



Predictors of residual pulmonary vascular obstruction after pulmonary embolism: Results from a prospective cohort study

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Abstract

Background: We aimed to determine the prevalence of residual pulmonary vascular obstruction (RPVO) after symptomatic pulmonary embolism (PE) and to identify risk factors for RPVO.

Methods: On the basis of a prospective cohort of patients with a documented symptomatic venous thromboembolism, we included patients who had an acute PE and underwent a ventilation/perfusion lung scan at 3 to 24 months during the follow-up after PE. RPVO score was assessed for each patient. Initial pulmonary vascular obstruction at PE diagnosis was also assessed when available. Univariable and multivariable analyses were performed with preselected data to identify predictors for persistent defect defined as $RPVO \geq 5\%$.

Results: Among the 537 included patients, 278 (51.8%) had $RPVO \geq 5\%$, and 191 (35.6%) had $RPVO \geq 10\%$. In primary multivariate analysis on overall population, age ≥ 65 years (Odds Ratio [OR] 2.25, 95%CI, 1.45-3.52) and chronic respiratory failure (OR 3.19, 95%CI, 1.22-10.04) were independent predictors of $RPVO \geq 5\%$. In secondary multivariate analysis restricted to 256 patients with available initial pulmonary vascular obstruction score at index PE (IPVO), age ≥ 65 years (OR 2.78, 95%CI, 1.41-5.53), unprovoked PE (OR 2.11, 95%CI, 1.11-4.07) and $IPVO \geq 20\%$ (OR 2.94, 95%CI, 1.68-5.20) were found to be independent risk factors for $RVPO \geq 5\%$.

Conclusion: In this selected population of patients with an acute PE, age ≥ 65 years, unprovoked PE and $IPVO \geq 20\%$ at PE diagnosis appeared to be risk factors for residual pulmonary vascular obstruction measured at three to 24 months.

Keywords:

Pulmonary embolism, Ventilation/Perfusion lung scan, residual pulmonary vascular obstruction, follow-up

Introduction

Pulmonary embolism (PE) is the most severe clinical presentation of venous thromboembolism (VTE).¹⁻³ The main complications are recurrent VTE, fatal and non-fatal, and chronic thromboembolic pulmonary hypertension (CTEPH). Beyond the initial three to six months of anticoagulation, anticoagulant treatment is either pursued or not, based on the presence or the absence of clinical risk factors. When PE is provoked by a major transient risk factor (e.g. surgery), the risk of recurrent VTE is low ($\leq 3\%$) and anticoagulation should not be prolonged.¹ Conversely, in the absence of major transient risk factors, the risk of recurrence is high (no identifiable clinical risk factors) or intermediate (presence of minor risk factors). Several randomized trials comparing different anticoagulation durations have demonstrated that extending anticoagulation up to 1 or 2 years was effective in these patients, but the benefit was lost after stopping anticoagulation.⁴⁻⁶ Thus, current guidelines recommend indefinite anticoagulation.^{1,7} However, as the risk of bleeding might outweigh the risk of recurrent VTE over time, it remains uncertain whose patients will really benefit from indefinite anticoagulation. Hence, identification of predictors for recurrence is a major issue.^{1,5-9}

Recently, several studies found that residual pulmonary vascular obstruction (RPVO), assessed by ventilation/perfusion (V/Q) lung scan, was an independent predictor of recurrent VTE.⁹⁻¹³ However, V/Q lung scan is a costly examination, with unequal accessibility, and the radiation exposure remains to be considered. Consequently, establishing criteria for targeting patients at increased risk of RPVO, who may therefore benefit from a V/Q lung scan in the follow-up of a PE, is clinically relevant.

In a recent sub-analysis of the PADIS-PE randomized trial, we found that age ≥ 65 years, chronic respiratory disease, initial pulmonary vascular obstruction (IPVO) at PE diagnosis and elevated Factor VIII were independent predictors of RPVO $\geq 5\%$ in a population

of unprovoked PE.¹⁴ Another study found that age and unprovoked PE were risk factor of RPVO.¹⁵ In this prospective cohort study, we aimed to determine the prevalence of RPVO on V/Q lung scans performed at 3 to 24 months during the follow-up after an acute episode of PE, provoked or not. Secondary objective was to identify predictors for RPVO.

Methods

Cohort Design and population

This study is based on our previously described single-center prospective cohort of patients with VTE.¹⁶ Since January 1st 1992, consecutive patients who had been hospitalized or referred to Brest University Hospital outpatient VTE clinic for management of symptomatic VTE were included if they were 18 years old or older and were able to sign the written consent. After inclusion, all cases were followed up without scheduled stopping date. Patients were managed according to current guidelines and physician's experience.

Identification of study population

In the present analysis, patients were eligible if they had a symptomatic acute PE (with or without associated DVT) and if they underwent a planned V/Q lung scan at 3 to 24 months (90 to 745 days) during the follow-up after PE diagnosis. The diagnosis of index PE was based on objective, standardized and validated criteria.^{1,7} Symptomatic PE was confirmed if there was: (i) a high clinical probability and a high-probability ventilation-perfusion lung scan according to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria; or (ii) a positive computed tomography pulmonary angiography (CTPA) showing a central filling defect outlined by contrast material, or a complete occlusion in a segmental or more proximal pulmonary artery; or (iii) a proximal DVT evidenced by ultrasonography in a patient with symptoms of PE.

To identify all the subjects who underwent planar V/Q lung scan during their follow-up as intended, a search by the ICD-10 (International Classification of Diseases, tenth edition) code and keywords was conducted in the Brest University Hospital database and crossed with our cohort study database. All imaging tests were then collected from medical records, and, when available, were printed to establish the RPVO retrospectively.

Patients were excluded if they had: (i) an evaluation at 3 to 24 months with tomography V/Q lung scintigraphy, V/Q single photon emission computed tomography (SPECT) or CTPA instead of planar V/Q lung scan; (ii) a history of pneumonectomy; (iii) a diagnosis of recurrent PE at the time of V/Q lung scan assessment at 3 to 24 months; or (iiii) if the imaging was not available for printing.

Outcome

The main outcome was to determine the prevalence of RPVO $\geq 5\%$ on V/Q lung scan performed 3 to 24 months after PE diagnosis. The cut-off of 5% was based on our previously published post-hoc analysis of the PADIS PE trial.⁹ RPVO was calculated for each perfusion scan by an experienced and three independent nuclear medicine physicians (P.R., PY.LR. PY. S.), blinded to patients' characteristics and using the score previously described by Meyer *et al* (see supplement data).¹⁷

For the main outcome, RPVO was assessed whether a CTEPH was diagnosed or not at the time of follow-up evaluation by V/Q lung scan. In our cohort, all patients with a suspicion of CTEPH were investigated according to international recommendations and CTEPH was confirmed by a reference team specialized in pulmonary hypertension. In a sensitivity analysis, patients with CTEPH were excluded (see statistic section).

The identification of potential risk factors for the primary outcome (RPVO $\geq 5\%$ with or without CTEPH) was based on the following predefined and prospectively collected data at the time of index PE and during follow-up: demographics, risk factors for VTE, comorbid

conditions and therapeutic management of VTE. Chronic respiratory failure was defined by oxygen partial pressure inferior to 60 mmHg on two occasions on arterial blood gaz. Index PE was classified as provoked by a major transient risk factor in the presence of at least one of the following: surgery, hospitalization longer than 3 days, leg trauma with immobilization (including plaster cast), estrogen-containing contraception, hormone replacement therapy or treatment for assisted reproduction, pregnancy or postpartum within the past 3 months and active cancer at the time of PE diagnosis. VTE was considered as unprovoked in the absence of these risk factors.¹

In addition, when available, initial pulmonary vascular obstruction (IPVO) score at index PE was calculated either on CTPA imaging (using Qanadli score) (see supplement data)¹⁸ or on V/Q lung scan (using Meyer score)¹⁷.

Statistical methods

The main analysis (first model) was conducted on the whole population included in the study where RPVO was available. A secondary analysis (second model) was conducted only on patients whose RPVO and IPVO were available. Lastly, two sensitivity analyses were performed: (1) after exclusion of patients with a documented CTEPH; and (2) on the study population for the risk factors of $RPVO \geq 10\%$. For each model, an univariable analysis was performed in order to evaluate the association between each potential predictor and the occurrence of RPVO measured at 3 to 24 months after PE diagnosis. Proportion and p-values were calculated for each variable, using Chi-squared test or Student test when appropriate.

Variables were then included in multivariable models if they respected the following criteria: (1) a p-value < 0.20 in univariable analysis, (2) a prevalence $\geq 3\%$, and (3) a clinical relevance. Discriminant threshold values of continuous variables were established based on clinical relevance and previous studies on RPVO, age and BMI.^{9,14} For IPVO, it was based on the calculation of area under the curve (AUC) of receiver operating curve (ROC) and Youden

index calculation. The multivariable analyses were then conducted using a logistic regression model. All tests were two-sided and a p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using the R-studio software (R Development Core Team (2005). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: <http://www.R-project.org>.)

Results

Patients

On July 31st 2018, among the 5449 included patients with VTE in the Brest cohort, 3056 had PE, of whom pulmonary imaging test during follow-up was available in 674 PE patients. Among those, 137 presented one or more exclusion criteria (Figure 1): 10 had CTPA and 55 had SPECT instead of V/Q lung scan during follow-up, 18 were recurrent PE at the time of V/Q lung scan during follow-up, 4 had pneumonectomy and 50 V/Q lung scans were not available for RPVO assessment. Finally, 537 patients were included in the main study analysis. For the secondary analysis, IPVO scores at the time of PE diagnosis were available for 256 patients.

Baseline characteristics of population and index PE (Table 1)

Mean (SD) age of the study population was 60.6 (16.9) years; women were 292 (54.4%).

Index PE was provoked in 182 patients (33.9%), in whom 30 had an active cancer and 152 had at least one major transient risk factor. At the acute phase of PE, 9 patients had thrombolysis (1.7%), initial anticoagulant therapy was direct oral anticoagulant in 82 (15.3%), vitamin K antagonist (VKA) (with initial heparin) in 420 (78.7%) and low-molecular weight heparin alone in 32 (6.0%). Regarding anticoagulation duration, 525 patients (98.3%) received anticoagulation for at least 3 months and 405 (75.8%) for at least 6 months. 419

patients (78.5%) were still on anticoagulant treatment at V/Q lung scan date, whereas 115 (21.5%) had stopped it. In the 256 patients with available IPVO at the time of PE diagnosis, IPVO was established on CTPA for 49 (18.4%) patients and on V/Q lung scans for 207 (81.6%).

Residual pulmonary vascular obstruction (RPVO) (Table 3)

Mean (SD) time from index PE to lung scan evaluation was 8.1 (4.3) months. Median (IQR) RPVO was 5.00% (0.00 – 15.75). During follow-up, 278 patients (51.8%) had $RPVO \geq 5\%$ (main outcome) and 191 (35.6%) had $RPVO \geq 10\%$. CTEPH was diagnosed in 17 patients (3.3%) through follow-up.

Assessment of predictors for $RPVO \geq 5\%$ 3 to 24 months from PE (primary outcome)

In the univariable analysis on the whole population (n=537), age and chronic respiratory failure were associated with a significant increased risk of $RPVO \geq 5\%$ (Table 1), which was confirmed in multivariable analysis (OR 2.25 [95%CI, 1.45-3.52] and OR 3.19 [95%CI, 1.22-10.04], respectively) (Table 3).

Secondary outcome and sensitivity analyses

In the 256 patients with available IPVO at the time of PE diagnosis, mean (SD) IPVO and RPVO were 30.9% (21.7) and 10.5% (13.7), respectively ($p < 0.001$). ROC analysis yielded the most discriminant value of IPVO according to $RPVO \geq 5\%$ at 20% (AUC: 0.67, 95%CI, 0.61-0.74) (Figure 2). In univariable analysis, IPVO was found to be a significant risk factor for $RPVO \geq 5\%$ ($p < 0.001$) (Table 1). In multivariable analysis, age ≥ 65 years, unprovoked PE and $IPVO \geq 20\%$ were found to be independent predictors for $RPVO \geq 5\%$ (OR 2.78 [95%CI, 1.41-5.53], OR 2.11 [95% CI, 1.11-4.07] and OR 2.94 [95% CI, 1.68-5.20], respectively) (Table 3).

Sensitivity analyses in which the 17 patients with CTEPH were excluded or outcome was defined by $RPVO \geq 10\%$ were consistent with our main and secondary analyses (see supplement data).

Discussion

In this large prospective study, based on 537 patients who had suffered from a symptomatic acute PE and who underwent a lung scan evaluation at 3 to 24 months during follow-up for reason other than recurrent PE, we found that age ≥ 65 years and chronic respiratory failure were independent predictors of persistent pulmonary vascular obstruction, as defined by $RPVO \geq 5\%$. In the subgroup of 256 patients in which IPVO was available, age ≥ 65 years, $IPVO \geq 20\%$ and unprovoked PE were independent predictors of RPVO. These results were consistent across sensitivity analyses.

During a mean follow-up period of 8 months for acute PE, 51.8% of patients had $RPVO \geq 5\%$ and 35.6% had $RPVO \geq 10\%$ using planar V/Q lung scan. Despite heterogeneity in literature regarding the type of imaging assessment, time from PE diagnosis, population's characteristics or RPVO definition, this prevalence of perfusion sequelae is consistent with other studies that used planar V/Q lung scan, that is more accurate than CT scan for pulmonary vascular obstruction assessment.^{10,11,14,15,19-23} We chose a threshold value of 5% for RPVO based on previous studies demonstrating that this cutoff was the most discriminant for predicting the risk of recurrent PE.¹⁴ This cut-off has anatomical relevance as it reflects vascular obstruction of one pulmonary segment.^{9,12,24}

Among potential predictors for $RPVO \geq 5\%$, we confirmed that age of 65 years or older was the strongest, in the main as well as in the secondary and sensitivity analyses. Several studies reported age as a risk factor for RPVO, which is confirmed by our results.^{10,11,14,15,25} One potential explanation is that advancing age is correlated with more important inflammation as well as pulmonary and vascular deterioration.^{26,27}

1 The second important finding is the observation of a 3-fold increased risk of RPVO
2 $\geq 5\%$ in patients having IPVO $\geq 20\%$ at PE diagnosis. This was observed on a subgroup of
3 patients whose IPVO was available and a selection bias leading to over- or under-estimation
4 could not be excluded. However, the baseline characteristics of this sample were very similar
5 to that of the overall study population, especially regarding comorbid conditions, PE risk
6 factors, initial management and prevalence of RPVO (supplementary Table S1), which is in
7 agreement with other studies^{10,14,15}. In addition, the 20% cutoff of IPVO, yielded by ROC
8 curve analysis, is concordant with our previous study showing that 25% is the most
9 discriminant threshold value.¹⁴

10 Interestingly, we observed a trend towards an increased risk of RPVO $\geq 5\%$ in patients
11 with unprovoked PE as compared to those with PE provoked by a major transient risk factor.
12 This result was also statistically significant when the analysis was restricted to patients with
13 available IPVO at the time of PE diagnosis. Although this association was weak, it is
14 supported by clinical and biochemical data. In a large prospective cohort study of 647 patients
15 with acute PE, Pesavento *et al* found a statistically significant association between
16 unprovoked PE and RPVO assessed by perfusion lung scan 6 months after an acute PE.⁽¹¹⁾ In
17 addition, there is evidence that patients with unprovoked VTE are more likely to have an
18 underlying thrombophilia, which might increase the risk of unresolved PE.²⁸ Nevertheless,
19 further trials are needed to confirm this observation.

20 In contrast to others, some potential risk factors were not associated with RPVO. First,
21 results about chronic respiratory diseases were not consistent across models. In our
22 prospective cohort, chronic pulmonary disease was actually defined as chronic respiratory
23 failure, which does not include common respiratory conditions such as non-severe COPD or
24 asthma. In addition, the prevalence of this condition was very low. However, when excluding
25 patients with chronic respiratory failure, results on other predictors were unchanged (data not

shown). Furthermore, the impact of chronic respiratory disease on RPVO might not be negligible, not only because of the functional impairment of the respiratory system but also by intrinsic characteristics. In our large double-blind randomized trial PADIS-PE, we previously found that chronic respiratory disease was an independent predictor for RPVO.¹⁴ Indeed, several publications suggest that moderate to severe COPD is associated with an increased thrombotic risk due to increased levels of proinflammatory cytokines, notably interleukin-6, that increase thrombogenicity of endothelial surface and coagulation cascade induction.³⁰⁻³³ Second, personal history of previous PE and presence of cancer were not associated with an increased risk of RPVO. This is likely due to a selection bias as patients with such past history may have been proposed more often indefinite anticoagulation.

Our findings may have important implications for daily clinical practice and for future clinical research studies. The underlying question of the study was to identify which patients would benefit from a V/Q lung scan during their follow-up after an acute episode of PE. This imaging test may have an important weight, when faced both to the question of optimal anticoagulation duration and follow-up modalities. First, there is evidence that RPVO is an important predictor of recurrent VTE.⁹⁻¹² Second, V/Q lung scan is a key test for the detection and the diagnosis of CTEPH, in association with transthoracic echocardiography and right heart catheterization. Third, it has been shown that about one third of patients with an acute PE will have persistent dyspnea and physical performances and quality of life alteration, mostly related to residual pulmonary vascular obstruction.^{15,29} In this setting, recent international guidelines emphasized on the necessity to provide an integrated model of patient care including searching for the entire spectrum of post-PE symptoms and functional limitations.^{1,4, 34-37} Thus, screening for RPVO using lung scan reassessment around 3 to 6 months from an acute PE may be part of risk/benefit balance for continuing anticoagulation and may detect patients who require a close follow-up and complementary tests to detect

1 chronic thromboembolic disease or CTEPH. However, V/Q lung scan cannot be proposed to
2 every patient after PE, for reasons such as cost, radiation exposure or accessibility.⁷ Although
3 validation studies are needed, particularly in patients with persistent dyspnea, our results,
4 based on a selected population, provide evidence to help identifying patients at risk of RPVO
5 in clinical practice.

6 Our work has several strengths: (1) it is one of the largest prospective cohort on this
7 scientific area; (2) enrolment of patients was prospective with objectively diagnosed and
8 adjudicated symptomatic PE and long term follow-up; (3) the main outcome (i.e. RPVO) was
9 measured by experienced physicians blinded to patients' characteristics; and (4), results were
10 consistent across models and sensitivity analyses.

11 Some limitations should be underlined. First, the inclusion method of the overall
12 population, based on patients who underwent V/Q lung scan in their follow-up, might have
13 led to selection bias. Hence, V/Q lung scan for the screening of RPVO may have been used
14 mostly in severe patients or in case of persistent dyspnea despite anticoagulation months after
15 an acute PE. However, baseline characteristics, as well as results, were consistent with other
16 studies in which V/Q lung scan was systematically performed for every patient, including a
17 randomized trial.^{11,14,15} Second, one could argue that inclusion of CTEPH patients in the
18 analysis might invalid conclusions because of a potentially different pathophysiology with
19 chronic thrombo-embolic disease. However, in practice, V/Q lung scan at distance of acute
20 PE is often performed in patients who remain symptomatic despite anticoagulation, whether
21 CTEPH is suspected or not. Furthermore, proven CTEPH diagnoses represented a small
22 sample of our population (17 patients (3.3%)) and the impact was negligible: when excluding
23 patients with documented CTEPH, the results were unchanged and consistent across all
24 statistical models (Supplementary Table S2-S3, Figure S1). Finally, we were unable to

1 include biological data in the analysis, such as elevated Factor VIII or antiphospholipid
2 antibodies.^{14,37}

3 **CONCLUSION**

4 In summary, in this selected population of patients with an acute PE, we found that
5 age ≥ 65 year and IPVO $\geq 20\%$ at diagnosis were independent predictors of RPVO $\geq 5\%$,
6 assessed with V/Q lung scan performed between 3 to 24 months after symptomatic PE. We
7 also observed a trend towards an increased risk of RPVO in patients with unprovoked PE.
8 These results reinforce previous findings and have the potential to help clinicians targeting
9 patients at risk of RPVO in the follow-up of an acute PE. However, it remains to be
10 confirmed in dedicated clinical trials.

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19

Table 1. Baseline characteristics and risk factors for residual pulmonary vascular obstruction $\geq 5\%$ in univariable analysis

	Overall N =537
Population characteristics	
Age	60.62 (16.89)
Age	
<50 years	146 (27.2)
50-65 years	142 (26.4)
≥ 65 years	249 (46.4)
Female	292 (54.4)
BMI (NA=10)	27.81 (5.85)
BMI ≥ 30 (NA=10)	141 (26.8)
Diagnostic method of pulmonary embolism	
CTPA	375 (69.9)
V/Q lung scan	150 (27.9)
Proximal deep vein thrombosis on CUS	12 (2.2)
Characteristics of pulmonary embolism	
Unprovoked	355 (66.1)
Provoked by active cancer	30 (5.6)
Provoked by a major transient factor	152 (28.3)
Hospitalization	68 (12.7)
Surgery <3 months	40 (7.4)
Lower limb cast immobilization	8 (1.5)
Pregnancy*	4 (1.4)
Postpartum *	5 (1.7)
Oral contraception with estrogen *	53 (18.2)
Hormone replacement therapy *	9 (3.1)
Therapy for assisted reproduction *	1 (0.3)
Associated DVT	263 (49.0)
IPVO (2nd model, N=256)	
IPVO $\geq 20\%$, n (%)	158 (61.7)
IPVO, mean (SD)	30.9 (21.7)
IPVO on V/Q lung scan (N=49), mean (SD)	30.2 (19.1)
IPVO on CTPA (N=207), mean (SD)	31.1 (22.2)
Medical history and conditions	
History of cancer	37 (6.9)
Congestive heart failure	12 (2.2)
Coronary heart disease (NA=2)	20 (3.7)
Atrial fibrillation (NA=7)	8 (1.5)
Chronic respiratory failure	24 (4.5)
Stroke	14 (2.6)
History of VTE (PE and/or DVT)	72 (13.4)
History of PE	20 (3.7)
Therapeutics	
Thrombolytic therapy (NA=7)	9 (1.7)
Initial anticoagulant therapy (NA=2)	
DOAC	82 (15.3)
VKA [#]	420 (78.7)
Heparin only (LMWH or UFH or fondaparinux)	32 (6.0)
Duration of anticoagulant therapy (NA=3)	
≥ 3 months	525 (98.3)
≥ 6 months	405 (75.8)

Data are presented as n (%) or mean (Standard Deviation, SD). Number of missing data are reported as NA: Not available

BMI: Body mass index; CTPA: computed tomography pulmonary angiography; V/Q lung scan: ventilation perfusion lung scan; CUS: compression ultrasound IPVO: initial pulmonary vascular obstruction; VTE: Venous thromboembolism; PE: Pulmonary embolism; DVT: Deep vein thrombosis; DOAC: Direct oral anticoagulant; VKA: Vitamin K antagonists; LMWH: Low molecular weight heparin, UFH: Unfractionated heparin
A heparin treatment was initiated concomitantly to VKA until reaching targeted International Randomized Ratio

* % related to number of females

1 **Table 2. Residual pulmonary vascular obstruction**

Time from PE to lung scan (months), median (IQR))	6.36 (5.78 – 9.39)
RPVO (%), median (IQR)	5.00 (0.00 – 15.8)
RPVO $\geq 5\%$, n (%)	278 (51.8)
RPVO $\geq 10\%$, n (%)	191 (35.6)
CTEPH n (%) (NA=16/537)	17 (3.3)

2 PE: Pulmonary embolism; IQR: Interquartile range; RPVO: residual pulmonary vascular obstruction; CTEPH:
3 Chronic thromboembolic pulmonary hypertension
4 Number of missing data are reported as NA: Not available
5

Table 3. Risk factors for residual pulmonary vascular obstruction $\geq 5\%$ in univariable analysis

	RPVO $<5\%$ N=259	RPVO $\geq 5\%$ N=278	p-value
Population characteristics			
Age	56.13 (16.58)	64.80 (16.12)	$<0.001^+$
Age			
<50 years	89 (34.4)	57 (20.5)	
50-65 years	82 (31.7)	60 (21.6)	$<0.001^+$
≥ 65 years	88 (34.0)	161 (57.9)	
Female	136 (52.5)	156 (56.1)	0.45
BMI (NA=10)	27.85 (5.99)	27.77 (5.72)	0.88
BMI ≥ 30 (NA=10)	69 (27.1)	72 (26.5)	0.96
Characteristics of pulmonary embolism			
Unprovoked	160 (61.8)	195 (70.1)	
Provoked by active cancer	13 (5.0)	17 (6.1)	$0.051^{+\S}$
Provoked by a major transient factor	86 (33.2)	66 (23.7)	
Hospitalization	30 (11.6)	38 (13.7)	0.54
Surgery <3 months	26 (10.0)	14 (5.0)	0.041
Lower limb cast immobilization	5 (1.9)	3 (1.1)	0.65
Pregnancy*	4 (2.9)	0 (0.0)	0.098
Postpartum *	5 (3.7)	0 (0.0)	0.050
Oral contraception with estrogen *	33 (24.3)	20 (12.8)	0.017
Hormone replacement therapy *	7 (5.1)	2 (1.3)	0.12
Therapy for assisted reproduction *	1 (0.7)	0 (0)	0.99
Associated DVT	120 (46.3)	143 (51.4)	0.27
IPVO (2nd model, N=256)			
IPVO $\geq 20\%$, n (%)	54 (46.2)	104 (74.8)	$<0.001^+$
Medical history and conditions			
History of cancer	14 (5.4)	23 (8.3)	0.25
Congestive heart failure	2 (0.8)	10 (3.6)	0.055^+
Coronary heart disease (NA=2)	9 (3.5)	11 (4.0)	0.95
Atrial fibrillation (NA=7)	3 (1.2)	5 (1.8)	0.78
Chronic respiratory failure	5 (1.9)	19 (6.8)	0.011^+
Stroke	4 (1.5)	10 (3.6)	0.22
History of VTE (PE and/or DVT)	27 (10.4)	45 (16.2)	0.067^+
History of PE	8 (3.1)	12 (4.3)	0.60
Therapeutics			
Thrombolytic therapy (NA=7)	3 (1.2)	6 (2.2)	0.76
Initial anticoagulant therapy (NA=2)			
DOAC	42 (16.3)	40 (14.5)	
VKA [#]	202 (78.3)	218 (79.0)	0.56
Heparin only (LMWH or UFH or fondaparinux)	14 (5.4)	18 (6.5)	
Duration of anticoagulant therapy (NA=3)			
≥ 3 months	254 (98.8)	271 (97.8)	0.57
≥ 6 months	200 (77.8)	205 (74.0)	0.35

Data are presented as n (%) or mean (Standard Deviation, SD). Number of missing data are reported as NA: Not available

BMI: Body mass index; OR: Odds Ratio, CI: Confidence interval; IPVO: initial pulmonary vascular obstruction; VTE: Venous thromboembolism; PE: Pulmonary embolism; DVT: Deep vein thrombosis; DOAC: Direct oral anticoagulant; VKA: Vitamin K antagonists; LMWH: Low molecular weight heparin, UFH: Unfractionated heparin

A heparin treatment was initiated concomitantly to VKA until reaching targeted International Randomized Ratio

* % related to number of females

+ These variables were integrated into multivariate analysis

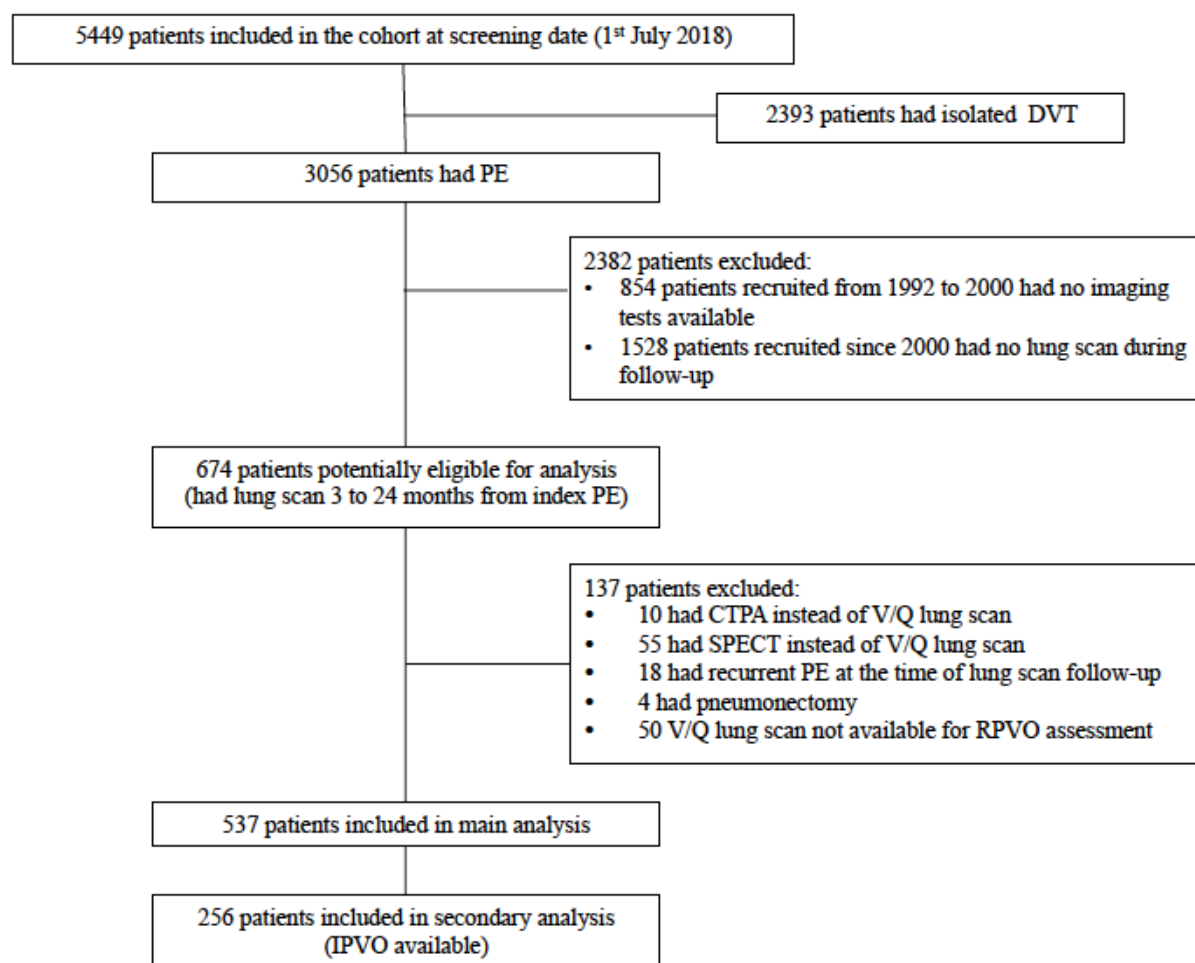
§ This P-value was calculated for the distribution of three variables: Unprovoked / Provoked by active cancer / Provoked by a major transient factor

Table 4. Risk factors for residual pulmonary vascular obstruction $\geq 5\%$ in multivariable analysis

	First model: overall population, N=537		Second model: population with available IPVO N=256	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age				
< 50 years	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
50-65 years	0.93 (0.57-1.52)	0.78	0.90 (0.43-1.8)	0.77
≥ 65 years	2.25 (1.45-3.52)	0.0003	2.78 (1.41-5.53)	0.0034
Medical history and conditions				
Congestive heart failure	4.57 (1.14-30.62)	0.056	NA	0.99
Chronic respiratory failure	3.19 (1.22-10.04)	0.028*	1.47 (0.35-7.58)	0.61
History of VTE (PE and/or DVT)	1.51 (0.89-2.58)	0.13	1.20 (0.52-2.90)	0.66
Characteristics of pulmonary embolism				
Provoked by a major transient factor	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
Unprovoked	1.48 (0.98-2.25)	0.063	2.11 (1.1-4.07)	0.024
Provoked by active cancer	1.61 (0.70-3.74)	0.26	2.59 (0.53-15.32)	0.26
Initial pulmonary vascular obstruction $\geq 20\%$	NA	NA	2.94 (1.68-5.20)	0.0002

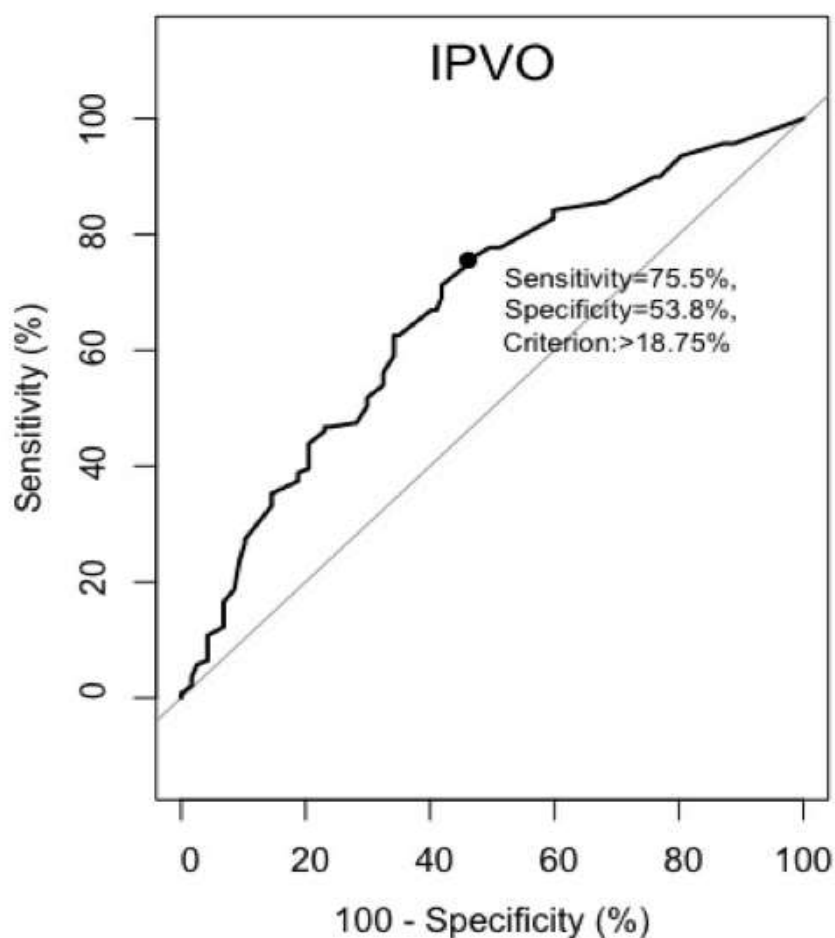
OR: Odds Ratio, CI: Confidence interval; IPVO: Initial pulmonary vascular obstruction; VTE: Venous thromboembolism; PE: Pulmonary embolism; DVT: Deep vein thrombosis. Ref: reference
NA = Not applicable

Figure 1. Flow chart



VTE: Venous thromboembolism; SPECT: tomography ventilation/perfusion scintigraphy; PE: Pulmonary embolism; DVT: Deep vein thrombosis; RPVO: Residual pulmonary vascular obstruction; IPVO: Initial pulmonary vascular obstruction (at PE diagnosis)

Figure 2. ROC curve for the initial pulmonary vascular obstruction at pulmonary embolism diagnosis, according to risk factor for Residual vascular obstruction $\geq 5\%$



Abbreviations: IPVO, Initial Pulmonary Vascular Obstruction at pulmonary embolism diagnosis; AUC, area under the curve; ROC, receiver operating curve

N=256 patients whose IPVO was available for analysis.

Area under the ROC curve (AUC (95% CI)): 0.672 (0.606 - 0.739)

Youden Index: 18.75