



**Universiteit  
Leiden**  
The Netherlands

## **Pulmonary embolism : diagnostic management and prognosis**

Klok, F.A.

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## Chapter 13

### **Quality of life after pulmonary embolism: validation of the PEmb-QoL questionnaire**

F.A. Klok<sup>†</sup>, D.M. Cohn<sup>†</sup>, S. Middeldorp, M. Scharloo, H.R. Büller, K.W. van Kralingen,  
A.A. Kaptein and M.V. Huisman

<sup>†</sup>Equally contributed

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## ABSTRACT

### Background

Even though quality of life (QoL) has become a key component of medical care, there is no instrument available that specifically measures QoL after pulmonary embolism (PE). Recently, the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire has been developed to address this gap. We have evaluated the validity of this questionnaire.

### Methods

The PEmb-QoL questionnaire and the Short Form-36 (SF-36) questionnaire were distributed twice among consecutive subjects with a history of objectively confirmed acute PE. Internal consistency reliability, test-retest reliability, convergent and criterion validity, and correlations between the PEmb-QoL and clinical patient characteristics were assessed using standard-scale construction techniques.

### Results

90 participants completed the questionnaires twice. Internal consistency was adequate (Cronbach's  $\alpha$  0.62-0.94), as well as test-retest reliability (intra-class correlation coefficients 0.78-0.94). Furthermore, correlation between the PEmb-QoL questionnaire and the SF-36 questionnaire supported the convergent and criterion validity of the PEmb-QoL. Age, obesity, cardiopulmonary comorbidity, centrally located PE and a family history of venous thromboembolism were shown to be independent determinants of disease-specific QoL.

### Conclusion

The PEmb-QoL questionnaire is a reliable instrument to specifically assess QoL following PE, which is helpful in the identification of patients with decreased QoL following acute PE.

## INTRODUCTION

Pulmonary embolism (PE) is a common disorder characterized by the obstruction of the pulmonary arterial tree by floating thrombi predominantly originating from the leg or pelvic veins.<sup>1</sup> Although PE has traditionally been considered to be an acute disease, the long term natural course in patients surviving the acute thromboembolic event can be complicated by recurrent episodes of PE or deep vein thrombosis, bleeding complications caused by anticoagulant treatment, arterial cardiovascular events and in rare cases by chronic thromboembolic pulmonary hypertension (CTEPH).<sup>1-4</sup> CTEPH may present as fatigue, limited exercise tolerance or shortness of breath and might even affect 3.8% of PE patients within 2 years following the initial event.<sup>3</sup> In addition, patients often have residual dyspnea complaints years after the acute thromboembolic event.<sup>5</sup>

Quality of life (QoL) has become an important outcome aspect of medical care. QoL can be assessed by generic or disease-specific questionnaires. The latter are more sensitive than generic questionnaires to detect and quantify small changes that are relevant to patients. Several disease-specific QoL instruments have been developed for deep venous thrombosis (DVT), a condition closely related to PE and considered a manifestation of the same disease entity.<sup>6-10</sup> Furthermore, there are several specific questionnaires for symptoms of the respiratory tract, such as the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)<sup>11</sup> or the Chronic Respiratory Disease Questionnaire (CRQ).<sup>12</sup> However, since respiratory or other symptoms that affect QoL after PE have never been purposely studied, we have developed a new measure -the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire-, based on symptoms as reported by 10 interviewed participants with severe complaints following PE. Details on the development of the PEmb-QoL questionnaire have been described previously.<sup>13</sup>

The PEmb-QoL was modelled on the quality of life after DVT (VEINES-QOL/Sym) questionnaire.<sup>6,7,9</sup> Both questionnaires assess the frequency of symptoms, the time of day at which the complaints are at their worst and activities of daily living (ADL) as well as work related problems. However, the PEmb-QoL questionnaire is distinct from the VEINES-QOL/Sym in the inclusion of pulmonary specific symptoms, adding questions on limitations in daily physical activities, and extending the number of questions on emotional functioning. Moreover, in order not to lose valuable information, we decided to assess the different areas of limitations as separate dimensions, instead of combining items into two subscales (symptoms and QoL), as is the case in the VEINES-QOL questionnaire. In the present paper, we report results from the validation study that was performed to assess the psychometric and clinical characteristics of the questionnaire.

## METHODS

### Participants

The PEmb-QoL in Dutch was distributed among consecutive participants of a large follow-up study of patients with a history of acute PE referred to the Leiden University Medical Center. Inclusion criteria were objectively confirmed PE diagnosed between January 1<sup>st</sup> 2001 and July 1<sup>st</sup> 2007. All surviving patients were invited for a control visit in our outpatient clinic. We asked a random, consecutive subsample of 93 participants to complete the PEmb-QoL and Short-Form 36 (SF-36) questionnaires shortly before this visit. After first review, incomplete questionnaires were completed at the study visit. For assessment of test-retest reliability, participants were instructed to complete both questionnaires for a second time (within a two week period) at home shortly after the visit and return these by mail. Incomplete returned questionnaires were completed by the patients following contact by telephone. We excluded participants with language barriers who could not complete the questionnaires in Dutch. The study protocol was approved by the Institutional Review Board of the Leiden University Medical Center and all patients provided written informed consent.

### PEmb-QoL questionnaire

We applied the disease specific PEmb-QoL questionnaire which we developed to assess QoL in patients with PE.<sup>13</sup> The PEmb-QoL questionnaire contains 6 dimensions: frequency of complaints, ADL limitations, work related problems, social limitations, intensity of complaints and emotional complaints. Higher scores indicate worse outcome.

### SF-36 questionnaire

The SF-36 is a generic QoL measure containing 8 scales (physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, and general health), scoring 0 to 100, with higher values indicating better health.<sup>14</sup> Two summary scores are created by combining scales into a physical health summary score and mental health summary score.

### Outcome measures

We expected that the PEmb-QoL dimensions frequency of complaints, ADL limitations, work related problems, social limitations and intensity of complaints would have higher correlations with the physical health summary score of the SF-36, whereas emotional complaints would have a higher correlation with the mental health summary score. Furthermore, we did not expect that patient characteristics at time of the acute PE would be important determinants of the results of the PEmb-QoL, given the results of a previous study.<sup>15</sup> This study showed that QoL after deep vein thrombosis as assessed by the VEINES-QOL and SF-36 was mostly determined by the presence of the postthrombotic syndrome and less by severity of the acute clinical event,

comorbid conditions, sex or age. To test this hypothesis, we assessed the following patient characteristics and correlated those to the results from the PEmb-QoL: age, sex, obesity (body mass index >30kg/m<sup>2</sup>), active malignancy (cancer with ongoing treatment, treatment within the previous 6 months or in the palliative stages), cardiopulmonary comorbidity (clinically relevant obstructive or restrictive pulmonary function impairment, or systolic or diastolic ventricular dysfunction), centrally located PE according to the original radiological reports, family history of venous thromboembolism and the duration of follow-up from the index thromboembolic event to study inclusion.

The outcome measures of this analysis were internal consistency reliability (which assesses whether several items that propose to measure the same general construct produce similar scores), test-retest reliability, convergent validity, criterion validity (as assessed by comparing the PEmb-QoL dimensions with the dimensions of the SF-36 disease generic questionnaire) and the association of patient demographics, comorbid conditions and PE characteristics with higher or lower QoL in our patient population.

### Statistical Analyses

Means and standard deviations were calculated for normally distributed variables. Skewed distributed variables were expressed in medians with ranges. We performed a factor analysis on the items of the PEmb-QoL with varimax rotation to examine the underlying constructs. Internal consistency reliability was calculated with Cronbach's  $\alpha$ .<sup>16</sup> Following the recommendations of DeVellis, internal consistency reliability was considered adequate if Cronbach's  $\alpha$  was higher than 0.7.<sup>17</sup> Test-retest reliability was expressed as intra-class correlation coefficients. We calculated inter-dimension correlations and criterion validity with bivariate Spearman correlation coefficients. For the assessment of significant predictors of QoL in our patient cohort, backward conditional linear regression analyses with direct entry were performed to identify independent determinants of QoL. A p-value <0.05 was considered statistically significant.

## RESULTS

### Patients

The questionnaires were distributed amongst 93 participants, of whom 90 completed the questionnaire after a median period of 38 months (range 10–91 months) following PE. Three participants (3.2%) were excluded due to inability to complete this questionnaire in Dutch because of language barriers. The number of missing items was very low; however the exact number could not be calculated as all missing items were completed by the respondents following contact by phone with the researchers. The included participants were 56  $\pm$ 14 years old, 44 (47%) were males, 19 (20%) had cardiopulmonary comorbidity, 12 (13%) had active malignancy, 36 (39%) were obese, 31 (33%) were diagnosed with centrally located PE,

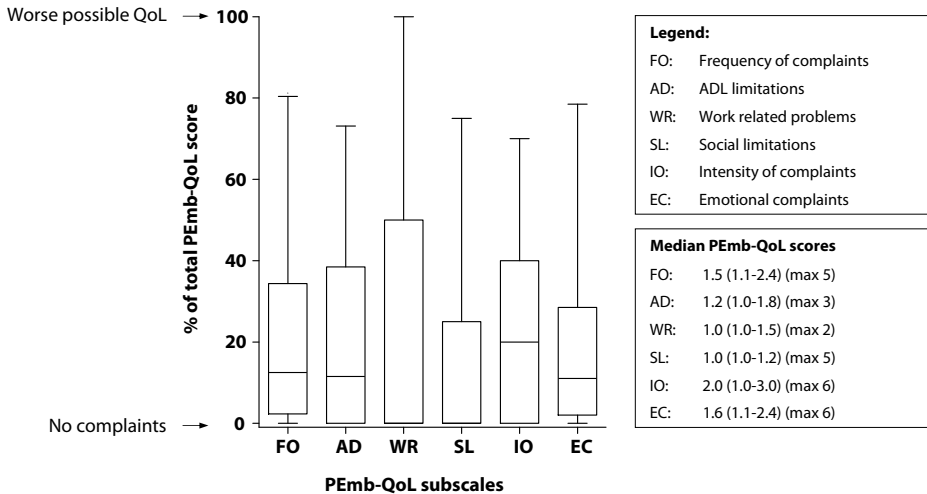
**Table 1.** Demographics of included patients.

	Study patients (n=90)
Male sex (n, %)	43 (48)
Age (years $\pm$ SD)	56 $\pm$ 14
Cardiopulmonary comorbidity (n, %)	18 (20)
Active malignancy (n, %)	12 (13)
Obesity* (n, %)	35 (39)
Centrally located PE (n, %)	31 (34)
Invasive treatment for PE <sup>†</sup> (n, %)	6 (6.7)
Recurrent PE (n, %)	18 (20)
Time to registration event <sup>‡</sup> (range)	3 years and 2 months (10 months – 7 years and 7 months)

\*Body mass index  $>30\text{kg}/\text{m}^2$ ; <sup>†</sup>thrombolysis, Surgery or VCF for first acute PE; <sup>‡</sup>time span between registration acute PE and study inclusion. PE=pulmonary embolism, n=number.

6 (6.5%) received invasive treatment for PE and 19 (20%) suffered from recurrent episodes of PE (Table 1).

Scores of the 6 dimensions of the PEmb-QoL were 1.5 (interquartile range 1.1-2.4; max 5 points) for frequency of complaints, 1.2 (1.0-1.8; max 3 points) for limitations in activities of daily living (ADL), 1.0 (1.0-1.5; max 2 points) for work related problems, 1.0 (1.0-1.2; max 5 points) for social limitations, 2.0 (1.0-3.0; max 6 points) for intensity of complaints and 1.6 (1.1-2.4; max 6 points; Figure 1). For all dimensions, a score of 1 point designates no complaints.



**Figure 1.** Results of the PEmb-QoL scores of patients with a history of acute pulmonary embolism. Scores are presented as median with interquartile range. Minimum score for all 6 subscales was 1, maximum scores are presented between brackets. Higher PEmb-QoL scores are associated with decreased quality of life. ADL=activities of daily living, QoL=quality of life.

### Psychometric characteristics of the PEmb-QoL questionnaire

Factor analysis (with varimax rotation) supported the underlying dimensions producing 6 factors which accounted for 72% of the total variance. Table 2 lists the internal reliabilities of the dimensions, as expressed by Cronbach's  $\alpha$ , as well as test-retest reliability and inter-dimension correlations between the PEmb-QoL dimensions. Internal reliability was high ( $\alpha \geq 0.87$ ) for the dimensions frequency of complaints, ADL limitations, work related problems, and emotional complaints but lower for the dimension intensity of complaints ( $\alpha = 0.62$ ). We assessed whether deletion of any of the items in the various dimensions could increase the internal reliability of any of the dimensions and hence, whether the PEmb-QoL questionnaire could be abridged. However, deletion of any of the items from the various dimensions did not lead to substantial improvements of the dimensions' internal consistency reliability.

**Table 2.** Internal consistency reliability, test-retest reliability and correlations between PEmb-QoL dimensions.

PEmb-QoL dimensions	PEmb-QoL questions	Number of items	Cronbach's $\alpha$	Intra-class correlation coefficient	Frequency of complaints	ADL limitations	Work related problems	Social limitations	Intensity of complaints
Frequency of complaints	Question 1*	8	0.90	0.94***	-	-	-	-	-
ADL limitations	Question 4*	13	0.94	0.87***	0.67**	-	-	-	-
Work related problems	Question 5*	4	0.87	0.78***	0.49**	0.66**	-	-	-
Social limitations	Question 6	1	NA	0.83***	0.62**	0.69**	0.64**	-	-
Intensity of complaints	Questions 7/8	2	0.62	0.85***	0.82**	0.73**	0.60***	0.66**	-
Emotional complaints	Question 9*	10	0.91	0.81***	0.60**	0.60**	0.56**	0.63**	0.71***

\*Items reversely scored (higher scores indicate more complaints); \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ . ADL=activities of daily living, NA=not applicable.

Intra-class correlation coefficients for test-retest analysis varied between 0.78 for work related problems and 0.94 for frequency of complaints, indicating adequate test-retest validity. The highest correlations between dimensions were found between intensity of complaints and all other dimensions ( $0.60 \leq r \leq 0.82$ ). Except for work related problems and frequency of complaints ( $r = 0.49$ ), all dimensions were moderately correlated ( $0.56 \leq r \leq 0.82$ ).

The results of the criterion validity are reported in Table 3. As expected, the PEmb-QoL dimensions frequency of complaints, ADL limitations, work related problems, social limitations and intensity of complaints had higher associations with the physical health summary score of the SF-36 questionnaire, whereas emotional complaints were most strongly associated with the



**Table 3.** Correlations between PEmb-QoL dimensions and SF-36 subscales.

PEmb-QoL	SF-36									
	Physical function- ing	Social function- ing	Physical role func- tioning	Emotional role func- tioning	Mental health	Vitality	Bodily pain	General health	Physical health summary	Mental health summary
Frequency of complaints	-0.46**	-0.55**	-0.33**	-0.28**	-0.45**	-0.56**	-0.42**	-0.55**	-0.44**	-0.42**
ADL limitations	-0.78**	-0.61**	-0.53**	-0.39**	-0.45**	-0.66**	-0.49**	-0.63**	-0.66**	-0.39**
Work related problems	-0.53**	-0.50**	-0.58**	-0.43**	-0.40**	-0.54**	-0.29**	-0.53**	-0.51**	-0.39**
Social limitations	-0.54**	-0.55**	-0.45**	-0.31**	-0.38**	-0.53**	-0.35**	-0.51**	-0.50**	-0.35**
Intensity of complaints	-0.62**	-0.66**	-0.44**	-0.32**	-0.55**	-0.67**	-0.49**	-0.60**	-0.55**	-0.48**
Emotional complaints	-0.45**	-0.60**	-0.38**	-0.43**	-0.57**	-0.69**	-0.41**	-0.59**	-0.40**	-0.57**

\*\*p<0.01.

mental health summary score. Frequency of complaints was most strongly correlated with vitality ( $r=-0.56$ ), social functioning ( $r=-0.55$ ) and physical functioning ( $r=-0.46$ ). The strongest correlations for ADL limitations were physical functioning ( $r=-0.78$ ), social functioning ( $r=-0.61$ ) and vitality ( $r=-0.66$ ). Work-related problems most strongly correlated with physical role functioning ( $r=-0.58$ ) and physical functioning ( $r=-0.53$ ). The dimension social limitations was correlated with several SF-36 dimensions. We observed strong correlations with physical functioning ( $r=-0.54$ ), social functioning ( $r=-0.55$ ) and vitality ( $r=-0.53$ ). Intensity of complaints was strongly correlated with the same SF-36 dimensions as frequency of complaints, but with higher correlation coefficients. The strongest correlations for emotional complaints were mental health ( $r=-0.57$ ), vitality ( $r=-0.69$ ) and social functioning ( $r=-0.60$ ).

#### Associations between clinical characteristics and the PEmb-QoL

After multivariate analysis including all patient demographics, comorbid conditions and PE-characteristics, younger age, obesity, cardiopulmonary comorbidity and centrally located PE were shown to be independent predictors for decreased disease-specific QoL (Table 4). Inversely, a family history of venous thromboembolism independently predicted lower intensity of complaints and emotional complaints and also was a predictor of better social function. Markedly, the multivariate models including these independent determinants of QoL predicted the measured QoL in the individual dimensions of the PEmb-QoL only for 5.7% to 16% (linear regressions' coefficient of determination).

**Table 4.** Multivariate linear regression of PEmb-QoL dimensions and SF-36 subscales.

	Frequency of complaints	ADL limitations	Work related problems	Social limitations	Intensity of complaints	Emotional complaints
Gender <sup>‡</sup>						
Age (per year)	-0.15*					
Obesity <sup>‡b</sup>		0.26**	0.18*	0.36*	0.49*	
Cardiopulmonary comorbidity <sup>†</sup>		0.26*			0.21*	
Active malignancy <sup>†</sup>						
Centrally located PE <sup>†</sup>	0.45*	0.23*				
Follow-up period (per day) <sup>‡</sup>						
Family history of VTE <sup>†</sup>				-0.40*	-0.50*	-0.55*

Unstandardized regression (beta) coefficients with p-values only of independently significant determinants of quality of life are displayed. Higher PEmb-QoL scores are associated with decreased quality of life. †0=not present, 1=present; ‡1=male, 2=female; <sup>a</sup>body mass index >30kg/m<sup>2</sup>; †0=not present, 1=present; ‡time span between registration acute pulmonary embolism and study inclusion in days; \*p<0.05, \*\*p<0.01. ADL=activities of daily living.

## DISCUSSION

The results from this validation study indicate that this newly developed disease-specific health-related QoL instrument PEmb-QoL is a valid and reliable instrument to assess QoL following PE. Internal reliability for all dimensions (except intensity of complaints) was adequate and comparable to the reliability of the VEINES-QOL/Sym scales.<sup>6</sup> Test-retest reliability was also adequate. The inter-correlations between the PEmb-QoL dimensions demonstrated logical relationships. Intensity of complaints correlated with a worse outcome in all other dimensions. This was expected as this dimension might actually affect a person's well-being in general. Also, its association with frequency of complaints is high, suggesting these dimensions could be taken together to form one summary score for symptom severity, comparable to the VEINES-QoL/Sym summary score.

We observed a tendency towards small floor and ceiling effects in some of the PEmb-QoL dimensions. This was assumed to be attributable to the time between the events and completion of the questionnaires. Therefore, we expect that other patient samples including those with a more recent event will show less floor or ceiling effects. Furthermore, we observed that work related problems most strongly correlated with physical role functioning and physical functioning. We hypothesized that this observation is explained by the fact that both dimensions focus on the extent of limitations performing work or physical exercise. Emotional complaints were more strongly associated with mental health and vitality than to emotional role functioning. This is also conceivable, as the wording of the items of this PEmb-QoL dimension closely match the items of the SF-36 dimensions mental health and vitality. Also, the correlation between social limitations and social functioning was (almost) as high as the correlation with physical

functioning and vitality. This is a plausible observation as well, since social activities are also influenced by the capability to perform exercises such as climbing stairs or walking a certain distance.

After multivariate analysis, several demographic and symptom factors associated with better or worse health related QoL were identified. Higher age, obesity and comorbid conditions predicted decreased QoL in our study population. This is to be expected, as these factors have previously been shown to be important determinants of health status in healthy persons and patients suffering from various diseases.<sup>15,18,19</sup> Notably, the presence of family members who have a history of the same condition was associated with improved social status, decreased intensity of complaints and a smaller amount of emotional complaints. We hypothesized that this phenomenon might be attributed to enhanced social support which is an important aspect of QoL.<sup>20,21</sup> Although we were able to identify several significant determinants of QoL in our patient population, combining these in multivariate prediction models did not result in precise prediction of the QoL for individual patients since our models predicted only 5.7% to 16% of the variance in PEmb-QoL scores. This observation is in accordance with the result of a previous study, which indicated limited effects of patient demographics and comorbid conditions on the QoL of patients with DVT.<sup>15</sup>

Limitations of our study comprise the exclusion of 3 participants due to language barriers and the lack of detailed comparison to healthy subjects. This comparison is difficult since the PEmb-QoL was designed for patients with acute PE and is by definition not applicable to subjects without this disease. Finally, we were unable to assess responsiveness in this cohort.

This disease specific questionnaire was developed to assist physicians in monitoring treatment interventions after acute PE. The advantage of disease specific questionnaires over generic instruments of QoL is that these can be considered to have higher sensitivity for detecting subtle but clinically relevant alterations in QoL caused by the studied condition or treatment.<sup>22</sup> Although we were able to show correlations between the outcome of the PEmb-QoL and the condition of patients with a history of acute PE, our study design did not allow assessing whether this QoL instrument could be used in treatment decisions. Hence, further studies are needed.

In summary, the PEmb-QoL is a valuable instrument for determining the disease-specific QoL in patients with previous acute PE. This questionnaire is a valid and reliable instrument of QoL following acute PE and discriminates patients with impaired health perception. The clinical applicability of the PEmb-QoL and its potential role in the management of patients with acute PE remains to be studied in clinical outcome studies.

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