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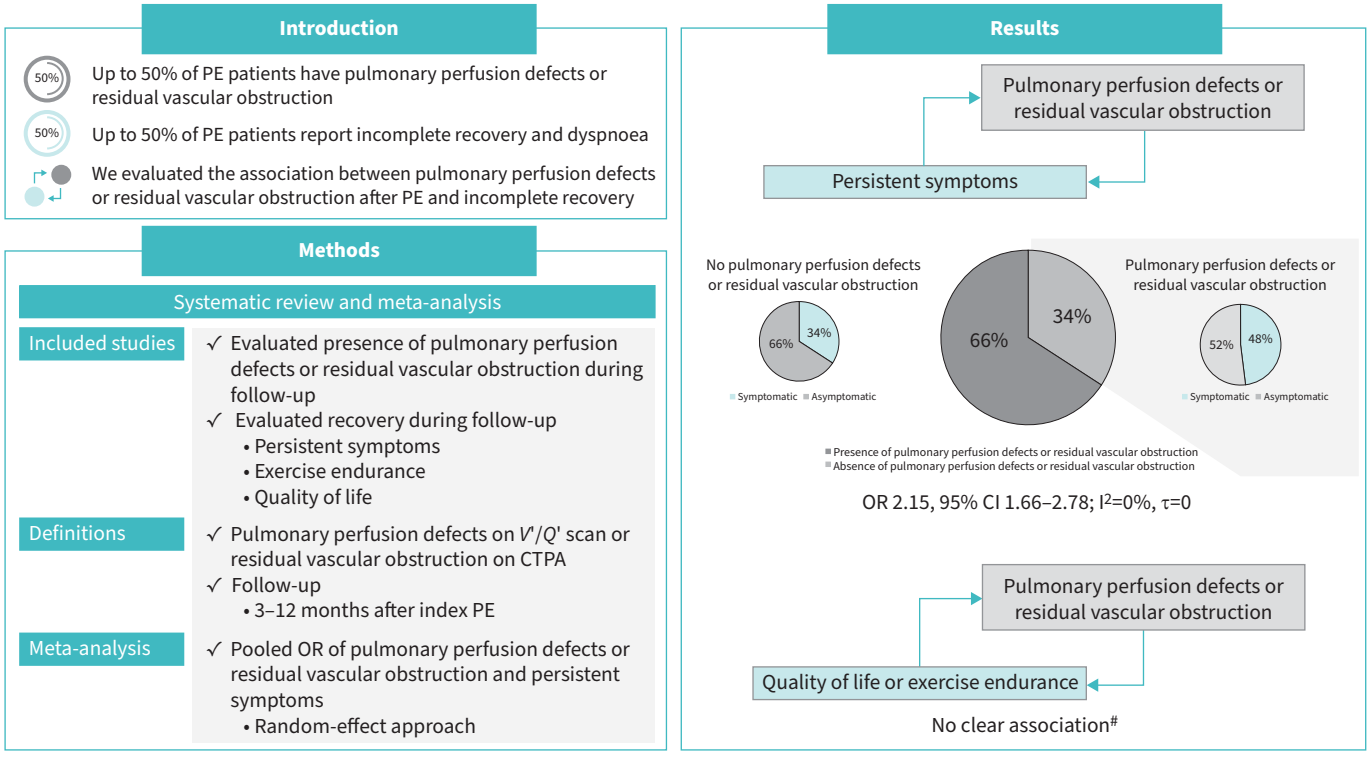

GRAPHICAL ABSTRACT PE: pulmonary embolism; *V'/Q'*: ventilation/perfusion; CTPA: computed tomography pulmonary angiography. #: no meta-analysis performed due to heterogeneity.

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Shareable abstract (@ERSpublications)
Perfusion defects or residual vascular obstruction are associated with persistent symptoms after acute pulmonary embolism with a pooled odds ratio of 2.15, although direct causality could not be proven https://bit.ly/4cvHc5h

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Abstract

Introduction: Up to 50% of pulmonary embolism (PE) patients have perfusion defects or residual vascular obstruction during follow-up despite adequate anticoagulant treatment, and a similar percentage experience chronic functional limitations and/or dyspnoea post-PE. We aimed to evaluate the association between pulmonary perfusion defects or residual vascular obstruction and functional recovery after PE.

Methods: We performed a systematic review and meta-analysis including studies assessing both the presence of perfusion defects or residual vascular obstruction and functional recovery (*i.e.* persistent symptoms, quality of life, exercise endurance). An odds ratio was pooled for perfusion defects or residual vascular obstruction and persistent symptoms using a random-effect model.

Results: 12 studies were included totalling 1888 PE patients; at a median of 6 months after PE (range 2–72 months), 34% had perfusion defects or residual vascular obstruction and 37% reported persistent symptoms. Among patients with perfusion defects or residual vascular obstruction, 48% (95% CI 37–60%, I^2=82%) remained symptomatic during follow-up, compared to 34% (95% CI 20–51%, I^2=96%) of patients without such defects. Presence of perfusion defects or residual vascular obstruction was associated with persistent symptoms (OR 2.15, 95% CI 1.66–2.78; I^2=0%, τ=0). Notably, there was no association between these defects and quality of life or cardiopulmonary exercise test parameters.

Conclusion: While the odds of having persistent symptoms was higher in patients with perfusion defects or residual vascular obstruction after acute PE, a significant proportion of these patients reported no limitations. A possible causality between perfusion defects or residual vascular obstruction and residual functional limitation therefore remains to be proven.

Introduction

Up to 50% of acute pulmonary embolism (PE) survivors have persistent symptoms or alterations of cardiocirculatory function, as well as a reduction in the quality of life (QoL) [1–4]. Patients who remain symptomatic despite receiving a minimum of 3 months of adequate anticoagulant treatment, are considered to have the post-PE syndrome (PPES) [5]. PPES consists of various aetiologies explaining a lack of recovery from acute PE: chronic thromboembolic pulmonary hypertension (CTEPH) (*i.e.* patients with 1) mismatched perfusion defects on ventilation/perfusion (V'/Q') scan and specific diagnostic signs for CTEPH on computed tomography pulmonary angiography (CTPA) in combination with 2) mean pulmonary artery pressure at rest >20 mmHg, pulmonary artery wedge pressure of ⩽15 mmHg and a pulmonary vascular resistance of >2 Woods Units [6]); chronic thromboembolic pulmonary disease (CTEPD) without pulmonary hypertension (PH) (*i.e.* patients present mismatched perfusion defects on V'/Q' scan and specific signs of organised fibrotic clots on CTPA, magnetic resonance imaging or conventional pulmonary cineangiography, without increased pulmonary artery pressure at rest [7, 8]); post-PE cardiac dysfunction (characterised by persistent right ventricle impairment after PE); post-PE functional impairment (possibly related to deconditioning); or other cardiopulmonary comorbidities [6, 8–10]. PPES is a large burden for patients and society, as these patients have decreased QoL [1]; healthcare utilisation searching for an explanation for incomplete recovery is associated with high costs [11]; and work-related productivity loss due to PPES is the main driver for the economic burden of acute PE [12].

CTEPD is the overarching term for CTEPH and CTEPD without PH, and is characterised by persistent thrombi. CTEPH is the most serious presentation of PPES and has clear diagnostic criteria; however, only 2.7% of acute PE survivors are diagnosed with CTEPH during follow-up [10]. CTEPD without PH is characterised by persistent thrombi and normal pulmonary artery pressure at rest. However, the current definition does not distinguish between patients who show exercise-induced haemodynamic limitations and those who don't, despite having persistent thrombi. This lack of specific diagnostic criteria during exercise leads to a homogeneous classification of these potentially diverse patient groups under CTEPD without PH. Some therefore suggest that CTEPD without PH should only be classified in patents with limited exercise tolerance which is attributed to an increased slope of pulmonary artery pressure–flow relationship during exercise of dead space ventilation [8]. It remains unknown what proportion of acute PE survivors suffer from incomplete recovery due to CTEPD without PH, and whether CTEPD without PH is an early presentation of CTEPH or an "end-stage disease". Interestingly, recent studies have suggested that incidence of CTEPD without PH is comparable to that of CTEPH and disease progression is hardly observed [13, 14]. The clinical relevance of incomplete thrombus resolution as assessed by pulmonary perfusion defects or residual vascular obstruction in acute PE patients who do not have CTEPH, as well as its association with recovery after acute PE, is debated and remains unknown.

In this systematic review and meta-analysis, we aimed to evaluate the association between pulmonary perfusion defects or residual vascular obstruction and recovery (*i.e.* symptom burden, exercise endurance, QoL).

Methods

Study selection, data extraction and quality assessment

PubMed, Web of Science, Cochrane Library, Emcare and Embase were searched from inception to February 2023 (complete search string available in the supplementary material: appendix S1) focusing on cohort studies that evaluated presence of pulmonary perfusion defects or residual vascular obstruction and recovery during acute PE follow-up. Two authors (L.A. Cimini and D. Luijten) independently reviewed the search list by title and abstract and determined study eligibility. Full-text candidate records were subsequently reviewed and selected for data retrieval. Disagreements were resolved through discussion or by consulting a third author (F.A. Klok).

Inclusion criteria were as follows. 1) Prospective or retrospective cohort studies, 2) with ⩾50 patients included, 3) that systematically assessed presence of pulmonary perfusion defects by routine repeat V'/Q' scan, perfusion (Q') scan or residual vascular obstruction on CTPA after ⩾3 months of adequate anticoagulation therapy, and 4) performed a systematic assessment of symptom burden, QoL and/or functional outcomes (*i.e.* cardiopulmonary exercise test (CPET), 6-min walk test (6MWT) and/or incremental shuttle walk test (ISWT)) at the time of imaging assessment. Only articles in English language were considered. If more than one study reported on the same cohort, the most appropriate one for our study question was included.

Two authors (L.A. Cimini and D. Luijten) independently performed quality assessment and data extraction for each included study using standardised extraction forms. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies. Individual study quality was assessed according to the following

domains: cohort study selection, comparability, outcome assessment and overall study quality (range 1–9; 1–3 indicates low quality, 4–6 indicates moderate quality and 7–9 indicates high quality) [15]. Disagreements were resolved through discussion or by consulting a third author (F.A. Klok). Extracted data included information on study design, patient characteristics, timing of the follow-up, type of imaging assessing pulmonary perfusion defects or residual vascular obstruction, clinical outcome assessment and results of functional tests. Study authors were contacted whenever data for meta-analysis could not be extrapolated from the text.

The study was registered at www.crd.york.ac.uk/prospero/ (identifier CRD42023397676).

Study outcome and measurements

The primary outcome was the association between presence of pulmonary perfusion defects or residual vascular obstruction and symptoms in acute PE patients during follow-up. Secondary outcomes were the associations between presence of pulmonary perfusion defects or residual vascular obstruction and other functional outcomes, *i.e.* 6MWT, CPET (*e.g.* oxygen consumption (V'_{O_2}), minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) slope), ISWT and/or QoL data. Pulmonary perfusion defects or residual vascular obstruction during follow-up could be evaluated by CTPA, V'/Q' or Q' scan independent of size of perfusion defect or vascular obstruction at index PE (table 1). Patients without pulmonary perfusion defects or residual vascular obstruction were considered to have a normal V'/Q' scan or CTPA during follow-up.

Statistical analysis

To evaluate the association between presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms, we performed a meta-analysis in which we calculated the pooled prevalence of persistent symptoms in patients with and without pulmonary perfusion defects or residual vascular obstruction using a generalised linear mixed-effect model, as well as the pooled odds ratio with 95% confidence intervals using a random-effect model (according to Mantel–Haenszel method with restricted maximum likelihood). The following subgroups were subsequently evaluated, according to 1) type of imaging technique (V'/Q' scan, Q' scan or CTPA); 2) timing of imaging during follow-up (3, 6 or 12 months); and 3) study design (retrospective or prospective).

To evaluate the association between presence of pulmonary perfusion defects or residual vascular obstruction and the 6MWT, we calculated the mean distance (m) achieved for patients with and without pulmonary perfusion defects or residual vascular obstruction within each study and calculated the standardised mean difference. The standardised mean difference was subsequently pooled across studies using a random-effect model. For all other outcomes we reported the incidence or median values in patients with and without pulmonary perfusion defects or residual vascular obstruction per individual study.

The appropriateness of pooling data across studies was assessed using the I^2 test for heterogeneity [31]. Heterogeneity was defined as low in when $I^2<25\%$, moderate when $I^2=25–75\%$ and high when $I^2>75\%$. The presence of publication bias was evaluated by visually inspecting funnel plots. The statistical analyses, forest plots and publication bias analyses were performed using R version 4.2.1. (metabin, metacont, metaprop).

Results

Study selection

The primary search identified 1420 records; 413 duplicate records were removed and another 901 were excluded after screening title and abstract (figure 1). An additional 94 papers were excluded after full-text examination, mainly for the lack of (systematic and standardised) assessment of persistent symptoms or functional outcomes (n=54). Overall, 12 studies provided data on presence of pulmonary perfusion defects or residual vascular obstruction during acute PE follow-up as well as functional outcomes and were included in this systematic review [16–28].

Quality assessment and risk of bias

Results of the NOS scale assessments are reported in supplementary table S1. Only one study was judged as high quality [20]. The other studies were judged as moderate quality. The main reasons for moderate quality of studies were 1) potential bias in selection (*e.g.* retrospective design); 2) potential bias in outcome (*e.g.* unclear if follow-up procedures were systematically performed according to a predefined standardised protocol); and 3) lack of adjustment for potential confounders.

Included studies

The main characteristics of the included studies are reported in table 1. Eight studies were prospective. Four studies provided the localisation of emboli (central/peripheral) at the baseline PE imaging test [16,

TABLE 1 Characteristics of the included studies

First author, year [reference]	Prospective/ retrospective	Single-centre/ multicentre	Study design	Included patients	Age years	Prior VTE	Malignancy	Cardiopulmonary disease	Centrally located PE	Reperfusion therapy	RVD at TTE/ CTPA at index PE	Timing of follow-up after acute PE months	Imaging during follow-up	Definition of presence of pulmonary perfusion defects or residual vascular obstruction	Definition of persistent symptoms
Alblas, 2022 [16]	Retrospective[¶]	Single-centre	Observational	179	56 (18–88)	29 (16)	13 (7)	18 (10)	75 (42)	28 (16)		6	*Q′*	Residual abnormalities according to the revised PISA-PED criteria [29]; coded as the following: complete reperfusion and incomplete or absent reperfusion	Patients reported dyspnoea/ shortness of breath
Amato, 2017[#] [17]	Prospective	Single-centre	Observational	166								6	*V′*/*Q′*	Persistent perfusion defects	
Aranda, 2021 [18]	Retrospective	Single-centre	Observational	150	61±18		13 (9)		52 (34)[+]		35 (24)[§]	12	CTPA	Presence of filling defects (occlusive or partial) were defined as visualisation of thrombus on follow-up CTPA	Symptoms suggestive of CTEPH
Aranda, 2021 [19]	Retrospective	Single-centre	Observational	241	64 (48–80)		45 (19)		59 (25)[f]		42 (18)[§]	6–12[##]	CTPA	Visualisation of thrombus on follow-up CTPA	Clinical resolution
Chopard, 2017 [20]	Prospective	Multicentre	Observational	241	65±16		20 (8)	0			160 (66)[¶¶]	3	*V′*/*Q′*[++]	RPVO >15%	Heart failure or worsening dyspnoea
George, 2015[#] [21]	Prospective	Single-centre	Observational	67								3	*V′*/*Q′*	Persistent perfusion defects	
Golpe, 2012 [22]	Prospective	Single-centre	Observational	91								6	CTPA	Residual intraluminal filling defects	Patients reported dyspnoea/ shortness of breath
Jervan, 2022[#] [23]	Prospective		RCT	274								6–72	*V′*/*Q′*	Residual perfusion defect According to the EANM criteria	mMRC score ⩾1

Continued

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TABLE 1 Continued

First author, year [reference]	Prospective/ retrospective	Single-centre/ multicentre	Study design	Included patients	Age years	Prior VTE	Malignancy	Cardiopulmonary disease	Centrally located PE	Reperfusion therapy	RVD at TTE/ CTPA at index PE	Timing of follow-up after acute PE months	Imaging during follow-up	Definition of presence of pulmonary perfusion defects or residual vascular obstruction	Definition of persistent symptoms
Lachant, 2020 [24]	Retrospective[¶]	Single-centre	Observational	104	60 (47–72)	23 (22)	7 (7)		31 (31)	14 (13)	64, (63)[§§]	2–4	*V′*/*Q′*	Mismatched or partly mismatched segmental *V′*/*Q′* defects	Reported self-limited activities
Ma, 2018 [25]/Kahn, 2017 [26]	Prospective	Multicentre	Observational	100	50±15		1 (1)	13 (13)		2 (2)	32 (32)[§]	12	*Q′*/CTPA	*Q′*: Persistent perfusion defects defined as persistent vascular obstruction score >0% CTPA: CT obstruction score of >0% (Qanadli score [30])	UCSD Shortness of Breath Questionnaire >5 points
Nakano, 2022 [27]	Prospective	Multicentre	Observational	43[ff]	59±16	8 (19)	4 (9)			2 (5)	7 (17)[###]	12	CTPA	CT obstruction score >0% (Qanadli score [30])	NYHA class ⩾2
Sanchez, 2010 [28]	Prospective	Single-centre	Observational	254	61±18	58 (23)	32 (15)	37 (15)		14 (6)	36 (14)[¶¶¶]	12	*V′*/*Q′*	Perfusion defects defined as residual pulmonary vascular obstruction ⩾10% (modified Qanadli score [30])	NYHA class ⩾1

Data are presented as n, median (interquartile range), mean±SD or n (%), unless otherwise stated. VTE: venous thromboembolism; PE: pulmonary embolism; RVD: right ventricular dysfunction; TTE: transthoracic echocardiogram; CTPA: computed tomography pulmonary angiogram; *Q′*: perfusion scan; PISA-PED: Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis; *V′*/*Q′*: ventilation/perfusion scan; CTEPH: chronic thromboembolic pulmonary hypertension; RPVO: residual pulmonary vascular obstruction; RCT: randomised controlled trial; EANM: European Association of Nuclear Medicine; mMRC: modified Medical Research Council; CT: computed tomography; UCSD: University of California, San Diego; NYHA: New York Heart Association. [#]: abstract only; [¶]: initially retrospective and subsequently prospective; [+]: massive/submassive PE; [§]: right ventricle (RV)/left ventricle (LV) >1; [f]: massive PE; [##]: CTPA at 6 months, assessment of symptoms at 12 months; [¶¶]: RV/LV >1, systolic pulmonary arterial pressure >30 mmHg or paradoxical septal motion; [++]: residual vascular obstruction >15%; [§§]: moderate to severe RVD (not further classified); [ff]: 52 patients were enrolled in this study; seven were unable to visit the outpatient clinic at the 1-year point, and two died; therefore, 43 patients were included in this meta-analysis. Since originally 52 patients were included, we concluded the exclusion criterion of <50 patients included was not met and we included this study in our systematic review and meta-analysis; [###]: tricuspid regurgitation pressure gradient >60 mmHg; [¶¶¶]: signs of RV failure (not further classified).

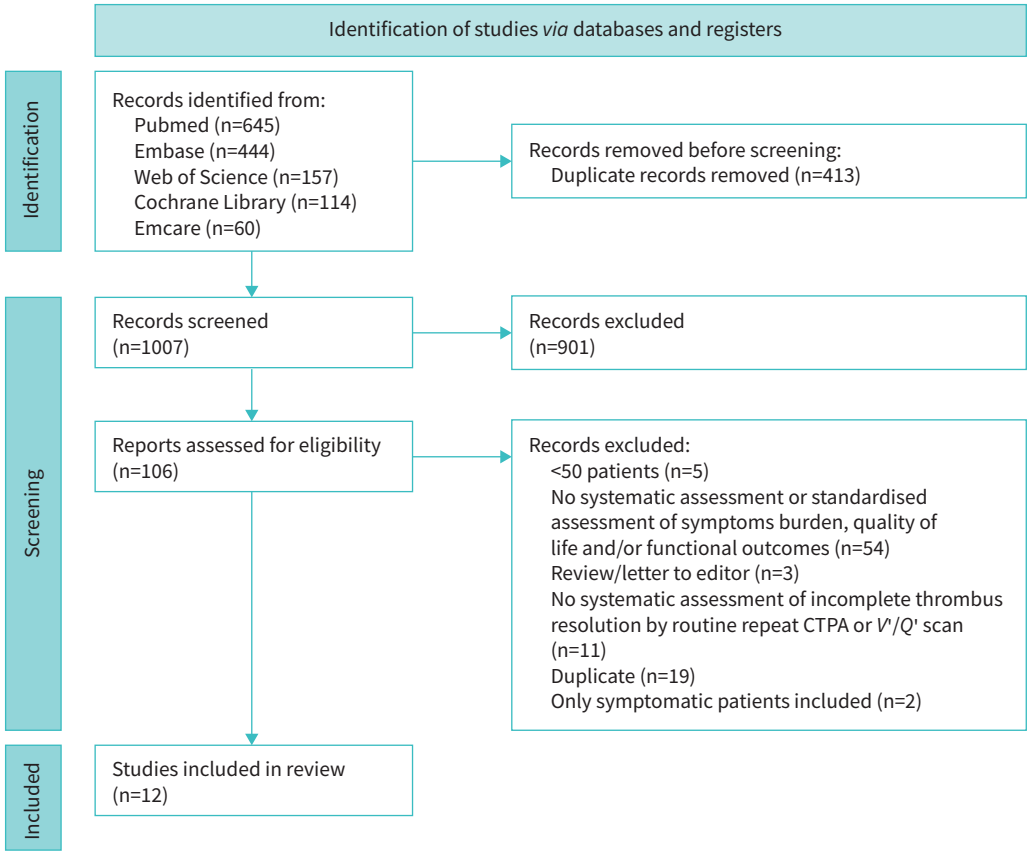

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study. CTPA: computed tomography pulmonary angiogram; V'/Q': ventilation/perfusion.

18, 19, 24]. Five studies reported on the number of patients who underwent reperfusion treatment (range 2–16%) [16, 24–28]. Seven studies reported the number of patients with right ventricular dysfunction at index PE; the proportion ranged from 17% to 66% [18–20, 24–28]. The timing of the follow-up procedures ranged from 2 months after the index PE episode up to 72 months, but were mostly within 3–12 months (11 out of 12 studies). Presence of pulmonary perfusion defects or residual vascular obstruction during follow-up was assessed in four studies by CTPA to evaluate residual vascular obstruction; six studies used V'/Q' scan to evaluate perfusion defects and one study used a Q' scan only. The presence of pulmonary perfusion defects or residual vascular obstruction was mostly defined as no residual thrombi/vascular obstruction on CTPA and/or no persistent perfusion defects on (V'/)Q' scan (supplementary table S3). Only one study used a threshold for residual vascular obstruction of >15% [20]. In the Evaluation of Long-term Outcomes after PE (ELOPE) cohort study, the presence of pulmonary perfusion defects or residual vascular obstruction was assessed by both CTPA and Q' scan [25, 26]. The most common assessment of persistent symptoms was patient-reported dyspnoea, used in two studies [16, 22].

Association between presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms

12 studies reported on the number of patients with pulmonary perfusion defects or residual vascular obstruction during follow-up: the pooled proportion was 34% (95% CI 24–46%, I^2=91%; supplementary figure S1). When using (V'/)Q' scan, 38% of the patients had persistent perfusion defects during follow-up; this was only 29% when using CTPA to evaluate residual vascular obstruction (supplementary figure S1). Nine studies reported on the number of patients with persistent symptoms during follow-up: the pooled proportion was 37% (95% CI 24–53%, I^2=97%; supplementary figure S2). Nine studies reported on the number of symptomatic/asymptomatic patients with pulmonary perfusion defects or residual vascular obstruction and the number of symptomatic/asymptomatic patients with a normal V'/Q' scan/CTPA during follow-up: among patients with pulmonary perfusion defects or residual vascular obstruction, the pooled proportion of persistent symptomatic patients was 48% (95% CI 37–60%, I^2=82%), compared to 34%

(95% CI 20–51%, I^2=96%) of patients with a normal V'/Q' scan/CTPA. The ELOPE cohort study reported the frequency of pulmonary perfusion defects or residual vascular obstruction assessed by both CTPA and Q' scan [25, 26]. In pooled analyses, patients with pulmonary perfusion defects or residual vascular obstruction had an increased odds of having persistent symptoms during follow-up (when including the CTPA data of the ELOPE cohort: OR 2.12, 95% CI 1.63–2.75; I^2=32% (figure 2); when including the Q' scan data of the ELOPE cohort: OR 2.15, 95% CI 1.66–2.78; I^2=0%, τ=0 (supplementary figure S3).

A subgroup analysis based on the modality of imaging used showed comparable odds ratios, although for CTPA the 95% confidence intervals included 1.0 (V'/Q' or Q' scan 2.03, 95% CI 1.54–2.68; I^2=9%; CTPA 1.80, 95% CI 0.59–5.49; I^2=67%; supplementary figure S5). When performing a subgroup analysis based on the timing of imaging after acute PE, pulmonary perfusion defects or residual vascular obstruction were associated with persistent symptoms at 3 months (OR 2.04, 95% CI 1.25–3.30; I^2=0%, τ=0), 6 months (OR 2.44, 95% CI 1.33–4.50; I^2=0%, τ=0) and 12 months (OR 2.00, 95% CI 0.69–5.77; I^2=70%; supplementary figure S6).

When pooling data separately for prospective *versus* retrospective studies, we found comparable results (supplementary figure S7). Funnel plot analysis illustrated asymmetry, which was most likely due to between-study heterogeneity, but without a clear indication of publication bias (supplementary figure S4).

Quality of life and functional tests

Three studies reported QoL, using three different tools: the Pulmonary Embolism Quality of Life questionnaire, EuroQol Five-Dimension questionnaire and 36-item Short-Form Health Survey (table 2) [16, 23, 27]. The heterogeneity between assessment of QoL was too large to pool data across studies. However, when looking at the QoL outcomes per individual study, we observed no clear difference between QoL in patients with pulmonary perfusion defects or residual vascular obstruction *versus* in patients with a normal V'/Q'-scan/CTPA.

Three types of functional tests were reported: CPET in two studies [21, 25, 26], ISWT in one study [23] and 6MWT in three studies [17, 27, 28]. For CPET outcomes, the percentage of predicted V'_{O_2} at maximal exercise (V'_{O_2peak}) reported was higher in patients with pulmonary perfusion defects or residual vascular obstruction in one study, but the difference was not significant, while another study reported significantly lower V'_{O_2peak} (table 2) [21, 25, 26]. Patients with pulmonary perfusion defects or residual vascular obstruction had a higher V'_E/V'_{CO_2} ratio compared to patients with a normal V'/Q' scan/CTPA, reflecting decreased ventilatory efficiency due to increased dead space ventilation (table 2) [21]. Patients with pulmonary perfusion defects or residual vascular obstruction had a lower ISWT compared to patients with a normal V'/Q' scan/CTPA (table 2) [23]. We observed no difference in the outcome of 6MWT between patients with pulmonary perfusion defects or residual vascular obstruction and patients with a normal V'/Q' scan/CTPA (pooled standardised mean difference −0.20, 95% CI −1.05–0.65; I^2=74%; supplementary figure S8).

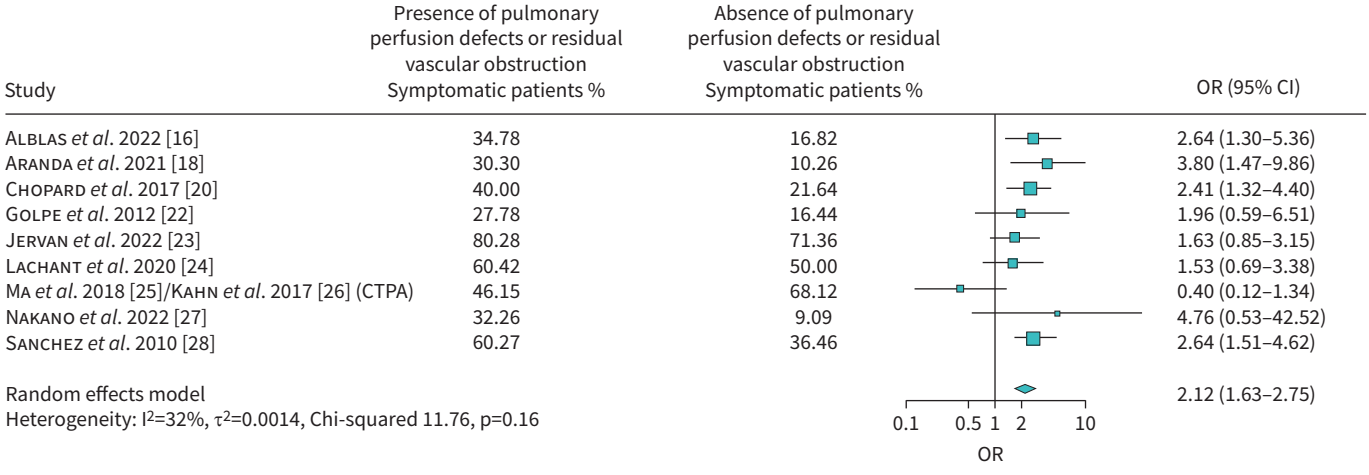

FIGURE 2 Presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms during follow-up. CTPA: computed tomography pulmonary angiogram.

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TABLE 2 quality of life and functional test in patients with or without pulmonary perfusion defects or residual vascular obstruction

First author, year [reference]	Quality-of-life assessment	Functional tests	Patients with pulmonary perfusion defects or residual vascular obstruction	Patients without pulmonary perfusion defects or residual vascular obstruction	p-value
Alblas, 2022 [16]	PEmb-QoL[¶] (%)		16 (7.4–38)	13 (4.5–32)	0.424
Jervan, 2022 [23]	EQ-5D visual analogue scale (0–100%)		65 (50–80)	71 (60–80)	0.02
	EQ-5D index value		0.94 (0.80–1.0)	0.92 (0.81–1.0)	0.86
Nakano, 2022 [27]	HRQoL (SF-36) Physical component summary Mental component summary Role/social component summary		47.4 (38.0–53.7) 59.8 (50.7–65.6) 54.3 (45.6–57.0)	42.5 (29.4–48.0) 53.8 (45.9–55.4) 57.9 (53.6–64.3)	Not reported
Amato, 2017 [17]		6MWT (m)	504±99	486±142	Not reported
George, 2015 [21]		$V'_{O_{2peak}}$ (% predicted) V'_E/V'_{CO_2} (ratio)	80.26±3.36 31.34±1.07	99.93±8.77 27.19±0.74	<0.05 <0.005
Jervan, 2022[#] [23]		ISWT (m)	660	805	0.01
Ma, 2018 [25]/Kahn, 2017 [26] (CTPA)		$V'_{O_{2peak}}$ (% predicted)	95.7	81.8	0.098
Nakano, 2022 [27]		6MWT (m)	454±112	480±145	Not reported
Sanchez, 2010 [28]		6MWT (m)	374±122	427±99	0.004

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. CTPA: computed tomography pulmonary angiogram; PEmb-QoL: Pulmonary Embolism Quality of Life questionnaire; EQ-5D: EuroQol Five-Dimension questionnaire; HRQoL: health-related quality of life; SF-36: 36-item Short-Form Health Survey; 6MWT: 6-min walk test; V'_{O_2peak}: oxygen consumption at maximal exercise; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; ISWT: incremental shuttle walk test. [#]: abstract only; [¶]: at 5 years; (a higher number presents lower quality of life).

Discussion

In the studies included in this meta-analysis, 34% of acute PE patients had pulmonary perfusion defects or residual vascular obstruction during follow-up. Among patients with pulmonary perfusion defects or residual vascular obstruction, 48% reported persistent symptoms during follow-up, indicating incomplete recovery, compared to 34% of patients with a normal V'/Q' scan/CTPA. Our data showed a moderate association between presence of pulmonary perfusion defects or residual vascular obstruction and incomplete recovery: patients with pulmonary perfusion defects or residual vascular obstruction had two-fold increased odds for persistent symptoms, which was irrespective of timing of imaging during follow-up or imaging modality.

Our findings do not clearly support a causal relation between persistent clots visualised by pulmonary perfusion defects on V'/Q' scan or residual vascular obstruction on CTPA (in patients without CTEPH) and incomplete recovery for several reasons. First, half the patients with pulmonary perfusion defects or residual vascular obstruction had completely recovered (*i.e.* were asymptomatic). Second, most of the included studies did not subject the study patients to systematic screening for CTEPH. In CTEPH, patients with persistent clots have increased pulmonary artery pressure due to an increase in pulmonary vascular resistance caused in part by intravascular fibrotic obstruction and in part by arteriopathy [6, 7]. In CTEPH a causal relationship between persistent clots and symptoms has been demonstrated, as treatment focusing on the removal of clots results in an improvement in pulmonary artery pressure resulting in an improvement of symptoms [32]. For daily practice it is important to understand the association between persistent clots, visualised by presence of pulmonary perfusion defects or residual vascular obstruction, and incomplete recovery in patients who do not have CTEPH, as the causality between and the clinical implication of having persistent clots in patients without CTEPH remains unknown. The possible involvement of CTEPH patients in the pooled odds ratio may have led to an overestimation of the odds ratio. Third, it could be argued that the expected relationship between pulmonary perfusion defects or residual vascular obstruction and altered haemodynamics (as measured by CPET) would be stronger than the relationship between pulmonary perfusion defects or residual vascular obstruction and persistent symptoms. After all, the causal mechanism would be that pulmonary perfusion defects or residual vascular obstruction as a surrogate marker for residual thrombi lead to altered haemodynamics, causing persistent symptoms. Of note, patients with chronic thrombi might less frequently report the presence of persistent symptoms, as they may have become "used" to these symptoms. However, haemodynamic changes are not affected by the patient's perspective. Importantly, the studies included in this systematic review did not find a clear and consistent association between presence of pulmonary perfusion defects or residual vascular obstruction and quality of life or exercise capacity. Specifically, the ELOPE cohort study showed no differences in functional limitation in patients with pulmonary perfusion defects or residual vascular obstruction and patients with a normal Q' scan/CTPA at 1-year follow-up. In this prospective follow-up study, having pulmonary perfusion defects or residual vascular obstruction was not associated with a decreased V'_{O_2} peak measured using CPET [26]. Finally, if a causal relationship were to be present, it is to be expected that patients receiving reperfusion therapy may show better recovery than those who received anticoagulation alone. However, the randomised Pulmonary Embolism Thrombolysis [33] trial showed that primary reperfusion by full-dose systemic thrombolysis did not improve long-term outcomes: among 709 patients who had long-term follow-up, there was no difference in the proportion of patients with persistent symptoms, the degree of functional limitations or echocardiographic measures between patients who received tenecteplase *versus* placebo.

What are the clinical implications of our findings? Current guidelines suggest to first perform echocardiography in PE survivors with persistent symptoms to rule out CTEPH, as minimising the diagnostic delay of CTEPH results in improved outcomes [6, 7, 34]. In patients without CTEPH, CPET can be considered to evaluate potential causes of persistent symptoms. CTEPH or CTEPD without PH can be expected if there is an increase dead space volume/tidal volume ratio or insufficient increase in oxygen pulse during exercise (reflecting poor stroke volume augmentation) on CPET [35]. Only in cases of suspected CTEPH or CTEPD without PH (based on clinical presentation as well as the results of echocardiography and/or CPET), imaging tests to qualify and quantify persistent vascular obstruction and perfusion defects should be performed, to avoid finding nonrelevant residual thrombi and thus "false positive" results for which there is no treatment option, and to avoid unnecessary costs and exposure to radiation and contrast media. Our findings do not give any evidence to deviate from these recommendations and therefore do not suggest routinely repeating imaging tests in (symptomatic) PE survivors, as causality and clinical implication of presence of pulmonary perfusion defects or residual vascular obstruction in acute PE patients without CTEPH or CTEPD without PH remains unclear. Additionally, in recent years, there is an increasing focus on advanced reperfusion techniques to improve the short-term outcomes of PE care, both in high- and intermediate-risk PE patients. However, improved

short-term outcomes of catheter-directed treatment in these patients as well as benefits for long-term prognosis remain to be proven. Future randomised studies on advanced reperfusion treatment of acute PE should incorporate dedicated long-term follow-up, to inform decision making in the acute setting [36, 37].

The strengths of this study are the large cohort of patients studied, as well as the inclusion of unpublished data from the selected studies. Moreover, we found a consistent association between presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms with low to moderate heterogeneity in most analyses. This study has some limitations: first, there is heterogeneity in the definition of presence of persistent symptoms across the included studies as almost all studies used a different definition. In addition, there is heterogeneity in the definition of pulmonary perfusion defects or residual vascular obstruction. Three types of imaging techniques have been used: CTPA, V'/Q' scan and Q' scan. Studies using $(V')/Q'$ scans evaluated persistent perfusion defects and studies using CTPA evaluated residual vascular obstruction. It should be noted that persistent perfusion defects might also occur in absence of a thrombus. When comparing CTPA to V'/Q' scan, persistent perfusion defects are more frequently identified by V'/Q' scan than residual vascular obstruction by CTPA [38]. This is also confirmed in our study: $(V')/Q'$ scan identified 38% of the patients as having persistent perfusion defects during follow-up, while this was only 29% when using CTPA to identify residual vascular obstruction. Furthermore, the residual vascular obstruction assessed by CTPA was mostly defined as persistent thrombi. Other signs of chronic thrombi such as arterial retraction or intravascular webs might not have been included [39, 40]. Even so, we observed no clear difference in the association between presence of pulmonary perfusion defects or residual vascular obstruction and persistent symptoms when comparing CTPA to $(V')/Q'$ scan. Besides different imaging techniques, different proportions of vascular obstruction were used, but mostly presence of one (small) perfusion defect or vascular obstruction was sufficient to classify as presence of pulmonary perfusion defects or residual vascular obstruction. We had no data on the severity of pulmonary perfusion defects or residual vascular obstruction; smaller defects leading to no symptoms could have diluted the association. Due to the lack of data we could not investigate a dose–response association to support a causal association between pulmonary perfusion defects or residual vascular obstruction and recovery. Also, as we did not have patient-level imaging data available, we could not further investigate thrombus morphology or thrombus resolution relative to thrombotic burden at index PE in relation to recovery. Second, patients with CTEPH were not systematically excluded, resulting in possible overestimating of the association between pulmonary perfusion defects or residual vascular obstruction and symptoms in patients without CTEPH. Third, despite our efforts, it was not possible to correct for potential confounders such as index PE severity, since data were lacking. Finally, studies included in our meta-analysis were of moderate quality, as only one study included in our meta-analysis had a low risk of bias.

In conclusion, we found increased odds of persistent symptoms in patients with pulmonary perfusion defects or residual vascular obstruction after acute PE, compared to those with a normal V'/Q' scan/CTPA. However, our meta-analysis of observational studies cannot support any causal relationship. The fact that presence of pulmonary perfusion defects or residual vascular obstruction displayed varying degrees of association with quality of life and functional tests indicates that the clinical and functional recovery after PE is dependent on many factors, which may possibly include thrombus resolution.

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