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ORIGINAL ARTICLE

Quality of life and functional limitations after pulmonary embolism and its prognostic relevance

Karsten Keller[1] | Clara Tesche[2,3] | Aslihan Gerhold-Ay[1,4] | Stefan Nickels[1,5] | Frederikus A. Klok[1,6] | Lisa Rappold[2,7] | Gerd Hasenfuß[2,8] | Claudia Dellas[9] | Stavros V. Konstantinides[1,10] | Mareike Lankeit[1,2,11,12]

[1]Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Mainz, Germany

[2]Clinic for Cardiology and Pulmonology, Heart Center, University Medical Center, Goettingen, Germany

[3]Department of Anesthesiology, University Hospital Duesseldorf, Duesseldorf, Germany

[4]Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Mainz, Germany

[5]Department of Ophthalmology, University Medical Center Mainz, Mainz, Germany

[6]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands

[7]Clinic for Internal Medicine, Siloah St. Trudpert Clinic, Pforzheim, Germany

[8]German Center for Cardiovascular Research (DZHK), Partner Site Goettingen, Goettingen, Germany

[9]Department of Paediatric Cardiology and Intensive Care, GUCH Center, University Medical Center, Goettingen, Germany

[10]Department of Cardiology, Democritus University Thrace, Alexandroupolis, Greece

[11]Department of Internal Medicine and Cardiology, Campus Virchow Klinikum (CVK), Charité – University Medicine Berlin, Berlin, Germany

[12]German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany

Correspondence
Mareike Lankeit, Department of Internal Medicine and Cardiology, Campus Virchow Klinikum (CVK), Charité – University Medicine Berlin, Augustenburger Platz 1, 13353 Berlin, Germany.
Email: mareike.lankeit@charite.de

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Abstract

Background: While the importance of patients' quality of life (QoL) in chronic cardiac or pulmonary disease is uncontroversial, the burden of an acute pulmonary embolism (PE) on QoL has received little attention thus far.

Objectives: We aimed to validate the German PEmb-QoL questionnaire, identify associations between QoL and clinical/functional parameters, and investigate the prognostic relevance of QoL for long-term survival in survivors of an acute PE episode.

Patients/Methods: Patients were invited for a clinical follow-up visit including assessment of QoL using the German PEmb-QoL questionnaire 6 months after an objectively confirmed PE at a single center. Internal consistency reliability, construct-related validity, and regressions between PEmb-QoL and clinical patient-characteristics were assessed using standard scale construction techniques.

Results: Overall, 101 patients [median age, 69 ([interquartile range] IQR 57-75) years; women, 48.5%] were examined 208 (IQR 185-242) days after PE. Internal consistency reliability and construct-related validity of the PEmb-QoL questionnaire were acceptable. As many as 47.0% of patients reported dyspnea, 27.5% had right

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ventricular (RV) dysfunction on transthoracic echocardiography (TTE), and 25.3% were diagnosed with post-PE impairment (PPEI) at 6-month follow-up. Furthermore, 15.9% of patients were diagnosed with depression 6 months after an acute PE. The QoL was affected by dyspnea, preexisting pulmonary disease, and PPEI, and a reduced QoL was associated with an increased risk for long-term mortality after an observation period of 3.6 years.

Conclusions: The German PEmb-QoL questionnaire is a reliable instrument for assessing QoL 6 months after PE. The QoL was affected by dyspnea, preexisting pulmonary disease, and PPEI and was associated with long-term mortality.

1 | INTRODUCTION

The long-term course of PE is complicated by several adverse events including recurrent venous thromboembolism (VTE), development of chronic thromboembolic pulmonary hypertension (CTEPH), and major bleeding due to anticoagulant therapy.[1-3] Furthermore, methodically heterogeneous studies demonstrated that residual perfusion defects can be detected in up to 50% of the patients after 6 months using ventilation-perfusion lung scan[4-6] and that approximately 50% of patients suffer from persisting symptoms and cardiopulmonary functional limitations up to 1 year after the initial PE.[3,7-9] While the long-term hemodynamic and functional consequences of an acute PE have received increasing attention during the past years, the burden of an acute PE on patients' psychological-emotional well-being and QoL has remained insufficiently studied thus far.[10,11] Health-related crises such as an acute PE can result in emotional distress and negative emotional reactions, which may manifest as anxiety, anger, depression, and posttraumatic stress disorder.[10] In patients with chronic heart failure and pulmonary artery hypertension, a reduced QoL has been shown to be associated with poor prognosis[12,13] and thus has become a treatment target in chronic heart failure.[12,14,15]

Although QoL can be assessed using generic questionnaires such as the 36-item Short Form Health Survey, disease-specific questionnaires promise higher sensitivity in detecting and quantifying disease-specific changes in QoL.[16] The first disease-specific QoL questionnaire for patients with PE, the so-called Pulmonary Embolism-Quality of Life (PEmb-QoL) questionnaire, was developed in 2009[17] and consists of nine questions with a total of 38 items summarized in six categories related to activities and emotional/social complaints. Subsequently, the PEmb-QoL was validated in different cohorts and languages.[16,18-21] However, limitations of these studies encompass the inclusion of patients at various time points after the initial PE event and the lack of investigating association between QoL and clinical parameters or prognosis. Thus, we aimed (i) to validate the German version of the disease-specific PEmb-QoL questionnaire in survivors of acute PE 6 months after the initial event, (ii) to identify associations between QoL and clinical and functional parameters, and (iii) to investigate the prognostic relevance of QoL for long-term survival.

Essentials

- The burden of a PE on QoL has received little attention. The PEmb-QoL questionnaire is a reliable instrument for assessing QoL in PE survivors.
- QoL is affected by dyspnea, pre-existing pulmonary disease and post-PE impairment and reduced QoL associated with an increased risk of long-term mortality.

2 | METHODS

2.1 | Study design

Consecutive patients aged ≥18 years with objectively confirmed acute PE diagnosed at the University Medical Center, Goettingen, Germany (January 2011-August 2013) were included in an ongoing prospective cohort study (Pulmonary Embolism Registry of Goettingen). The study protocol has been described in detail previously.[22] All treatment decisions were made by the physicians caring for the patients according to current guidelines and were not influenced by the study protocol at any time. The study was conducted in accordance with the amended Declaration of Helsinki and the study protocol was approved by the local independent ethics committee. All patients provided written informed consent.

At baseline, detailed information on initial presentation including symptoms, findings from risk stratification, comorbidities, and VTE risk factors; treatment and in-hospital outcomes were obtained using a standardized case report form. Details on diagnostic procedures, definitions used for risk stratification, and laboratory measurements are provided in the Data S1. An adverse in-hospital outcome was defined as PE-related death, cardiopulmonary resuscitation, mechanical ventilation, or need for catecholamine administration.

Patients were invited to participate in a 6-month routine follow-up visit at the outpatient clinic of the Clinic of Cardiology and Pulmonology of the University Medical Center, Goettingen, Germany. Exclusion criteria and study flow are shown in Figure 1. At the follow-up visit, information on adverse events [including recurrent VTE, clinically relevant bleeding (defined according to the

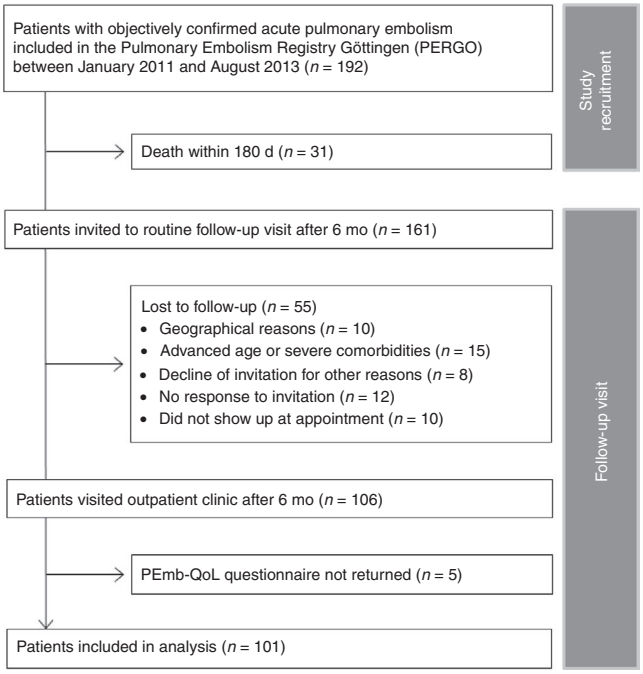

FIGURE 1 Flow diagram of exclusion criteria. PE, pulmonary embolism; PEmb-QoL, pulmonary embolism-quality of life; PERGO, Pulmonary Embolism Registry Goettingen

International Society of Thrombosis and Hemostasis)[23] new diagnosis of depression, cancer, and CTEPH (confirmed according to current guideline recommendations)[24]] were recorded. Additionally, all patients received a conventional 12-lead electrocardiogram, TTE, physical examination, and laboratory testing and were asked to complete the German version of the PEmb-QoL questionnaire and questions related to their socioeconomic status (Figure S1, Table S1). Long-term survival status was assessed by contacting the responsible registration office at various time points (generally at 2-year intervals).

2.2 | PEmb-QoL questionnaire

The disease-specific PEmb-QoL questionnaire[16-20] consists of nine questions with a total of 38 included items summarized in six categories (dimensions): frequency of complaints (FO, 8 items), activities of daily living limitations (AD, 13 items), work-related problems (WR, 4 items), social limitations (SL, 1 item), intensity of complaints (IO, 2 items), and emotional complaints (EC, 10 items). Two additional questions (questions 2 and 3) are descriptive only and not scored in the dimensions. The minimum score is 1 (indicating no complaints) and thus, higher scores are associated with a more complaints and decreased QoL.

The German PEmb-QoL questionnaire (Figure S1) is a linguistically validated translation of the Dutch PEmb-QoL questionnaire[16,17] provided by the MAPI institute (Lyon, France). The validation process included forward and backward translation, clinicians' review, and cognitive interview of five patients with PE. For the present study, question 3 (referring to the change of symptoms over time) was adapted to the 6-month follow-up period.

2.3 | Study outcomes at 6-month follow-up

Study outcomes at 6-month follow-up include (i) severe dyspnea [defined as New York Heart Association (NYHA) class III/IV], (ii) depression (defined as confirmed diagnosis by a physician or administration of antidepressive drugs), (iii) RV dysfunction on TTE, and (iv) PPEI.

Right ventricular dysfunction on TTE was defined according to Rudski et al[25] and Konstantinides et al[26] as the presence of one or more of the following parameters: RV basal diameter >4.2 cm, tricuspid annular plane systolic excursion <1.6 cm, elevated right atrial pressure based on the absence of an inspiratory collapse of the inferior vena cava, tricuspid regurgitant velocity ≥2.8 m/s. and presence of pericardial effusion.

Post-pulmonary embolism impairment was defined as a combination of one or more echocardiographic sign(s) of RV dysfunction plus presence of one or more clinical/laboratory sign(s) including peripheral edema, dyspnea (NYHA class ≥ II), or an elevated sex-specific and age-adjusted N-terminal pro brain natriuretic peptide level (Table S2).[26]

2.4 | Statistical analyses

Dichotomous and nominal variables are presented as absolute numbers and proportions and were compared using McNemar's test. Continuous variables are presented as median and IQR and were compared using Wilcoxon rank sum test.

The PEmb-QoL scores were calculated for each dimension by summing up the item values divided by the number of items. Calculation of the "activities of daily living limitations" (AD) score was dependent on the answer for question 4a; if the answer was "I do not work," the item sum was divided by 12, otherwise by 13 items. In the case of missing items, no score for the respective dimension was calculated.[27] Quality criteria of the PEmb-QoL questionnaire that were tested comprised outcome measures validity, reliability with internal consistency, and reproducibility and interpretability.[28,29] The detailed statistical approach is provided in the Data S1. Briefly, to evaluate construct-related validity, we assessed the associations of single items with proposed PEmb-QoL dimensions using linear regression models with single items as outcomes and scores as predictors adjusted for age and sex (Table S3). We further used linear regression models to evaluate the impact of patients' baseline characteristics (adjusted for sex and age, Table S4), socioeconomic status (Table S5), and increasing NYHA classes (Table S6) on PEmb-QoL dimensions. The results are presented as beta coefficients (β) with 95% confidence intervals (CIs). To evaluate internal consistency reliability, we calculated Cronbach's α for each PEmb-QoL dimension (Table 2).[28-30] For examination of floor and ceiling effects, we presented the proportion of participants with minimal and maximal possible scores of single dimensions (Table 2).[16,18-20]

Univariate logistic regression models were used to assess the impact of study outcomes (Table 3) and socioeconomic status on PEmb-QoL dimensions (Table S5) and the impact of patients' baseline characteristics on clinical outcomes at 6-month follow-up (Table S7).

The results were presented as odds ratios with 95% CIs. Cox regression models (univariate and adjusted for sex and age) were used to evaluate the prognostic impact of PEmb-QoL dimensions and study outcomes on long-term mortality (Table 4). The results were presented as hazard ratios with 95% CIs.

All analyses were explorative analyses. No adjustments for multiple testing were conducted. *P* values were provided for descriptive reasons only and should be interpreted with caution and in connection with the effect estimates. We used SPSS (versions 21.0-23.0) and R (version 3.0.3) for the statistical analyses.

3 | RESULTS

3.1 | Patients' characteristics

Overall, 192 patients were enrolled in the Pulmonary Embolism Registry Goettingen between January 2011 and August 2013; of those, 31 patients (16.1%) died within the first 180 days. Thus, 161 patients were invited to the routine clinical follow-up visit after 6 months. After applying the exclusion criteria shown in Figure 1, 101 patients [62.7%; median age, 69 (IQR, 57-75) years; 48.5% women] completed the 6-month follow-up visit and were included in the present analysis.

Patients' characteristics at baseline (time of initial PE) are shown in Table 1, left column. The majority of patients (61.4%) had an unprovoked PE event, 14.0% had chronic heart failure, and 13.0% chronic pulmonary disease. A TTE within 48 h after admission was performed in 68 (67.3%) patients; of those, 49.3% of patients were diagnosed with RV dysfunction. According to the 2014 European Society of Cardiology guideline algorithm, 9 patients (8.9%) were classified as high-risk, 28 (27.7%) as intermediate-high-risk, 52 (51.5%) as intermediate-low-risk, and 12 (11.9%) as low-risk. Overall, 11 patients (10.9%) received systemic thrombolysis; of those, 4 patients received early systemic thrombolysis (within 24 h) and 7 patients were included in the PEITHO study and randomized to either single-bolus tenecteplase or placebo.[31] Nine patients (8.9%) had an adverse in-hospital outcome. Median in-hospital stay was 9 days (IQR, 6-13 days).

The median time to the follow-up visit was 208 (IQR, 185-242) days. At the time of follow-up, 85.1% of the patients still received therapeutic anticoagulation, no patient was diagnosed with recurrent VTE, 2 (2.0%, *n* = 100) had developed clinically relevant bleeding (excluding bleeding events occurring during the in-hospital stay), 13 (13.4%, *n* = 97) were diagnosed with postthrombotic syndrome, and 4 (4.3%, *n* = 94) with CTEPH. As shown in Table 1, right column, 6.0% (*n* = 100) of patients had a new diagnosis of cancer.

3.2 | Validation of the PEmb-QoL questionnaire: Psychometric characteristics

Overall, 86.1% of the patients completed the PEmb-QoL questionnaire in adequate quality for analyses. Median PEmb-QoL scores of the six dimensions were 1.4 (IQR, 1.0-1.8; maximum 5 points) for "frequency of complaints" (FO), 1.3 (1.1-2.0; maximum 3 points) for "activities of daily living limitations" (AD), 1.0 (1.0-1.8; maximum 2 points) for "work-related problems" (WR), 1.0 (1.0-2.0; maximum 5 points) for "social limitations" (SL), 2.0 (1.0-3.0; maximum 6 points) for "intensity of complaints" (IO), and 1.8 (1.3-2.7; maximum 6 points) for "emotional complaints" (EC) (Figure 2). For "work-related problems" (WR) and "social limitations" (SL), the median was equal to the lowest possible score, indicating that the usability of these two dimensions might be limited. All dimensions revealed distinct floor effects, ranging from 12.0% for "emotional complaints" to as high as 59.2% for "social limitations." Ceiling effects were especially observed in "work-related problems" (Table 2).

Construct-related validity was evaluated using linear regression models, which showed an acceptable association of single items with the proposed scores (Table S3). Three items (9.e, 9.h, and 9.i) assigned to "emotional complaints" revealed their strongest associations with other scores ("work-related problems" and "activities of daily living limitations," respectively) and three items (1.h, 7 and 8) assigned to "intensity of complaints" showed strong associations with "work-related problems." In summary, these findings support good construct-related validity of the PEmb-QoL questionnaire.

Most patients' baseline characteristics (Table S4) and self-reported socioeconomic status (Table S5) had only minor impact on PEmb-QoL scores except pulmonary disease, which was associated with increased "activities of daily living limitations" and "work-related problems" scores.

Cronbach's α coefficients for the different dimensions were in the acceptable range, except for the "intensity of complaints" score (0.54) (Table 2). Therefore, the reliability of the PEmb-QoL questionnaire was mainly confirmed.

3.3 | Study outcomes

As shown in Table 1, right column, as many as 47.0% of patients reported persisting dyspnea (NYHA class ≥II) at the time of follow-up; of those, 19 patients (40.4%) were in NYHA class III/IV. Severe dyspnea (NYHA class III/IV) was associated with obesity, duration of hospital stay at baseline, and chronic pulmonary diseases (Table S7). Furthermore, 14 patients (15.9%) were diagnosed with depression (compared to 10.2% at the time of PE, *P* = .063). Depression at follow-up was associated with female sex and the duration of hospital stay at baseline (Table S7). Although a higher number of patients was diagnosed with cancer and depression at follow-up compared to baseline (Table 1), depression at follow-up was not more prevalent in the patients with cancer compared to those without (5.9% vs. 18.1%, *P* = .253).

Overall, 91 patients (90.1%) underwent TTE at 6-month follow-up; of those, 25 (27.5%) were diagnosed with echocardiographic signs of RV dysfunction and 23 (25.3%) with PPEI. Surprisingly, acute RV dysfunction at the PE index event was neither predictive of RV dysfunction or PPEI nor of severe dyspnea (NYHA class III/IV) at follow-up (Table S7). An adverse in-hospital outcome was associated with PPEI (Table S7).

TABLE 1 Patients' characteristics at baseline (time of PE event) and 6-month follow-up

All study patients (*n* = 101)	Baseline (admission for acute PE event)	Follow-up (6 months after PE event)	*P* value
Age at PE event (years)	69.0 (56.5-75.0)	-	-
Male sex	52 (51.5%)	-	-
BMI (kg/m^2)	28.1 (25.4-31.4) (n = 100)	28.4 (25.0-31.3) (n = 97)	.229
Risk factors for VTE			
Previous deep vein thrombosis	29 (29.0%) (n = 100)	-	-
Previous pulmonary embolism	12 (12.0%) (n = 100)	-	-
Thrombophilia	5 (5.0%) (n = 100)	-	-
Trauma/surgery[a]	15 (14.9%)	-	-
Immobilization or recent long travel[a]	19 (19.0%)	-	-
Pregnancy/postpartum period[b]	0 (0%)	-	-
Cancer[c]	11 (11.0%) (*n* = 100)	17 (17.0%) (n = 100)	.031
Comorbidities			
Chronic (left) heart failure	14 (14.0%) (*n* = 100)	-	-
Heart failure with reduced LVEF (<40%) (HFrEF)	3 (21.4%)		
Heart failure with midrange reduced LVEF (40%-49%) (HFmrEF)	5 (35.7%)		
Heart failure with preserved LVEF (≥50%) (HFpEF)	4 (28.6%)		
LVEF unkown	2 (14.3%)		
Coronary artery disease	18 (18.0%) (*n* = 100)	-	-
Peripheral artery disease	7 (8.5%) (*n* = 82)	-	-
Arterial hypertension	65 (64.4%)	-	-
Diabetes mellitus	12 (11.9%)	-	-
Hyperlipidemia	30 (29.7%)	-	-
Previous stroke	5 (5.0%)	-	-
Chronic pulmonary disease[d]	13 (13.0%) (*n* = 100)	-	-
Renal insufficiency[e]	10 (10.6%) (*n* = 94)	-	-
Depression[f]	9 (10.2%) (n = 88)	14 (15.9%) (*n* = 88)	.063
Symptoms			
Acute onset of symptoms (<24 h before admission)	46 (45.5%)	-	-
Dyspnea (NYHA ≥II)	94 (93.1%)	47 (47.0%) (*n* = 100)	<.001
NYHA class II	-	28 (28.0%) (*n* = 100)	-
NYHA class III	-	18 (18.0%) (*n* = 100)	-
NYHA class IV	-	1 (1.0%) (*n* = 100)	-
Chest pain	59 (59.0%) (*n* = 100)	20 (20.6%) (*n* = 97)	<.001
Syncope	14 (14.0%) (*n* = 100)	-	-
Leg swelling or leg pain	31 (31.0%) (*n* = 100)	37 (38.5%) (*n* = 96)	.568
Vital signs			
Systolic blood pressure (mm Hg) < 100 mm Hg	12 (12.0%) (*n* = 100)	0 (0%) (*n* = 85)	Not calculable
Tachycardia (heart rate ≥ 100 bpm)	36 (36.0%) (*n* = 100)	1 (1.1%) (*n* = 90)	<.001
Hypoxia[f]	23 (27.7%) (*n* = 83)	-	-
Transthoracic echocardiography			
RV > LV	24 (44.4%) (*n* = 54)	3 (3.6%) (*n* = 84)	<.001
RV D1 > 4.2 cm	-	9 (26.5%) (*n* = 34)	-
Paradoxical septal movement	19 (43.2%) (*n* = 44)	2 (2.3%) (*n* = 87)	<.001
Absence of the inspiratory collapse of the IVC	21 (40.4%) (*n* = 52)	2 (2.7%) (*n* = 75)	<.001

(Continues)

TABLE 1 (Continued)

All study patients (*n* = 101)	Baseline (admission for acute PE event)	Follow-up (6 months after PE event)	*P* value
TAPSE <1.6 cm	-	2 (3.1%) (*n* = 65)	-
TR jet velocity ≥2.8 m/s	16 (50.0%) (*n* = 32)	17 (25.4%) (*n* = 67)	.219
Systolic PA pressure >50 mm Hg	14 (33.3%) (*n* = 42)	7 (10.9%) (*n* = 64)	.125
Reduced LV EF (<50%)	10 (18.2%) (*n* = 55)	7 (7.7%) (*n* = 91)	.016
Electrocardiogram			
S_IQ_{III}-type pattern	33 (34.7%) (*n* = 95)	4 (4.4%) (*n* = 90)	<.001
Negative T-waves in leads V1 to V3	38 (40.0%) (*n* = 95)	9 (10.0%) (*n* = 90)	<.001
Incomplete or complete RBBB	17 (17.9%) (n = 95)	16 (17.8%) (*n* = 90)	.554
Laboratory biomarkers			
hsTnT ≥14 pg/mL	52 (62.7%) (n = 83)	15 (24.2%) (*n* = 62)	<.001
NT-proBNP ≥600 pg/mL	43 (55.8%) (*n* = 77)	7 (11.3%) (*n* = 62)	<.001

Notes: Abbreviations: BMI, body mass index; EF, ejection fraction; hsTnT, high sensitive troponin T; IVC, inferior vena cava; LV, left ventricle; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PE, pulmonary embolism; RBBB, right bundle branch block; RV, right ventricle; RVD1, right ventricle diameter 1; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitant; VTE, venous thromboembolism.

[a]Within 4 weeks prior to PE index event.

[b]Postpartum period of within 6 weeks prior to PE index event.

[c]Active or within 6 months prior to PE event.

[d]Chronic obstructive pulmonary disease, asthma, and interstitial lung disease.

[e]Glomerular filtration rate of ≤60 mL/min/1.73 m^2.

[f]O_2 saturation of <90% or partial pressure of O_2 <60 mm Hg (8 kPa) in arterial blood gas analysis.

3.4 | Association of study outcomes and QoL

While PEmb-QoL dimensions were not affected by depression, cancer, and RV dysfunction on TTE at follow-up, PPEI was associated with higher scores in "work-related problems" [odds ratio, 3.4 (95% CI, 1.1-10.8); *P* = .041] (Table 3). Severe dyspnea (NYHA class III/IV) affected all PEmb-QoL dimensions except "emotional complaints" (Table 3) and increasing NYHA classes were strongly related to all PEmb-QoL dimensions (Table S6).

Long-term survival status was available for all patients and 12 patients (11.9%) died during the observation period of 3.6 (IQR, 3.1-4.5) years (range: 276-1888 days). Interestingly, the PEmb-QoL dimensions "activities of daily living limitations," "work-related problems," "social limitations," and "emotional complaints" were associated with an increased risk for long-term mortality (Table 4, left column). In multivariable Cox regression analyses adjusted for sex and age, patients with poorer QoL in "activities of daily living limitations" and "work-related problems" showed a more than four-fold increased risk for long-term mortality (Table 4, right column). In contrast, all clinical study outcomes at the 6-month follow-up, including PPEI and RV dysfunction on TTE, had no relevant impact on long-term survival.

4 | DISCUSSION

The main study findings can be summarized as follows: (i) the German PEmb-QoL questionnaire is a valid and reliable instrument for assessing disease-specific QoL 6 months after an acute PE; (ii) as many as 47.0% of patients presented with dyspnea, 27.5% with RV dysfunction on TTE, and 25.3% with PPEI at 6-month follow-up; (iii) 15.9% were diagnosed with depression 6 months after an acute PE; (iv) QoL was affected by dyspnea and PPEI; and (v) reduced QoL was associated with an increased risk for long-term mortality.

4.1 | Validation of the German PEmb-QoL questionnaire

The results of this present validation study indicate that the German PEmb-QoL questionnaire is a valid and reliable tool for assessing disease-specific QoL 6 months after an acute PE. However, some weaknesses were identified: Although its construct-related validity was acceptable (Table S3) and its criterion-related validity was previously confirmed by other studies[16,18-20] (and therefore not tested in the present study again), the internal consistency measured by Cronbach's α coefficients was in an acceptable range for all dimensions except for "intensity of complaints." Nevertheless, the reliability of the questionnaire was widely confirmed. Of note, the reproducibility as the test-retest stability of the PEmb-QoL questionnaire was not tested again because its stability was already confirmed in several previous studies.[16,18-20] Although Klok et al.[16] reported only small floor and ceiling effects, we identified, similarly to previous studies,[18-20] distinct floor and ceiling effects of up to 59.2% (Table 2). Thus, the ability of the PEmb-QoL questionnaire to detect small changes in QoL of mildly affected patients might be limited especially in the dimensions "work-related problems" and "social limitations." However, since QoL is operationalized as the absence of subjective impairments, 53.0% of our patients reported that they never experienced lung symptoms and 22.1%

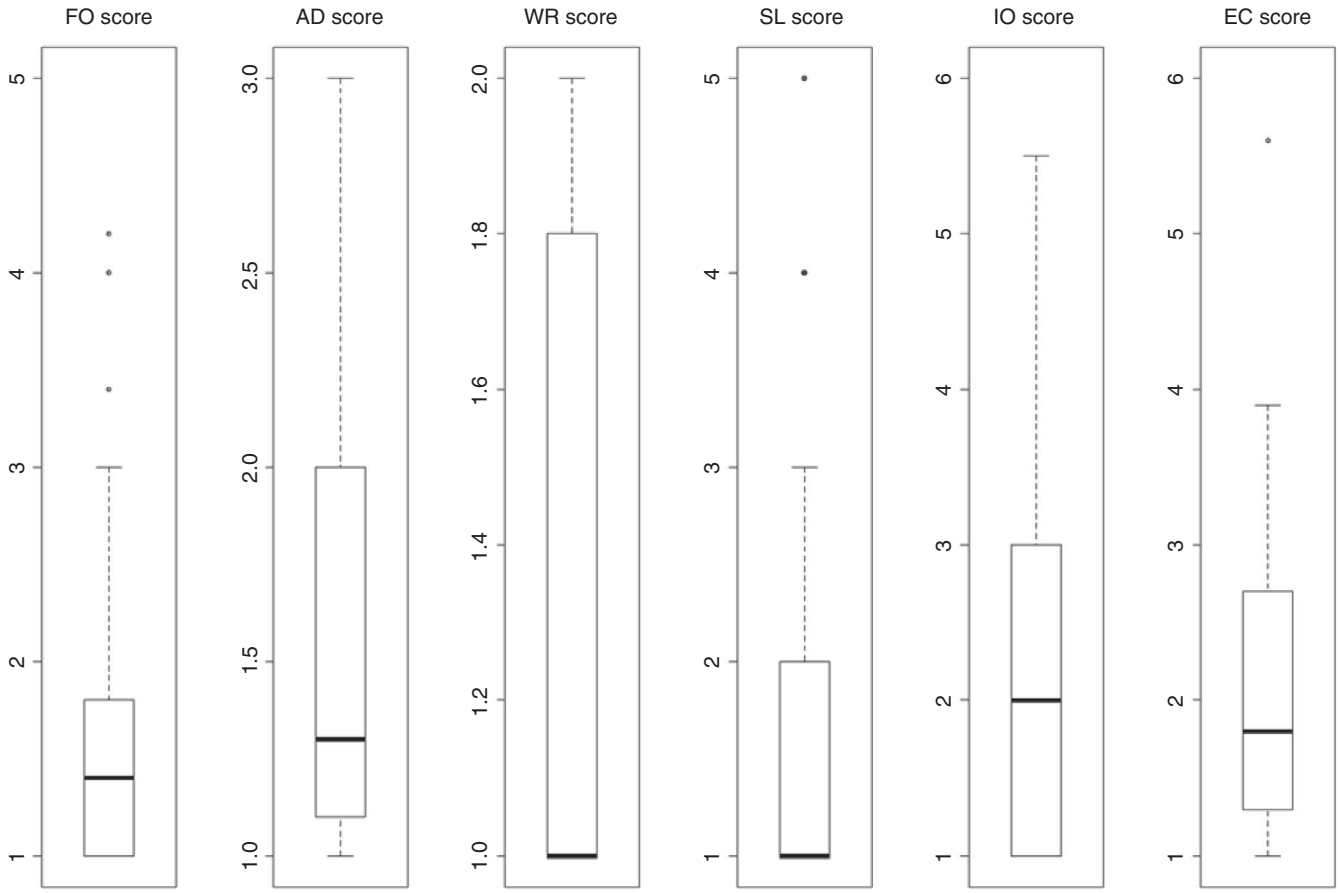

FIGURE 2 PEmb-QoL dimension scores. Higher scores indicate decreased QoL. AD, activities of daily living limitations; EC, emotional complaints; FO, frequency of complaints; IO, intensity of complaints; SL, social limitations; WR, work-related problems

TABLE 2 Internal validation of the PEmb-QoL questionnaire

Dimensions	Missing % (*n*)	Cronbach's α	Floor effects % (*n*/*N*)	Ceiling effects % (*n*/*N*)
Frequency of complaints (FO)	6.9% (7)	0.77	25.5% (24/94)	0% (0/94)
Activities of daily living limitations (AD)	23.8% (24)	0.90	22.1% (17/77)	3.9% (3/77)
Work-related problems (WR)	10.9% (11)	0.91	55.6% (50/90)	21.1% (19/90)
Social limitations (SL)	3.0% (3)	-	59.2% (58/98)	2.0% (2/98)
Intensity of complaints (IO)	2.0% (2)	0.54	32.3% (32/99)	0% (0/99)
Emotional complaints (EC)	8.9% (9)	0.86	12.0% (11/92)	0% (0/92)

negated the presence of any lung problems at follow-up visit. Hence, the prevalence of distinct floor effects in our study seems plausible and unavoidable rather than a major limitation.

4.2 | Symptoms and functional limitations 6 months after acute PE

It is increasingly acknowledged that a (single) PE event can cause restricting and profound alterations such as persisting symptoms and cardiopulmonary functional limitations over the long term.[3,8] In accordance with the literature, in the present study, every second patient suffered from persisting symptoms 6 months after PE: as many as 47.0% of patients reported dyspnea (NYHA class ≥II), which was severe (NYHA class III/IV) in 19.0% of all patients. Unexpectedly, and probably because of the small sample size, although higher NYHA classes have been shown to be associated with increased mortality in patients with chronic heart failure,[32] in the present study, severe dyspnea at 6-month follow-up had no prognostic impact with regard

to long-term mortality (Table 4). Furthermore, every fourth patient was diagnosed with RV dysfunction on TTE at 6-month follow-up. In comparison, RV dysfunction on TTE was observed by Stevinson et al[9] in 16.5% of 109 previously healthy (free of cardiopulmonary diseases or other disabling processes) patients 6 months after a first-time PE, by Golpe et al[33] in 17.8% of 95 initially hemodynamic stable PE patients after 6 months, by Samaranayake et al[34] in 14.3% of 42 patients with "submassive" PE after a mean follow-up of 7.6 months, and by Held et al[35] in 11.5% of 130 symptomatic patients 6 months after newly diagnosed PE. The higher prevalence in our study might be related to different definitions of RV dysfunction in the respective studies. Consistent with our observation that RV dysfunction on TTE at 6-month follow-up was no predictor of long-term mortality (Table 4), Golpe et al.[33] as well as Samaranayake et al.[34] reported that RV dysfunction at follow-up was not associated with long-term mortality after a mean of 2.8 ± 1.1 years and after 1 year, respectively.

Since RV dysfunction on TTE constitutes an unspecific finding that may also be related to underlying comorbidities such as cardiopulmonary diseases, a number of attempts have been undertaken in the past to define long-term sequelae of PE more precisely. For example, the term "post-PE syndrome" has been introduced and proposed to be defined as (i) persistence or worsening of cardiac or pulmonary function in combination with (ii) deterioration of the clinical symptoms, functional status, or patients' quality of life (iii) in the absence of an obvious alternative explanation.[3] However, diagnostic criteria and thresholds to define "post-PE syndrome" are not available thus far. The ongoing "FOllow-up after aCUte pulmonary emboliSm" (FOCUS) study aims to determine the incidence of CTEPH and persisting or progressive functional and/or hemodynamic PPEI over a 2-year follow-up period after an index episode of acute symptomatic PE.[26] For this purpose, a definition of PPEI was introduced by the FOCUS steering committee[26] and was used in slight modification in the present study. Overall, in the present study, 25.3% of patients were diagnosed with PPEI at 6-month follow-up. In comparison, in the Evaluation of Long-Term Outcomes after PE (ELOPE) study, following 100 patients 1, 3, 6, and 12 months after acute PE at five Canadian hospitals between 2010 and 2013, 46.5% of patients had functional limitations (defined as peak oxygen consumption <80% on cardiopulmonary exercise testing) 1 year after the PE event.[7] The authors concluded that deconditioning might have contributed to this notably high prevalence. Data from Germany indicate that 35.3% of symptomatic patients with a normal echocardiogram have functional limitation on cardiopulmonary exercise testing 3 months after an episode of acute PE.[35]

Assuming that persisting or progressive functional and/or hemodynamic impairment after acute PE is an early indicator of the subsequent development of CTEPH, PPEI has been defined as a coprimary outcome in the FOCUS study.[26] Indeed, a recent cohort study demonstrated that patients fulfilling all diagnostic criteria of CTEPH despite elevation of mean pulmonary artery pressure (a condition called "chronic thromboembolic disease") showed similar objective functional impairment using cardiopulmonary exercise testing compared to patients with CTEPH.[36] These assumptions become of clinical importance if aiming to define who, when, and

TABLE 3 Prognostic impact of study outcomes on PEmb-QoL dimensions

Study outcomes	Dyspnea (NYHA class III/IV) (19/101 [18.8%])		RV dysfunction on TTE (25/91 [27.5%])		Post-PE impairment (23/91 [25.2%])		Depression (14/89 [15.7%])		Cancer (17/100 [17.0%])	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Frequency of complaints (FO)	5.2 (2.0-13.3)	.001	1.3 (0.6-2.6)	.500	1.5 (0.7-3.0)	.283	1.1 (0.5-2.5)	.820	1.0 (0.4-2.2)	.933
Activities of daily living limitations (AD)	10.6 (3.0-36.9)	<.001	1.1 (0.5-2.7)	.793	1.4 (0.6-3.6)	.423	2.6 (0.7-9.2)	.134	2.1 (0.8-5.6)	.150
Work-related problems (WR)	49.0 (7.2-332.5)	<.001	2.5 (0.8-7.7)	.109	3.4 (1.1-10.8)	.041	1.7 (0. 4-7.1)	.501	1.3 (0.4-4.6)	.670
Social limitations (SL)	3.7 (2.1-6.6)	<.001	1.1 (0.7-1.7)	.660	1.2 (0.8-1.8)	.416	1.0 (0.6-1.7)	.979	1.0 (0. 6-1.6)	.910
Intensity of complaints (IO)	4.5 (2.3-9.0)	<.001	1.2 (0.8-1.8)	.451	1.3 (0.8-1.9)	.244	1.5 (0.9-2.4)	.112	1.0 (0.7-1.7)	.875
Emotional complaints (EC)	1.4 (0.8-2.7)	.242	0.9 (0.5-1.5)	.678	1.0 (0.5-1.7)	.862	1.3 (0.7-2.4)	.467	1.1 (0.6-2.1)	.671

Abbreviations: CI, confidence interval; NYHA, New York Heart Association; OR, odds ratio; PE, pulmonary embolism; PEmb-QoL, pulmonary embolism-quality of life; RV, right ventricular; TTE, transthoracic echocardiography.

TABLE 4 Prognostic value of the PEmb-QoL dimensions and study outcomes at 6-month follow-up with regard to long-term mortality

	Univariate Cox regression		Adjusted for age and sex	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PEmb-QoL dimensions				
Frequency of complaints (FO)	1.2 (0.5-2.9)	.707	1.2 (0.5-2.9)	.669
Activities of daily living limitations (AD)	5.4 (1.9-15.0)	.001	5.3 (1.6-17.8)	.007
Work-related problems (WR)	4.5 (1.2-16.8)	.024	4.2 (1.1-16.4)	.038
Social limitations (SL)	1.7 (1.1-2.7)	.010	1.7 (1.1-2.6)	.022
Intensity of complaints (IO)	1.5 (0.9-2.4)	.106	1.4 (0.8-2.3)	.146
Emotional complaints (EC)	1.8 (1.0-3.3)	.038	1.8 (1.0-3.3)	.048
Study outcomes at the 6-mo follow-up				
Dyspnea (NYHA class III/IV)	1.5 (0.7-3.0)	.309	1.4 (0.7-2.9)	.364
RV dysfunction on TTE	1.1 (0.3-4.3)	.850	1.0 (0.3-4.0)	.956
Post-PE impairment	1.3 (0.3-4.8)	.742	1.2 (0.3-4.5)	.809
Depression	1.3 (0.3-6.0)	.775	1.0 (0.2-5.2)	.963

Abbreviations: CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association; PE, pulmonary embolism; PEmb-QoL, pulmonary embolism-quality of life; RV, right ventricular; TTE, transthoracic echocardiography.

how patients should be followed after acute PE. At present, current guidelines concordantly state that screening for CTEPH in asymptomatic survivors of PE is not recommended.[2,24] However, the present study findings and the increasing body of evidence may indicate that, even in the absence of "typical" symptoms, patients with PPEI might benefit from closer follow-up.[37]

4.3 | Associations between QoL and study outcomes

In the present study, every sixth patient was diagnosed with depression at 6-month follow-up. While depression was associated with female sex and a longer duration of in-hospital stay, no higher prevalence was observed in cancer patients. Interestingly, and in contrast to previous studies using more "global" questionnaires,[38,39] depression and cancer did not affect QoL assessed by the PEmb-QoL questionnaire in the present analysis (Table 3). Thus, the PEmb-QoL questionnaire appears less useful to detect depressive episodes. Since an acute PE may result in emotional distress reactions reaching from anxiety to posttraumatic stress disorder, screening for depression using validated methods (for example, the Hospital Anxiety and Depression Scale[40]) should be included in routine follow-up of PE patients.

As shown in Figure 2, patients' QoL 6 months after PE was especially reduced in the PEmb-QoL dimensions "activities of daily living limitations," "intensity of complaints," and "emotional complaints." The strongest association with PEmb-QoL dimensions was observed for dyspnea: increasing severity of dyspnea did affect all PEmb-QoL dimensions (Table S6); the only baseline variable affecting PEmb-QoL dimensions was preexisting pulmonary disease (Table S4). This observation is not surprising since all questions in the PEmb-QoL refer to "lung problems."[16] Post-pulmonary embolism incident was the only other outcome related to QoL (Table 3); however, only the dimension "work-related problems" appeared to be affected [median score in patients with PPEI 1.5 (95% CI 1.0-2.0) compared to 1.0 (95% CI 1.0-1.7) in patients without PPEI, $P = .055$]. Study design and patients' characteristics may substantially affect the interpretation of study findings related to QoL. In the present analysis, most patients' baseline characteristics and self-reported socioeconomic status had only minor impact on PEmb-QoL dimensions (Tables S4 and S5), as reported previously.[16] In contrast to previous studies with large follow-up periods of >6 years,[16,20] the present cohort consists of consecutive patients who underwent follow-up examination after 208 (IQR, 185-242) days, allowing for analysis of a homogeneous study population. Since previous studies assessed QoL in median >2 years after a PE event,[16,18,27] comparability might be limited.

This is the first study demonstrating that a reduced QoL in survivors of an acute PE episode was associated with an increased risk for long-term mortality after a median observation period of 3.6 years (Table 4). Highest odds ratio was observed for the PEmb-QoL dimension "activities of daily living limitations" [odds ratio 5.3 (95% CI 1.6-17.8)], while other clinical outcomes were not identified as predictors of long-term mortality. This finding is in accordance with studies investigating patients with heart failure, stroke, and coronary artery disease.[12,41,42] At first sight, it appears confusing that on the one hand most of the PEmb-QoL dimensions were influenced by dyspnea and a reduced QoL was associated with a

reduced probability of long-term survival, while on the other hand severe dyspnea at 6-month follow-up had no impact on long-term survival. However, this discrepancy might be explained by the fact that the PEmb-QoL questionnaire contains questions about physical capacity (daily living and working) that might reflect the overall patients' condition and, in case of a low score in these dimensions, frailty. Thus, by providing information on "overall physical condition," it appears less surprising that the prognostic performance of the PEmb-QoL questionnaire with regard to long-term mortality is superior to that of dyspnea.

4.4 | Limitations

Although the number of patients included in the present study was comparable to previous studies investigating quality of life after acute PE,[7,16,19,20] the small sample size constitutes a potential limitation of our study.

5 | CONCLUSION

The results of the present study indicate that dyspnea, RV dysfunction on TTE, PPEI, and reduced QoL are frequent findings in survivors of PE 6 months after the acute event. Quality of life is associated with an increased risk of long-term mortality and can reliably be assessed by the German PEmb-QoL questionnaire. Thus, assessment of presence and severity of symptoms, functional limitations, QoL, and screening for depression after an episode of acute PE should be implemented in future outcome trials in short-term and long-term management of acute PE.

ADDENDUM

K. Keller analyzed the data and drafted and revised the manuscript critically for important intellectual content. C. Tesche acquired and analyzed the data and revised the manuscript critically for important intellectual content. A. Gerhold-Ay analyzed the data and revised the manuscript critically for important intellectual content. S. Nickels analyzed the data and revised the manuscript critically for important intellectual content. F. A. Klok interpreted the data and revised the manuscript critically for important intellectual content. L. Rappold acquired and interpreted the data and revised the manuscript critically for important intellectual content. G. Hasenfuß interpreted the data and revised the manuscript critically for important intellectual content. C. Dellas acquired and interpreted the data and revised the manuscript critically for important intellectual content. S. Konstantinides interpreted the data and revised the manuscript critically for important intellectual content. M. Lankeit designed and supervised the study, acquired and analyzed the data, and drafted and revised the manuscript critically for important intellectual content. All authors gave final approval of the version of the manuscript to be published and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTERESTS

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ORCID

Karsten Keller https://orcid.org/0000-0002-0820-9584
Frederikus A. Klok https://orcid.org/0000-0001-9961-0754
Mareike Lankeit https://orcid.org/0000-0001-5211-7997

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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