE syndrome will in the future be diagnosed with abnormal cardiorespiratory performance due to their PE.

5.2.3.3 HRQoL

As in Paper II, both dyspnea and unemployment were observed to be significantly associated with the PEmb-QoL sum score. Interestingly, we also found ongoing anticoagulation to be correlated with disease-specific HRQoL, a finding that was not observed in Paper II. It has been described in the literature that VKA therapy is associated with reduced HRQoL because it mandates regular testing, which may be inconvenient for patients [194]. A further explanation may be that ongoing anticoagulation is perceived by the patients as an indication that they have not been cured of the disease, consequently affecting their HRQoL.

However, studies evaluating HRQoL in patients receiving "chronic" anticoagulation have reported conflicting results. Whereas in some populations anticoagulation does not seem to affect HRQoL[195], others have reported covariates, e.g., bleeding events, interactions with other medications, educational status and comorbidities, as possible explanation for the reduced HRQoL rather than the anticoagulative treatment itself [196].

5.2.3.4 Echocardiographic evaluation

Echocardiographic evaluation was performed in 159 patients (78%). There were no clinically significant differences in left ventricular function between dyspneic and non-dyspneic patients. TAPSE was found to be significantly associated with the 6MWT results, indicating that the observed exercise limitation could be explained by impaired right ventricular function. Studies evaluating persistent signs of RVD and impaired exercise capacity in PE patients have reported similar results, albeit with other echocardiographic parameters [88,197]. According to international guidelines, an abnormal value of TAPSE is highly suggestive of RVD [198]. However, it is important that this finding is interpreted with caution. Generally, as opposed to the left ventricle, the right ventricle has a complex shape, which contributes to difficulties in establishing fixed reference values. In addition, although international guidelines have attempted to quantify echocardiographic evaluations by determining reference values [198], ultrasonography as a diagnostic modality is highly operator dependent. Because the echocardiographic results were not confirmed by a second observer in our study, we cannot rule out possible over- or underestimation of the presented values. Furthermore, defining RVD based on the abnormal

threshold of a single parameter and dichotomizing all echocardiographic variables based on reference values may be inappropriate. Finally, because we did not have available echocardiographic data at diagnosis, we cannot rule out the possibility of a pre-existing RVD. However, from a different perspective, a more important finding in this regression analysis is that the functional exercise capacity in our cohort was not due to left-sided heart disease.

6 Contribution to current and past knowledge

The work in this thesis is in line with the developing knowledge regarding the long-term course of PE. This thesis describes the characteristics of a large cohort of PE survivors and provides additional insights into post-PE recovery. Our studies have identified important knowledge gaps in current scientific literature and highlighted possible areas that need further investigation. Previous to this thesis, it was debatable whether post-PE recovery and in particular impaired post-PE recovery existed (CTEPH excluded). Now, however, owing to some extent to the present work along with work done by others, the scientific community is not only familiar with the concept of post-PE recovery but is working to discover the pathophysiological mechanisms and exploring possible treatment options.

7 Future perspectives

Several noteworthy obstacles exist regarding post-PE recovery. First, the definitions of impaired post-PE recovery/post-PE syndrome and CTED need to be formally established. To do so, the prevalence of persistent dyspnea needs further clarification. In addition, studies need to explore whether there is a cause-and-effect relationship between persistent dyspnea and PE and whether this dyspnea can be objectified. Second, studies need to evaluate whether the high prevalence of dyspnea and impaired HRQoL will remain with the introduction of DOACs. The obvious advantages of DOACs are the absence of regular testing, more reliable drug concentration levels (as opposed to VKA therapy with varying time in the therapeutic range), and reduced bleeding rates. Theoretically, these benefits may alter current reported outcomes of dyspnea and impaired HRQoL. Third, an exceedingly large number of patients diagnosed with low-risk PE will perhaps be managed as outpatients in the future, given that the current literature is in favour of this strategy. As such, it could very well be the case that the perception of the PE diagnosis by the patients will be different, thereby impacting the HRQoL. This needs to be clarified. Fourth, if deconditioning is the key element contributing to exercise limitation and dyspnea, the possible advantages of thorough information regarding the disease, treatment, treatment-related side effects and initiation of early exercise need to be evaluated.

Management-associated questions need further clarification by future studies. It needs to be addressed whether exercise testing adds further value as an adjunct to current recommended assessment strategies of persistent dyspnea in PE survivors. Furthermore, the optimal timing for these evaluations must be established.

Issues regarding available treatment options need to be explored as well. Recent studies have implied that the treatments available for CTEPH may also be applicable to certain CTED patients.

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Appendices

The Norwegian version of the PEmb-QoL questionnaire

Norsk versjon av "The PEmb-QoL Questionnarie"

Spørreskjema om livskvalitet

Instruksjoner for utfylling av spørreskjemaet:

Hvert spørsmål besvares ved å markere svaret som beskrevet. Dersom du er usikker på hvordan du skal besvare spørsmålet, vennligst velg det svaralternativet som passer best.

Disse spørsmålene handler om **lungene** dine. Svarene dine skal beskrive hvordan du føler deg. Du kan også angi i hvilken grad du er i stand til å utføre en del normale aktiviteter.

1. I løpet av de siste 4 ukene, hvor ofte har du hatt noen av de følgende symptomene fra lungene? (Sett ring rundt ett svar på hver linje)

	Hver dag	Flere ganger i uken	Omtrent 1 gang i uken	Mindre enn 1 gang i uken	Aldri
Smerte mellom skulderbladene?	1	2	3	4	5
Smerter i brystet?	1	2	3	4	5
Smerter i ryggen?	1	2	3	4	5
Trykkfølelse?	1	2	3	4	5
Følelse av at det "fortsatt er noe der"?	1	2	3	4	5
"Brennende følelse" i lungene?	1	2	3	4	5
En "irriterende" følelse i lungene?	1	2	3	4	5
Pustevansker eller andpustenhet?	1	2	3	4	5

2. På hvilken tid av døgnet er **symptomene fra lungene** dine mest intense? (Sett ring rundt 1 svar)
    1. Når du våkner
    2. Midt på dagen
    3. Mot slutten av dagen
    4. I løpet av natten
    5. Til alle døgnets tider
    6. Aldri

3. Sammenlignet med for ett år siden, hvordan vil du si at dine **lungers tilstand** generelt sett er nå? (Sett ring rundt ett svar)
    1. Mye bedre enn for ett år siden
    2. Litt bedre nå enn for ett år siden
    3. Omtrent det samme som for ett år siden
    4. Litt dårligere nå enn for ett år siden
    5. Mye verre nå enn for ett år siden
    6. Jeg har ingen problemer med lungene mine.

Norsk versjon av "The PEmb-QoL Questionnarie"

4. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Begrenser dine nåværende lungesymptomer disse aktivitetene? Hvis ja, hvor mye?
(Sett ring rundt ett svar på hver linje)

	Jeg jobber ikke	**JA, begrenser meg mye**	**JA, begrenser meg litt**	**NEI, begrenser med ikke i det hele tatt**
a. **Daglige aktiviteter på jobben**	0	1	2	3
b. **Daglige aktiviteter hjemme** (f.eks. husarbeid, stryke klær, utføre småjobber/reparere ting i huset, hagearbeid osv…)		1	2	3
c. **Sosiale aktiviteter** (slik som dra på reiser, gå på kino, selskaper, shopping)		1	2	3
d. **Anstrengende aktiviteter**, som å løpe, løfte tunge gjenstander, delta i anstrengende sports/fritids aktivitet		1	2	3
e. **Moderate aktiviteter** som å flytte et bord, støvsuge, svømme eller sykle		1	2	3
f. Løfte eller bære en pose med matvarer		1	2	3
g. Gå opp trappen **flere** etasjer		1	2	3
h. Gå opp trappen **én** etasje		1	2	3
i. Bøye deg, knele eller sitte på huk		1	2	3
j. Gå **mer enn en kilometer**		1	2	3
k. Gå **et par hundre meter**		1	2	3
l. Gå ca **hundre meter**		1	2	3
m. Vaske eller kle på deg		1	2	3

5. I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av lungesymptomene? (Sett ring rundt ett svar på hver linje)

	JA	**NEI**
a. Du har måttet **kutte ned på den tiden** du har brukt på arbeid eller på andre aktiviteter	1	2
b. Du har **utrettet mindre** enn du hadde ønsket	1	2
c. Du har følt begrensning i å utføre **visse typer** arbeid eller gjøremål	1	2
d. Du har hatt **vanskeligheter** med å utføre arbeidet eller andre gjøremål (f.eks. det krevde ekstra anstrengelser)	1	2

6. I løpet av de siste 4 ukene, i hvilken grad har lungesymptomene påvirket dine normale sosiale aktiviteter sammen med familie, venner, naboer eller grupper? (Sett ring rundt ett svar)
   1. Ikke i det hele tatt
   2. Litt
   3. Moderat
   4. Ganske mye
   5. Svært mye

7. Hvor mye smerter i området rundt skulderbladene/smerter i brystet har du hatt i løpet av de siste 4 ukene? (Sett ring rundt ett svar)
    1. Ingen
    2. Ubetydelig
    3. Moderat
    4. Ganske mye
    5. Sterke
    6. Meget sterke

8. I hvilken grad har du opplevd andpustenhet i løpet av de siste 4 ukene? (Sett ring rundt ett svar)
    1. Ingen
    2. Meget liten
    3. Liten
    4. Ganske mye
    5. Stor
    6. Meget stor

9. Disse spørsmålene handler om hvordan du føler deg og hvordan tilstanden din har vært de siste 4 ukene som resultat av dine lungesymptomer. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du…
   (Sett ring rundt ett svar på hver linje)

	Hele tiden	**Nesten hele tiden**	**Mye av tiden**	**En del av tiden**	**Litt av tiden**	**Ikke i det hele tatt**
Vært bekymret for å ha fått en ny lungeemboli?	1	2	3	4	5	6
Følt deg irritabel?	1	2	3	4	5	6
Ville du vært bekymret dersom du måtte slutte å ta blodfortynnende legemidler?	1	2	3	4	5	6
Følt at du blir lettere følelsesmessig påvirket ?	1	2	3	4	5	6
Har det plaget deg at du blir raskere følelsesmessig påvirket ?	1	2	3	4	5	6
Følt deg nedfor eller i dårlig humør?	1	2	3	4	5	6
Har du følt at du har vært til bry for familie og venner?	1	2	3	4	5	6
Vært redd for å anstrenge deg?	1	2	3	4	5	6
Følt deg hindret til å dra på en reise?	1	2	3	4	5	6
Vært redd for å være alene?	1	2	3	4	5	6

Takk for samarbeidet.
Vennligst returner spørreskjemaet i vedlagt konvolutt

Erratum list

In Paper I, the frequency of obesity was reported as 5 patients (2.3%). This is incorrect. The correct frequency was 73 patients (34%). A request for an erratum correction has been sent to the journal of Quality of Life Research.

Papers I-III

I

Qual Life Res
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Quality of life after pulmonary embolism: first cross-cultural evaluation of the pulmonary embolism quality-of-life (PEmb-QoL) questionnaire in a Norwegian cohort

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Abstract
Purpose The aim of the current study was to translate and test the psychometrical properties of the disease-specific pulmonary embolism quality-of-life questionnaire (PEmb-QoL).
Methods Patients with a prior history of pulmonary embolism (PE) were identified from the thrombosis registry at Østfold Hospital Trust, Fredrikstad, Norway. All eligible patients were asked to complete the generic EuroQol 5-dimension (EQ-5D) QoL questionnaire as well as the disease-specific PEmb-QoL at baseline and after 2 weeks. Construct validity was tested using principal component factor analysis. Criterion validity was tested using Spearman's correlation coefficients (rho) between EQ-5D and PEmb-QoL. Internal consistency reliability was calculated using Cronbach's alpha coefficient, while test–retest reliability was calculated using the intra-class correlation coefficients (ICC).
Results A total of 213 participants had complete datasets and were included in further analyses. Factor analysis with varimax rotation yielded six factors explaining 71 % of the cumulative variance. Cronbach's alpha coefficient was found to be 0.94, indicating a very good intercorrelation of items. Of the 213 participants, 145 (68 %) completed the questionnaire a second time. The ICC ranged from 0.75 to 0.86, indicating good test–retest reliability. All factors were found significant with p values <0.001. The criterion validity of the PEmb-QoL was confirmed through good correlation with other similar health-related quality-of-life constructs in the EQ-5D.
Conclusions Findings of the current study indicate that Norwegian version of the PEmb-QoL is both valid and reliable, thus representing an important supplement in subjective outcomes measurement among patients sustaining PE.

Keywords PEmb-QoL · HRQoL · Pulmonary embolism · Psychometric evaluation · Disease-specific questionnaires

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Introduction

Pulmonary embolism (PE) is a common medical emergency resulting from the obstruction of the pulmonary vasculature by a clot most often originating in deep veins of the lower extremities or the pelvis [1]. The short-term outcomes after PE are well defined. These outcomes range from transient dyspnea and chest pain to hemodynamic instability and death [2, 3]. The long-term outcomes include persistent dyspnea and development of chronic thromboembolic pulmonary hypertension [4]. Adding the risk of bleeding associated with the use of anticoagulation, these outcomes may have an impact on various aspects related to health-related quality of life (HRQoL).

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While the early clinical outcomes after PE have been extensively studied, there has been little focus on long-term outcomes including psychological functioning. HRQoL after PE is a novel research field, which has recently gained increasing interest [5–7]. HRQoL is measured either by generic and/or disease-specific questionnaires, where a combined generic and disease-specific approach is known to increase sensitivity [8]. Disease-specific HRQoL questionnaires are often regarded as more sensitive than generic questionnaires, at least for outcomes that might be clinically relevant in specific patient populations [9]. Until recently, no disease-specific questionnaire was available for PE. The pulmonary embolism quality-of-life (PEmb-QoL) questionnaire was developed to close this gap [10]. It has recently been used and validated in a Dutch study [7, 11], and to our knowledge, it still remains the only available disease-specific questionnaire in this particular group of patients [11].

The aim of the present study was to translate the PEmb-QoL questionnaire into Norwegian and to validate it in a cohort of patients with a history of PE.

Materials and methods

Patients

Patients who were diagnosed and treated for PE at the Østfold Hospital Trust, Fredrikstad, Norway, between January 2002 and December 2011 were identified from the thrombosis registry of the Østfold Hospital and by searching hospital databases for ICD-10 codes of PE (ICD-10 I26.0 and I26.9). All living patients who had an objectively confirmed diagnosis of PE by ventilation–perfusion scan or computed tomography pulmonary angiogram (CTPA) scan were invited to participate. Patients were excluded if they were <18 or >90 years, deemed incapable of complying with the study procedure, such as language barriers, cognitive problems, or dementia, and if they were geographically unavailable. Moreover, patients living in nursing homes and those who had a major psychiatric diagnosis, including schizophrenia and major depression, were excluded. Five patients from the original cohort were erroneously not invited to participate in the study. The study was performed according to the principles founded in the revised Declaration of Helsinki, and written informed consent was obtained from each individual before entering the study. The study was approved by the Regional Committee for Medical and Health Research Ethics, Norway (REK 2011/2557).

Questionnaires

The pulmonary embolism quality-of-life (PEmb-QoL) questionnaire and the EuroQol 5-dimension, 3-level (EQ-5D-3L) forms were sent to the patients either by e-mail or by post. Patients were asked to complete the questionnaires at home and return them at scheduled study visits. Incomplete forms were completed during the visit at the hospital. In order to determine test–retest reliability, patients were asked to complete the forms a second time. These were sent to the patients 2 weeks after the physical evaluation. Incomplete forms were completed by telephone interview.

The pulmonary embolism quality-of-life (PEmb-QoL) questionnaire

The PEmb-QoL questionnaire is a disease-specific QoL questionnaire [10, 11], which consists of nine questions with a total of 38 single items. A hypothesized dimensional structure was created based on the contents of the items consisting of *frequency of complaints* (PEmb question one, consisting of eight items), *activities of daily life limitations* (ADL) (PEmb question four, consisting of 13 items), *work-related problems* (PEmb question five, consisting of four items), *social limitations* (PEmb question six, consisting of one item), *intensity of complaints* (PEmb question seven and eight, consisting of two items), and *emotional complaints* (PEmb question nine, consisting of ten items). Two items (i.e., items two and three) are descriptive. In the dimensions frequency of complaints (question one), ADL limitations (question four), work-related problems (question five), and emotional complaints (question nine) items are reversely scored. The mean dimensional scores are calculated by dividing the respondents score in that particular dimension by the number of the items in the dimension. Consequently, the minimum and maximum score of, for example, the frequency of complaints dimension will be ranging from one (lowest possible score) to five (highest possible score). The questionnaire was found both valid and reliable in its original validation [11] and has been translated into English according to the standard guidelines [12].

EuroQoL-5 dimension-3 level (EQ-5D-3L) questionnaire

The EQ-5D-3L is a generic HRQoL questionnaire that is widely used [13, 14]. It contains one descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The EQ-VAS is self-rated health on a vertical visual analogue scale (0–100) where the end points are labelled "best imaginable health state" and "worst imaginable health state." The questionnaire has been found valid and reliable in several languages as well as in Norwegian.

Translation procedure

In order to develop a Norwegian version of the PEmb-QoL questionnaire, a forward–backward translation procedure from English into Norwegian was performed according to the recommendations in the literature [12]. Two independent translations into Norwegian were performed by two professional bilingual translators, one with a medical background and both having Norwegian as their mother tongue. Furthermore, four observers synthesized one translation by merging the two versions. The questionnaire subsequently underwent a backward translation to English by a translator with English as her mother tongue. Finally, three independent individuals evaluated the questionnaire by comparing the English and Norwegian versions with regard to semantic, idiomatic, experiential, and conceptual equivalence. Following these procedures, a final version was approved and tested.

Statistical analysis

Means and standard deviations were used to express normally distributed variables, while medians and interquartile range (IQR) were used to express non-normally distributed variables. Construct validity of the PEmb-QoL was tested by factor analysis using principal component analysis with varimax rotation. A criterion cutoff at eigenvalues >1 was used, and factorial loadings >0.40 were considered high. Criterion validity was determined by correlating the dimensions of the PEmb-QoL with the generic EQ-5D-3L. Inter-dimension correlations and criterion validity were calculated using Spearman's rho correlation coefficient.

Internal consistency reliability was calculated with Cronbach's alpha [15] and was considered adequate at the 0.7 level or above [16]. Test–retest reliability was analyzed using intra-class correlation coefficients (ICC) between the two different measurements at different time points. Missing values were treated in accordance with the recommendations in the literature; if data for half of the items or fewer within a dimension were missing, they were replaced by the mean value of the respondent's completed items in the same dimension [17]. Cases with more than 50 % of items missing within a dimension were excluded from the analyses.

Potential multicollinearity between PEmb-QoL dimensions was determined by calculating variance inflation factor (VIF) and tolerance. A VIF value >5 and a tolerance value <0.20 were regarded indicative of multicollinearity according to the published recommendations [18].

All tests were two-sided with a 5 % significance level. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS INC; Chicago, IL).

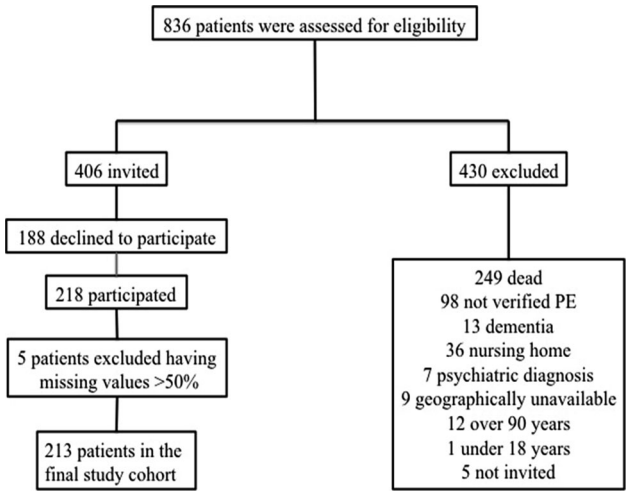

Fig. 1 Flowchart of the patients

Results

A total of 836 patients were identified and assessed for eligibility in this study. A detailed description of the study cohort is given in Fig. 1. Of the 406 eligible patients, 218 agreed to participate and completed the questionnaires at a median time of 3.6 years (IQR 1.8–6.5) after the diagnosis of PE. Five questionnaires had missing values exceeding 50 % and were consequently omitted from the analysis. In seven questionnaires, there were less than 50 % of items missing and these were consequently calculated. In total, 213 patients had evaluable HRQoL data and were included in further analyses. Sociodemographic and clinical characteristics of the patient cohort are summarized in Table 1.

Using the original dimensional structure reported by Klok et al. [11], median scores of the six PEmb dimensions were 1.6 (IQR 1.1–2.4, max 5 points) for the dimension frequency of complaints, 1.3 (IQR 1.0–1.8, max 3 points) for the limitations of activities in daily living, 1.3 (IQR 1.0–2.0, max 2 points) for work-related problems, 1.0 (IQR 1.0–2.0, max 5 points) for social limitations, 2.5 (IQR 1.5–3.0, max 6 points) for intensity of complaints, and 1.5 (IQR 1.2–2.2, max 6 points) for emotional complaints.

Psychometrical characteristics

Validity

Factor analysis (principal component method) with varimax rotation yielded six factors explaining 71 % of the cumulative variance. Factorial loadings are presented as a pattern matrix in Table 2 and scree plot in Fig. 2. After organizing the items according to highest factorial loadings (>0.40), factor one loaded mostly for items concerning activities of daily life.

Table 1 Sociodemographic and clinical characteristics

Variable	$N = 213$
Female, *n* (%)	95 (44.6)
Age in years, mean (SD)	56.7 (15.1)
Age at inclusion, mean (SD)	60.1 (15.3)
Years since diagnosis, median (IQR)	3.6 (1.8–6.5)
Sick leave, *n* (%)	12 (5.8)
Disability pension, *n* (%)	35 (16.4)
Retired, *n* (%)	85 (39.9)
Diagnosis, *n* (%)	
PE	150 (70.4)
PE + DVT	63 (29.6)
PE localization, *n* (%)	
Unilateral	57 (26.8)
Bilateral	142 (66.7)
Not specified	14 (6.5)
Risk factors, *n* (%)	
Prior DVT	29 (13.6)
Prior PE	9 (4.2)
Hereditary disposition	40 (18.8)
Contraceptive pills/HRT	25 (11.7)
Immobilization	24.4 (24.4)
Cancer/chemotherapy last 6 months	16 (7.5)
BMI >30	5 (2.3)
Treatment, *n* (%)	
LMWH only	22 (10.3)
LMWH + warfarin	182 (85.4)
Additional systemic thrombolysis	3 (1.4)
Treatment complications, *n* (%)	
No hemorrhage	207 (97.2)
Hemorrhage	2 (0.9)

SD standard deviation, *IQR* interquartile range, *PE* pulmonary embolism, *DVT* deep venous thrombosis, *HRT* hormone replacement therapy, *LMWH* low-molecular-weight heparin

Factor two loaded predominantly for emotional complaints. Factor three appeared to load mainly for work-related problems, as did factor six, and difficulties performing regular activities. Factor four loaded for remnant discomfort or pain in the chest and/or back. Factor five was assessed as being associated with pain and fear associated with the sensation that the disease was not fully healed. Factor six consisted merely of item 4a, and a total of 61.5 % of the respondents ($n = 131$) reported that they did not work.

All correlations between the items and their hypothesized scales were above 0.40 (item internal consistency), and the correlation between the items and their hypothesized scales was statistically higher (>2 standard errors) than the correlation between the items and the other scales (item discriminant ability).

For the calculation of criterion validity, Spearman's correlation coefficient was used to compare the extracted factors in PEmb-QoL to the EQ-5D-3L dimensions. Factors one, three, five, and six had strong correlations to usual activities in EQ-5D-3L, whereas factor two (emotional complaints) correlated with anxiety and factor four (pain) correlated with pain/discomfort (Table 3).

Floor and ceiling effects were calculated by estimating the proportion of patients scoring either the lowest or highest possible score in each of the factors. No ceiling effects were observed, but in factors two to six, floor effects above the recommended limit of 20 % were observed (Table 4) [19].

A sum score of the PEmb-QoL was calculated by summarizing each patient's dimensional crude score divided by the number of dimensions reported by Klok et al. [11]. A possible scale score thus ranged from 6 to 27; higher score indicated a worse HRQoL. The median sum score in the current study was found to be 9.5 (IQR 7.5–13.0), range 6.2–24.3.

Test for multicollinearity revealed satisfactory values for both VIF and tolerance and within the recommended limits of <5 and >0.20, respectively. The range of VIF and tolerance was 1.9–3.2 and 0.32–0.54, respectively.

Reliability

The Cronbach's alpha coefficient measuring internal consistency reliability was found to be 0.94 prior to calculating missing items ($n = 7$). The alpha increased further to 0.95 after correction of these items, indicating a very good intercorrelation of items. Cronbach's alpha values are shown in Table 5.

All participants ($n = 213$) were invited to complete the questionnaires a second time. Of all invited patients, 145 (68 %) completed and returned the second questionnaire. There were no differences between responders and non-responders related to gender, but non-responders were significantly younger and had shorter disease duration than responders ($p < 0.05$). The ICC is used to quantify the extent in which the results from measurements at two different time points resemble each other. A score of 0 and 1 in ICC values represents no and high reliability, respectively. The factorial solution of the Norwegian PEmb-QoL was used to evaluate test–retest reliability between the two time points. The ICC in the current study varied from 0.75 for factor five to 0.86 for factor one, indicating good test–retest reliability. All factors were found significant with p values <0.001. The details of ICCs are presented in Table 5.

Table 2 Factorial structure of the Norwegian version of the PEmb-QoL questionnaire

PEmb items	Factorial loadings					
	F1	F2	F3	F4	F5	F6
Factor 1: *Limitations in activity I*						
1h. Difficulty in breathing or breathlessness	**0.44**		0.40			
4b. Daily activities at home	**0.66**		0.53			
4c. Social activities	**0.56**					
4e. Moderate activities	**0.73**					
4f. Lifting and carrying groceries	**0.71**		0.42			
4g. Climbing several flights of stairs	**0.66**		0.43			
4h. Climbing one flight of stairs	**0.73**					
4i. Bending, kneeling, and squatting	**0.62**					
4j. Walking more than half a mile	**0.76**					
4k. Walking a couple of hundred yards	**0.83**					
4l. Walking about one hundred yards	**0.84**					
4m. Washing or dressing yourself	**0.54**					
8. How much breathlessness have you experienced in the past 4 weeks?	**0.50**				0.42	
Factor 2: *Emotional complaints*						
1f. Burning sensation in the lungs		**0.46**		0.43		
6. During the past 4 weeks, to what extent have your lung symptoms interfered with your normal social activities with family, friends, neighbors, or groups?		**0.57**				
9a. Where you worried about having another pulmonary embolism?		**0.52**			0.41	
9b. Did you feel irritable?		**0.71**				
9d. Did you become emotional more readily?		**0.84**				
9e. Did it bother you that you became emotional more quickly?		**0.88**				
9f. Were you depressed or in low spirits?		**0.82**				
9g. Did you feel that you were a burden to your family and friends?		**0.74**				
9h. Were you afraid to exert yourself?	0.49	**0.53**				
9i. Did you feel limited in taking a trip?	0.49	**0.60**				
9j. Were you afraid of being alone?		**0.62**				
Factor 3: *Limitations in activity II*						
4d. Vigorous activities	0.43		**0.56**			
5a. Cut down the amount of time you spent on work or other activities	0.48		**0.60**			
5b. Accomplished less than you would like			**0.73**			
5c. Were limited in the kind of work or other activities			**0.76**			
5d. Had difficulty performing the work or other activities	0.42		**0.75**			
Factor 4: *Pain*						
1a. Pain behind or between the shoulder blades				**0.78**		
1b. Pain on or in the chest				**0.75**		
1c. Pain in the back				**0.71**		
1d. Sensation of pressure		0.42		**0.46**		
7. How much pain around your shoulder blades/pain in your chest have you experienced during the past 4 weeks?				**0.79**		
Factor 5: *Treatment*						
1e. Feeling that there is still "something there"					**0.57**	
1g. Nagging feeling in the lungs					**0.57**	
9c. Would you have been worried if you had to stop taking anticoagulant medication?					**0.65**	
Factor 6: *Professional work*						
4a. Daily activities at work						**0.72**

Principle component analysis performed using varimax rotation and eigenvalues >1, coefficients <0.40 were omitted from the Table, highest factorial loadings are in bold face

PEmb-QoL pulmonary embolism quality of life

Discussion

The current study was performed to translate the PEmb-QoL questionnaire into Norwegian and to evaluate its

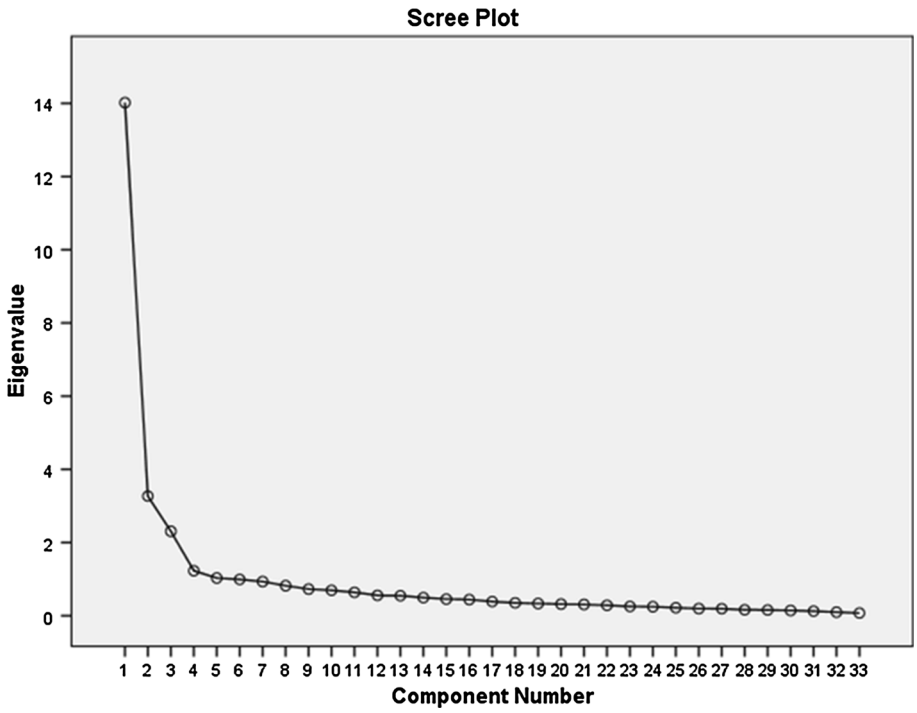

Fig. 2 Scree plot of the Norwegian version of the pulmonary embolism quality-of-life questionnaire (Pemb-QoL)

Table 3 External validity of the Norwegian version of the PEmb-QoL questionnaire, using Spearman's correlation analysis with the EQ-5D-3L questionnaire

EQ-5D-3L factors	F1	F2	F3	F4	F5	F6
Mobility	0.46$^{\pm}$	0.44$^{\pm}$	0.45$^{\pm}$	0.29$^{\pm}$	0.18¶	−0.27$^{\pm}$
Self-care	0.33$^{\pm}$	0.25$^{\pm}$	0.33$^{\pm}$	0.15¶	0.07^{+}	−0.22*
Usual activities	**0.63$^{\pm}$**	0.56$^{\pm}$	**0.62$^{\pm}$**	0.49$^{\pm}$	**0.35$^{\pm}$**	**−0.29$^{\pm}$**
Pain/discomfort	0.54$^{\pm}$	0.52$^{\pm}$	0.44$^{\pm}$	**0.64$^{\pm}$**	0.27$^{\pm}$	−0.23*
Anxiety/depression	0.31$^{\pm}$	**0.59$^{\pm}$**	0.30$^{\pm}$	0.33$^{\pm}$	0.31$^{\pm}$	−0.21*
EQ-VAS	−0.67$^{\pm}$	−0.55$^{\pm}$	−0.61$^{\pm}$	−0.51$^{\pm}$	−0.35$^{\pm}$	−0.28$^{\pm}$

Factors displaying the highest correlations are in bold face

PEmb-QoL pulmonary embolism quality of life

Significance levels: $^{\pm}$ <0.001, * < 0.01, ¶ < 0.05, $^{+}$ nonsignificant

psychometrical properties. To our knowledge, this is the first cross-cultural evaluation [10, 11]. Our findings indicate that the Norwegian version is both valid and reliable, thus representing an important supplement for measuring subjective outcomes in patients who have sustained PE.

Klok et al. [11] established a hypothesized dimensional structure, consisting of six dimensions, which concur with a majority of questions in the questionnaire (except from questions two and three). Basing the construct of a questionnaire merely on a postulated structure may be debateable, since no consideration is made about the underlying structure. Even though it might be assumed that the items are highly correlated, such a structure can only be confirmed and tested by performing a factor analysis. Formal factor analysis consequently plays a major role in construct validation [17]. Deciding which factors to retain is crucial.

Table 4 Median values and floor effects of factors extracted in the Norwegian PEmb-QoL

PEmb factors	Median	Interquartile range	Floor effects (%)
F1	1.5	1.2–2.2	16
F2	1.4	1.1–2.0	20.2
F3	1.4	1.0–2.2	26.3
F4	1.6	1.0–2.4	33.8
F5	1.7	1.7–2.7	28.6
F6	0.0	0.0–1.0	61.5

PEmb-QoL pulmonary embolism quality of life, *F1–F6* extracted factors 1–6 based on principle component analysis

Over- or under-extraction may have deleterious effects on the results [20, 21]. It is debated which method to be used in the factor-retaining process [22], but generally it is

Table 5 Test–retest reliability of the Norwegian version of the PEmb-QoL questionnaire ($n = 146$)

PEmb N factors	Median (SD)		Cronbach's alpha	ICC^{+}	p value
	Baseline	Retest			
F1	1.5 (0.60)	1.4 (0.58)	0.93	0.86	<0.001
F2	1.4 (0.79)	1.3 (0.75)	0.88	0.79	<0.001
F3	1.4 (0.49)	1.4 (0.46)	0.89	0.81	<0.001
F4	1.6 (0.96)	1.4 (0.90)	0.90	0.83	<0.001
F5	1.7 (1.07)	1.7 (0.97)	0.86	0.75	<0.001
F6	0.0 (0.60)	0.0 (0.61)	0.88	0.78	<0.001

PEmb-QoL pulmonary embolism quality of life, *ICC* intraclass correlation coefficient, + two-way mixed model—single measures, *SD* standard deviation

recommended that eigenvalue >1 should be accompanied by another method, e.g., scree plot [20]. However, retaining factors based on only eigenvalue is still an extensively applied approach [17, 23]. In the original article by Klok et al. [11], it is not stated which method was used. The principal component analysis in the current study yielded six factors explaining 71 % of the cumulative variance. The varimax rotation clustered the items fairly consistent with the original dimensional structure, except for factors five and six. Factor five loaded for items 1e, 1g, and 9c, respectively. The first two of these items originate from the frequency of complaints dimension and the last one from the emotional complaints dimension. A logical explanation may be that these questions are interpreted as if the disease has not been fully recovered. Factor six had its highest loading in item 4a, which originate from the ADL limitations dimension, and it could have been expected to load in factor three, clustering items about work-related problems. The reason for this is not clear, but a potential explanation may be that 4a is the only item addressing work per se, which of course not necessarily applies to a large amount of the patients in this population. The latter is underscored by the fact that 61.5 % of patients included in this study reported that they did not work.

Moreover, it is well known from studies performed in different patient populations [24] that the number of factor in the same questionnaire may differ across various studies in different countries. Furthermore, discrepancies may be found related to which items that relates to the various factors. The same phenomenon was seen in this study, reproducing the same amount of factors as in the original validation, but with a different item loading. It might be speculated whether observed differences in factorial structure and score may be related to potential differences in clinical and sociodemographic variables between the current study and the study by Klok et al. [11]. Compared to the study by Klok et al. [11], our study had more patients included ($n = 213$ vs. $n = 90$), less patients had active malignancy and less patients were obese. Patients in our cohort were, however, slightly older at the time of inclusion compared to patients in the study by Klok et al. [11] (60 vs. 56 years). Even though not directly comparable, we cannot exclude that these factors may potentially have contributed to the observed differences. There are obvious problems related to such findings. In particular, it may limit the possibility of comparison across studies and boundaries. A possible solution to circumvent this problem may be to calculate and compare a PEmb-QoL sum score. The sum score was, however, not reported in the original validation [11]. It may also be debateable to merely report the sum score on the basis that HRQoL is generally viewed as a multidimensional construct [17].

Sample size is much debated in exploratory factor analysis, and there is no unanimous understanding or presented algorithms for adequate sample size [25, 26]. Strict rules about sample size have mostly disappeared [20, 27]. Traditionally, it has been considered that "the more the better" [25]. Several guidelines mention the subject to item ratio as a common method to be used [28]. Our subject to item ratio was 5.5:1, which is a ratio that is advocated by some and commonly used in several other studies [23, 29].

Internal consistency reliability showed excellent results, way over the recommended limit [24]. However, an excellent Cronbach's alpha may be a marker for redundancy [21]. In other words, one or more items are basically asking the same question or at least the subject is interpreting the questions in the same way. Very high Cronbach's alpha can also be found in scales with large number of items, because it is dependent upon the number of items in a scale [27]. In order to investigate whether the PEmb-QoL dimensions displayed ambiguous multicollinearity, both variance inflation factor (VIF) and tolerance were calculated. No questionable values were displayed indicating that no problematic multicollinearity was found.

There is no general consensus as to how long the between-assessment time gap should be when measuring test–retest reliability. It is generally agreed, however, that a too short test–retest period can result in patients' recalling their answers from baseline, and a too long period may allow true change in the patients' clinical condition [17]. In our study, questionnaires were sent to patients in order to calculate test–retest reliability after 2 weeks, meaning that patients completed them at a minimum of 14 days after our initial assessment. In comparison with, e.g., cancer where one would anticipate HRQoL to vary over time, the risk of such variations in the present population was viewed to be low. Furthermore, a retest interval of minimum 14 days was judged as adequate to avoid a recall bias. Findings indicated that the test–retest reliability was good with ICC values consistently over 0.70, which is recommended by some guidelines [27, 30]. Thus, the questionnaire seems to

have adequate reproducibility and consequently suitable for longitudinal comparisons.

Criterion validity was confirmed by rather good correlations between the PEmb-QoL factors and the EQ-5D-3L dimensions. Factors one, three, five, and six (related to ADL and work/regular activity) correlated with EQ-5D-3L's dimension for usual activities. Factor four (pain) correlated significantly with pain in EQ-5D-3L. Finally, factor two (emotional complaints) correlated significantly with anxiety in EQ-5D-3L.

The main limitations of the study are the retrospective patients' identification and the incomplete participation of the original cohort. One might speculate that higher percentage of patients with both reduced health-related quality of life and increased symptom burden agreed to participate. However, given the fact that a marked floor effect was observed in five out of six factors (indicating minor HRQoL problems), this seems unlikely. Problematic floor effects were also reported by Klok et al. [11], and the most plausible explanation seems to be related to the fact that patients in the current study were recruited from a hospital registry, with a median time since diagnosis being 3.6 years. Consequently, a majority of these patients may no longer have troubling symptoms. Furthermore, patients did not rate their symptoms at the two measurement times, which would have been valuable in order to calculate responsiveness (sensitivity to change). Indeed, responsiveness is an indicator of the ability of a questionnaire to detect changes over time and should consequently be evaluated in longitudinal studies [17]. Given the rather long time since the diagnosis of PE, real changes in patients' health condition may have occurred at an earlier stage, and it is difficult to know whether a symptom score would in fact be related to the PE diagnosis. Moreover, the potential improved level of function over time may have resulted in a response shift among these patients [31]. On the other hand, since this study had a fairly large sample size and inclusion criteria were broad, we judge this cohort to be a representative sample of prior PE patients. We recommend, however, that floor effects and sensitivity to change should be further investigated in future longitudinal follow-up studies of patients with PE. In the current study, EQ-5D-3L was the chosen generic HRQoL instrument. This choice was based on the brevity of the EQ-5D-3L and consequently the potential positive influence this may have on patients' compliance and completeness of scores. In retrospect, however, the Short-Form 36 (SF-36) might have been more a better choice because of its comprehensiveness for measuring generic HRQoL. There are also some limitations attached to the translation procedure of the PEmb-QoL. Indeed, response choice ratings could have been used in order to test the conformity of the response choices to their hypothesized ordinality. Besides, even though no differences were seen related to response rates when distributing questionnaires either by post or e-mail, questions may be raised related to potential influence on validation. In our view, this seems to be a minor problem, given the fact that questionnaires (regardless of receiving them by post or e-mail) were completed at home. Consequently, having some patients filling them out in the hospital and some at home would have constituted a greater problem.

In conclusion, the results from the psychometrical testing of the PEmb-QoL in this Norwegian cohort are promising and indicate overall good reliability, validity, and reproducibility; however, further studies are warranted to evaluate the questionnaire with regard to sensitivity to change (responsiveness) and potential response shifts [32]. Currently, there are no longitudinal follow-up studies from the time of diagnoses of PE using disease-specific measures. Such studies are warranted as well as the need to test the PEmb-QoL in studies aiming to evaluate various treatment effects and interventions.

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Health-related quality of life after pulmonary embolism: a cross-sectional study

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ABSTRACT

Objectives: The psychological effects of acute pulmonary embolism (PE) have scarcely been studied. The aims of this study were to evaluate health-related quality of life (HRQoL) in patients with a history of PE compared with that of the general population and buddy controls, and to explore factors that may predict impaired HRQoL.

Design: Cross-sectional.

Setting: Haematology and thrombosis unit in Fredrikstad, Norway.

Participants: 213 consecutive patients treated for PE were identified from hospital registries. Eligible patients were scheduled for a single study visit, including a functional capacity test (6 min walking test). HRQoL was assessed using the EuroQol 5D dimensions 3-level (EQ-5D-3L) questionnaire, of which the results were compared with Danish population norms and age-matched and sex-matched buddy controls. The buddy controls were recruited by asking every patient to hand over the EQ-5D questionnaire to 2 age-matched and sex-matched friends or relatives. Multivariable regression analyses were used to examine possible determinants of reduced HRQoL.

Results: Mean age was 61 years (SD 15), 117 (55%) were males, and median time since diagnosis was 3.8 years (range 0.3–9.5). Mean EuroQol visual analogue scale (EQ VAS) was 67 in PE as compared with 81 in the general population (p<0.005) and corresponding EQ-5D index values were 0.80 and 0.86 (p<0.005). Patients reported more problems in all 5 EQ-5D compared with both the buddy controls and the general population, p<0.05. Shorter 6 min walking distance (β=0.09, p<0.005) and patient-reported dyspnoea (β=11.27, p<0.005) were independent predictors of lower EQ VAS scores.

Conclusions: Our findings show that patients with a history of PE have impaired HRQoL when compared with the general population and buddy controls. Reduced functional capacity and persistent dyspnoea were the main predictors of this impairment.

Strengths and limitations of this study

- This study describes the long-term health-related quality of life, functional capacity and prevalence of dyspnoea in patients with a history of pulmonary embolism, which have scarcely been studied.
- A large sample size in which all aspects of a generic health-related quality of life questionnaire is reported combined with functional capacity assessment.
- The findings of this study may encourage future studies to evaluate the susceptibility of these patients to cardiopulmonary rehabilitation.
- The low response rate and the retrospective design may hamper external validation.

INTRODUCTION

Health-related quality of life (HRQoL) after deep vein thrombosis (DVT) has been extensively studied. The interest in studying HRQoL in DVT is believed to be related to the well-characterised frequent detrimental chronic condition of post-thrombotic syndrome (PTS) that affects 30–50% of patients with DVT.[1] Unlike DVT, long-term effects of acute pulmonary embolism (PE) on HRQoL are understudied. The equivalent long-term complication of acute PE is chronic thromboembolic pulmonary hypertension (CTEPH).[2] This condition has been shown to affect 2–4% of the patients with a history of PE.[3] This relatively low frequency of CTEPH may be the reason for the limited number of studies focusing on HRQoL and the psychological well-being of patients with PE.[4–9] It has been suggested that CTEPH itself is the extreme manifestation of a much more common phenomenon of permanent changes in pulmonary haemodynamics, cardiac function and pulmonary gas exchange after acute PE, which is associated with dyspnoea and decreased exercise capacity. Additionally, several studies have shown that up to 50% of the patients with a history of PE report persistent dyspnoea a long time after PE.[4 10] By analogy with PTS after DVT, it was recently

proposed to refer to this phenomenon as the 'postpulmonary embolism syndrome'.[11] Moreover, a recent Scandinavian study reported the overuse of antidepressants in adolescents with a history of PE, indicating that PE may develop into a chronic illness in a relevant number of patients.[12] Indeed, the few existing studies all report an impaired HRQoL in patients with a history of PE compared with that of the normal population,[4 6] although the results concerning possible predictors of reduced HRQoL are divergent.[7] A more detailed knowledge of the determinants of HRQoL is needed to allow for identification of treatment targets and implementation of this important end point in future outcome studies.

The aims of this study were to compare HRQoL in patients with a history of PE to that of the general population and age-matched and sex-matched controls, and to evaluate possible determinants of HRQoL.

MATERIALS AND METHODS

Participants and setting

Consecutive patients who were diagnosed and treated for PE at the Østfold Hospital Trust, Fredrikstad, Norway, between January 2002 and December 2011 were identified from the hospital's registries including the thrombosis registry by searching for International Classification of Diseases (ICD)-10 codes of PE (ICD-10 I26.0 and I26.9). All patients alive at the beginning of March 2012, and with a PE diagnosis confirmed by CT pulmonary angiogram or high probability perfusion scintigraphy, were eligible for study participation.

Patients were excluded if they were aged <18 or >90 years or deemed incapable of complying with study procedures, including language barriers, geographical unavailability, known dementia, psychiatric diagnosis such as major depression as well as affective disorders or any degree of psychotic disorder. Patients living in nursing homes or receiving major help from social care services were excluded as well.

Written informed consent was obtained for all patients.

Study design

All eligible patients were contacted by telephone and invited to participate in the study. Patients who responded to our invitation were scheduled for a visit during which they underwent physical examination and functional capacity test using the 6 min walking test. The 6 min walking test is a standardised functional capacity test, which is widely used to objectively assess patients' cardiopulmonary capacity.[13] The test was performed according to published guidelines,[14] by one of the study investigators (MT). For each patient, we derived predicted values from the recommendations of the literature.[15] Evaluation of patients comprised blood tests including brain natriuretic peptide (BNP), which were obtained at the study visit. Sociodemographic data were recorded on standardised case record forms.

Prior to the study visit, the HRQoL questionnaire was sent to the patients either by email or post. Patients were asked to complete the form at home and return it at the scheduled study visit. Incomplete forms were completed during the visit at the hospital.

Quality of life questionnaire

The validated Norwegian version of the EuroQol five-dimension three-level (EQ-5D-3L) questionnaire was used in order to assess quality of life (QoL). EQ-5D-3L consists of a descriptive system and the EuroQol visual analogue scale (EQ VAS).[16 17] The EQ-5D-3L is a validated, generic, preference-based, health status measure consisting of five descriptive questions encompassing five domains of HRQoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question is answered based on three response options (1='no problems', 2='moderate problems', 3='severe problems'). The 243 (3^5) potential patterns of responses each indicate a unique health state ranging from 11 111 for perfect health to 33 333 for the worst possible state. The health states can then be converted into a single summary index value, which ranges from 1 (state of full health) to values lower than 0 (states regarded as worse than being dead).

The EQ VAS is a self-rated health on a vertical visual analogue scale (0–100) where the end points are labelled 'worst imaginable health state' and 'best imaginable health state'.

Control groups

Although several European countries have established normative population data for the EQ-5D instrument, these are not available for Norway. Therefore, we compared our results to the Danish population norms that were established in 2009.[18]

To correct for incident cases with venous thrombosis in the normative population, we included a second control group by asking our study participants to recruit two age-matched (±5 years) and sex-matched relatives or friends without a history of venous thrombosis, hereafter referred to as buddy controls, to complete the EQ-5D form. Buddy controls were asked to return the anonymous questionnaire in prepaid envelopes. Owing to the anonymity of the buddy controls, further baseline characteristics were not accessible.

Predictors

On the basis of clinical experience and previous research, we hypothesised that the following determinants may be relevant predictors of HRQoL after PE: (1) age, (2) sex, (3) disease duration (time in years from PE diagnosis to study visit), (4) body mass index (kg/m^2), (5) recurrent venous thromboembolism, (6) occupation, (7) persistent patient-reported dyspnoea, (8) performance at 6 min walking test, (9) BNP, (10)

active malignancy, (11) ongoing anticoagulant treatment, (12) known cardiopulmonary comorbidity, including interstitial pulmonary diseases, congestive heart failure and chronic obstructive pulmonary disease and (13) proximal clot location at PE diagnosis as assessed by a previously published radiological score by Ghanima *et al*.[19]

STATISTICAL ANALYSES

Continuous variables were expressed as means and SDs if normally distributed and as medians with ranges if the distribution was skewed. Categorical variables were presented as percentages and/or frequencies. Comparisons were made using Student's t-test or Mann-Whitney U test (depending on normal or skewed distribution) for continuous variables and χ^2 tests for categorical variables.

Since very few patients and controls had 'extreme problems', the EQ-5D were dichotomised to either 'no problems' or 'problems'.

Age and gender adjustment of controls was made by weighing the population norm EQ-5D index values and EQ VAS with the distribution of our sample, as recommended by Hjermstad *et al*.[20]

Variables deemed predictive of HRQoL were first screened using univariate analysis (Spearman's r). Correlations below the significance level of α=0.1 were retained for the multivariate regression analysis. Potential multicollinearity was checked before inclusion in the multivariate models. Then multivariate regression analyses comprising both standard linear regression and binary logistic regression models were performed. For the former, the possible determinants were tested for independency against EQ VAS and r^2 was used to estimate the percentage of effect explained by the model. For the latter, retained determinants from the univariate analysis were tested for independency against each of the EQ-5D dimensions. The Hosmer and Lemeshow test was used to estimate the goodness of fit of the model.

The multiple imputation model was used in order to deal with missing values in the EQ-5D questionnaires of the buddy controls in whom we did not have the possibility to check and complete the questionnaires during a study visit.[21] Cases with more than 50% of the items or EQ VAS missing were omitted. All analyses were performed using the Statistical Package for Social Science V.22.0 (SPSS, Chicago, Illinois, USA), and considered significant at a two-sided α of $\leq$0.05.

RESULTS

Study flow

A total of 836 patients were identified and assessed for eligibility in this study. As shown in the study flow chart (figure 1), 430 (51%) patients were excluded according to the predefined exclusion criteria. Of the 406 remaining and thus invited patients, 189 (46%) declined to participate. Of the remaining 217 eligible patients, 213 completed both the EQ-5D questionnaire and underwent the 6 min walking test. Hence, the response rate for our study cohort was 52%.

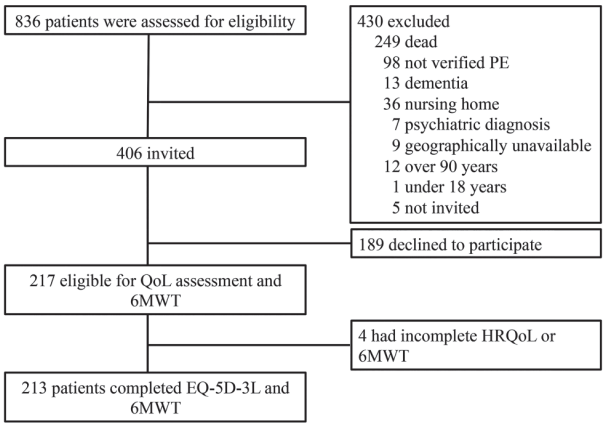

Figure 1 Study flow chart. 6MWT, 6 min walking test; EQ-5D-3L, EuroQol five-dimension three-level; HRQoL, health related quality of life; PE, pulmonary embolism; QoL, quality of life.

The number of buddy controls who returned the EQ-5D form was 205, of whom 28 returned questionnaires had more than 50% of data missing. After excluding these 28, 177 were left for analysis. The response rate for the buddy controls was thus 42%, assuming all study patients indeed forwarded the questionnaire to two 'buddies'.

Study patients

Patients had a mean age of 61 years (SD 15) and 55% were men (n=117). Sociodemographic characteristics are presented in table 1. Median time since diagnosis was 3.8 years (range 0.3–9.5) with 89% being diagnosed with PE more than a year prior to study inclusion.

Mean distance covered on the 6 min walking test by the study cohort was 449 m (SD 135). The mean 6 min walking distance was 97 m (95% CI 76 to 117) less in male patients and 84 m (95% CI 65 to 104) less in female patients as compared with their gender-predicted value, p<0.005.

Comparison of HRQoL between patients, population controls and buddy controls

Table 2 shows the frequency of reported problems by dimension as well as mean and median values for EQ VAS and EQ-5D index values stratified by age group. The dimensional difference between patients and both of the control groups yielded statistically significant differences across all dimensions (figure 2). Comparisons of EQ-5D index values and EQ VAS between patient and control groups are presented in table 3. A comparison with the male proportion of our sample to that of the Danish population norms regarding EQ-5D index values initially showed a statistically significant difference, p=0.04 (0.84 vs 0.88). However, after adjusting for outliers, the statistical significance disappeared (0.85 vs 0.87, p=0.13).

Table 1 Sociodemographic and clinical characteristics of the study sample

Variable	Study sample n (%)
Female	96 (45)
Age in years, mean (SD)	61 (15)
Years since diagnosis, median (range)	3.8 (0.3–9.5)
Occupation	
Unemployed	50 (24)
Working	71 (33)
Retired	92 (43)
Diagnosis	
PE	149 (70)
PE+DVT	64 (30)
Recurrent VTE	34 (16)
Cardiopulmonary comorbidity	19 (9)
BMI, mean (SD)	28.7 (4.9)
Obesity	73 (34)
Active malignancy	15 (7)
Reporting dyspnoea	99 (46)
Smoking	
Current	38 (18)
Former	52 (24)
Ongoing AC treatment	81 (38)
6MWT, mean (SD)	
Total	449 (135)
Men	488 (124)
Women	402 (134)
Laboratory tests at study visit	203
BNP, mean (SD)	48.6 (72.4)
F-score	192
Median (range)	3 (1–4)

6MWT, 6 min walking test measured in metres; BMI, body mass index (kg/m^2), obesity=BMI>30 kg/m^2; BNP, brain natriuretic peptide (mg/l); F-score, Fredrikstad radiological score (higher scores associated with a more proximal location of the thrombus); Ongoing AC treatment, ongoing anticoagulant treatment at inclusion; PE, pulmonary embolism; PE+DVT, concomitant deep vein thrombosis reported in hospital records at PE diagnosis; Unemployed, unemployed or unemployment because of long-term illness or disability retirement; Working, working or studying.

The differences in mean EQ-5D index values were 0.11 and 0.06 between patients and buddy controls and between patients and the general population, respectively.

Predictors of HRQoL

Table 4 summarises the results of the univariate analysis. The 6 min walking test was significantly correlated with all the EQ-5D dimensions as well as EQ VAS (p<0.005), indicating that patients with lower scores on EQ VAS or reporting problems in the EQ-5D tended to walk shorter distances. Similar associations were found concerning dyspnoea, as those reporting dyspnoea reported problems in four out of five EQ-5D dimensions (p<0.05; table 4). Patients reporting dyspnoea also tended to cover shorter distances on the 6 min walking test (481 vs 413 m, p<0.005). In the multiple linear regression model, the following variables were shown to be independently predictive of the dependent variable EQ VAS: performance on 6 min walking test (β=0.09, p<0.005), symptoms of dyspnoea (β=−11.27, p<0.005) and unemployment (β=−8.98, p<0.005; table 5). In addition to the EQ VAS, performance on the 6 min walking test consistently proved to be an independent determinant of every EQ-5D dimension, except for the dimension anxiety and depression. Dyspnoea was a significant predictor of the dimension usual activities and pain and discomfort. However, regarding the latter, the goodness of fit of the model showed a value beneath the significance level of 0.05 (Hosmer and Lemeshow=0.02), indicating the poor fit of the model. None of the other evaluated variables were significant determinants of HRQoL. The results from both the multiple linear and binary logistic regression analyses are displayed in table 5.

DISCUSSION

In this population-based cross-sectional study, we found that the long-term HRQoL assessed by EQ-5D-3L was significantly impaired among patients with PE compared with buddy controls and population norms. Moreover, we found that poorer performance on the 6 min walking test, persistent patient-reported dyspnoea and unemployment were independent predictors of reduced HRQoL. To the best of our knowledge, this is the second largest study to compare long-term HRQoL after PE to a control group and the first one to incorporate a validated functional capacity test to a more comprehensive evaluation of HRQoL in patients with PE. Despite using a different instrument (EQ-5D-3L vs Short-Form 36 (SF-36)), our results of impaired HRQoL after PE confirm previously published studies.[6 7]

The challenge of QoL studies is to judge whether identified differences are clinically relevant or not. Across various HRQoL research papers using the EQ-5D instrument, authors have suggested threshold values for minimal (clinical) important difference (MID/MCID), that is, the least amount of difference suggesting clinical relevance or mandating a change in clinical practice,[22] ranging from 0.04 to 0.08.[23–25] In our study, the δ EQ-5D index value between the study population and buddy controls was 0.11 and between the study population and the general population was 0.06. This indicates that we have identified the clinically relevant difference in HRQoL between the patients and both control cohorts. Of note, the cut-off value for MID/MCID is various and probably depends on the disease and valuation sets used. Moreover, since we did not include a longitudinal within-person measurement of QoL, the differences must be interpreted with caution.[26]

Compared with those without dyspnoea, 46.5% of our study patients who reported persistent dyspnoea performed worse in the 6 min walking test, objectively verifying this symptom. As for the whole study cohort, both male and female patients walked significantly shorter distances than their gender predicted value. In the

Table 2 Frequency of patients (n=213) reporting problems in the EQ-5D dimensions, means and medians for EQ VAS and EQ-5D index values. All displayed by age groups

	Age groups							
	18–29	30–39	40–49	50–59	60–69	70–79	80+	Total
EQ-5D								
Mobility, N (%)	2 (1)	4 (2)	6 (3)	8 (4)	12 (6)	13 (6)	10 (5)	55 (26)
Self-care, N (%)	0 (0)	0 (0)	2 (1)	3 (1)	3 (1)	5 (2)	1 (0.5)	14 (7)
Usual activities, N (%)	2 (1)	4 (2)	9 (4)	10 (5)	20 (9)	11 (5)	12 (6)	68 (32)
Pain and discomfort, N (%)	3 (1)	8 (4)	15 (7)	21 (10)	28 (13)	24 (11)	17 (8)	116 (54)
Anxiety and depression, N (%)	3 (1)	4 (2)	9 (4)	8 (4)	23 (11)	13 (6)	10 (5)	70 (33)
EQ VAS								
Mean (SD)	61 (22)	65 (23)	67 (23)	70 (22)	70 (21)	70 (18)	57 (21)	67 (21)
Median	60	73	70	75	70	70	51	70
25th	45	49	50	50	53	51	40	50
75th	80	84	85	87	90	82	75	83
EQ-5D index values								
Mean (SD)	0.67 (0.40)	0.81 (0.26)	0.81 (0.23)	0.84 (0.21)	0.81 (0.16)	0.80 (0.25)	0.74 (0.18)	0.80 (0.22)
Median	0.27	0.73	0.76	0.77	0.71	0.73	0.71	0.72
25th	0.82	0.82	0.82	0.82	0.79	0.82	0.77	0.82
75th	1.00	1.00	1.00	1.00	1.00	1.00	0.82	1.00

EQ-5D,EuroQol five-dimension; EQ VAS, EuroQol visual analogue scale.

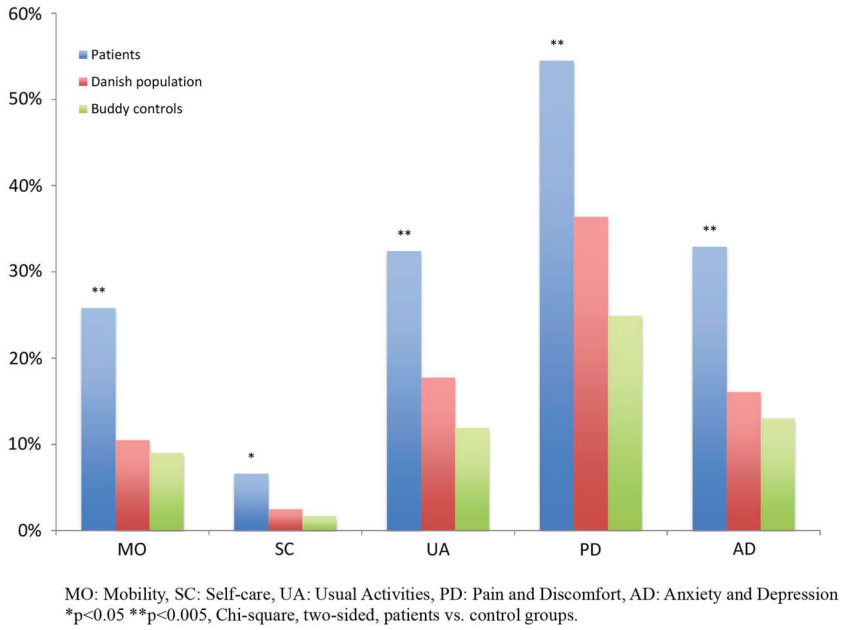

Figure 2 Proportion of patients, Danish population and buddy controls reporting problems stratified by EQ-5D dimensions. EQ-5D, EuroQol five-dimension.

multivariable analyses, performance on the 6 min walking test and persistent dyspnoea appeared to be independent predictors of worse HRQoL. This may indicate that patients with PE suffer from a reduced functional capacity that persists for many years after the event and that the declining functional capacity is one of the main determinants of impaired HRQoL in patients with a history of PE. The finding that patients on average underperformed in the 6 min walking test may thus be an important explanation for their overall reduced HRQoL. This finding could be further supported by a qualitative study in patients with PE revealing that modification of physical activity and exertion (avoidance or reduction) was the most common behaviour change reported by the interviewed patients.[8] Again, however, cut-off values for the clinically relevant abnormal 6 min walking test performance regarding PE are lacking, which makes it difficult to put the observed results in further perspective. Furthermore, we cannot exclude that this correlation also could be reversed,

Table 3 Comparisons of mean EQ-5D index values and EQ VAS between patients versus Danish population and patients versus buddy controls

	Patients			Danish population*			Buddy controls
	Male	Female	Total	Male	Female	Total	Total
EQ-5D index							
Mean (SD)	0.85 (0.21)	0.75 (0.23)	0.80 (0.22)	0.87	0.84	0.86	0.91 (0.16)
p Value				0.13†	<0.005†	<0.005†	<0.005‡
EQ VAS							
Mean (SD)	71 (20)	62 (22)	67 (21)	81	80	81	80 (19)
p Value				<0.005†	<0.005†	<0.005†	<0.005‡

*Age-adjusted and sex-adjusted values.
†One sample t-test with the age-adjusted and sex-adjusted value as test value (two-sided).
‡Mann-Whitney U test (two-sided).
EQ-5D, EuroQol five-dimension; EQ VAS, EuroQol visual analogue scale.

meaning that the reduced HRQoL is due to the low physical performance.

Numerous studies have shown the beneficial effects of pulmonary rehabilitation in other cardiovascular diseases, resulting in improved functional capacity as well as HRQoL.[27–30] In this context, our findings support the hypothesis that patients with PE with persistent dyspnoea and poor functional status may benefit from cardiopulmonary rehabilitation programmes.[31]

Although the majority of studies focusing on the long-term effects of PE have not excluded patients with established CTEPH diagnosis, there is consistent reporting that approximately half of the patients assessed more than 6 months after experiencing an episode of acute PE report dyspnoea, which is also correlated to a decline in physical performance measured by the 6 min walking test.[4 10 32 33] Our results confirm these findings and support the concept of 'post-PE syndrome', which has recently been presented as an analogy to PTS, referring to the persistent dyspnoea and reduced functional capacity after PE.[11] The authors discuss whether PE could in some cases, CTEPH excluded, be classified as a chronic illness and postulate the 'post-PE syndrome' being a state just prior to development of CTEPH. This reasoning is further strengthened by a Danish study reporting the overuse of antidepressants in adolescents long after they experienced their first episode of PE.[12] However, whether persistent dyspnoea after PE should be the subject of further standardised workup including HRQoL questionnaires and the 6 min walking test is still debatable since some studies attribute the high prevalence of dyspnoea to pre-existing comorbidities.[34] The final independent predictor of worse HRQoL in our study was unemployment. Several sociodemographic variables have previously been shown to affect HRQoL, regardless of the underlying disease or condition.[35] The fact that 24% of the study population were unemployed could possibly have contributed to the overall lower HRQoL scores in our patient cohort. Furthermore, we hypothesise that the association between impaired HRQoL and unemployment may be subject to reverse correlation, that is, impaired HRQoL leading to unemployment. However, owing to missing data on other social factors, we could not investigate this further.

Of the predefined determinants being evaluated, we found only a selected proportion predictive of worse HRQoL and, to our surprise, malignancy appeared not to be a significant determinant of HRQoL. Previous studies have found cardiopulmonary disease, active malignancy as well as obesity being independent predictors of HRQoL.[6 36] However, the proportions of these subgroups reported in the aforementioned studies are higher than in ours and the presented multivariate regression analysis yielded rather low r^2 percentages indicating the models not being precise.[6] This may indicate, as van Es *et al*[7] postulate, that in this study the patients are somewhat healthier and subsequently, perhaps emphasising the findings regarding the reported differences in HRQoL between study participants and the general population. Nevertheless, in our view, these contradictions exemplify the heterogeneous effects of PE as a disease on HRQoL and physical capacity and consequently rendering cumbersome the evaluation of determinants of HRQoL in patients with PE.

Limitations

Our study has some limitations. The low response rate may hamper the external validity of our results. Moreover, since the final study cohort comprised one-quarter of the patients being assessed for eligibility, a possible bias towards recruitment of patients with more persistent symptoms cannot be ruled out. However, the 6 min walking test results and proportion reporting dyspnoea in our sample are similar to those of prior PE follow-up studies,[10 33 37] highlighting that our cohort is a representative PE population. Also, the buddy control group could not be assessed for potential confounders because we did not assess their characteristics. Therefore, we cannot rule out a bias towards 'extremely' healthy buddies or poor matching. Furthermore, owing to the study's retrospective design, which carried missing data concerning the index event of the PE, we could not classify the PE episode as being of low or intermediate risk.

Table 4 Univariate analysis displaying correlations of the predefined determinants to EQ-5D dimensions and EQ VAS

		EQ-5D										EQ VAS	
		MO		SC		UA		PD		AD			
	N	Corr.coef	p Value	Corr.coef	p Value	Corr.coef	p Value	Corr.coef	p Value	Corr.coef	p Value	Corr.coef	p Value
Age	213	0.09	0.19	0.05	0.49	0.07	0.32	0.06	0.39	0.06	0.38	−0.06	0.31
Sex	213	−0.20*	<0.05	−0.03	0.70	−0.23*	<0.05	−0.13*	0.06	−0.27*	<0.05	0.23*	<0.05
6MWT	213	−0.43*	<0.05	−0.28*	<0.05	−0.42*	<0.05	−0.30*	<0.05	−0.25*	<0.05	0.51*	<0.05
BMI	213	0.13*	0.06	0.14*	0.04	0.10	0.16	0.03	0.71	0.05	0.50	0.22*	<0.05
BNP	203	0.19*	0.01	0.01	0.89	0.15*	0.03	0.13*	0.07	0.19*	0.01	−0.10	0.14
Ongoing AC	213	0.09	0.19	−0.05	0.45	0.02	0.73	0.02	0.80	−0.01	0.85	−0.06	0.38
Cardiopulmonary comorbidity	213	0.15*	0.03	0.05	0.47	0.17*	0.01	0.09	0.20	0.06	0.20	−0.19*	0.01
Active cancer	213	0.09	0.20	0.01	0.99	0.01	0.90	−0.01	0.93	0.01	0.97	−0.02	0.77
Reporting dyspnoea	213	0.16*	0.02	0.13*	0.05	0.29*	<0.05	0.40*	<0.05	0.11	0.11	−0.37*	<0.05
F-score	192	0.06	0.42	0.15*	0.04	0.11	0.13	0.07	0.36	−0.01	0.94	−0.12*	0.09
Recurrent VTE	213	0.01	0.93	−0.06	0.35	−0.02	0.73	0.06	0.35	−0.01	0.95	−0.02	0.77
Unemployed	213	0.10	0.13	0.08	0.27	0.22*	<0.05	0.24*	<0.05	0.27*	<0.05	−0.24*	0.01
Disease duration	213	−0.02	0.77	−0.02	0.79	−0.03	0.64	−0.04	0.58	−0.07	0.32	0.13*	0.05

*All values with α<0.10 retained for multiple regression analysis, explanatory variables recoded to 0=not having the condition and 1=having the condition, dimensions dichotomised in reporting problems=1 and not reporting problems=0.
6MWT, 6 min walking test; AD, anxiety and depression; Age, age at inclusion, male sex=1; BMI, body mass index (kg/m^2); BNP, brain natriuretic peptide; Corr. coef, Spearman's r correlation coefficient; EQ-5D, EuroQol five-dimension; EQ VAS, EuroQol visual analogue scale; F-score, Fredrikstad radiological score (higher scores associated with a more proximal location of the thrombus); MO, mobility; Ongoing AC, ongoing anticoagulant treatment; PD, pain and discomfort; SC, self-care; UA, usual activities; Unemployed, unemployed or unemployment because of long-term illness or disability retirement and disease duration=time in years from PE diagnosis to study inclusion.

Table 5 Multiple binary logistic and standard linear regression models with retained determinants from the univariate analysis for possible independency tested against EQ-5D dimensions and EQ VAS

	EQ-5D										EQ VAS	
	MO		SC		UA		PD		AD			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	β†	SE‡
6MWT	0.991	0.987 to 0.995**	0.990	0.984 to 0.997**	0.991	0.988 to 0.995**	0.996	0.992 to 0.999*	0.997	0.994 to 1.000	0.09	0.01**
BMI	1.04	0.97 to 1.12	1.06	0.94 to 1.19	–	–	–	–	–	–	−0.07	0.26
BNP	1.00	1.00 to 1.01	–	–	1.00	1.00 to 1.01	1.00	0.99 to 1.00	1.00	1.00 to 1.01	–	–
Cardiopulmonary comorbidity	0.57	0.14 to 2.30	–	–	0.78	0.20 to 3.07	–	–	–	–	1.63	4.69
Reporting dyspnoea	1.33	0.63 to 2.81	1.74	0.38 to 8.07	2.33	1.14 to 4.78*	3.74	1.97 to 7.08**	–	–	−11.27	2.56**
F-score	–	–	3.12	0.79 to 5.69	–	–	–	–	–	–	1.71	1.13
Unemployed	–	–	–	–	2.55	1.15 to 5.67*	2.76	1.24 to 6.15*	3.94	1.88 to 8.26**	−8.98	2.97**
Disease duration	–	–	–	–	–	–	–	–	–	–	−0.19	0.47
Hosmer and Lemeshow	0.08		0.87		0.35		0.02		0.62			
r^2											0.46	

*p Value <0.05 all regression models adjusted for age and sex, explanatory variables recoded to 0=not having the condition and 1=having the condition, dimensions dichotomised in reporting problems=1 and not reporting problems=0.
**p Value <0.005, all regression models adjusted for age and sex, explanatory variables recoded to 0=not having the condition and 1=having the condition, dimensions dichotomised in reporting problems=1 and not reporting problems=0.
†Unstandardised β coefficient.
‡SE of β.
6MWT, 6 min walking test; AD, anxiety and depression, higher scores in EQ VAS associated with better health related quality of life; BMI, body mass index (kg/m^2); BNP, brain natriuretic peptide; EQ-5D, EuroQol five-dimension; EQ VAS, EuroQol visual analogue scale; F-score, Fredrikstad radiological score (higher scores associated with a more proximal location of the thrombus); MO, mobility; PD, pain and discomfort; SC, self-care; UA, usual activities; Unemployed, unemployed or unemployment because of long-term illness or disability retirement, disease duration=time in years from diagnosis to study inclusion.

The EQ-5D was used based on its simplicity and potential positive influence on patients' completeness of scores. It could be argued, however, that the SF-36 might have been a good choice as well, due to its comprehensiveness and in order to compare our results with previous studies. Finally, we did not apply a disease-specific questionnaire of QoL.

The strong points of this study are the sample size and the long-term follow-up period with 89% of the patients being diagnosed with PE more than 1 year prior to inclusion. Furthermore, this study is one of the largest studies to present a more comprehensive evaluation of HRQoL by reporting all aspects of a generic QoL questionnaire as well as incorporating a functional capacity test (6 min walking test) in order to objectify the findings.

CONCLUSIONS

Patients with a history of acute PE were found to have a worse HRQoL compared with age-matched and sex-matched venous thromboembolism-free buddy controls and population controls. Underperformance and patient-reported dyspnoea were independent predictors of decreased HRQoL. Further studies are necessary to further evaluate the course and determinants of HRQoL after acute PE, as well as interventions aimed at improving HRQoL in these patients.

Contributors MT and WG were responsible for study concept, design and data acquisition. MT, HSW and WG performed the statistical analyses. MT wrote the first draft of the manuscript. All authors were responsible for critical revision of the manuscript, interpretation of the results, had full access to all the data in the study, and take responsibility of the integrity of the data and the accuracy of data analysis.

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Health-related quality of life after pulmonary embolism: a cross-sectional study

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Full Length Article

The impact of post-pulmonary embolism syndrome and its possible determinants

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ABSTRACT

Introduction: Recent studies suggest that up to 50% of patients surviving pulmonary embolism (PE) may suffer from post-PE syndrome, which is defined by persistent dyspnea, impaired exercise capacity and/or decreased health-related quality of life (HRQoL). The possible determinants of post-PE syndrome are however not fully established.

Aims: To describe the differences between dyspneic and non-dyspneic PE-patients and to explore determinants of dyspnea, 6-min walking test (6MWT) and HRQoL.

Material and methods: In this cross-sectional study, consecutive patients diagnosed with PE between 2002 and 2011 at Østfold Hospital, Norway were identified from hospital registries. Patients were scheduled for clinical examination and a 6MWT. Dyspnea was assessed by the New York Heart Association (NYHA) classification. HRQoL was assessed with PEmb-QoL questionnaire. PE severity was assessed with PESI score, mean bilateral proximal extent of the clot and right-/left ventricle-ratio (RV/LV-ratio).

Results: 203 patients participated in this study, of which 96 patients reported dyspnea (47%). Median time from diagnosis was 3.6 years (IQR 1.9–6.5). Patients without dyspnea performed better on 6MWT (488 m vs 413 m, $p < 0.005$) and had better HRQoL results ($p < 0.005$). None of the variables we examined, including Charlson comorbidity index, was independently associated with dyspnea. However, higher RV/LV ratio at diagnosis was significantly associated with reduced 6MWT at follow-up. Further, ongoing anticoagulation and unemployment were independently associated with impaired HRQoL.

Conclusions: PE-survivors complaining of dyspnea suffer from impaired HRQoL and reduced exercise capacity. Although PE-severity factors were associated with reduced exercise capacity, none of the examined factors were found to be independent determinants of dyspnea.

Abbreviations: PE, pulmonary embolism; HRQoL, health-related quality of life; 6MWT, 6-min walking test; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiogram; V/Q-scan, ventilation/perfusion scintigraphy; BMI, body mass index; PESI, pulmonary embolism severity index score; RV/LV-ratio, right ventricle to left ventricle ratio; BNP, brain natriuretic peptide; CCI, Charlson comorbidity index; PEmb-QoL, Pulmonary embolism quality of life questionnaire; NYHA, New York heart association; $Sp0_2$, peripheral oxygen saturation; ADL, activities of daily living; TTE, transthoracic echocardiography; TAPSE, tricuspid annular plane systolic excursion; estPASP, estimated pulmonary artery systolic pressure; pTRV, peak tricuspid regurgitation velocity; RVGLS, the global longitudinal strain of the RV free wall; LVEF, left ventricle ejection fraction; LVGLS, left ventricular global longitudinal strain; LAVI, left atrial volume index; MBPEC, mean bilateral proximal extension of the clot; SD, standard deviation; IQR, interquartile range; VIF, variance inflation factor; SPSS, statistical package for social science; CI, confidence interval

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1. Introduction

Pulmonary embolism (PE) has classically been regarded as a curable disease with the majority of patients expected to fully recover without any sequelae. However, during the last decade several reports have revealed that up to 50% of long term PE survivors suffer from dyspnea, reduced health-related quality of life (HRQoL) and/or impaired exercise capacity, e.g. by 6-min walking test (6MWT) or cardiopulmonary exercise test [1–4]. These observations have led to the proposition of a new syndrome called “post-PE syndrome” [5]. Although a clear definition of post-PE syndrome is still to be fully established, it is considered to be characterized by a combination of the following elements: persistent dyspnea, exercise capacity limitations and/or impaired HRQoL after a PE [5]. Chronic thromboembolic pulmonary hypertension (CTEPH), which also is suggested to fall under the post-PE syndromes umbrella, should be regarded as the most severe presentation of this ‘syndrome’ [6].

However, there are several knowledge gaps regarding post-PE syndrome. Firstly, the vast majority of studies reporting on possible long-term effects of PE have mainly focused on clinical outcome measures, e.g. recurrence, residual thrombosis and right ventricular dysfunction, rather than persistent dyspnea, which is the main manifestation of post-PE syndrome [7,8]. This is of particular clinical importance since it is the symptom of persistent dyspnea that mandates further evaluation in such patients [9,10]. Secondly, although associations between dyspnea, reduced exercise capacity and impaired HRQoL have been reported by previous studies, none have primarily aimed to evaluate independent associations between these measures. Thirdly, the pathophysiological basis and possible determinants of post-PE syndrome are still a subject of debate. Whereas some studies argue that the phenomenon is due to residual thrombosis, actual pathological remodeling of the pulmonary vasculature and the right side of the heart [11,12], other studies have suggested that the observed impairment is more likely due to patients' comorbidities and/or physical deconditioning [4,13,14]. From this perspective, there is a need for further research on post-PE recovery in order to better understand the impact, determinants and underlying pathophysiology of the post-PE syndrome.

The main purpose of this study was to characterize the post-PE syndrome. The specific objectives were: 1) To describe the differences in clinical, biochemical and radiological parameters as well as exercise capacity and HRQoL in patients with and without dyspnea; 2) To study whether there were independent associations between persistent dyspnea, reduced exercise capacity and impaired HRQoL; 3) To explore possible determinants of these measures; and 4) To evaluate if echocardiographic parameters were associated with either dyspnea and/or exercise capacity.

2. Materials and methods

2.1. Study design

The details regarding inclusion and exclusion criteria of this cross-sectional study has previously been reported [3]. Briefly, patients who were objectively diagnosed with PE (i.e. by computed tomography pulmonary angiogram (CTPA) or high probability perfusion scintigraphy (V/Q-scan)) at Østfold Hospital Trust, Norway, between January 2002 and December 2011 and who were still alive in March 2012 were eligible for study participation. If patients had multiple separate episodes of PE between 2002 and 2011, the first one occurring during this period was considered as the index episode. Patients were excluded if they were < 18 or > 90 years old or deemed incapable to comply with study procedures, including language barriers, geographical unavailability, known dementia, psychiatric diagnosis, such as any psychotic disorder, or living in nursing homes.

The study was approved by the southeastern Norway Regional Committee for Medical and Health Research Ethics (Approval no 2011/2557b), and written informed consent was obtained for all patients.

2.2. Study procedure

Patients who agreed to participate were invited to a scheduled study visit during which they underwent the following assessments: 1) Clinical examination; 2) Exercise capacity test; 3) Blood tests; 4) Echocardiographic examination; and 5) Assessment of HRQoL. Further, clinical and socio-demographic data were retrieved from the patients' history and medical records and recorded on a standardized case report form by one of the study authors (M.T.).

Prior to the study visit, the HRQoL questionnaire was sent to the patients either by e-mail or post. Patients were asked to complete and return these at their scheduled study visit. In case of missing questionnaire data, patients were asked to complete these during their visit at the hospital.

2.3. Study outcomes

As one of the main components of the post-PE syndrome is persistent dyspnea, the primary objective was to study the differences in clinical, biochemical and radiological variables as well as exercise capacity and HRQoL in patients with and without dyspnea. Based on previous published studies [13,14] and clinical experience following variables were thus recorded for all patients: age, sex, body mass index (BMI; kg/m^2), occupation, smoking, pulmonary embolism severity index (PESI) score [15], right to left ventricle diameter ratio (RV/LV-ratio), mean bilateral proximal extension of the clot [16], disease duration (time in years from PE diagnosis to study visit), recurrence (any PE or deep vein thrombosis prior to study inclusion or after the index episode), blood tests at study visit including hemoglobin (g/L) and brain natriuretic peptide (BNP; ng/L), ongoing anti-coagulation at follow-up, non-age-adjusted Charlson comorbidity index at follow up (fibromyalgia was classified as a connective tissue disease) [17].

The second objective included assessment of possible determinants of dyspnea, 6MWT and Pulmonary Embolism Quality of life questionnaire (PEmb-QoL) sum score. As such, variables mentioned above, were examined for associations with these measures. In addition, we analyzed if there was an independent association between the outcomes of dyspnea, 6MWT and PEmb-QoL sum score. The final objective was to evaluate if right or left ventricular dysfunction had any association with the presence of shortness of breath and/or reduced exercise capacity. In order to do so, echocardiographic parameters were explored for possible independent associations with dyspnea and 6MWT.

In addition, in order to reduce the possible confounding effect of comorbidities, a subgroup analysis was done in patients with no known comorbidities, i.e. Charlson comorbidity index = 0.

2.4. Study measures

2.4.1. Dyspnea

Dyspnea was considered present if the patients experienced any persistent symptom of shortness of breath after their diagnosis of PE. Although not developed for or validated in PE-patients the New York Heart Association (NYHA) classification has been used in several studies evaluating the long-term effects of PE [11,13]. We graded dyspnea with NYHA and persistent dyspnea was scored as NYHA > I.

2.4.2. Exercise capacity

Exercise capacity was assessed with 6MWT according to published guidelines [18]. Based on previous reports we sought to assess the frequency of patients covering 85% of their predicted walking distances [12]. In order to do so, predicted walking distances were derived from the literature for each patient [19]. Moreover, pulse oximetry was used to measure resting peripheral oxygen saturation ($Sp0_2$) as well as $Sp0_2$ during the 6MWT. The mean decrease of $Sp0_2$ was calculated by subtracting resting $Sp0_2$ with the lowest value measured during the 6MWT.

2.4.3. Disease-specific health-related quality of life

HRQoL was assessed using the validated Norwegian version of PEmb-QoL questionnaire [20]. This instrument consists of 40 single items including six dimensions: frequency of complaints, activities of daily living (ADL) limitations, work-related problems, social limitations, intensity of complaints and emotional complaints. Two items are descriptive [21]. A sum score, ranging from 6 to 27 where higher scores indicate a worse HRQoL, was calculated by summarizing each patient's dimensional crude score divided by the number of dimensions.

2.4.4. Echocardiographic evaluation

Patients were evaluated at follow-up with a standardized transthoracic echocardiography (TTE) according to the American society of echocardiography and the European association of cardiovascular imaging recommendations [22,23], using a Vivid E9 machine (GE Vingmed Ultrasound, Horten, Norway). Right ventricular function was assessed by the following four measurements: 1) Tricuspid annular plane systolic excursion (TAPSE; cm) and a value < 1.7 cm was considered abnormal; 2) Estimated pulmonary artery systolic pressure (mm Hg), a value > 36 mm Hg was considered abnormal; 3) Peak tricuspid regurgitation velocity (m/s), a value > 2.9 m/s considered abnormal and 4) The global longitudinal strain of the right ventricular free wall (%), a value > −20% (i.e., < 20% in absolute value) was considered abnormal. Right ventricular dysfunction was considered present if any of these four parameters were abnormal. The left ventricular systolic function was assessed measuring the left ventricular ejection fraction (%) by 3D echo and global longitudinal strain (%). Values below 53% and −20% (i.e., < 20% in absolute value) respectively were considered abnormal. Diastolic function of the left ventricle was assessed by analysis of the left atrial volume index (mL/body surface area) and a value > 34 mL/m^2 was considered abnormal. Left ventricular dysfunction was considered present if any of these three measurements was abnormal.

2.4.5. Mean bilateral proximal extension of the clot

The mean bilateral proximal extension of the clot was first described in 2007 and proposed as a new score to assess the embolic burden of pulmonary embolisms diagnosed with CTPA. The mean bilateral proximal extension of the clot score is calculated by assigning a number to each of the four main vessels: 1 for sub-segmental, 2 for segmental, 3 for lobar, and 4 for main pulmonary artery. The mean score of the largest affected vessel in each lung, ranging from 1 to 4, is calculated and adjusted to the higher whole number [16].

2.5. Statistical analyses

Continuous variables were expressed as means and standard deviations (SD) if normally distributed and medians with interquartile range (IQR) if skewed distributed. Categorical variables were presented as frequencies and percentages. Comparisons were made using Students *t*-test or Mann-*U*-Whitney (depending on normal or skewed distribution) for continuous variables and Chi-square tests for categorical variables.

In order to analyze possible determinants of the outcomes of dyspnea, 6MWT and PEmb-QoL sum score (dependent variables), three regression models were performed (one logistic and two linear respectively). Independent variables with a significance level below alpha 0.1 in the univariate regression models were retained for multivariate regression analysis using the enter model. Of note, among our study objectives were to evaluate if there was an independent association between dyspnea, 6MWT and PEmb-QoL sum score. As such, dyspnea was included in the models having 6MWT and PEmb-QoL sum score as dependent variables and 6MWT in the model having PEmb-QoL sum score as dependent variable. The Hosmer and Lemeshow test and r^2 were used to estimate the goodness of fit of the model for logistic and linear models respectively.

Since the PEmb-QoL sum score was not normally distributed we log-transformed it in a first step. Hereafter variables were tested for independency in a multivariate linear regression analysis (enter model).

For the above mentioned analyses, the p-value was adjusted in the final multivariate model according to the Bonferroni correction and a two-sided alpha of < 0.017 (0.05/3) was considered significant.

The echocardiographic parameters were evaluated as possible determinants of dyspnea and 6MWT in a similar fashion as mentioned above. The parameters were dichotomized based on the abnormality thresholds. All models were adjusted for age, gender and BMI as well as Charlson comorbidity index. Since we used two dependent variables in these analyses, the p-value was adjusted according the Bonferroni correction and a two-tailed alpha < 0.025 was considered significant.

For all regression analyses, multicollinearity was checked using Variance inflation factor (VIF).

All analyses were performed using the Statistical Package for Social Science version 24.0 (SPSS Inc., Chicago, IL, USA). A two-sided alpha of < 0.05 was considered significant except for the regression analyses as mentioned previously.

3. Results

3.1. Patients

The study flow chart is shown in Fig. 1. A total of 836 patients were identified for eligibility. After excluding 430 (51%) according to predefined exclusion criteria, 406 patients were found eligible and invited. Of these, 203 patients completed both the 6MWT and the HRQoL questionnaire. The index PE diagnosis was confirmed by CTPA in 186 patients and V/Q scan in 17 patients. Complete data for blood tests at follow up were obtained in 196 patients. Although the entire cohort was referred for echocardiographic examination, this was performed in only 159 patients (78%).

3.2. Patient characteristics at diagnosis and follow up

Characteristics of the 203 patients categorized by dyspnea (NYHA > I) vs no dyspnea are provided in Table 1. After a median follow up of 3.6 (IQR 1.9–6.5) years, 96 (47%) patients reported dyspnea. The majority of the patients (86.5%) reported mild dyspnea, i.e. NYHA II. Although patients with dyspnea had shorter duration from diagnosis to study inclusion (median 3.6 (IQR 1.6–5.1) vs 4.6 (IQR 2.2–7.5) years, p < 0.05), the frequency of patients having their disease diagnosed < 1 year was equal between the groups (Table 1). PE-related severity parameters at baseline including the mean bilateral extension of the clot, RV/LV-ratio and PESI score did not differ between the groups. In contrast, significantly higher mean BMI and unemployment were observed in the dyspnea group (p = 0.009). The clinical characteristics revealed that dyspneic patients had a higher comorbid burden according to Charlson comorbidity index and more cardiopulmonary comorbidities (Table 1).

Of the 113 patients identified without any comorbidities (Charlson comorbidity index = 0), 44 patients (39%) reported dyspnea. In this subgroup analysis, the only observed significant difference between non-dyspneic and dyspneic patients was median time from diagnosis to study inclusion, 4.8 (IQR 2.3–7.8) vs 2.9 (1.4–4.6) years, p = 0.005.

3.3. 6-min walking test

Patients with dyspnea walked significantly shorter distances on the 6MWT, 413 (SD 133) meters vs 488 (SD 131) meters (Table 2). Although, 48% of the patients in the whole cohort had walking distances below 85% of their predicted values, non-dyspneic patients were more likely to cover longer than their 85% predicted distances (Table 2). In the subgroup of patients without comorbidities (n = 113), dyspneic patients had still significantly reduced 6-min walking distances compared to non-dyspneic, 452 (SD 102) meters vs 503 (SD 131) meters, p = 0.03.

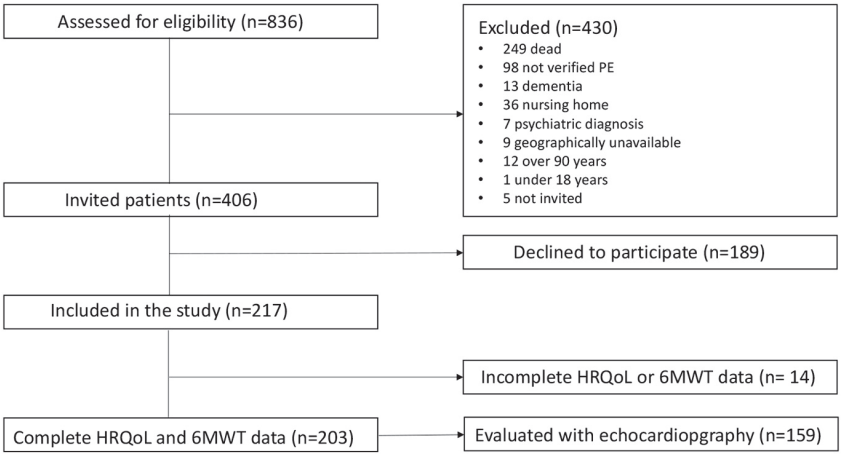

Fig. 1. Study flow chart.
HRQoL: Health-related quality of life.
6MWT: 6-min walking test.
Psychiatric diagnosis: any degree of psychotic disorder.

Pulse oximetry measurements revealed that the mean decrease in $Sp0_2$ during the 6MWT walking test did not differ significantly between patients with and without dyspnea, 2.5 (SD 1.8) vs 2.4 (SD 1.8) %, p = 0.75 (Table 2).

3.4. Disease-specific health-related quality of life

HRQoL was worse in dyspneic patients compared to non-dyspneic (Table 2). This impairment in HRQoL was also observed in the

Table 1
Patient characteristics at PE diagnosis and follow-up.

Variable	Total N = 203	No Dyspnea N = 107	Dyspnea N = 96	p-Value
Demographics				
Female, n (%)	92 (45.0)	46 (43.0)	46 (47.9)	0.57
Age (years), mean (SD)	60.1 (14.9)	59.9 (14.8)	61.6 (15.0)	0.40
BMI (kg/m2), mean (SD)	28.6 (4.8)	27.7 (4.8)	29.5 (4.7)	0.009
Obesity (BMI > 30), n (%)	70 (34.5)	30 (28.0)	40 (41.7)	0.05
Occupation, n (%)				
-Retired	84 (41.4)	43 (40.2)	41 (42.7)	
-Working	69 (34.0)	46 (43.0)	23 (24.0)	
-Unemployed	50 (24.6)	18 (16.8)	32 (33.3)	0.009
Smoking, n (%)				
-Former or current	88 (43.3)	45 (42.1)	43 (44.8)	0.78
-Package years, mean (SD)	21.9 (12.6)	22.0 (12.9)	21.7 (12.5)	
Characteristics				
Disease duration, years, median (IQR)	3.6 (1.9–6.5)	4.6 (2.2–7.5)	3.6 (1.6–5.1)	0.008
Disease < 1 year, n (%)	26 (12.8)	13 (12.1)	13 (13.5)	0.83
MBPEC, median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.65
RV/LV ratio, mean (SD)	1.1 (0.34)	1.1 (0.3)	1.1 (0.4)	0.84
RV/LV ratio > 0.9, n (%)	155 (76.4)	82 (76.6)	73 (76.0)	1.0
PESI, mean (SD)	72.7 (23.4)	70.3 (22.9)	75.5 (23.8)	0.12
Recurrence, n (%)	61 (30.0)	31 (29.0)	30 (31.3)	0.76
Cardiopulmonary comorbidities, n (%)	19 (9.4)	4 (3.7)	15 (15.6)	0.007
Malignancy and/or chemotherapy, n (%)	14 (6.9)	5 (4.7)	9 (9.4)	0.27
CCI, mean (SD)	0.78 (1.2)	0.53 (0.98)	1.05 (1.39)	< 0.005
CCI > 1, n (%)	90 (44.3)	38 (35.5)	52 (54.2)	0.01
Ongoing AC, n (%)	79 (38.9)	42 (39.3)	37 (38.5)	1.0

Dyspnea: NYHA > I at follow-up.
BMI: Body mass index at follow-up.
Working: Working or studying at follow-up.
Unemployed: Unemployed, long-term sick-leave or disability pension at follow-up.
Disease duration: Time from PE diagnosis to study inclusion.
MBPEC: Mean bilateral proximal extension of the clot at PE diagnosis.
PESI: Pulmonary embolism severity index score at diagnosis.
Recurrence: Any PE or deep vein thrombosis prior to study inclusion or after the index PE episode.
Cardiopulmonary comorbidities: documented chronic heart failure and non-asthmatic chronic obstructive pulmonary disease at follow-up.
Malignancy and/or Chemotherapy: Active malignancy and/or chemotherapy within past 6 months at follow-up.
CCI: Charlson comorbidity index, non-age adjusted at follow-up.
Ongoing AC: Ongoing anticoagulation at follow-up.

Table 2
The differences in physical examination, blood tests, 6MWT and HRQoL at follow up in in non-dyspneic and dyspneic patients.

Variable	Total N = 203	No dyspnea N = 107	Dyspnea N = 96	p-Value
Physical exam and blood test characteristics				
Systolic blood pressure (mm Hg), mean (SD)	147.9 (20.9)	146.2 (21.0)	149.7 (20.8)	0.24
Diastolic blood pressure (mm Hg), mean (SD)	89.3 (10.8)	89.0 (11.1)	89.7 (10.5)	0.69
Resting Sp02 (%), mean (SD)	97.2 (2.1)	97.5 (0.9)	96.9 (2.9)	0.07
Hemoglobin (g/L), mean (SD)	142.3 (20.0)	145.8 (12.9)	139.7 (26.1)	0.04
P-BNP (ng/l), mean (SD)	48.4 (72.8)	42.8 (57.9)	54.4 (85.9)	0.27
6MWT characteristics				
6MWT (meters), mean (SD)	453 (137)	488 (131)	413 (133)	< 0.005
6MWT below 85% of predicted, n (%)	97 (48)	43 (40)	54 (56)	0.03
Sp02 (%) decrease, mean (SD)	2.5 (1.8)	2.4 (1.8)	2.5 (1.8)	0.75
HRQoL characteristics				
PEmb-QoL sum score, median (IQR)	9.5 (7.5–12.8)	8.0 (7.0–9.5)	12.5 (9.9–15.0)	< 0.005

Dyspnea: NYHA > 1.
P-BNP: plasma-brain natriuretic peptide.
6MWT: 6-min walking test.
Mean Sp02 decrease: Decrease in Sp02% during 6MWT.
PEmb-QoL sum score: Pulmonary embolism quality of life sum score. Higher scores indicating worse HRQoL.

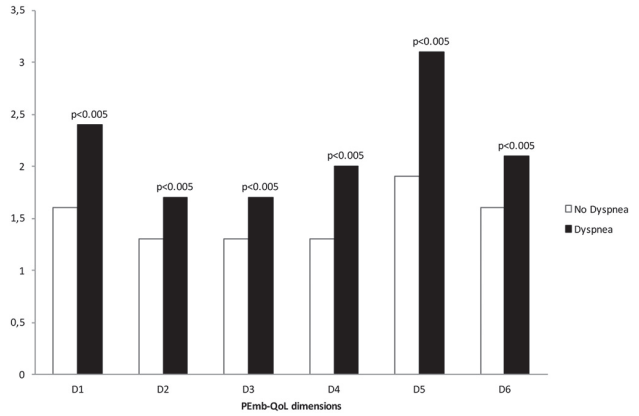

Fig. 2. Mean dimensional PEmb-QoL scores in patients with and without dyspnea.
Independent sample Student *t*-test, two-sided.
D1: Frequency of complaints.
D2: Activities of daily living limitations.
D3: Work-related problems.
D4: Social limitations.
D5: Intensity of complaints.
D6: Emotional complaints.

subgroup of patients with no comorbidities, PEmb-QoL sum score 12.2 (IQR 9.6–14.9) vs 7.8 (IQR 6.8–8.8), p < 0.005. Fig. 2 displays the differences between patients with and without dyspnea stratified by the PEmb-QoL dimensions. The largest mean differences were observed in dimension one (frequency of complaints, questions 1; mean difference 0.86), dimension four (social limitations, question 6; mean difference 0.74) and dimension five (intensity of complaints, question 7 and 8; mean difference 1.19). Interestingly for example in dimension four, 89% of the patients not having dyspnea had a mean score of 1, indicating that their "lung symptoms" did not interfere at all with social activities. For the group with dyspnea however, 74% had reported some degree of inhibition from their lung symptoms.

3.5. Possible determinants of dyspnea, 6MWT and PEmb-QoL

The results from multiple binary logistic and linear regression analyses for possible determinants of dyspnea, 6MWT and PEmb-QoL sum score are given in Table 3. None of the variables was found to be independently associated with dyspnea per se. Dyspnea had a significant independent association with higher PEmb-QoL sum score (i.e. worse HRQoL) and lower 6MWT results. In addition to age, gender and BMI, RV/LV-ratio at baseline was found to be associated with 6MWT results at follow-up, p < 0.017 (Table 3). Unemployment and ongoing oral anticoagulation were significantly associated with PEmb-QoL sum score (Table 3). Interestingly, Charlson comorbidity index was a significant determinant of dyspnea, impaired HRQoL and reduced exercise capacity in the univariate analysis. However, it failed to show any significant association with these measures in the multivariate models (Table 3).

3.6. Echocardiographic evaluation

There was no significant difference in patient characteristics examined with echocardiography (n = 159) compared to the whole cohort. Although patients having dyspnea had lower left ventricular ejection fraction and reduced left ventricular global strain, there was no statistically significant difference observed regarding the proportion of patients having an ejection fraction < 53% or left ventricular global strain < 20% between the groups, Table 4. In total 9 patients had TAPSE below 1.7 cm. TAPSE was not statistically different between the groups (p = 0.3). Of the 18 patients with peak tricuspid regurgitation velocity > 2.9 m/s, three patients, all of whom reported dyspnea, had peak tricuspid regurgitation velocity > 3.4 m/s suggesting pulmonary hypertension being probable according to guidelines [24]. One of these patients had already established CTEPH diagnosis. The other two were referred to further work-up and were not found to have CTEPH.

Multiple regression analysis failed to reveal that any of the echocardiographic parameters were associated with dyspnea. However, in the model evaluating possible echocardiographic determinants of 6MWT, a significant association was observed between TAPSE and 6MWT results adjusted for age, gender, BMI and Charlson comorbidity index. Patients having an abnormal TAPSE (i.e., TAPSE < 1.7 cm) walked on average 88 m less (unstandardized beta −88, SE 36, p = 0.015, r^2 = 46%). This significance remained when we performed the analysis on the subgroup of patients with no comorbidities (n = 87 with available echocardiographic data), unstandardized beta −164, SE 65, p = 0.014, r^2 = 42%. Of note, peak tricuspid regurgitation velocity and estimated pulmonary artery systolic pressure revealed high VIF values indicating a multicollinearity issue. Hence, the variable with the highest VIF value, i.e., estimated pulmonary artery systolic pressure, was excluded from the adjusted model.

Table 3
Adjusted multiple regression analysis for possible determinants of dyspnea, 6-min walking test and PEmb-QoL sum score.

	Dyspnea		6MWT			PEmb-QoL sum score		
	Odds ratio	95% CI	B	S.E.	p-value	B	S.E.	p-value
Gender	1.11	0.57-2.16	-79.1	16.2	< 0.005*	0.018	0.039	0.65
Age	1.01	0.99-1.03	-2.6	0.8	< 0.005*	-0.003	0.002	0.11
BMI	1.07	0.99-1.15	-6.2	1.6	< 0.005*	0.000	0.004	0.94
Smoking	†	†	†	†	†	0.010	0.035	0.78
Unemployed	1.80	0.86-3.76	†	†	†	0.135	0.041	< 0.005*
Disease duration	0.90	0.81-1.01	†	†	†	-0.007	0.006	0.25
Ongoing anticoagulation	†	†	†	†	†	0.085	0.034	0.01*
Recurrence	†	†	†	†	†	†	†	†
PESI score	†	†	-1.2	0.5	0.02	-0.001	0.001	0.54
MBPEC	†	†	-1.8	7.7	0.82	†	†	†
RV/LV-ratio	†	†	-63.7	23.3	0.007*	†	†	†
BNP (ng/l)	†	†	-0.2	0.1	0.22	0.001	0.000	0.03
Hemoglobin (g/l)	0.99	0.97-1.01	0.77	0.5	0.13	0.000	0.001	0.91
CCI	1.32	0.98-1.79	-5.3	6.9	0.45	0.007	0.017	0.86
6MWT	‡	‡	‡	‡	‡	-0.001	0.000	< 0.005*
Dyspnea	‡	‡	-38.0	15.2	0.01*	0.242	0.035	< 0.005*
Hosmer and Lemeshow, (%)		55.7						
R^2, (%)					50.8			58.1

All models adjusted for gender and age.
Gender: female = 1.
BMI: Body mass index (kg/m^2) at follow-up (continuous).
Smoking: current or former smoker at follow-up = 1
Unemployed = unemployed, long-term sick leave or disability pension at follow-up = 1.
Disease duration = Time from PE diagnosis in years (continuous).
Ongoing anticoagulation: Ongoing anticoagulation at follow-up = 1.
PESI score: Pulmonary embolism severity index score at PE diagnosis.
MBPEC: Mean bilateral proximal extension of the clot at PE diagnosis (continuous).
RV/LV ratio: right to left ventricle diameter ratio at PE diagnosis (continuous).
BNP: Brain natriuretic peptide (ng/l) at follow-up (continuous).
CCI: non age-adjusted Charlson comorbidity index at follow-up (continuous).
Dyspnea: NYHA > I at follow-up = 1.
6MWT: 6-minute walking test at follow-up (continuous).
PEmb-QoL sum score: Pulmonary embolism quality of life questionnaire summary score at follow-up (continuous).
* : indicating significance at alpha < 0.017.
B : Unstandardized Beta.
S.E .: Standard error.
† : Variables not significant in the univariate analysis.
‡ : Not included in the model.

Table 4
Echocardiographic findings at follow-up.

Variable	Total N = 159	No dyspnea N = 72	Dyspnea N = 87	p-Value
Echocardiographic characteristics				
LVEF (%), mean (SD)	60.9 (9.2)	62.6 (6.4)	59.5 (10.8)	0.03
LVEF < 53%, n (%)	16 (10.1)	4 (5.6)	12 (13.8)	0.11
LVGLS (%), mean (SD)	−19.8 (3.4)	−20.6 (2.7)	−19.1 (3.8)	0.005
LVGLS < 20%, n (%)	75 (47.2)	29 (40.3)	46 (53.5)	0.11
LAVI (mL/m^2), mean (SD)	27.8 (11.4)	27.4 (10.7)	28.1 (12.0)	0.70
LAVI > 34 mL/m^2, n (%)	35 (22.0)	16 (22.2)	19 (21.8)	1.00
pTRV (m/s), mean (SD)	2.3 (0.6)	2.2 (0.43)	2.3 (0.64)	0.53
pTRV > 2.9 m/s, n (%)	18 (11.3)	5 (6.9)	13 (14.9)	0.14
EstPASP (mm Hg), mean (SD)	26.9 (9.9)	25.4 (6.9)	28.2 (11.7)	0.08
EstPASP > 36 mm Hg, n (%)	19 (11.9)	5 (6.9)	14 (16.1)	0.09
TAPSE (cm), mean (SD)	2.4 (0.4)	2.4 (0.4)	2.3 (0.4)	0.30
TAPSE < 1.7 cm, n (%)	9 (5.7)	2 (2.8)	7 (8.0)	0.18
RVGLS (%), mean (SD)	−24.8 (6.2)	−26.3 (5.6)	−23.6 (6.4)	0.006
RVGLS < 20%, n (%)	29 (18.2)	6 (8.3)	23 (26.4)	0.004

LVEF: Left ventricular ejection fraction. Abnormality threshold < 53%.
LVGLS: Left ventricular longitudinal global strain. Abnormality threshold < 20% in absolute value.
LAVI: Left atrial volume index. Abnormality threshold > 34 mL/m^2.
pTRV: Peak tricuspid regurgitation velocity. Abnormality threshold > 2.9 m/s.
EstPASP: Estimated pulmonary artery systolic pressure. Abnormality threshold > 36 mm Hg.
TAPSE: Tricuspid annular plane systolic excursion. Abnormality threshold < 1.7 cm.
RVGLS: Global longitudinal strain of the right ventricular free wall. Abnormality < 20% in absolute value.

4. Discussion

In this study, we found that 47% of the patients had persistent dyspnea 3.6 years after an episode of PE. Patients with dyspnea had reduced exercise capacity and HRQoL compared to those without dyspnea. Further, an independent association was observed between these measures, hence objectively confirming the presence of the yet uncharacterized condition called post-PE syndrome. None of the predefined variables was found to be associated with dyspnea. However, we found that unemployment and ongoing oral anticoagulation were significantly associated with PEmb-QoL sum score whereas RV/LV-ratio at baseline was associated with 6MWT. Of the echocardiographic parameters only TAPSE was associated with reduced 6MWT results.

In line with previous reports, our study revealed an independent association between dyspnea, limitations in exercise capacity and reduced HRQoL in the regression models, elucidating the negative impact of post-PE syndrome on several aspects of the patients post-PE recovery [5,25]. However, there has been a debate regarding whether parameters determining persistent dyspnea, which is the main element of post-PE syndrome, lie within patient-related, e.g. comorbidities, or PE-related factors [12,13]. Our study did not find comorbidities independently associated with dyspnea or HRQoL. Importantly, Charlson comorbidity index was not found to be associated with 6MWT results and even in the subgroup analysis of patients with no comorbidities, dyspneic patients had significantly lower 6MWT results. Furthermore, we found no significant differences between dyspneic and non-dyspneic patients in resting $Sp0_2$ and mean decrease in $Sp0_2$ during 6MWT. These findings indicate that the post-PE syndrome cannot simply be explained by comorbid conditions.

In the PEmb-QoL questionnaire the two dimensions of “frequency and intensity of complaints” evaluate the amount of pain and/or discomfort including breathlessness the patients have from their chest, whereas the “social limitations” dimension evaluates how much these symptoms, interfere with daily social activities. The largest differences in PEmb-QoL between dyspneic and non-dyspneic were observed in these three domains, suggesting that patients with dyspnea have various persistent complaints from their thoracic region, and that these symptoms limit them to engage in usual and social activities of daily life. Whether or not this truly is related to their PE is however hard to assess. Nevertheless, this finding may imply that designated rehabilitation programs, as shown for other cardiopulmonary diseases [26,27], could perhaps alleviate these symptoms also in PE-patients. Furthermore, we found that ongoing anticoagulation was significantly associated with PEmb-QoL sum score – a finding that has not been previously reported. A plausible explanation is that ongoing anticoagulation potentially enhances the notion of active disease in PE patients and hence reducing their HRQoL. However, we cannot rule out factors such as depression and chronic pain influencing the reduced HRQoL in patients with ongoing anticoagulation. Unemployment, which previously have been shown to be associated with reduced generic HRQoL both in PE patients and other diseases [3,28], was also significantly associated with reduced disease-specific HRQoL. This is an important observation since the observed impaired HRQoL in PE-patients is perhaps not due to the PE itself but rather to other socio-demographic factors.

The characteristics in patients evaluated with echocardiography were comparable to that of the whole cohort of 203 patients. Although, affected right ventricle, i.e. TAPSE, was associated with impaired exercise capacity in the whole cohort as well as in the subgroup of patients without comorbidities, none of the echocardiographic parameters revealed an association with dyspnea or reduced HRQoL. This may indicate that, whereas the notion of dyspnea is perhaps not due to structural cardiac or physiological changes, the patients reduced exercise capacity may be.

It should be mentioned however, that although we failed to reveal any association between PE-related factors and dyspnea, PESI (not adjusted according to Bonferroni) and RV/LV-ratio had significant associations with long-term exercise capacity. Moreover, several reports including the current study have revealed close associations between dyspnea, impaired HRQoL and reduced exercise capacity [3,4,11,14]. As such, this finding may indicate that patients with high PESI scores or RV/LV-ratio at diagnosis should be evaluated more thoroughly during the follow-up period in order to identify patients with post-PE syndrome. However, the possibility of discrepancy between patient-reported outcomes (e.g. dyspnea and HRQoL) and physical performance should also be considered as a potential explanation of these findings. In this context, perhaps post-PE syndrome should be characterized as a syndrome consisting of several affected elements with more than one underlying cause. Moreover, there may be other factors (which no study to date have included) such as depression, chronic pain and/or social status, that may influence the impaired post-PE recovery in patients with post-PE syndrome.

4.1. Strength and limitations

The major strengths of this study are its sample size and a comprehensive evaluation of patients at follow-up, including physical and echocardiographic examination, exercise capacity test and evaluation of HRQoL. In addition, the inclusion of the Charlson comorbidity index has allowed us to assess comorbidities which has been shown to have a prognostic value regarding mortality in PE [29].

The study has some limitations: The possibility of a selection bias cannot be excluded since not all data were complete for the whole cohort and 47% (189/406) of the invited patients did not participate. This may have led to including a “survivor cohort” with less prevalence of cancer and cardiopulmonary comorbidity. However, our Charlson comorbidity index, 6MWT and PEmb-QoL results are comparable to prior studies [11,12,30], reflecting the cohort being representative of PE patients at large. Moreover, we assessed dyspnea using NYHA classification, which is not a validated measure of dyspnea in PE-patients, as opposed to other validated comprehensive dyspnea scales, such as the San Diego Shortness of Breath Questionnaire or S:t Georges respiratory questionnaire. However, as these questionnaires were either not available in Norwegian or not validated for PE this was not possible. Furthermore, we did not perform a pulmonary function test or follow-up imaging in order to properly assess the patients' pulmonary status and screen for possible residual thrombosis. Additionally, we cannot rule out the possibility of a ceiling effect in the 6MWT results, i.e. even in young, healthy patients without comorbidities it is difficult to walk > 500 m. Hence, minimizing the true difference between dyspneic and non-dyspneic patients. However, again, our 6MWT results are comparable to previous studies [11,12]. Lastly, only 78% (159/203) were evaluated with echocardiography, which could argue that patients having more problems met up for the echocardiographic examination. However, very few patients had for example an ejection fraction below 53% and overall our echocardiographic parameters are comparable to previous studies [12,14].

5. Conclusion

In conclusion, our study revealed that dyspnea is a frequent symptom in long-term PE survivors and that it is independently associated with limited exercise capacity and reduced HRQoL. These findings emphasize the existence and relevance of the post-PE syndrome and its impact on several aspects of the patients' well-being after PE. The underlying cause of post-PE syndrome seems, however, to be multifaceted and further research is needed in order to more clearly define this condition. Future studies should evaluate whether designated rehabilitation programs could indeed reduce the prevalence of post-PE syndrome in order to improve post-PE recovery.

Conflict of interest

The authors state that they have no conflict of interest, except W. Ghanima, P.A. Sirnes and L.P. Jelsness-Jørgensen. W. Ghanima reports research grants from Bayer, Novartis and BMS and lecture and advisory board honoraria from Bayer, Amgen and Novartis. PA Sirnes reports lecture and advisory board honoraria from Novartis, Sanofi, Bayer and Merck Sharp & Dohme – none of which is relevant for the submitted work. L.P. Jelsness-Jørgensen reports unrestricted grants from Ferring pharmaceuticals and Tillots pharma, and personal fees from Abbvie, not relevant for the submitted work.

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