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ABSTRACT

Background: Pulmonary infarction (PI) is relatively common in pulmonary embolism (PE). The association between PI and persistent symptoms or adverse events is largely unknown.
Aim: To evaluate the predictive value of radiological PI signs at acute PE diagnosis on 3-month outcomes.
Methods: We studied a convenience cohort with computed tomography pulmonary angiography (CTPA)-confirmed PE for whom extensive 3-month follow-up data were available. The CTPAs were re-evaluated for signs of suspected PI. Associations with presenting symptoms, adverse events (recurrent thrombosis, PE-related readmission and mortality) and self-reported persistent symptoms (dyspnea, pain and post-PE functional impairment) at 3-month follow-up were investigated using univariate Cox regression analysis.
Results: At re-evaluation of the CTPAs, 57 of 99 patients (58 %) had suspected PI, comprising a median of 1 % (IQR 1–3) of total lung parenchyma. Patients with suspected PI more often presented with hemoptysis (11 % vs. 0 %) and pleural pain (OR 2.7, 95%CI 1.2–6.2), and with more proximal PE on CTPA (OR 1.6, 95%CI 1.1–2.4) than patients without suspected PI. There was no association with adverse events, persistent dyspnea or pain at 3-month follow-up, but signs of PI predicted more functional impairment (OR 3.03, 95%CI 1.01–9.13). Sensitivity analysis with the largest infarctions (upper tertile of infarction volume) yielded similar results.
Conclusions: PE patients radiologically suspected of PI had a different clinical presentation than patients without those signs and reported more functional limitations after 3 months of follow-up, a finding that could guide patient counselling.

1. Introduction

Pulmonary infarction occurs when pulmonary vascular occlusion leads to ischemia, alveolar hemorrhage and, if the latter cannot be resorbed, eventually pulmonary tissue necrosis [1]. Pulmonary infarction is most often caused by pulmonary embolism (PE; Fig. 1), and has been reported in 10–50 % of all PE cases [2,3]. Signs of pulmonary infarction are best detected on computed tomography (CT). Parenchymal abnormalities suggestive for infarction include a subpleural wedge-shaped consolidation in a region of PE [4]. In the acute phase of PE, no distinction between reversible alveolar hemorrhage and true necrosis can be made, and formally a pulmonary infarction can only be confirmed with the presence of a fibrotic scar on follow-up imaging, weeks to months after the acute event [5]. In acute PE, the diagnosis is limited to suspected pulmonary infarction because follow-up is not yet available. Notably, the term pulmonary infarction as used in the

Abbreviations: CI, confidence interval; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; DVT, deep-vein thrombosis; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; OR, odds ratio; PE, pulmonary embolism; PEmb-QoL, Pulmonary Embolism Quality of Life (questionnaire); PI, pulmonary infarction; PVFS, post-VTE functional status; RV/LV ratio, right ventricle-to-left ventricle diameter ratio; SD, standard deviation; VTE, venous thromboembolism.

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literature includes the whole spectrum of ischemic injury of pulmonary tissue.

Radiological signs of pulmonary infarction may be associated with presenting symptoms, i.e. pleural pain (due to the subpleural location of infarction) and/or hemoptysis (due to alveolar hemorrhage), and by itself predict slower or incomplete recovery from the acute event [6]. The impact of PI on clinical outcomes is however largely unknown. Several studies have shown that the presence of an infarction is not related to increased mortality [2,7], nor to measurable pulmonary dysfunction because of the often limited residual parenchymal lesions [8]. However, the impact on other patient-relevant outcomes, including need for initial or chronic pain medication, need for oxygen therapy, (re) hospitalization or long-term complications such as the post-PE syndrome have not been studied. This is valuable information for optimal patient counselling and the organization of the acute and chronic care for PE patients, i.e. need for hospitalization or optimal timing of follow-up visits. The aim of this study was to explore the predictive value of radiologically suspected pulmonary infarction at acute PE diagnosis on 3-month clinical outcomes.

2. Methods

2.1. Patients, outcomes and design

This was an exploratory study, using an existing convenience cohort of 99 adult patients (≥18 years old) with hemodynamically stable CT pulmonary angiography (CTPA) confirmed acute PE in the Leiden University Medical Centre (LUMC) between July 2017 and October 2019 [9,10]. Anticoagulant treatment was started in all patients, or modified in patients already on anticoagulant treatment according to international standards. Patients were followed for three months as part of routine clinical practice, and data on persistent symptoms and adverse outcomes at 3-month follow-up were systematically assessed. Persistent symptoms included self-reported 1) dyspnea; 2) chest pain; or 3) post-PE functional impairment. The latter was defined as new or progressive dyspnea leading to exercise intolerance and/or diminished functional status following PE which was adequately treated with anticoagulation for at least 3 months, without an apparent non-PE alternative explanation [11]. Chronic thromboembolic pulmonary hypertension (CTEPH) was diagnosed (based on the guideline recommendations at that time) when at least one mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning after 3 months of adequate treatment was present, in combination with a resting mean pulmonary arterial pressure ≥ 25 mmHg and pulmonary capillary wedge pressure ≤ 15 mmHg measured by right heart catheterization [11]. Adverse outcomes included recurrent venous thromboembolism (VTE), PE-related readmission and all-cause mortality. PE-related readmission was defined as readmission to the hospital due to PE-related complications, such as dyspnea, chest pain, anticoagulation-related bleeding or (suspected) recurrent VTE. The study protocol was approved by the institutional

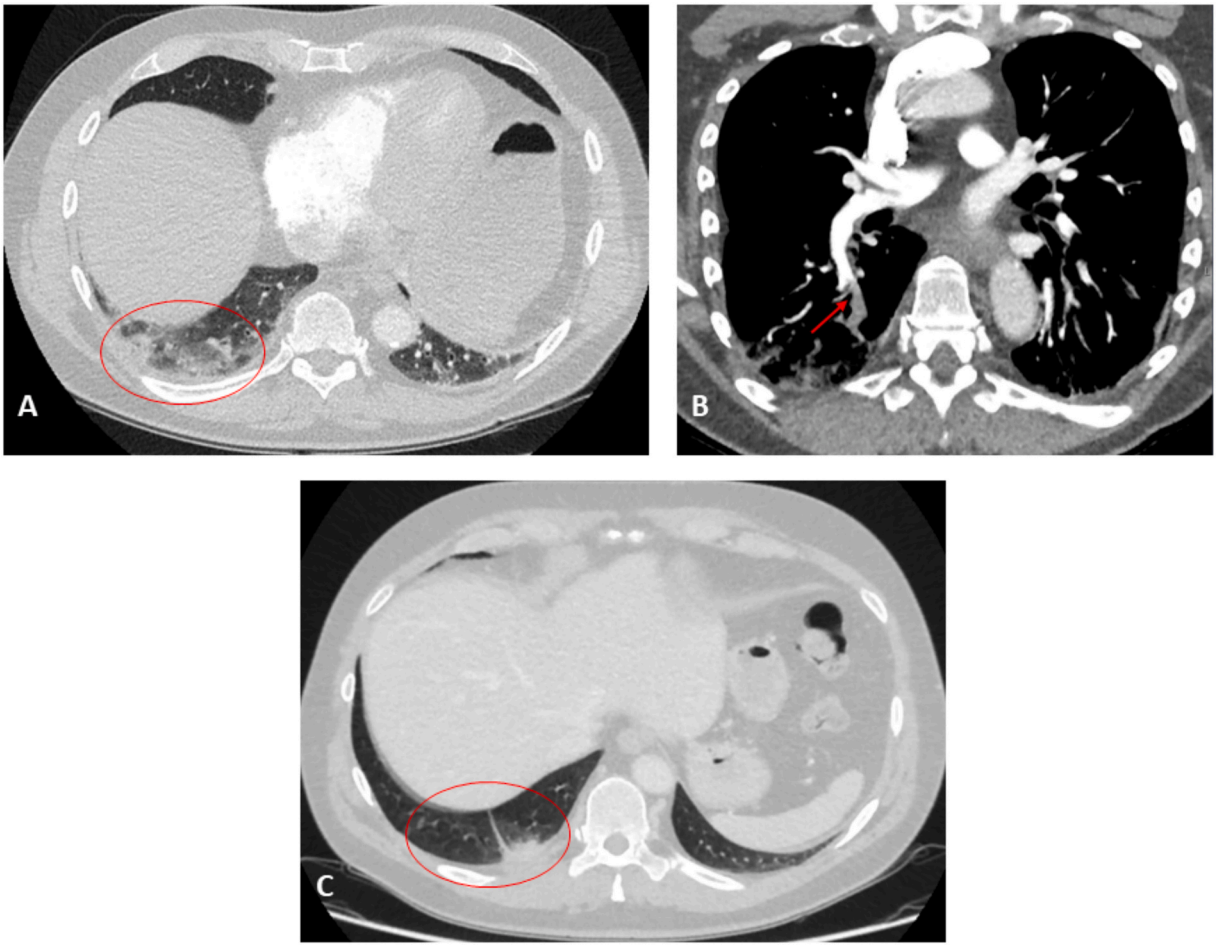

Fig. 1. Clinical evaluation of a pulmonary infarction in a patient with acute pulmonary embolism.
Figure text: 58-year-old male patient presenting with acute pulmonary embolism. A: CT pulmonary angiography in lung setting showing patchy consolidation in the posterior and lateral basal segment area of the right lower lobe suspected of pulmonary infarction. B: Soft tissue setting in oblique transverse reconstruction at presentation, occlusion of the segmental pulmonary artery to the infarcted area. C: CT 10 months later showing a pleural-based residual scar in the same area as proof of infarction.

review board of the LUMC (the Medical Research Ethics Committee Leiden-The Hague-Delft; MREC LDD), and informed consent requirement was waived due to the observational nature of the study.

The initial CT scans at acute PE diagnosis were performed on a 320-multislice detector row CT scanner (Canon) and re-evaluated on a standard diagnostic PACS workstation for parenchymal abnormalities of any size suggestive for pulmonary infarction by an expert thoracic radiologist (LMJK), hereafter referred to as 'reader', who was blinded for the presenting symptoms and clinical outcomes. A suggestive lesion usually included a peripheral wedge-shaped consolidation in a region of PE, with decreased contrast enhancement. The presence of a pulmonary infarction was assessed as being 'likely' (with all typical imaging findings as aforementioned), 'possible' (some, but not all, of the typical imaging findings are present) or 'absent' (none of the typical imaging findings are present, or, if some are present, an alternative diagnosis is in fact far more likely). The locations and sizes of presumed infarctions were annotated on a predefined score form. Per presumed infarction, the size was determined by measuring the two maximal perpendicular sizes on axial view, with the corresponding perpendicular size in craniocaudal direction on coronal view. The approximate volume was calculated as the product of the 3 perpendicular (axial, sagittal and coronal) measurements divided by three (as the consolidations were generally wedge-shaped) and expressed in milliliters (mL). The size was also visually estimated as percentage of total lung parenchyma. Also, it was described whether pulmonary artery obstruction was present in the area of presumed infarction, and whether atelectasis or alternative gross pathology, such as tumor or emphysema, was present. Information on right ventricular overload (maximum right-to-left ventricular diameter >1.0) and CT obstruction index according to Qanadli [12] was available as well for all patients.

2.2. Statistical methods

Patient characteristics were described using standard descriptive statistics. Suspected infarctions refer to all lesions assessed as a 'likely' or 'possible' infarction by the reader. Association of PI and the study outcomes were estimated using univariate logistic regression, and presented as odds ratio (OR) with corresponding 95 % confidence intervals (CI). A sensitivity analysis including only 'large infarctions', i.e. those in the upper tertile of the percentage of total lung parenchyma, was performed. All statistical analyses were performed in SPSS version 25 (IBM, Armonk, NY, USA).

3. Results

The cohort of 99 patients included 52 males (53 %), and the mean age was 62 (SD 16) years old. Most patients had bilateral pulmonary embolism (n = 72, 72 %). In 31 patients, the initial CTPA was re-evaluated as 'infarction likely' and in 26 patients as 'infarction possible' by the reader, resulting in a suspected infarction in 57 (58 %) of the patients. In the original radiology reports of the initial CTPA, a pulmonary infarction was described in 25 patients (25 %, 1 inconsistent with the study assessment).

Often multiple locations with signs of infarction were present (23/57, 40 %), for a total of 90 locations (range 1–5 per patient). These suspected infarctions were usually small, with a median estimated volume per patient of 8.3 mL (range 0.08–212.3), and a median percentage of total lung volume of 1.0 % (range 0.1–10.0). Most infarctions were located in the right lung (n = 56), especially in the right lower lobe (n = 41, 46 %). In 54 patients with suspected infarction, a thrombus in the supplying vessel to the affected area was identified, and in 3 patients this could not be assessed, as the vessel was either deemed too small or obscured by pulsation or respiration artifacts. Atelectasis was frequently observed too (n = 80, 81 %), and in 41 patients (41 %) other gross pathology was annotated, most frequently pleural effusion (n = 26) or emphysema (n = 10).

The baseline characteristics of patients with suspected pulmonary infarction on the CTPA versus those without suspected infarction, are shown in Table 1. No significant differences between demographics or comorbidities were observed. Patients with suspected infarction presented more often with pleuritic pain (OR 2.7, 95%CI 1.2–6.2) and hemoptysis (n = 6 vs. n = 0, infinite OR). Furthermore, radiologically suspected infarction was associated with more proximal located PE (OR 1.6, 95%CI 1.1–2.4; relative to a more distal PE location, categorized as 'central', 'lobar', 'segmental' or 'subsegmental').

At time of acute PE diagnosis, in total 40 patients (40 %) had treatment at home and 59 patients (60 %) were admitted to the hospital, of which 4 (4 %) to the intensive care unit (ICU). Twenty-four patients (24 %) required supplemental oxygen therapy and 6 patients (6 %) intravenous pain medication for >24 h. One patient developed cavitation and secondary infection in the infarction region during admission, leading to (intravenous) antibiotic treatment.

During the 3 months of follow-up, 20 patients (20 %) were

Table 1
Baseline symptoms and outcomes in PE patients with and without suspected pulmonary infarction.

	Suspected PI (n = 57)	No PI (n = 42)	Odds ratio (95%CI)
Baseline characteristics			
Female sex (n, %)	24 (42.1 %)	23 (54.8 %)	0.60 (0.27–1.34)
Age (mean, SD)	65.0 (16.0)	59.4 (16.2)	0.98 (0.95–1.0) per year
Duration of complaints in days (median, IQR)	2 (1–12.5)	1.5 (1–5)	0.93 (0.87–1.0)
Outpatient (n, %)	33 (78.6 %)	46 (80.7 %)	1.1 (0.43–3.1)
Recurrent PE (n, %)	6 (14.3 %)	10 (17.5 %)	1.3 (0.42–3.8)
Provoked PE (n, %)	32 (56 %)	24 (57 %)	0.96 (0.43–2.1)(
– Active malignancy (n, %)	13 (22.8 %)	14 (33.3 %)	0.59 (0.24–1.4)
– Surgery, trauma and/or immobility (n, %)	19 (33.3 %)	15 (35.7 %)	0.90 (0.39–2.1)
– Active inflammation/infection (n, %)	2 (3.5 %)	1 (2.4 %)	1.5 (0.13–17)
– Hormone therapy (n, %)	6 (10.5 %)	1 (2.4 %)	4.8 (0.56–42)
– Known thrombophilia (n, %)*	0	0	N/A
– Pregnancy (n, %)	0	0	N/A
Presenting symptoms and signs			
– Dyspnea	47 (82.5 %)	36 (85.7 %)	0.78 (0.26–2.4)
– Chest pressure	14 (24.6 %)	10 (23.8 %)	1.0 (0.41–2.6)
– Pleuritic pain	37 (64.9 %)	17 (40.5 %)	2.7 (1.2–6.2)
– Hemoptysis	6 (10.5 %)	0	N/A
– Signs of DVT	2 (3.5 %)	4 (9.5 %)	0.30 (0.051–1.7)
– Hemodynamic instability	4 (7.0 %)	2 (4.8 %)	1.5 (0.26–8.7)
– D-dimer level in mg/L (mean, SD)	3.13 (1.64)	2.73 (1.57)	1.2 (0.87–1.6)
– Location PE			1.6 (1.1–2.4) (relative to a more distal PE location)
o Central	25 (43.9 %)	12 (28.6 %)	
o Lobar	7 (12.3 %)	2 (4.8 %)	
o Segmental	23 (40.4 %)	19 (45.2 %)	
o Subsegmental	2 (3.5 %)	9 (21.4 %)	
– CT obstruction index in % (median, IQR)	35 (10.0–53.8)	15 (5.0–48.1)	1.1 (0.99–1.2) per 5 %
– RV/LV diameter ratio > 1.0	30 (52.6 %)	18 (42.9 %)	1.5 (0.66–3.3)
– Presence of atelectasis	49 (86.0 %)	31 (73.8 %)	2.2 (0.79–6.0)
– Presence of other gross pathology	19 (33.3 %)	22 (52.4 %)	0.46 (0.20–1.0)

Note: PI: pulmonary infarction, CI: confidence interval, DVT: deep-vein thrombosis, PE: pulmonary embolism, RV: right ventricle, LV: left ventricle, ICU: intensive care unit, IV: intravenous, N/A: analysis not possible.

* Known thrombophilia included antiphospholipid antibodies, factor V Leiden, protein C or S deficiency, hyperhomocysteinemia, prothrombin mutation or antithrombin deficiency.

readmitted to the hospital, of whom 11 for PE-related reasons. Post-PE symptoms were reported by 28 patients (28 %), usually including dyspnea (n = 22) and/or functional impairment (n = 22). Six patients (6 %) died during follow-up, of whom 2 due to the acute PE.

Table 2 shows the adverse outcomes in patients with versus patients without signs of infarction at acute PE. There were no differences between the groups with regard to hospital or ICU admission, the need for intravenous analgesics or need for oxygen treatment. Three patients with suspected pulmonary infarction required vasopressor therapy, versus none of the patients without infarctions (OR infinite). During follow-up, there was no difference in the incidence of recurrent VTE, rehospitalization or all-cause mortality. Notably, all instances of rehospitalizations of PE-related symptoms (progressive pain and/or dyspnea) occurred in patients with suspected pulmonary infarction (n = 4 vs. n = 0). Two patients had fatal acute PE, one with and one without signs of infarction. Self-reported persistent symptoms were generally similar, although patients with suspected pulmonary infarction reported persistent functional impairment more frequently (30 % vs 12 %, OR 3.0, 95%CI 1.0–9.1). None of the patients in our cohort was diagnosed with CTEPH.

The 'large infarction' group included suspected lesions with a median of 3.0 % of total long volume (range 2.0–10.0) and a median estimated volume of 37.8 mL (range 10.7–212.3). The sensitivity analysis with only large infarctions showed similar results to the total cohort with regard to symptoms and acute outcomes. The association with PE symptom-related readmission was lost, probably due to loss of power (Supplementary Table 1).

4. Discussion

In this study, CT signs of pulmonary infarction were found in more than half of the patients presenting with acute PE. Most lesions were small (median 1 % of the total lung parenchyma). Suspected infarction was associated with specific presenting symptoms and impacted the prognosis of the patients. Mortality and symptom burden after 3 months were not different between patients with or without CT suspected infarction.

We found a higher prevalence of suspected pulmonary infarctions in acute PE than hitherto reported (58 % vs. 10–30 % with CT-based diagnosis [8,13]). This is likely attributable to the dedicated post-hoc reading of the CT images by an expert reader in research setting, focused on identifying pulmonary infarction, irrespective of possible clinical relevance, resulting in a relatively sensitive assessment. For reference, the routine radiology report only mentioned the presence of signs of pulmonary infarctions in 25 % of cases, presumably allocated to lesions with possible clinical relevance. Although measurement methods slightly vary in literature, the small dimensions of the parenchymal abnormalities in our cohort are comparable to those reported in previous studies (with mean longest dimensions of 4.2–4.7 cm vs. 4.8 cm in our cohort) [4,8,14].

We did not find an association between suspected pulmonary infarction and short-term clinical outcomes (e.g. mortality, need for pain medication, need for oxygen therapy). This may be explained by the small volume of the suspected infarctions: such small-sized parenchymal lesions indeed are probably less relevant in this specific context. Our findings are largely in line with a recently published cohort study, in which the presence of pulmonary infarction in PE did not correlate with the need for reperfusion therapy or poorer outcomes (e.g., hospital readmission, bleeding complications or death), either [15].

Notably, we could not differentiate between true pulmonary necrosis and reversible hemorrhage, as we did not systematically perform follow-up imaging tests that would show scar lesions after true infarction. It is generally thought that this distinction is not necessarily relevant, as residual lesions are much smaller than the initial ischemic area. Therefore, it may be argued that unless the infarct is 'massive', the impact on pulmonary function is negligible, regardless whether a suspected pulmonary infarction heals slowly leaving a peripheral scar, or disappears more quickly with resorption of alveolar hemorrhage without leaving a scar [8]. Furthermore, it has been reported that pulmonary infarction can be complicated by secondary infection and cavitation, which was seen in one patient in our cohort [16,17].

While patients with signs of pulmonary infarction at baseline were more likely to report persistent functional limitations during follow-up, we did not find differences in persistent dyspnea or pleural pain. Importantly, we assessed the presence and severity of persistent symptoms by asking the patients, but did not use specific patient-reported outcome measures, as is now for example recommended by the International Consortium for Health Outcomes Measurement (ICHOM) for all VTE patients [18]. More accurate and consistent quantification of pain, dyspnea, functional limitations and quality of life by using validated instruments as the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire [19] and Post-VTE Functional Status (PVFS) scale [20] would have resulted in a more reliable and reproducible outcome assessment than the used approach, and could have impacted our results.

Within the setting of an exploratory study, of which the findings need to be interpreted with caution, we observed several notable associations between CT signs of pulmonary infarction and presenting symptoms as well as prognosis, i.e. higher prevalence of hemoptysis and pleuritic pain, more PE-related hospital admissions and a higher incidence of post-PE impairment. As there are no specific therapeutic options available for pulmonary infarction, more accurate reporting of suspected CT abnormalities at acute PE diagnosis might not have direct implications for the initial treatment of PE patients. However, awareness of the presence of infarctions could be relevant in order to better inform and educate patients, possibly reducing anxiety and uncertainty. This might prevent unplanned visits to the emergency room and readmissions to the hospital, but also decrease the incidence and severity of the post-

Table 2
Adverse events and persistent outcomes, acute and at 3 months follow-up, in PE patients with and without suspected pulmonary infarction at baseline.

	Suspected PI (n = 57)	No PI (n = 42)	Odds ratio (95%CI)
Acute outcomes			
– Hospital admission	37 (64.9 %)	22 (52.4 %)	1.7 (0.75–3.8)
– Reperfusion therapy	3 (5.3 %)	1 (2.4 %)	2.3 (0.23–22)
– Vasopressor therapy	3 (5.3 %)	0	N/A
– ICU admission	5 (8.8 %)	2 (4.8 %)	1.9 (0.35–10)
– Oxygen therapy >24 h	16 (28.1 %)	8 (19.0 %)	1.6 (0.62–4.3)
– IV pain medication >24 h	3 (5.3 %)	3 (7.1 %)	0.71 (0.14–3.7)
3-month outcomes			
Adverse events			
– Recurrent VTE	0	1 (2.4 %)	N/A
– Rehospitalization	14 (24.6 %)	6 (14.3 %)	1.9 (0.67–5.6)
o PE-related	8 (14.0 %)	3 (7.1 %)	2.0 (0.50–8.2)
o Due to persistent PE-related symptoms	4 (7.0 %)	0	N/A
– Mortality	2 (3.5 %)	4 (9.5 %)	0.33 (0.057–1.9)
Self-reported persistent symptoms			
– Post-PE symptoms	17 (29.8 %)	11 (26.2 %)	1.13 (0.46–2.79)
o Dyspnea	13 (22.8 %)	9 (21.4 %)	1.02 (0.39–2.71)
o Chest pain	7 (12.3 %)	4 (9.5 %)	1.27 (0.34–4.67)
o Functional impairment	17 (29.8 %)	5 (11.9 %)	3.03 (1.01–9.13)

Note: PI: pulmonary infarction, CI: confidence interval, ICU: intensive care unit, IV: intravenous, VTE: venous thromboembolism, PE: pulmonary embolism, N/A: analysis not possible.

thrombotic panic syndrome contributing to better recovery [21]. Optimal patient information is increasingly recognized as one of the pillars of modern medicine. Insufficient information provision may indeed compromise ability to cope with the disease, difficulties in gaining control and non-compliance.

Our study has strengths and limitations. To our knowledge, this is the first study focusing on the complete spectrum of outcomes of pulmonary infarction. The images were accurately evaluated and detailed information was available for location, aspect and volume of the possible infarction, as well as location and extent of the clots. Limitations of our study include the absence of a reference standard to confirm pulmonary infarctions in general, and the lack of standardized measurement of persistent symptoms and functional limitations. Furthermore, as this was an exploratory study, we used a convenience cohort which was not specifically selected for answering our research question. No information was available on additional laboratory markers for coagulation, inflammation or fibrinolysis. The relatively small sample size resulted in large confidence intervals and inability to perform adjusted analysis. Lastly, we could not assess persistent symptoms and outcomes beyond the 3-month follow-up.

In conclusion, our results suggest that radiologically suspected pulmonary infarction in patients with acute PE on CT is prevalent and associated with specific symptomatology, higher rate of unscheduled readmissions and more long-term functional limitations. Our findings are a call to action to perform larger and prospective studies on this topic, as well as to improve patient tailored information provision in PE patients with signs of pulmonary infarction, which may facilitate shared decision-making regarding hospital admission, as well as the duration and frequency of follow-up visits.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.04.005.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The other authors have no conflicts of interest to declare.

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