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Pulmonary and cardiac variables associated with persistent dyspnea after pulmonary embolism

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ABSTRACT

Introduction: Persistent dyspnea is common in follow-up after pulmonary embolism (PE), but the underlying mechanisms are poorly understood.

Material and methods: This cross-sectional study included subjects aged 18–75 years with confirmed PE by computed tomography pulmonary angiography (CTPA) 6–72 months earlier. A total of 180 participants underwent clinical examination, incremental shuttle walk test, laboratory tests, transthoracic echocardiography, pulmonary function tests and ventilation/perfusion scintigraphy. In further analysis, we divided participants into two groups; "dyspnea" or "no dyspnea", based on interview and questionnaires at inclusion. The association of cardiac and pulmonary variables with persistent dyspnea was assessed using multiple logistic regression analysis.

Results: In total, 44% (95% CI: 39%–51%) of the participants reported persistent dyspnea after PE. Age (adjusted odds ratio (aOR) 0.93 per year, 95% CI: 0.90–0.97, $P = 0.001$), body mass index (BMI) (aOR 1.14 per kg/m^2, 95% CI: 1.04–1.25, $P = 0.004$), recurrent venous thromboembolism (VTE) (aOR 3.69, 95% CI: 1.45–9.38, $P = 0.006$) and diffusion capacity of the lung for carbon monoxide (DLCO) (aOR 0.95 per increase of 1%, 95% CI: 0.92–0.98, $P = 0.001$) were independently associated with persistent dyspnea.

Conclusions: Persistent dyspnea was prevalent after PE. Age, BMI and recurrent VTE were independently associated with dyspnea. Apart from reduced DLCO, no other cardiac or pulmonary variables were associated with persistent dyspnea.

1. Introduction

The possible long-term outcomes following pulmonary embolism (PE) span from full recovery without detectable cardiopulmonary sequela to chronic thromboembolic pulmonary hypertension (CTEPH). Persistent dyspnea, functional limitation and reduced health-related quality of life affect up to 50% of patients following PE [1–4], and the term "Post-PE syndrome" or "Post-PE impairment" has been suggested

Abbreviations: A, transmitral late diastolic filling peak velocity; BMI, body mass index; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; DLCO, diffusion capacity of the lung for carbon monoxide; E, transmitral early diastolic filling peak velocity; E', early diastolic annular mitral velocity; EF, ejection fraction; ESC, European Society of Cardiology; FVC, forced vital capacity; GLS, global longitudinal strain; ISWT, Incremental Shuttle Walk Test; LV, left ventricular; mMRC, modified Medical Research Council; PE, pulmonary embolism; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; V/Q, ventilation/perfusion; VTE, venous thromboembolism.

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as an umbrella to describe the whole spectrum of long-term consequences of PE [5].

Apart from CTEPH, our understanding of the underlying pathophysiology of persistent dyspnea and functional limitations after acute PE is poor. Some studies suggest an underlying cardiopulmonary impairment, such as persistent right ventricular dysfunction or impaired right ventricular contractile reserve, higher pulmonary vascular resistance, exercise-induced pulmonary hypertension or dead space ventilation as a consequence of residual thrombosis in the pulmonary vasculature [2,6–15]. However, other studies have failed to demonstrate such a relationship and argue that post-PE impairment is more likely caused by comorbidities and/or physical deconditioning after the PE event [3,4,16,17].

This study aimed to explore if persistent dyspnea was associated with impaired cardiac and/or pulmonary function in a cohort with a history of acute PE diagnosed 6–72 months earlier.

2. Material and methods

This was a cross-sectional sub-study of an ongoing project of pulmonary rehabilitation to improve physical capacity after PE (clinicaltrials.gov - NCT03405480). Patients were identified from the thrombosis registry (TROLL) at the Østfold Hospital Norway, which includes all patients with venous thromboembolism (VTE) diagnosed at Østfold Hospital since 2005.

Between January 1. 2018 and December 31. 2019, subjects that met the following inclusion criteria were invited by mail to participate in the study: 1- PE confirmed (greater than isolated subsegmental emboli) with computed tomography pulmonary angiography (CTPA), 2- age 18–75 years, and 3- PE diagnosed 6–72 months prior to inclusion. We excluded subjects with preexisting: 1- heart failure with reduced or preserved ejection fraction as defined by European Society of Cardiology (ESC) guidelines [18]), 2- significant valvular heart disease, 3- chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease stage >1), 4- restrictive lung disease (total lung capacity <80% of predicted), 5- CTEPH as defined in the Cologne Consensus guidelines of 2018 [19], 6- pregnancy, 7- active malignancy or 8- any psychiatric or cognitive disorder resulting in failure to comply with the study program. If the diagnostic tests performed in this study revealed conditions corresponding to the exclusion criteria, these subjects were also excluded. However, we did not exclude subjects with suspected or confirmed CTEPH during the diagnostic work-up of this study. We chose to do so, because unrecognized CTEPH is an important differential diagnosis for persistent dyspnea after PE.

We divided the participants into two groups, “dyspnea” or “no dyspnea”, based on interview and a self-completed questionnaire at inclusion. This questionnaire contained an item about shortness of breath or breathing problems that had appeared or worsened after the time of the PE episode: “do you experience shortness of breath or problems breathing that appeared or was worsened at the time of PE”? - Yes/No. This item was followed by the modified Medical Research Council (mMRC) dyspnea scale, which consists of five statements describing the patient’s respiratory disability, ranging from 0 to 4, where 4 represents the worst possible state [20]. Participants with new onset dyspnea after the acute PE episode and mMRC dyspnea scale score ≥ 1 comprised the “dyspnea” group.

All participants provided written informed consent. The project was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK 2017/1940).

2.1. Clinical assessments and examinations

All participants underwent clinical evaluation, assessment of dyspnea, incremental shuttle walk test (ISWT) and echocardiography. All subjects were then referred to further diagnostic work-up including pulmonary function tests, ventilation/perfusion (V/Q) scintigraphy and laboratory tests, including venous and arterial blood gas.

2.2. Incremental shuttle walk test

The ISWT is an externally paced, incremental field walking test to assess functional capacity in patients with cardiopulmonary disease [21]. The participants walk between two cones 9 m apart, with increasing speed according to a pre-recorded audio signal. The test was repeated after 20–30 min to account for a possible learning effect. The investigator performing the ISWT was not blinded to participants’ symptoms or group affiliation.

2.3. Pulmonary function tests

The pulmonary function tests included spirometry (without bronchodilator reversibility testing), whole body plethysmography and diffusion capacity of the lungs for carbon monoxide (DLCO). The tests were performed using Jaeger MasterScreen PFT (Program Sentry Suite Version 2.11) system with European Respiratory Society reference values [22]. The tests were conducted by an experienced technician who was blinded to patients’ group assignment.

2.4. Ventilation/perfusion scintigraphy

The V/Q scintigraphy was performed using 99mTechnetium-labeled macroaggregated albumin for perfusion scintigraphy and 99mTechnetium-labeled diethylene triamine pentaacetic acid aerosol for ventilation scintigraphy. Images were acquired using GE Discovery NM/CT 670 SPECT/CT (General Electric healthcare, Chicago, IL, USA). The images were analyzed by an experienced radiologist according to the European Association of Nuclear Medicine-criteria [23]; positive V/Q scintigraphy was considered present if there was V/Q mismatch in at least one segment or two subsegments conforming to the pulmonary vasculature.

2.5. Transthoracic echocardiography

The echocardiographic examination was performed using Vivid E95 (General Electric healthcare, Chicago, IL, USA). Image acquisition was performed during breath-hold, and three consecutive cardiac cycles were recorded. The echocardiographic evaluation included standard measurements of the cardiac chambers and function and was performed according to current guidelines [24].

Left ventricular (LV) ejection fraction (EF) was determined using Simpson’s biplane method and three-dimensional (3D) imaging. LV global longitudinal strain (GLS) was measured using speckle tracking imaging. LV diastolic function was assessed using transmitral early and late diastolic filling peak velocity (E and A), early diastolic annular mitral velocity (E′) and left atrial volume index. Echocardiographic diastolic dysfunction was considered present if >50% of the following findings were present; E/E′ (average) >14, septal E′ <7 cm/s or lateral E′ < 10 cm/s, left atrial volume index >34 mL/m^2 or tricuspid regurgitation peak velocity > 2.8 m/s [25].

The evaluation of the right ventricular (RV) function and hemodynamics included tricuspid annular longitudinal movement (TAPSE) and tricuspid regurgitation peak velocity, pulmonary valve acceleration time and tricuspid annular peak systolic myocardial velocity. RV myocardial performance index was measured using tissue velocity imaging. We performed two-dimensional speckle tracking strain analysis of the RV in an RV-focused apical four-chamber view, using three segments (RV free wall only) [24]. See Appendix B for full list of echocardiographic measurements and calculations.

The physician performing and analyzing the echocardiographic examinations was not blinded to the patients’ symptoms and group affiliation.

2.6. Statistical analysis

Data are reported as mean, median or proportions as appropriate. Normality of the data was assessed using Shapiro-Wilk's test and quantile-quantile (QQ) plots.

Two-sample *t*-test or Mann Whitney *U* test was used to compare continuous variables and Fisher's exact test to compare categorical variable between the dyspnea and no dyspnea group.

The potential association of pulmonary and cardiac variables with persistent dyspnea, was assessed using multiple logistic regression. The analysis was planned to include a maximum of 9 independent variables corresponding to a sample size with about ten subjects with dyspnea per independent variable. Several different domains of potentially associated factors were considered, including demographic characteristics, laboratory values, echocardiography and pulmonary function tests. Based on previous literature and clinical judgement, we assessed age, sex, BMI and recurrent VTE (yes/no) as relevant independent variables and thus included these in the model. In addition, we selected three "pulmonary" variables; forced vital capacity (FVC), DLCO, V/Q scintigraphy (significant perfusion defects present; yes/no) and two "cardiac" variables; TAPSE and RV free wall strain in the model. All variables were forced into the model. Missing data, which was most prevalent in the echocardiographic data because of reduced imaging quality, was handled by multiple imputation using chained equations (MICE), creating five imputed data sets. All variables in the regression model were included as covariates in the imputation process, including the dependent variable, i.e., dyspnea [26].The following variables were imputed (number of missing values); TAPSE (3), RV free wall strain (62), V/Q scintigraphy (5), FVC (17), DLCO (17). In addition, we performed a sensitivity analysis based on time from diagnosis of PE (6–18 months (n = 89) and > 18 months (n = 91)).

Multicollinearity was assessed using variance inflation factor, and a value >5 was considered as indicative of multicollinearity. Validity of the regression model, including linearity of continuous variables, was assessed by appropriate residual plots. Results from the multiple regression analysis are reported as odds ratio with 95% confidence interval. A P value <0.05 was considered statistically significant.

Statistical analysis was performed using Stata version 16.1 (StataCorp., College Station, TX, USA).

3. Results

A total of 673 subjects were identified in the TROLL registry and assessed for eligibility. After initial screening of electronic medical records, 289 were excluded according to the predefined exclusion criteria, geographic unavailability or uncertainty regarding the initial radiological diagnosis. Thus, 384 subjects were invited to participate, of whom 208 replied. Of these, 16 subjects withdrew their consent or were not available. A total of 192 were scheduled for primary evaluation.

All subjects underwent clinical examination and echocardiography (n = 192). Twelve subjects were during the diagnostic work-up found to have one or more of the predefined exclusion criteria, and thus excluded. The final cohort consisted of 180 participants (Fig. 1). Of these, completion of diagnostic work-up was as follows; echocardiography (n = 180), laboratory tests (n = 167), pulmonary function tests (n = 163), V/Q scintigraphy (n = 175).

Seventy-nine (44%, 95% CI: 37%–51%) of the participants reported persistent dyspnea corresponding to mMRC dyspnea scale ≥1, which was new onset or worsened at the time of the PE diagnosis. Eight participants (4%) reported new onset or worsened dyspnea after the PE event, but had only mild complaints corresponding to mMRC 0; these participants were included in the no dyspnea group.

Participants with dyspnea were younger, comprised less males, had a higher mean BMI and were more likely to have been diagnosed with recurrent VTE than those without dyspnea (Table 1). The median time since PE diagnosis was 19 months, with no difference between those

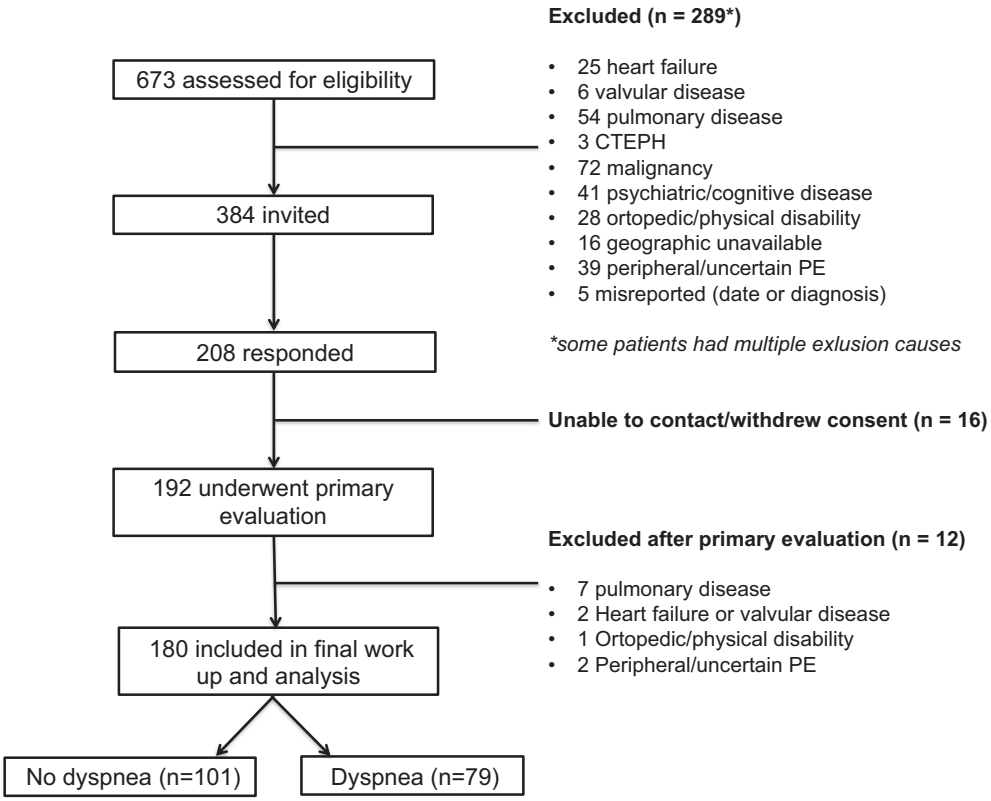

Fig. 1. Enrollment flowchart.
Abbreviations: CTEPH – chronic thromboembolic pulmonary hypertension; PE – pulmonary embolism.

Table 1
Comparison of clinical and historical data between those with and without dyspnea after PE, mean (SD) unless stated otherwise.

	No dyspnea (n = 101)	Dyspnea (n = 79)	P value
Age, years, median (IQR)	64 (17)	58 (17)	<0.001
Sex, males, number (%)	78 (77)	43 (54)	0.001
Body mass index, kg/m^2	27.6 (3.5)	29.9 (5.6)	<0.001
Time since diagnosis, months, median (IQR)	19 (15)	18 (27)	0.31
Duration anticoagulant therapy, months, median (IQR)	10 (13)	10 (15)	0.41
Charlson Comorbidity Index, number (%)			0.10
0	85 (84)	56 (71)	
1	12 (12)	16 (20)	
≥2	4 (4)	7 (9)	
Provoked pulmonary embolism, number (%)	41 (41)	35 (44)	0.65
Previous venous thromboembolism, number (%)	14 (14)	22 (28)	0.02
Smoking status, number (%)			0.46
Current smoker	3 (3)	5 (6)	
Former smoker	38 (38)	32 (41)	
Never smoker	60 (59)	42 (53)	

Abbreviations; IQR – interquartile range.

with and without dyspnea.

We found no differences in baseline values of arterial blood gas analyses and other laboratory tests (Table 2).

Those reporting dyspnea had a lower DLCO and carbon monoxide transfer coefficient than those without dyspnea (P = 0.001 and 0.005, respectively) but there was no difference in the proportions of residual perfusion defects by scintigraphy in the two groups (Appendix A, Table A.1). Participants reporting dyspnea performed significantly worse on ISWT when compared to those without dyspnea (P < 0.001). The echocardiographic evaluation showed that patients with dyspnea had reduced LV EF compared to those without dyspnea, 61.7% vs. 63.3%, respectively (P = 0.03) (Appendix A – Table A.2). However, there were no statistical differences observed concerning LV GLS or 3D LV EF. The group without dyspnea had a larger mean left atrial volume index than those with dyspnea, 29.3 mL/m^2 vs. 25.6 mL/m^2, respectively (P = 0.006). There were no differences in other echocardiography indices of diastolic function between the two groups. Only four participants had diastolic dysfunction as defined in the ESC/ASA guidelines [27]. Three of these were in the no dyspnea group and one in the dyspnea group.

Based on echocardiographic findings, symptoms and V/Q scintigraphy results, we performed right heart catheterization in five participants. Two of these had findings consistent with CTEPH. Both of these were in the group with dyspnea.

The logistic regression showed the following variables to be associated with persistent dyspnea (Fig. 2); age (aOR 0.93 per year, 95% CI: 0.90–0.97, P = 0.001), BMI (aOR 1.14 per kg/m^2, 95% CI: 1.04–1.25, P = 0.004), recurrent VTE (aOR 3.69, 95% CI: 1.45–9.38, P = 0.006) and DLCO (aOR 0.95 per increase of 1%, 95% CI: 0.92–0.98, P = 0.001). In the subgroup analysis (Fig. 3) age retained significant association with dyspnea in both strata. Furthermore, in subjects with PE ≥18 months prior to inclusion, the presence of residual perfusion defects was associated with dyspnea.

Table 2
Laboratory analyses at time of inclusion for subjects with and without dyspnea after pulmonary embolism, mean (SD) unless stated otherwise.

	No dyspnea (n = 85–96)	Dyspnea (n = 71–79)	P value
Hemoglobin, g/dL	14.5 (1.3)	14.3 (1.4)	0.35
NT-proBNP, ng/L, median (IQR)	83 (96)[a]	75 (77)[b]	0.13
D-dimer, number (%)			0.43
<0.5 mg/L	68 (71)	56 (78)	
0.5–1 mg/L	18 (19)	13 (18)	
>1 mg/L	9 (10)	3 (4)	
Troponin I, number (%)			0.12
<5 ng/L	73 (78)	64 (89)	
5–100 ng/L	20 (21)	8 (11)	
>100 ng/L	1 (1)	0 (0)	
Arterial pO_2, kPa	11.2 (1.3)[c]	11.2 (1.1)[d]	0.80

Abbreviations; IQR – interquartile range; NT-proBNP – N-terminal pro-brain natriuretic peptide.
[a] n = 76, [b]n = 58, [c]n = 58, [d]n = 54.

4. Discussion

In this study, the prevalence of persistent dyspnea was high, as 44% of the participants reported dyspnea after PE. Of a comprehensive cardiopulmonary work-up, only reduced DLCO was independently associated with dyspnea. In addition, those with dyspnea were younger, had higher BMI and were more likely to have recurrent VTE.

The prevalence of persistent dyspnea is comparable to that reported in previous studies [2,4,16,17]. However, the prevalence may depend on definitions of dyspnea, and may be affected by many physical, psychological and social experiences. The BOLD study revealed that the prevalence of dyspnea, defined as mMRC >0, was up to 27% in the general population and 16% in a sub-cohort with a normal spirometry and without relevant comorbidities [28]. Furthermore, time is an important factor when evaluating post-PE impairment, as the majority of symptoms and functional limitations gradually improves within 3 to 6 months after the acute event [3,4]. The present study included only subjects with a history of PE >6 months prior to inclusion, at a time when the symptoms are less likely to improve further.

We found no association between spirometry or plethysmography variables and persistent dyspnea. However, impaired DLCO was associated with dyspnea in the simple and the multiple regression analyses. This finding of reduced DLCO in a post-PE population is in line with another, albeit, small (n = 20) study, which showed that DLCO remained subnormal over 3 years of follow-up after PE [29]. Gas diffusion has rarely been performed in the setting of post-PE impairment, except for studies limited to patients with CTEPH. Acute PE causes a range of pathophysiological changes in the pulmonary vasculature, including increased pulmonary vascular resistance and mismatch of ventilation and perfusion [30,31]. All of these alterations may cause impaired gas diffusion capacity resulting in a reduced DLCO.

Residual perfusion defects were detected in 22% of the participants in our cohort, which compares well with a range of 20–50% reported in previous studies [32–36]. Perfusion defects have in other studies been linked to dyspnea and functional limitations [34], and often the term chronic thromboembolic pulmonary disease (CTEPD) is used [37]. The detection of significant perfusion defects/CTEPD may be highly clinically relevant, as these patients sometimes are offered the same surgical treatment as CTEPH [38]. Furthermore, residual perfusion defects have in several studies been linked to recurrent VTE and may thus impact anticoagulant treatment [36,39]. In the present study, there was a higher proportion of significant perfusion defects in participants reporting dyspnea, albeit not statistically significant. This may be due to the relative low number of perfusion defects present, and the dichotomization of the V/Q results. However, the presence of residual perfusion defects was associated with dyspnea in the subgroup analysis with subjects diagnosed with PE ≥ 18 months prior.

We experienced a considerable ceiling effect regarding the ISWT, as a substantial proportion of participants was able to complete the test up to its maximum walking distance of 1020 m. Still, those with dyspnea performed significantly worse when compared to those without dyspnea.

Mean LV EF was slightly reduced in the participants reporting

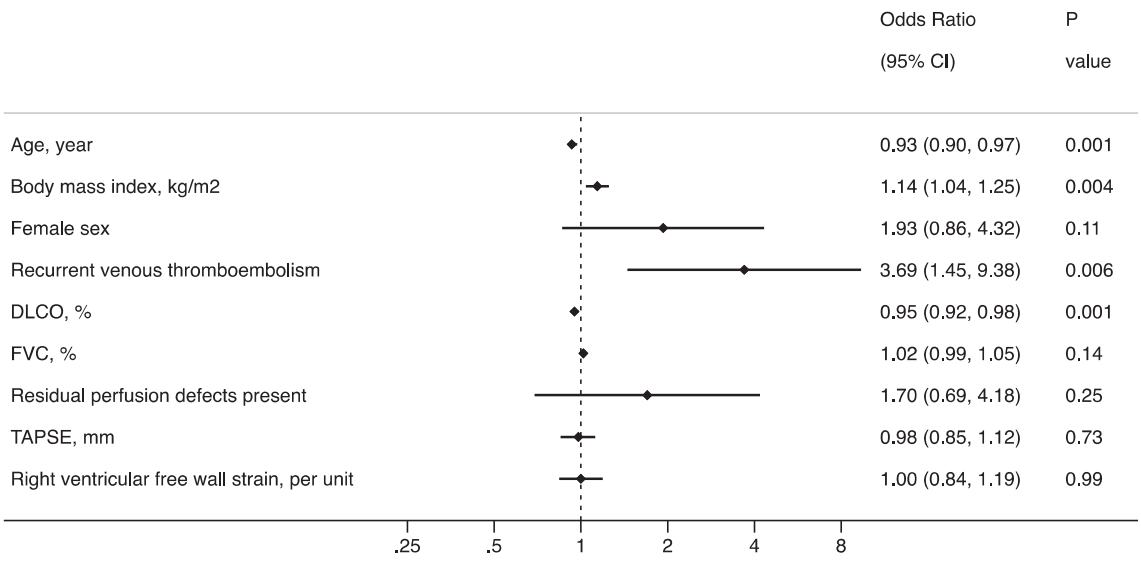

Fig. 2. Variables associated with persistent dyspnea after pulmonary embolism using multiple logistic regression analysis, presented as adjusted Odds Ratio, *P* value and corresponding forest plot (*N* = 180). Abbreviations; CI – confidence interval; DLCO – diffusion capacity of the lung for carbon monoxide; FVC – forced vital capacity; TAPSE – tricuspid annular plane systolic excursion.
Younger age (adjusted odds ratio (aOR) 0.93 per year, 95% CI: 0.90–0.97, $P = 0.001$), higher body mass index (aOR 1.14 per kg/m^2, 95% CI: 1.04–1.25, $P = 0.004$), recurrent venous thromboembolism (VTE) (aOR 3.69, 95% CI: 1.45–9.38, $P = 0.006$) and lower diffusion capacity of the lung for carbon monoxide (DLCO) (aOR 0.95 per increase of 1%, 95% CI: 0.92–0.98, $P = 0.001$) were independently associated with persistent dyspnea.

dyspnea in the univariate analysis. However, other LV function indices such as LV GLS and 3D LV EF, which are both considered to be more sensitive echocardiography indices for LV systolic function than Simpson's biplane EF, revealed no difference between those with and without dyspnea [40–42].

Diastolic dysfunction has been proposed as a major cause of post-PE impairment [43]. However, in the present study only four subjects fulfilled the predefined echocardiographic criteria for diastolic dysfunction, of which three (75%) reported no dyspnea. This study used the echocardiographic criteria from the ESC guidelines of 2016, which are deemed more conservative with regard to the prevalence of diastolic dysfunction than the earlier 2009 criteria [27,44–46].

There was no association between variables of right ventricular dimension or function with persistent dyspnea. While RV dysfunction is common in the long-term follow-up after PE [2], its impact on functional limitations and symptoms remains unclear; some studies have shown an association between echocardiographic findings and functional limitations [6–8], while others have not revealed such a relationship [3,4,16].

Subjects with dyspnea were younger than those without dyspnea both in the univariate and multivariable analysis. This finding may be explained by younger people in general having a higher activity level than older people [47] and thus more sensitive to a post-PE impairment and more likely to report dyspnea. Another possible explanation is recruitment bias; retired senior citizens may be more prone to participate in this sort of study, regardless of symptoms, while people with unexplained dyspnea may be more willing to participate regardless of work status. This finding is in contrast with other studies that have either shown a positive correlation between age and symptoms [7,17] or no association at all [16].

Participants reporting dyspnea had higher BMI than those without dyspnea, which supports previous studies in the field [3,16,17]. This finding is also in line with reported associations of overweight and obesity with dyspnea in a general population and in patients with chronic cardiopulmonary disease [48–50].

Out of a total of 673 subjects screened for eligibility, only 3 had previously been diagnosed with CTEPH. Additionally, two of the participants in the current study were diagnosed with CTEPH during the diagnostic work-up, yielding a prevalence of 0.7% (5/673). This is a low prevalence of CTEPH compared to other cohorts [51–53]. There are, however, several possible explanations to this; firstly, we included only participants up to 75 years of age, which may play some part as increasing age is a risk factor for CTEPH [54]. Secondly, we did not include patients who were reported dead in the eligibility screening, thus excluding all patients who might have developed CTEPH and died.

Strengths of this study include a comprehensive cardiopulmonary diagnostic work-up. Pulmonary gas diffusion has rarely been assessed in other studies concerning post-PE impairment. The echocardiographic examination and analysis included novel echocardiographic parameters not previously applied to a post-PE population.

Some limitations of the study should be noted. The dichotomization of subjects (i.e., dyspnea or no dyspnea) was based on a simple question at inclusion which has not been validated in other studies. The sensation and reporting of dyspnea may be prone to confirmation bias and recall bias, which may have affected the results. Subjects with symptoms may be more willing to participate in such a study as this, possibly contributing to selection bias. Not all tests were completed by all participants. The investigator performing the echocardiographic examination/analysis and shuttle walk tests was not blinded with regard to the participants' symptoms and group affiliation, which may cause information bias. The exclusion of several prevalent conditions, such as heart failure and obstructive pulmonary disease, restrict the generalizability of our results and make direct comparison with other post-PE studies difficult. The study assessed a large number of variables and did not adjust for multiple comparisons. In the multiple regression analysis, however, we restricted the number of variables and did not use a statistics-driven variable procedure. Finally, the time-interval from the date of diagnosis to inclusion was wide, from 6 months to 72 months, which may have yielded a heterogeneous study population. To address this, we performed subgroup analysis based on time from diagnosis.

The causes of post-PE impairment, including persistent dyspnea, which is the focus of this paper, have been much debated. Based on the findings of this study, we believe that the etiology of post-PE impairment is probably multifactorial, but our finding of reduced DLCO in those complaining of dyspnea, suggest some underlying respiratory impairment in at least some patients. Further studies are needed to validate this finding.

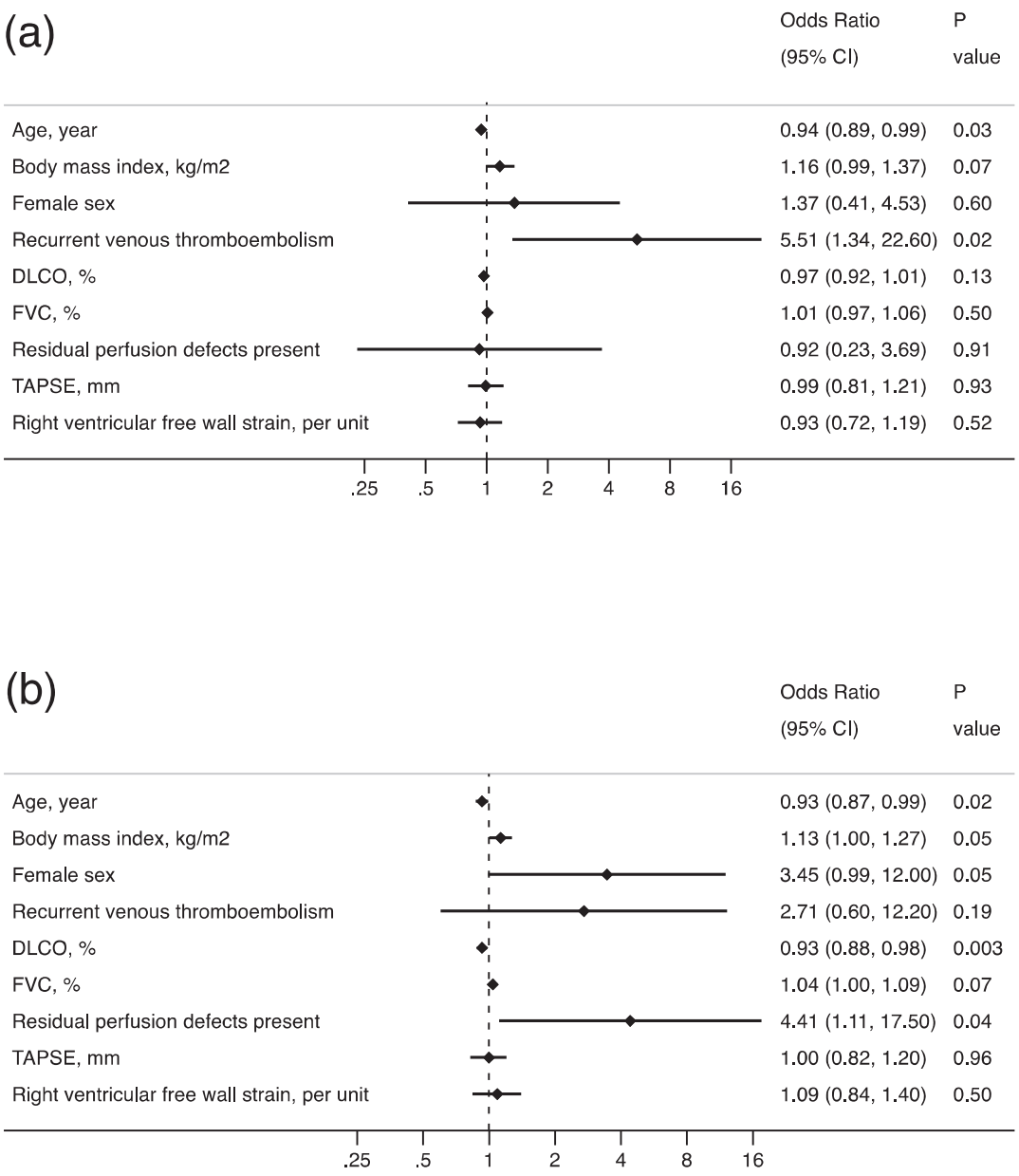

Fig. 3. Subgroup analysis; (a) participants with PE 6–18 months prior ($n = 89$) and (b) participants with PE $\geq$ 18 months prior ($n = 91$).
Abbreviations; CI – confidence interval; DLCO – diffusion capacity of the lung for carbon monoxide; FVC – forced vital capacity; TAPSE – tricuspid annular plane systolic excursion.

5. Conclusions

This study has shown that persistent dyspnea after PE is common, even in the absence of cardiopulmonary comorbidity, affecting almost half of PE survivors. Of our comprehensive diagnostic cardiopulmonary tests, reduced DLCO was the only abnormality that was independently associated with dyspnea, after adjusting for age, BMI and recurrent VTE.

CRedit authorship contribution statement

Ø.Jervan, J.Gleditsch, K.Stavem, K.Steine and W.Ghanima were responsible for the design of the study. Ø.Jervan had full access to all the data in the study and takes responsibility for all content of the manuscript, including data and analyses. D.Rashid interpreted the scintigraphic images. The statistical analyses were performed by Ø.Jervan with contribution by R.Holst. Ø.Jervan drafted the first manuscript. All authors contributed to the interpretation of the results and revision of the manuscript. All authors have read and approved the final version of the manuscript.

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Declaration of competing interest

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Appendix A

Table A.1
Pulmonary function tests, V/Q-scintigraphy and exercise test at time of inclusion for subjects with and without dyspnea after pulmonary embolism, mean (SD) unless stated otherwise.

	No dyspnea (n = 86–96)	Dyspnea (n = 77–79)	P value
Spirometry			
FEV1/FVC	0.77 (0.07)	0.76 (0.07)	0.71
FEV1, % of predicted	99 (13.3)	97.1 (12.7)	0.37
FVC, % of predicted	102.7 (14.6)	104 (13.8)	0.57
Carbon monoxide diffusion capacity			
DLCO, % of predicted	93.4 (14.6)	85.6 (15.1)	0.001
KCO, % of predicted	102.4 (16.0)	94.9 (17.1)	0.005
Whole body plethysmography			
TLC, % of predicted	100.4 (11.3)	99.3 (11.9)	0.56
RV, % of predicted	111.8 (24.4)	106.1 (20.8)	0.11
Ventilation/perfusion scintigraphy			
Significant perfusion defects present, number (%)	18 (19)	22 (28)	0.11
Exercise test			
ISWT, meters (median/IQR)	900 (310)	710 (330)	<0.001

Abbreviations; FEV1 – forced expiratory volume in one second; FVC – forced vital capacity; DLCO – diffusion capacity of the lung for carbon monoxide; KCO – carbon monoxide transfer coefficient; TLC – total lung capacity; RV – residual volume; ISWT – Incremental Shuttle Walk Test.

Table A.2
Echocardiographic findings for subjects with and without dyspnea after pulmonary embolism, mean (SD) unless stated otherwise.

	No dyspnea (n = 95–98)	Dyspnea (n = 73–79)	P value
LV ejection fraction (Simpson's biplane), %	63.3 (5.0)	61.7 (5.1)	0.03
LV ejection fraction (3D), %	58.9 (5.2)[a]	59.8 (6.5)[b]	0.25
LV global longitudinal strain	−19.5 (2.0)[c]	−19.6 (2.1)[d]	0.84
E/A ratio	0.96 (0.03)	0.95 (0.03)	0.82
E/E′, average	6.8 (1.8)	6.6 (2.0)	0.72
Left atrial volume index, ml/m^2	29.3 (9.9)	25.6 (7.1)	0.006
TAPSE, mm	25.4 (3.5)	24.4 (3.5)	0.06
RV S′, cm/s	12.9 (2.5)	12.4 (2.6)	0.18
RV myocardial performance index	0.39 (0.14)	0.41 (0.14)	0.41
RV free wall strain	−27.0 (4.0)[e]	−25.7 (3.4)[f]	0.06
Tricuspid regurgitation peak velocity, m/s	2.4 (0.3)[g]	2.5 (0.4)[h]	0.33
Pulmonary valve acceleration time, ms	136 (24)	131 (30)	0.18

Abbreviations; LV – left ventricle; RV – right ventricle; E – transmitral early diastolic filling peak velocity; A; transmitral late diastolic filling peak velocity E′ - Early diastolic annular velocity of the mitral valve; TAPSE – tricuspid annular plane systolic excursion; RV S′ – right ventricle tricuspid annular peak systolic velocity.

[a] n = 77.
[b] n = 55.
[c] n = 73.
[d] n = 49.
[e] n = 64.
[f] n = 54.
[g] n = 80.
[h] n = 52.

Appendix B. Echocardiographic recordings, measurements and calculations

All cineloops recorded with 3 cycles during breath hold, preferably end-expiration

View	Mode	Abbreviation/ short form	Full description	Comments
PLAX	M-mode	IVSd	Interventricular septum diameter end-diastolic	– Alternatively, PSAX – Angular M-mode if necessary
PLAX	M-mode	LVIDd	LV internal diameter end-diastolic	

(continued on next page)

(*continued*)

View	Mode	Abbreviation/ short form	Full description	Comments
PLAX	M-mode	LVPWd	LV posterior wall diameter end-diastolic	
PLAX	M-mode	IVSs	Interventricular septum diameter end-systolic	
PLAX	M-mode	LVIDs	LV internal diameter end-systolic	
PLAX	M-mode	LVPWs	LV posterior wall diameter end-systolic	
PSAX	PW	PV AT	Pulmonary valve acceleration time	– Sample volume proximal of PV
A4C/A2C	2D	LVEDV	LV end-diastolic volume	– Manual tracing and Simpson's biplane method
A4C/A2C	2D	LVESV	LV end-systolic volume	– Manual tracing and Simpson's biplane method
A4C/A2C/ A3C	2D	LV strain (GLS)	Global longitudinal strain of LV	– Speckle tracking imaging
A4C	2D	LAA	Left atrium area end-systolic	– Manual tracing
A4C	2D	LAV	Left atrium volume end-systolic	– LAVs calculated using Simpson's biplane method
A4C	PW	E	Transmitral early diastolic filling peak velocity	
A4C	PW	Edec	Transmitral early diastolic filling wave deceleration time	
A4C	PW	A	Transmitral late diastolic filling peak velocity	
A4C	TDI	E' lateral	Early diastolic lateral annular velocity of the mitral valve	
A4C	TDI	E' septal	Early diastolic septal annular velocity of the mitral valve	
A4C RV focus	2D	RAA	Area of the right atrium	– Manual tracing
A4C RV focus	M-mode	TAPSE	Tricuspid annular systolic excursion	
A4C RV focus	TDI	RV S'	Tricuspid annular peak systolic velocity	
A4C RV focus	TDI	RV IVRT	RV isovolumetric relaxation time	
A4C RV focus	TDI	RV ET	RV ejection time	
A4C RV focus	TDI	RV IVCT	RV isovolumetric contraction time	
A4C RV focus	2D	RV strain	Longitudinal strain of RV	– Speckle tracking imaging – 3 segments (RV free wall)
A4C RV	CW	TR V max	Tricuspidal regurgitation peak velocity	– If inadequate TR-signal, other views are attempted (PSAX, subcostal, RV inlet view)
Subcostal	2D			– Overview of chambers with color
A4C	3D	LVEDV (3D) LVESV (3D)		– Left ventricular volumes and ejection fraction using designated 3D software

Calculations.

Name	Calculation
LV EF	$\frac{LVEDV - LVESV}{LVEDV}$
EA ratio	$\frac{E}{A}$
E/E'avg	$\frac{E}{E'(average of lateral and septal measurements)}$
RV myocardial performance index (MPI)/tei-index	$\frac{RV\,IVCT + RV\,IVRT}{RV\,ET}$

Abbreviation list. A4C = apical four chamber view, A2C = apical two chamber view, A3C = apical three chamber view, PLAX = parasternal long axis view, PSAX = parasternal short axis view, PW = pulsed wave Doppler, CW = continuous wave Doppler, TDI = tissue Doppler imaging, LV = left ventricle, RV = right ventricle, LA = left atrium, RA = right atrium, PV = pulmonic valve, VCI = vena cava inferior

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