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Original article

Identification of chronic thromboembolic pulmonary hypertension on CTPAs performed for diagnosing acute pulmonary embolism depending on level of expertise

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ABSTRACT

Background: Expert reading often reveals radiological signs of chronic thromboembolic pulmonary hypertension (CTEPH) or chronic PE on computed tomography pulmonary angiography (CTPA) performed at the time of acute pulmonary embolism (PE) presentation preceding CTEPH. Little is known about the accuracy and reproducibility of CTPA reading by radiologists in training in this setting.
Objectives: To evaluate 1) whether signs of CTEPH or chronic PE are routinely reported on CTPA for suspected PE; and 2) whether CTEPH-non-expert readers achieve comparable predictive accuracy to CTEPH-expert radiologists after dedicated instruction.
Methods: Original reports of CTPAs demonstrating acute PE in 50 patients whom ultimately developed CTEPH, and those of 50 PE who did not, were screened for documented signs of CTEPH. All scans were re-assessed by three CTEPH-expert readers and two CTEPH-non-expert readers (blinded and independently) for predefined signs and overall presence of CTEPH.
Results: Signs of chronic PE were mentioned in the original reports of 14/50 cases (28%), while CTEPH-expert radiologists had recognized 44/50 (88%). Using a standardized definition (≥3 predefined radiological signs), moderate-to-good agreement was reached between CTEPH-non-expert readers and the experts' consensus (k-statistics 0.46; 0.61) at slightly lower sensitivities. The CTEPH-non-expert readers had moderate agreement on the presence of CTEPH (κ-statistic 0.38), but both correctly identified most cases (80% and 88%, respectively).
Conclusions: Concomitant signs of CTEPH were poorly documented in daily practice, while most CTEPH patients were identified by CTEPH-non-expert readers after dedicated instruction. These findings underline the feasibility of achieving earlier CTEPH diagnosis by assessing CTPAs more attentively.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is the only potentially curable form of pulmonary hypertension, but is currently underrecognized. [1, 2] CTEPH is a rare complication of acute pulmonary embolism (PE) [3], with increasing evidence showing that

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acute PE may be accompanied by acute-on-chronic thromboembolic disease leading to diagnostic misclassification. A French study showed that patients ultimately diagnosed with CTEPH had multiple concomitant signs of CTEPH at computed tomography pulmonary angiography (CTPA) and echocardiography at the time of a preceding PE. [4] Confirmation of prevalent findings suggestive of CTEPH have been confirmed by recent studies, although it has also been suggested that radiologists rarely report these signs. [1, 5-8]

More detailed assessment of index CTPAs may therefore lead to earlier identification of patients with (high risk of developing) CTEPH, which is associated with better prognosis. [9) In the InShape III study, three expert chest radiologists scored signs of chronic thrombi and pulmonary hypertension on CTPA scans performed for suspected acute PE in 50 PE patients who were subsequently diagnosed with CTEPH during follow-up ('cases'), and in 50 PE patients in whom sequential echocardiograms performed >2 years after the acute PE diagnosis had not shown any signs of pulmonary hypertension ('controls'). [5) This standardized assessment revealed six independent radiological signs that were most predictive of a future CTEPH diagnosis (**Fig. 1**). The overall judgement on the presence of CTEPH yielded a high diagnostic accuracy (sensitivity 72%, 95%CI 58-84%; specificity 94%, 95%CI 83-99%), confirming the hypothesis that careful evaluation of CTPA scans can identify the majority of patients that will be diagnosed with CTEPH in the course of PE.

Elaborating on this, it remains unknown whether readers with less experience in diagnosing CTEPH are also able to identify CTEPH patients to the same accuracy as the expert radiologists based on a routinely performed CTPA scan to diagnose acute PE. In the current study, we evaluated whether concomitant signs of CTEPH are reported spontaneously in routine clinical care, and whether CTEPH-non-expert readers, after being provided with a dedicated instruction, achieve comparable predictive accuracy to expert radiologists

2. Methods

2.1. Study design and patients

We studied the same study population included in the InShape III study, consisting of 50 post-hoc selected cases with a confirmed CTEPH diagnosis after acute PE from the Amsterdam University Medical Center – location VUmc, a Dutch CTEPH expertise center. [5] PE was defined as a contrast filling defect on CTPA. [11, 12] CTEPH was diagnosed according to current ESC Guidelines on Pulmonary Hypertension (PH] including right heart catheterisation. [13] The control group comprised 50 patients with an acute PE diagnosis in whom CTEPH was ruled out by echocardiography after 2-year follow-up according to current ESC/ERS Guidelines on PE. [14] These controls were diagnosed at the Leiden University Medical Center (LUMC] and were selected post-hoc from previous studies based on presence of associated right ventricular (RV] overload (i.e. CTPA-assessed RV/LV diameter ratio of >1.0] at the index PE diagnosis. [15-18] As such, we minimized bias concerning the assessment of CTPA scans in a blinded fashion.

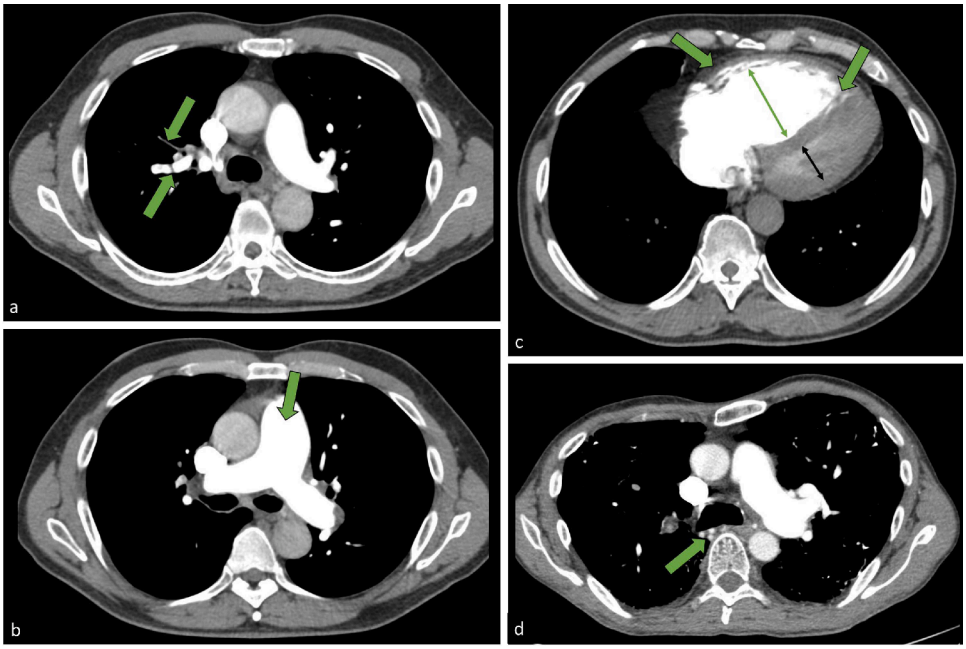
The institutional review board of both LUMC and VUmc approved the study protocol and waived the need for informed consent due to the observational nature of the study. All control patients had provided oral and written informed consent for inclusion in the two previous studies that included collection of all clinical and radiological parameters used in the current study.

2.2. Objectives

The objectives of this study were to use the original 100 CTPA scans used in the InShape III study 1] to evaluate the spontaneous reporting of radiological characteristics of chronic PE and PH according to the original radiology reports; 2] to assess the interobserver agreement between two CTEPH-non-expert readers for the standardized evaluation of the six predefined radiological predictors (**Fig. 1**] of CTEPH as well as the overall judgement on the presence of CTEPH; and 3] to assess the interobserver agreement between the CTEPH-non-expert readers and the consensus reading by the expert readers concerning both the evaluation of radiological characteristics and the overall judgement.

2.3. Procedures

All CTPA scans evaluated in the InShape III study were re-assessed in the current study. These scans had been performed using a CT scanner



a) intravascular web and arterial retraction; b) dilated main pulmonary artery;

c) flattening of the interventricular septum, RV hypertrophy and RV/LV diameter ratio >1.0; d) dilated bronchial arteries.

Fig. 1. CTPA image showing the 6 radiological predictors of CTEPH, in addition to RV/LV diameter ratio of >1.0

Abbreviations: CTPA, computed tomography pulmonary angiography; CTEPH, chronic thromboembolic pulmonary hypertension; RV, right ventricle; LV, left ventricle.

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with at least 64 slices and a slice thickness of 1 to 3 mm. Of both cases and controls, CTPA scans at the moment of index PE diagnosis, including the original radiology reports, were collected and fully anonymized. Their meta-data were removed, leaving the original axial data set only available for study procedures.

The original reports of the index CTPA scans were reviewed for documentation of aforementioned signs of chronic PE or PH by two independent reviewers (Y.E.V. and F.A.K.], two physicians with over 10 years of clinical experience, who were blinded to case or control status (**Fig. 2**]. The following precise formulations were included: 1] chronic PE, chronic vascular occlusion, chronic thrombus remnants, CTEPH; or 2] RV overload or PH. After independent scoring, consensus was reached by discussion. The presence of signs of CTEPH were compared to what was reported by the expert reading. [5]

Standardized assessment of the 100 scans was performed in a randomized order by two radiologists in their last year of training (P.M.J. and G.M.C.G.] at the time of evaluation (**Fig. 2**]. Both CTEPH-non-expert readers had no specific expertise in cardiothoracic radiology. They were unaware of case or control status, ratio of cases versus controls, origin of the scans, patient's characteristics and clinical outcomes. Independent scoring of the presence of radiological parameters suggestive of chronic thrombus remnants and PH was done using a scoring form identical to that of the derivation study (InShape III, **Appendix A**]. [5] Both readers received the same dedicated instruction as the three CTEPH-expert chest radiologists involved in the derivation study: they were all instructed to look for the particular signs suggestive of CTEPH according to the scoring form, and also to give an overall judgement on the presence of CTEPH for each patient. Both results were compared to the consensus reading by the three expert readers in the derivation study.

Radiological parameters incorporated for evaluating the presence of chronic thrombus remnants were: intravascular webs; residual thrombus attached to the vascular wall; complete arterial occlusion; arterial retraction; post-stenotic vascular dilatation; pulmonary infarction; and parenchymal bands. [19, 20] The following indicators of PH were evaluated: right atrial (RA] dilatation; RV dilatation; RV hypertrophy; flattening or inversion of the interventricular septum; dilatation of the main pulmonary artery; dilated bronchial arteries; and the presence of mosaic perfusion. The presence of RA dilatation was visually determined, RV dilatation was defined as RV/LV diameter ratio of >1.0, RV hypertrophy was defined as a wall thickness of >4 mm or visually determined, and main pulmonary artery dilatation was based on a diameter of >30 mm or a diameter larger than the diameter of the aorta. The readers scored each of the aforementioned items as present or not present. If present, these were interpreted as predictive for a future CTEPH diagnosis, as it could not be confirmed whether patients already had CTEPH at the time of index PE.

2.4. Statistical analysis

Descriptive analyses were used to show the results of the CTPA reading by the CTEPH-non-expert readers as well as of reviewing the original radiology reports. Baseline characteristics were described as mean with standard deviation (SD], median with interquartile range (IQR], or numbers with proportions if appropriate. Presence of radiological predictors was assessed using a predefined cut-off of ≥3 signs within the predetermined six independent signs with the highest predictive value for a future CTEPH diagnosis (i.e. presence of intravascular

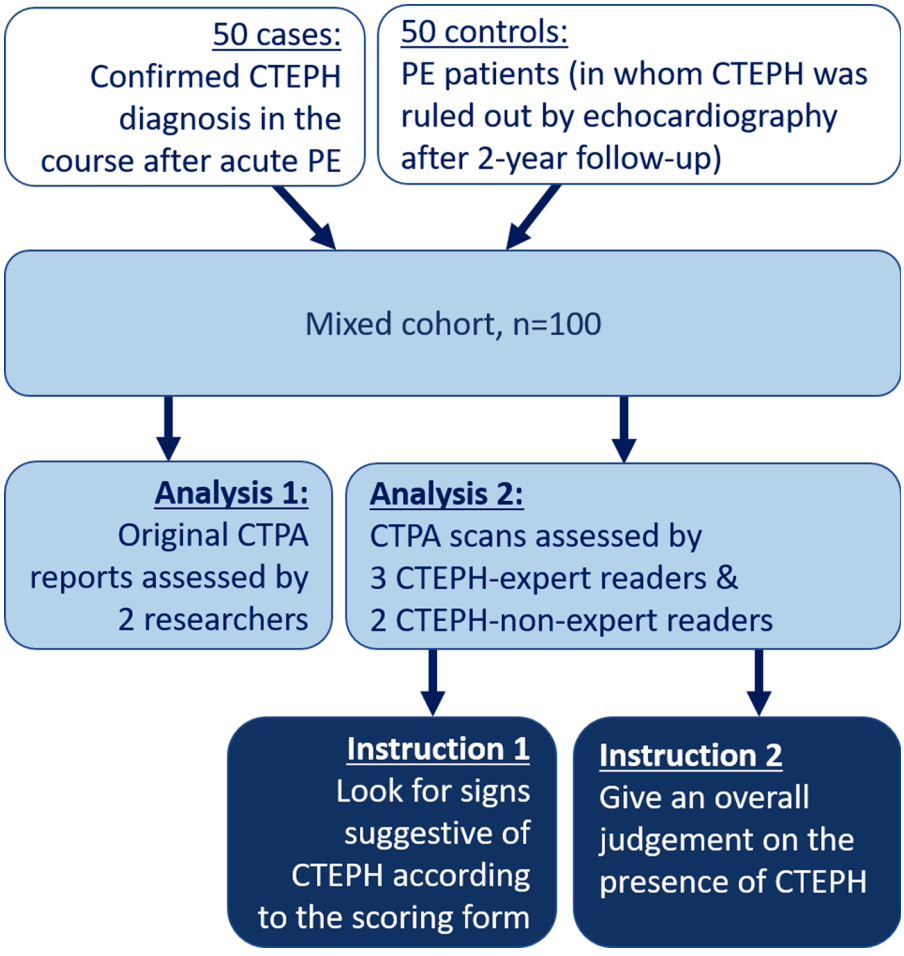

Fig. 2. Study procedures

webs; arterial retraction; dilatation of the bronchial arteries; dilatation of the pulmonary trunk; RV hypertrophy; and flattened interventricular septum. [5] The interobserver agreements of both the assignment of these predictors and the allocation of patients in either the case or control group was determined by using Cohen's kappa-statistics. The experts' consensus from the derivation study was used as a reference to determine interobserver agreements with both CTEPH-non-expert assessments. The k-statistic for agreement was interpreted as follows: poor (< 0.20], fair (0.21–0.40], moderate (0.41–0.60], good (0.61–0.80] or very good (0.81–1.00]. [21] Diagnostic accuracy was expressed by sensitivities, and specificities, and differences between the cases and controls by odds ratio's (ORs] with corresponding 95% confidence intervals (95%CI]. All statistical tests were performed using SPSS Statistics software (version 25.0, IBM].

3. Results

3.1. Study patients

Patients' characteristics at the time of initial CTPA scan for PE diagnosis are shown in Table 1. A total of 46% of cases and 34% of controls were men, mean age at time of PE diagnosis was 61 years (SD15] and 56 years (SD15], respectively. Of the cases, the index PE was an unprovoked event in 43 (86%] and a recurrent venous thromboembolism (VTE] in 20 (40%]; this was 29 (58%] and 10 (20%] in control patients, respectively. Before the acute PE was established, the duration of symptoms was more than 2 weeks in 43 (86%] cases versus in 6 (12%] controls. Cases were referred for diagnostic work-up for suspected CTEPH median 7.1 months (IQR 4.7−12] after their index PE diagnosis. Motion artifacts and/or inadequate contrast timing for optimally diagnosing acute PE was observed in 12 of the 100 CTPA scans, of which one could not be assessed for presence of chronic thrombi.

Table 1
Baseline characteristics

	PE patients with confirmed CTEPH during follow-up (n=50)	PE patients (CTEPH ruled out) (n=50)	Differences (95%CI)
Mean age at baseline	62 (SD 15)	56 (SD 15)	6.3 (0.25-12) [#]
Male	23 (46)	17 (34)	OR 1.7 (0.74-3.7)
Unprovoked PE	43 (86)	37 (74)	OR 5.2 (2.0-14)
Recurrent VTE	20 (40)	10 (20)	OR 2.7 (1.1-6.5)
Onset of symptoms >2 weeks before index PE diagnosis	43 (86) [*]	6 (12)	OR 45 (14-145)
Comorbidities at baseline			
COPD	10 (20)	4 (8)	OR 2.9 (0.84-9.9)
Chronic left heart failure	4 (8)	3 (6)	OR 1.4 (0.29-6.4)
Malignancy	7 (14)	14 (28)	OR 0.42 (0.15-1.1)

Note: continuous variables denoted as mean (± standard deviation), categorical variables as number (percentage). Baseline is defined as the moment of index PE diagnosis.

[#] Mean difference calculated by Student's T-test.

[*] Missing data in 3 patients.

Abbreviations: PE, pulmonary embolism; CTEPH, chronic thromboembolic pulmonary hypertension; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease.

3.2. Original radiology reports

Among the cases, 14 (28%] reports mentioned that signs of chronic PE were present, whereas the experts previously had recognized these signs in 44 (88%] (Table 2]. In two patients from the control group (4%], these signs of chronicity were also described, which was not confirmed by the experts. The presence of RV overload was reported in 17 (34%] cases and in 9 (18%] controls, against 49 (98%] and 45 (90%] described by the experts, respectively.

3.3. Objective radiological predictors

The six radiological predictors for chronic thrombus remnants and PH scored by the CTEPH-non-expert readers are presented in Table 2. The two readers assigned three or more of the six predefined radiological predictors in 20 and 39 cases, and in 1 and 5 controls, respectively. This yielded a sensitivity of 40% (95%CI 26-55] and 78% (95%CI 64-88] against a specificity of 98% (95%CI 89-99.9] and 90% (95%CI 78-97], respectively (Table 3]. Predetermined consensus reading by the expert radiologists had a sensitivity of 70% (95%CI 55-82] and a comparable specificity of 96% (95%CI 86-99.5]. The interobserver agreement between the two CTEPH-non-expert readers was 'fair' with a k-statistic of 0.33 (95%CI 0.16 – 0.50]. Between the CTEPH-non-expert readers and the consensus of three expert chest radiologists in the derivation study, a 'moderate-to-good' agreement was achieved for a k-statistic of 0.46 (95%CI 0.30-0.63] and 0.61 (95%CI 0.45-0.77].

3.4. Overall judgement on the presence of CTEPH

Forced to give an overall adjudication on the presence or absence of CTEPH, the two CTEPH-non-expert readers allocated 51 and 66 patients to the CTEPH patient group, respectively. Of those, 40 and 44 cases were identified correctly for a sensitivity of 80% (95%CI 66-90] and 88% (95%CI 76-95], against 72% (95%CI 58-84] by the experts' consensus (Table 3]. Their overall judgment reached a higher sensitivity than focusing on the six predefined radiological predictors only. Specificity was 78% (95%CI 64-88] and 56% (95%CI 41-70], compared to 94% (95%CI 83-99] by the experts' assessment. The mutual interobserver agreement concerning the overall judgment was 'fair' (κ-statistic of 0.38; 95%CI 0.21-0.55], whereas agreement with the experts' consensus was 'moderate' (κ-statistics of 0.44, 95%CI 0.27-0.61; and 0.50, 95%CI 0.35-0.64].

4. Discussion

We observed that concomitant signs of CTEPH on CTPA scans performed for suspected acute PE were insufficiently reported in daily practice, while the majority of CTEPH cases were recognized by two CTEPH-non-expert readers after dedicated instruction. Importantly and despite moderate interobserver agreements with the experts' consensus, the overall judgement on the presence of CTEPH by CTEPH-non-expert readers resulted in higher case finding than focusing on the previously established set of six radiological predictors only. These findings confirm that close CTPA reading in daily clinical practice outside expert centers could potentially play an important role in diagnosing CTEPH earlier.

The lack of awareness for CTEPH has been illustrated by its current diagnostic delay of up to 14 months as well as the insufficient use of healthcare resources. [9, 22-24] Reducing this delay is crucial in improving prognosis, which requires a thorough and internationally uniform approach of follow-up after acute PE. [25-29] Where dedicated reading of CTPA images of patients with acute PE may help in an earlier diagnosis of CTEPH, in daily practice, however, incomplete reporting of radiological signs suggestive of CTEPH occurs frequently. Similar results to ours were found in a previous study retrospectively evaluating CTPA reports in which (signs of] CTEPH were mentioned in only 9 of 35 (26%] reports. [7] Of note, in daily practice, CTPAs are frequently assessed by

Table 2
Presence of the predefined 6 independent radiological predictors for a future CTEPH diagnosis in the clinical course of acute PE

	CTEPH-non-expert reader 1			CTEPH-non-expert reader 2		CTEPH-experts' consensus (5)		Original CTPA reports	
	Scored in cases (n=50)	Scored in controls (n=50)	Univariate analysis (OR, 95%CI)	Scored in cases* (n=50)	Scored in controls (n=50)	Univariate analysis (OR, 95%CI)	Univariate analysis (OR, 95%CI)	Scored in cases (n=50)	Scored in controls (n=50)
Signs of chronic PE									
Intravascular webs	19 (38%)	10 (20%)	2.5 (0.998- 6.0)	36 (72%)	13 (26%)	7.3 (3.0-18)	48 (13-177)	14 (28%)	2 (4%)
Arterial retraction	22 (44%)	4 (8%)	9.0 (2.8-29)	36 (72%)	9 (18%)	12 (4.5-30)	26 (8.0-82)		
Signs of PH *									
Dilatation of the pulmonary trunk	23 (46%)	5 (10%)	7.7 (12-140)	38 (76%)	21 (42%)	4.4 (1.9-10)	18 (6.2-55)	17 (34%)	9 (18%)
RV hypertrophy	11 (22%)	2 (4%)	6.8 (1.4-32)	11 (22%)	3 (6%)	4.4 (1.2-17)	Infinite		
Flattening of the interventricular septum	37 (74%)	6 (12%)	21 (7.2-60)	40 (80%)	19 (38%)	6.5 (2.7-16)	18 (6.1-55)		
Dilated bronchial arteries	5 (10%)	0	12 (0.66-227)	28 (56%)	9 (18%)	4.0 (1.7-9.6)	13 (4.0-39)		

* *Notes: Concerning the evaluation of original CTPA reports, signs of PH and/or chronic RV overload are included in the numbers.*
Abbreviations: OR, odds ratio; RV, right ventricular; 95%CI, 95% confidence interval.

Table 3
Results of the assessment of radiological signs of CTEPH in controls and cases by two CTEPH-non-expert readers, compared to the experts' consensus

	CTEPH-non-expert reader 1	CTEPH-non-expert reader 2	Consensus reading by 3 CTEPH-expert readers
Presence of ≥3 of 6 predefined radiological predictors of CTEPH			
Sensitivity	40% (95%CI 26-55)	78% (95%CI 64-88)	70% (95%CI 55-82)
Specificity	98% (95%CI 89-99.9)	90% (95%CI 78-97)	96% (95%CI 86-99.5)
Overall judgment on the presence or absence of CTEPH			
Sensitivity	80% (95%CI 66-90)	88% (95%CI 76-95)	72% (95%CI 58-84)
Specificity	78% (95%CI 64-88)	56% (95%CI 41-70)	94% (95%CI 83-99)

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; 95% CI, 95% confidence interval.

radiologists without specific expertise in thoracic radiology since patients with suspected acute PE often present out of office hours. Concerning experience and time, this suggests that the most appropriate moment for assessing the presence of signs of chronic PE or RV overload is post-hoc by a dedicated expert reader.

We were largely able to reproduce the findings of the InShape III study in CTEPH-non-expert readers: most importantly, the large majority of cases was recognized. [5] Even so, the previously established set of 6 radiological predictors was highly specific but identified less cases than in the InShape III study, which may be due to less accurate assessment of these predictors by the CTEPH-non experts. By overall judgement of CTEPH-non-expert readers, more than 80% of CTEPH cases were identified correctly. However, both reviewers yielded a higher number of false positive diagnoses (specificity 56-78%] than was the case in the experts' assessment (specificity 94%]. As such, we must be vigilant for overreading and subsequent avoidable diagnostic work-up. At the same time, this type of assessment resulted in the highest case finding, emphasizing the relevance of pattern recognition beyond focusing on specific criteria only. Predicting a future CTEPH diagnosis, therefore, seems more appropriate based on the overall CTPA judgement than solely based on the set of six criteria.

Our findings add to the existing literature that vigilance on prevalent signs of CTEPH may play a pivotal role in diagnosing CTEPH earlier. Detecting these clues on a CTPA scan performed for diagnosing (recurrent] acute PE should prompt a high suspicion of CTEPH with the need for subsequent confirmatory testing. [1, 20, 30, 31] Still, expert radiologists were not able to identify all CTEPH cases, most likely because CTEPH was not yet present at the time of acute PE diagnosis in all cases. It has been hypothesized that CTEPH might either present as acute-on-chronic PE or develop in the course of acute PE. [4, 32] Particularly in the setting of pre-existing conditions that may also contribute to signs of PH, e.g. COPD or chronic heart failure, it should be emphasized that CTPA findings itself are not diagnostic for CTEPH. As such, we argue that CTPA should not replace other imaging techniques but may provide relevant and early guidance in differentiation between acute and chronic thrombi.

The 2019 European Society of Cardiology Guidelines on acute PE have proposed to routinely follow-up patients after acute PE including echocardiography in those with persistent dyspnea, functional limitations and/or predisposing conditions for CTEPH. [14] According to this guideline, the presence of radiological signs suggestive of CTEPH should be regarded as one of these predisposing conditions. The InShape II algorithm for follow-up after acute PE is an alternative strategy aimed at selecting specific PE patients at high risk of developing CTEPH who require further diagnostic testing. [32, 33] This risk stratification starts with assessment of the pre-test probability based on the CTEPH prediction score, combined with evaluation of the presence of symptoms suggestive of CTEPH and the application of the CTEPH rule-out criteria. [34-36] Replacing the 'simple' RV/LV diameter ratio with more comprehensive CTPA assessment in the CTEPH prediction score will likely result in improved diagnostic accuracy of the algorithm.

Importantly, the interobserver variability between the two CTEPH-non-expert readers as well as between the experts and non-experts remains a concern when considering implementation of refined CTPA assessment into routine care for patients with acute PE. Standardisation of the comprehensive CTPA assessment by providing a handle for radiology reports, including a statement on the presence of characteristics of chronic vascular occlusions and RV overload, contributes to complete reports with uniform terminology, ultimately enhancing communication with clinicians and patients. [37] Future integration of artificial intelligence-based software designed to quantify vascular morphology and perfusion may help in diagnosing CTEPH; the development and validation of such software is subject of ongoing studies. [38-41]

Strengths of our study include using the same set of CTPA scans and assessing these in an identical way as was done in the InShape III study, allowing direct comparison to the previous assessment by CTEPH-expert readers. Moreover, controls were selected upon presence of RV overload, which contributes to assessment in a complete blinded fashion. Some limitations of our study should also be acknowledged. The heterogeneity of the patient case mix in clinical practice is not fully reflected in the case-control design. Due to the observational nature of the

study, it remains uncertain whether the cases already had existing (yet undiagnosed] CTEPH at the moment of acute PE diagnosis, whereas we expect that this was the case in many patients. Also, the much higher prevalence of cases (50%] compared to clinical practice (3%] may have resulted in an overestimation of the specificity of the dedicated reading by both the CTEPH-experts as the CTEPH-non-expert readers. Notably, in the control group, complete CTEPH work-up including ventilation perfusion scanning, pulmonary angiography and RHC was not indicated in case of an echocardiographic low probability of PH. Therefore, misclassification might have occurred, although this approach was in line with the follow-up strategy proposed by the 2019 ESC Guidelines on PE. [14] Moreover, previous studies have not revealed any new symptomatic CTEPH patients later than two years after the index PE, further reducing the chances of missed cases. [42]

In conclusion, after dedicated instruction, CTEPH-non-expert readers were able to differentiate the majority of actual CTEPH patients from those with acute PE who did not develop CTEPH over time, while most of these signs of CTEPH were not included spontaneously in the original reports. Overall judgment outperformed a strategy focussing on six predefined radiological predictors. These findings underline the feasibility of achieving an earlier CTEPH diagnosis by closer CTPA reading in daily practice, which may ultimately improve prognosis.

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CJR has no disclosures.

YME has no disclosures.

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LJMK has no disclosures.

HJB has no disclosures.

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Authors' contribution

GJAMB and FAK had full access to all data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis (guarantors).

Acquisition of the data: GJAMB, PMJ, GMCG, CJR, YME, LFMB, LJMK, LJM, FAK.

Analysis and interpretation of the data: GJAMB, LFMB, LJMK, LJM, FAK.

Drafting of the manuscript: GJAMB, FAK.

Critical revision of the manuscript: GJAMB, PMJ, GMCG, CJR, YME, LFMB, LJMK, HJB, MVH, PS, AVN, LJM, FAK.

Final approval of the manuscript: GJAMB, PMJ, GMCG, CJR, YME, LFMB, LJMK, HJB, MVH, PS, AVN, LJM, FAK.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2021.07.001.

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