Prediction of long-term complications of venous thromboembolism

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Chapter 6

Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study

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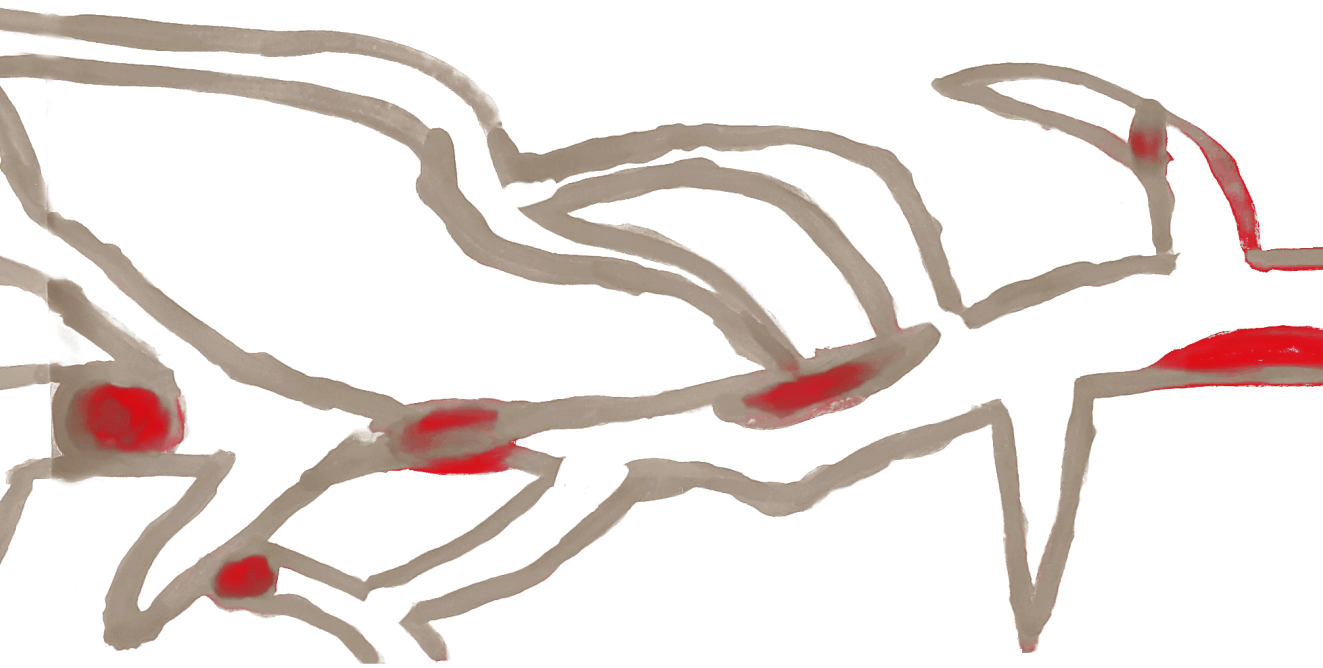
Journal of Heart and Lung Transplantation 2019; 38: 731-738



ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is often diagnosed after a long delay, even though signs of CTEPH may already be present on the CT pulmonary angiography (CTPA) used to diagnose a preceding acute pulmonary embolism (PE). In this setting of suspected acute PE, we evaluated the diagnostic accuracy of dedicated CTPA reading for the diagnosis of already existing CTEPH.

Methods: Three blinded expert radiologists scored radiological signs of CTEPH on initial CTPA scans with confirmed acute PE in 50 patients who were subsequently diagnosed with CTEPH during follow-up (cases), and in 50 patients, in whom sequential echocardiograms performed more than two years after the acute PE diagnosis did not show any signs of pulmonary hypertension (controls). All 50 control CTPA scans had signs of right ventricular (RV) overload. Sensitivity and specificity of expert CTPA reading was calculated, and best predicting radiological parameters were identified.

Results: The overall expert reading yielded a sensitivity of 72% (95%CI 58-84) and a specificity of 94% (95%CI 83-99%) for CTEPH diagnosis. Multivariate analysis identified six radiological parameters as independent predictors: intravascular webs, pulmonary artery retraction or dilatation, bronchial artery dilatation, RV hypertrophy and interventricular septum flattening. The presence of ≥3 of these parameters was associated with a sensitivity of 70% (95%CI 55-82), a specificity of 96% (95%CI 86-100%) and a c-statistic of 0.92.

Conclusion: Standardized reading of CTPA scans performed for acute PE can be useful for the diagnosis of CTEPH when structured identification of 6 characteristics are employed during interpretation. The use of this technique may help reduce diagnostic delay of CTEPH.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious, though potentially curable long-term complication of acute pulmonary embolism (PE), occurring in approximately 3.2% of PE survivors [1-4]. Relevance of optimal treatment and prognosis is clear [1, 2], yet early CTEPH diagnosis is a major clinical challenge as a median diagnostic delay of 14 months (inter quartile range (IQR) 7.5-32.8) was recently demonstrated in 679 patients included in the International CTEPH registry [5].

It has been suggested that a relevant proportion of patients with CTEPH with a prior history of acute PE already had radiological signs of pre-existing CTEPH on the initial computed tomography pulmonary angiography (CTPA) performed to diagnose the acute PE. Guerin et al showed in a retrospective evaluation of the initial CTPA scan of 146 acute PE patients, that all seven patients with an ultimate diagnosis of CTEPH had several radiological signs of CTEPH at the initial CTPA [6].

CTPA is the imaging test of choice for patients with suspected acute PE [7] and can be helpful in the diagnostic work-up of suspected CTEPH as well. Data from the Aspire registry assessing the spectrum of pulmonary hypertension (PH) showed that CTPA yielded a high sensitivity of 94% (95%CI 0.85-0.98) and high specificity of 98% (95%CI 0.88-0.99) for CTEPH in patients with clinically suspected CTEPH [8]. Typical CTPA parameters for right ventricular (RV) overload such as a right-to-left ventricle diameter (RV/LV) ratio >1.0 are often present in patients with acute PE [9]. More specific radiological clues for CTEPH include intravascular webs or bands, and wall-adherent thrombi. Mosaic attenuation and dilated bronchial arteries are less specific for CTEPH and can also be seen in other types of pulmonary hypertension [1, 10-13]. In contrast, on CTPA acute PE can manifest as a complete arterial occlusion, or centrally located in the vessel with contrast material present between the thrombus and the arterial wall, or as an eccentric filling defect that forms an acute angle with the arterial wall [14, 15]. Confirmation of the findings of Guerin et al [6] should prompt (more) targeted reading of CTPA scans performed for suspected acute PE, since recognition of concurrent signs of CTEPH may greatly help in achieving earlier CTEPH diagnosis.

We set out to evaluate the accuracy of extensive reading of CTPA scans performed in the setting of suspected acute PE, to assess concomitant CTEPH diagnosis. Moreover, we aimed to identify the most predictive radiological parameters for this purpose.

METHODS

Study population

Patient selection occurred post-hoc from the local registry of the VU university medical Center (VUmc) (cases) and previous prospective studies (controls) [9, 16, 17]. The assessment of the CTPA scans was performed prospectively. The cases consisted of 50 consecutive patients who were referred to the VUmc, Amsterdam, in the period between 2014 and 2016 for treatment of CTEPH, and had a prior diagnosis of acute PE. The CTEPH diagnosis was confirmed by right heart catheterisation (RHC) and pulmonary angiography in all patients, in accordance with current guideline recommendations [1]. The second group consisted of 50 control patients diagnosed in the Leiden University Medical Center (LUMC), Leiden, with acute PE and associated RV overload, defined as RV/LV diameter ratio of >1.0 as shown by the CTPA made for PE diagnosis, who had thereafter not developed CTEPH over the course of at least 2 years. These latter 50 patients were selected out of two prior studies and were prospectively subjected to baseline ECG-synchronized cardiac CTPA scanning at the moment of PE diagnosis and sequential echocardiography during a follow-up period of at least two years [9, 16, 17]. The echocardiograms did not show any signs of PH. We only included controls with signs of RV overload at baseline to minimize bias, since patients without any signs of RV overload at the moment of acute PE diagnosis are very unlikely to have concurrent CTEPH.

All initial CTPA scans for PE diagnosis were performed using a CT scanner with at least 64 slices and generally a reconstructed slice thickness of 1-3 mm. The institutional review board (IRB) of both the LUMC and VUmc approved the study protocol and waived the need for informed consent due to the observational nature of the study. All controls had previously provided oral and written informed consent for inclusion in the two prior studies that included assessment of all clinical and radiological parameters used in the current study [9, 16-18].

Study procedures

The CTPA images for PE diagnosis of both cohorts were collected and anonymized. All relevant information of the date of the CTPA scan and the specific scanner used were removed, as were additional image sequences and reformatted series other than the original axial data-set. All CTPA studies were distributed among three expert thoracic radiologists, who were unaware of the case or control status, patient characteristics or other clinical outcome. All three radiologists have broad expertise on diagnosis of acute PE and CTEPH (L.M, L.K and L.B). Each radiologist independently scored the presence of radiological parameters of both chronic thrombus remnants as well as of PH on a predesigned adjudication form according to predefined criteria. Moreover, after reading the scan and scoring all items, they were forced to classify each patient as having CTEPH or not.

The following radiological parameters were scored as 'yes, present' or 'no, not present' for assessment as indicators of PH: 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 following radiological parameters were scored for the presence of chronic thrombus remnants: intravascular webs, residual thrombus attached to the vascular wall, complete arterial occlusion, arterial retraction, post-stenotic vascular dilatation, pulmonary infarction and parenchymal bands (**Figures 1, 2 and 3**) [19, 20]. The presence of RA dilatation was visually determined, RV dilatation was defined as a RV/LV diameter ratio of >1.0, RV hypertrophy as a wall thickness of > 4mm or visually determined and main pulmonary artery dilatation was based on a diameter of > 30mm or a diameter larger than the diameter of the aorta. The readers scored each of the above mentioned items as present or not present.

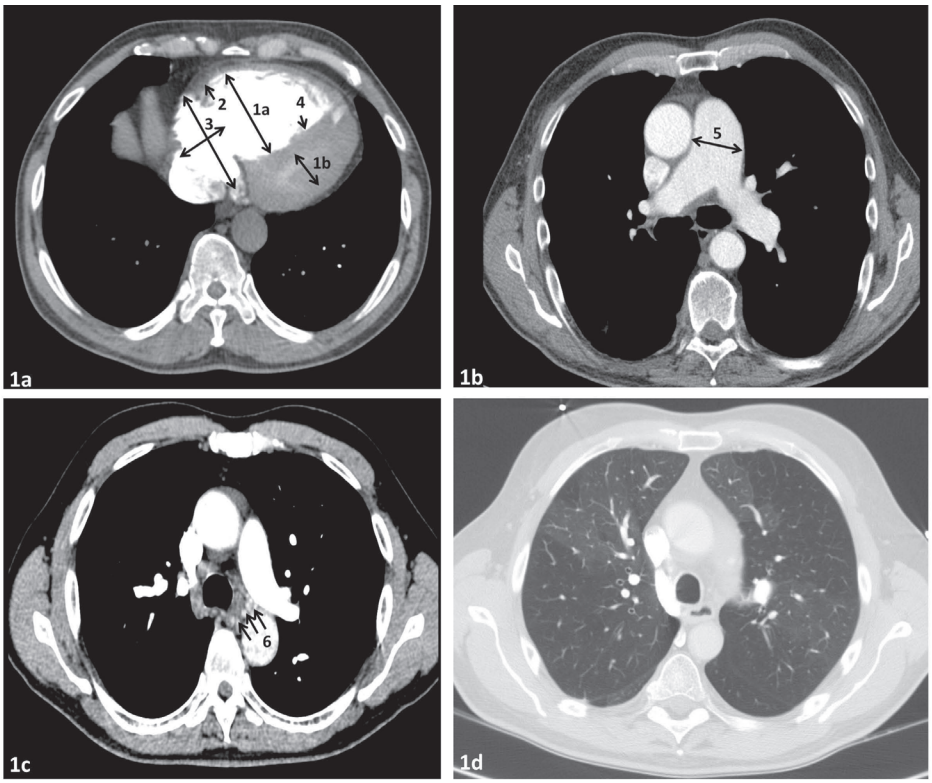


Figure 1. Pulmonary hypertension characteristics found on axial CTPA images.
Fig 1a: 1. Right ventricle dilatation based on right (1a) -to- left (1b) ventricle diameter ratio of >1.0; 2. Right ventricle hypertrophy ; 3. Right atrial dilatation ; 4. Flattening/inversion of the interventricular septum.
Fig 1b: 5. Dilatation of the main pulmonary artery.
Fig 1c: 6. Dilated bronchial arteries.
Fig 1d: Mosaic perfusion.
Note: CTPA: computed tomography pulmonary angiography.

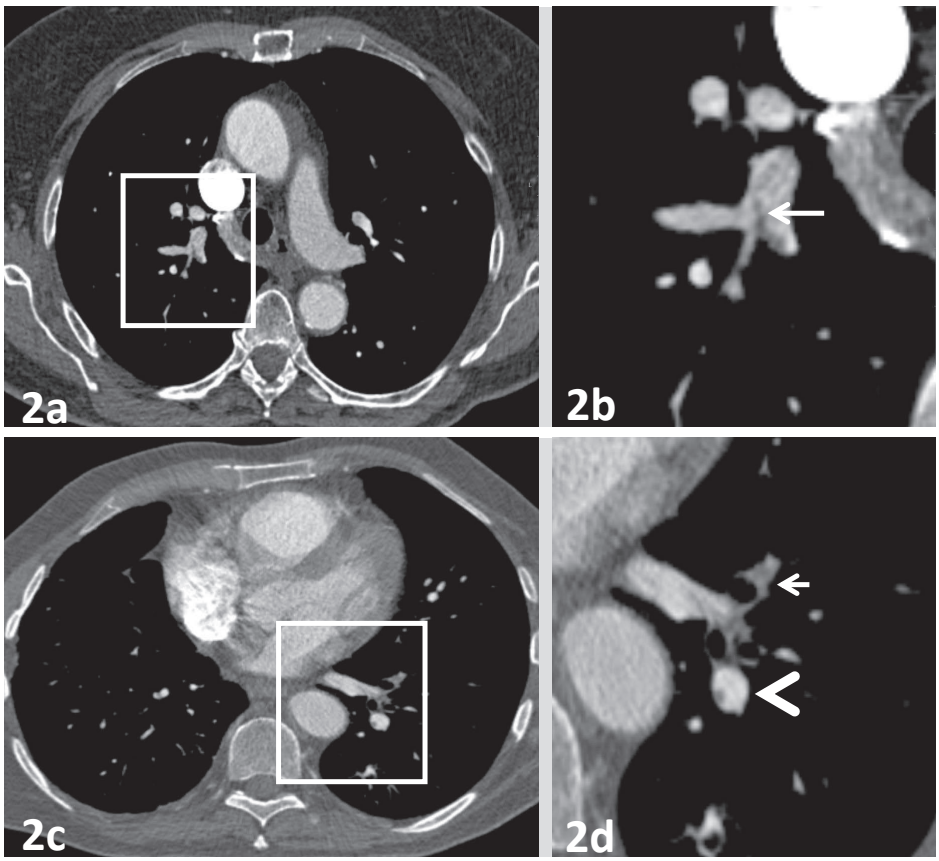


Figure 2. Chronic thrombus remnants characteristics found on axial CTPA images.
Fig 2a and b (zoomed-in): Intravascular webs in the right upper lobe artery (arrow).
Fig 2c and d (zoomed-in): Retraction of the anterobasal segment artery of the left lower lobe (arrow), note the difference in size compared with the segmental posterior artery of the left lower lobe (arrrowhead).
Note: CTPA: computed tomography pulmonary angiography.

Study outcome and definitions

The primary aim of the study was to assess whether careful reading of CTPA scans performed for suspected acute PE can differentiate patients with acute PE without CTEPH from those with already existing CTEPH. The secondary aims of the study were: 1) to evaluate the interobserver agreement of the three expert radiologists for the diagnosis of CTEPH and 2) to identify the best (set of) predictive radiological signs of CTEPH on CTPA for acute PE. To avoid misclassification bias, the radiological signs of CTEPH were indicated as predictive for CTEPH diagnosis, as it is impossible to prove that these patient already had CTEPH at that moment.

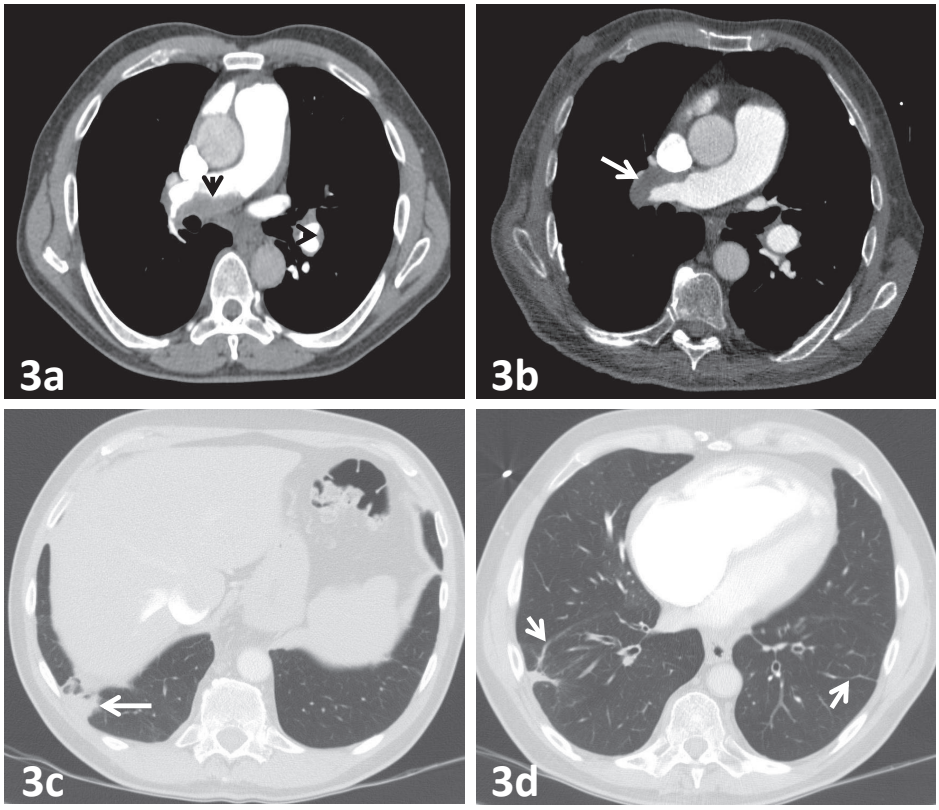


Figure 3. Chronic thrombus remnants characteristics found on axial CTPA images.
Fig 3a: Residual thrombus attached to the vascular wall (arrows).
Fig 3b: Total occlusion of the right pulmonary artery (arrow).
Fig 3c: Pulmonary infarction in the laterobasal segment of the right lower lobe (arrow).
Fig 3d: Parenchymal bands in the laterobasal segments of the left- and right lower lobe (arrows).
Note: CTPA: computed tomography pulmonary angiography.

Statistical analysis

Baseline characteristics of the patients are provided with corresponding frequencies. Differences between the two cohorts with regard to categorical variables were calculated using odds ratios (OR) with corresponding 95% confidence intervals (95%CI). Final patient allocation by the radiologists was based on majority rule. Odds ratio, sensitivity and specificity of the patient allocation were calculated with corresponding 95%CI. We predefined a sensitivity >80% and/or a specificity >80% as 'relevant' accuracy. The interobserver agreement for allocation of the patients in either of the two groups was determined by using Cohen's kappa-statistics. The kappa value 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].

Next, we determined the accuracy of all individual radiological signs studied for a future CTEPH diagnosis in univariate analysis by calculating ORs with corresponding 95%CI. The 10 strongest predictors from univariate analysis were included in a multivariable backward conditional stepwise logistic regression model. All items left in the final model were considered to be independently associated with a CTEPH diagnosis in the clinical course of acute PE. The predictive accuracy of the combination of the identified independent predictors was evaluated using receiver operating characteristic (ROC) curve analysis in all 100 study patients. Optimal threshold of the number of radiological signs for patients at high risk was determined based on comparison of the area under the curves (AUC). The sensitivity and specificity of this threshold was calculated for the complete study population. All analyses were performed using SPSS software version 23 for Windows IBM Corporation.

RESULTS

Patients

The patient characteristics at the moment of the initial CTPA scan for the PE diagnosis are provided in **Table 1.** Mean age at the time of PE diagnosis was 61 ± 15 years in cases and 56 ± 15 years in controls. A total of 43 (86%) cases had an unprovoked acute PE event and 20 (40%) had recurrent venous thromboembolism (VTE). In the control cohort, these numbers were 29 (58%) and 10 (20%) respectively for ORs of 5.2 (95%CI 2.0-14) and 2.7 (95%CI 1.1-6.5), respectively. Symptom onset was >2 weeks before PE diagnosis in 43 (86%) cases compared with 6 (12%) controls for an OR of 45 (95%CI 14-145). The median RV/LV diameter ratio at the time of the PE diagnosis was 1.5 ± 0.4 for the cases and 1.1 ± 0.2 for the controls. The cases were referred for CTEPH diagnosis after a median of 7.1 months (IQR 4.7-12.3) following the initial CTPA scan performed for diagnosing PE.

CTPA scan quality

Twelve of the 100 CTPA scans were judged to be of suboptimal quality due to motion artefacts and/or inadequate contrast timing for diagnosing acute PE. One of these latter CTPA scans could not be assessed for the presence of chronic thrombus remnants at all because of completely insufficient scan timing. This patient was therefore allocated to the control cohort by all three expert readers. All 100 scans were included in the primary analysis.

Table 1. Patient characteristics.

	Cases (patients diagnosed with CTEPH during follow-up after PE) (n=50)	Controls (patients who did not develop CTEPH after PE) (n=50)	Differences
Age at PE diagnosis (mean, SD)	61 (15)	56 (15)	0.04[#]
Male sex (n, %)	23 (46)	17 (34)	1.7 (0.74-3.7)[^]
Unprovoked PE (n, %)	43 (86)	27 (54)	5.2 (2.0-14)[^]
Recurrent VTE	20 (40)	10 (20)	2.7 (1.1-6.5)[^]
Onset of symptoms > 2 weeks before PE diagnosis	43 (86)[*]	6 (12)	45 (14-145)[^]
Comorbidities at the moment of PE			
COPD (n, %)	10 (20)	4 (8)	2.9 (0.84-9.9)[^]
Chronic left heart failure (n, %)	4 (8)	3 (6)	1.4 (0.29-6.4)[^]
Malignancy (n, %)	7 (14)	14 (28)	0.42 (0.15-1.1)[^]

Note: CTEPH: chronic thromboembolic pulmonary hypertension; PE: pulmonary embolism; SD: standard deviation; VTE: venous thromboembolism; COPD: chronic obstructive pulmonary disease.
Differences calculated by using: [#]students T test; [^]OR with corresponding 95% confidence interval; [*]missing in 3 patients.

Distinction of CTEPH from acute PE

The results of CTPA scoring are displayed in **Table 2.** A total of 39 patients were diagnosed as having CTEPH and 61 as not having CTEPH. The OR for a CTEPH diagnosis during follow-up for those former 39 patients was 40 (95%CI 11-151). This final diagnosis yielded a sensitivity of 72% (95%CI 58-84) and a specificity of 94% (95%CI 83-99%). Of the 50 CTEPH cases, any sign of acute PE was identified in 37 (74%) patients and signs of chronic thrombus remnants in 44 (88%). A total of 31 (62%) patients were scored as having both acute PE and chronic thrombus remnants. For the control cohort, these numbers of acute PE and chronic thrombus remnants were 46 (92%) and 11 (22%), respectively.

A total of 14 CTEPH cases were not identified. The CTPA scan in one of them was technically inadequate for diagnosis of CTEPH as described above. Moreover, in those 14 patients, the median duration between PE diagnosis and referral to the VUMC was 11 (IQR 4.9-19) months. In the 36 patients correctly identified, this time period was 6.7 (IQR 4.5-16) months (P=0.13 for difference). None of the patient characteristics available for analysis were associated with incorrect allocation (**Supplement 1**).

Radiological parameters for future CTEPH diagnosis

All radiological parameters for chronic thrombus remnants and PH were highly associated with a future CTEPH diagnosis in univariate analysis, with ORs ranging from 4.4 to

Table 2. Results of CTPA scoring by three expert radiologists based on majority rule.

	Signs of chronic thrombus remnants (n, %)	Signs of acute PE (n, %)	Signs of acute PE and chronic thrombus remnants (n,%)	Signs of PH (n,%)	Overall judgment CTEPH yes/no (n, %)
Cases: patients diagnosed with CTEPH during follow-up after PE (n=50)	44 (88)	37 (74)	31 (62)	43 (86)	36 (72)
Controls: patients who did not develop CTEPH after PE (n=50)	11 (22)	46 (92)	10 (20)	9 (18)	3 (6)

Note: PE: pulmonary embolism; PH: pulmonary hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; CTPA: computed tomography pulmonary angiography.

infinite (**Table 3**)**.** The latter indicates that the specific radiological parameter was not identified in any of the controls but in at least one of the cases. Signs of chronic thrombus remnants with the highest predictive value for CTEPH diagnosis were: presence of intravascular webs (OR 48; 95%CI 13-177), thrombus adherent to the vascular wall (OR 44; 95%CI 9.2-207), complete arterial occlusion (OR 5.0; 95%CI 1.8-14), arterial retraction (OR 26; 95%CI 8.0-82) and post-stenotic vascular dilatation (OR infinite). Signs of PH with the highest predictive value for a future CTEPH diagnosis were: dilatation of the main pulmonary artery (OR 18; 95%CI 6.2-55), RV hypertrophy (OR infinite), flattening of the interventricular septum (OR 18; 95%CI 6.1-55), mosaic perfusion (OR 20; 95%CI 6.0-69) and dilated bronchial arteries (OR 13; 95%CI 4.0-39).

Multivariate regression analysis revealed the following six radiological parameters to be independent predictors for a future CTEPH diagnosis: presence of intravascular webs (adjusted OR 209; 95%CI 4.2->1000), retraction (adjusted OR 47; 95%CI 1.9->1000), dilatation of the bronchial arteries (adjusted OR 19; 95%CI 0.71-516), dilatation of the pulmonary arteries (adjusted OR 14; 95%CI 0.82-248), RV hypertrophy (adjusted OR infinite) and flattening of the interventricular septum (adjusted OR 9.9; 95%CI 0.61-161). The overall AUC of the ROC curve for these six variables was 0.99 (95%CI 0.97-1.0). The most optimal threshold for a future CTEPH diagnosis was three or more of these radiological parameters, for a C-statistic of 0.92 (95%CI 0.86-0.99). Patients with three or more of these radiological parameters had a higher risk of a future CTEPH diagnosis than those with less than three parameters, for an OR of 56 (95%CI 12-261). This model yielded a sensitivity of 70% (95%CI 55-82) and a specificity of 96% (95%CI 86-100). Kappa values for the assessment of the individual 6 independent predictors of CTEPH ranged between 0.53 and 0.83, with 75% of all kappa's ≥ 0.7.

Table 3. Univariate and multivariate analysis on radiological parameters of a future CTEPH diagnosis in the clinical course of acute PE.

Scored radiological parameter	Scored in number of cases n=36	Scored in number of controls n=50	Univariate analysis		Multivariate analysis	
			OR	95%CI	OR	95%CI
Signs of chronic PE						
Intravascular webs	29	4	48	13-177	209	4.2->1000
Thrombus attached to the vascular wall	34	14	44	9.2-207		
Complete arterial occlusion	30	25	5.0	1.8-14		
Arterial retraction	28	6	26	8.0-82	47	1.9->1000
Post-stenotic vascular dilatation	2	0	Infinite			
Pulmonary infarction	21	12	4.4	1.8-11		
Parenchymal bands	10	4	4.4	1.3-16		
Signs of PH						
Dilatation of the main pulmonary artery	28	8	18	6.2-55	14	0.82-248
RV hypertrophy	14	0	Infinite		Infinite	
Flattening of the interventricular septum	27	7	18	6.1-55	9.9	0.61-161
Dilated bronchial arteries	21	5	13	4.0-39	19	0.71-516
Mosaic perfusion	23	4	20	6.0-69		

Note: OR: odds ratio; CI: confidence interval; PE: pulmonary embolism, PH: pulmonary hypertension; RV: right ventricular.

DISCUSSION

In this study we have demonstrated that expert radiologists were able to identify 36 of 50 patients with acute PE who were later diagnosed with CTEPH and correctly excluded CTEPH in 47 out of 50 patients from those who did not develop CTEPH after at least 2 years of follow-up, based on close reading of the CTPA scan performed for the initial PE diagnosis. The interobserver agreement between the three expert radiologists for the majority of the best predictive radiological parameters was good. The presence of three or more of these best predicting parameters was strongly predictive of a CTEPH diagnosis.

Our findings have two main explanations. First, it is likely that CTEPH was already present at the moment of the initial PE diagnosis but that CTEPH characteristics were not recognized when not sought for. Second, chronic thrombus remnants may increase

the risk of future CTEPH development. Although the design of our study does not allow differentiation between the two, we consider the first explanation the most likely. First, we found high diagnostic accuracy for all evaluated radiological parameters of CTEPH. This could not be explained by any other fact than that CTEPH was already developing or present, especially since the specificity we found in our cohort approximates the established specificity of CTPA for CTEPH [8]. Importantly, we did not set out to find *new* radiological signs for CTEPH but only evaluated established ones. Second, the vast majority of cases reported to have symptoms of dyspnoea for longer than two weeks before diagnosis of acute PE, in contrast to the controls. This is an argument supporting the presence of CTEPH in addition to acute PE as well [22, 23].

Interestingly, almost all cases had radiological signs of acute PE as well, which supports the validity of this diagnosis of 'acute on chronic' PE in these patients. On the other hand, a small number of the controls had signs of chronic thrombus remnants and/or PH as well, although PH was not confirmed by sequential echocardiography after 2 years of follow-up. Earlier studies also suggested that the prevalence of radiological parameters of chronic thrombus remnants and/or PH is 20% in patients who do not have echocardiographic signs of CTEPH after a 2-year follow-up period [6]. The clinical relevance of these findings is unknown, especially since it is unclear if these patients develop CTEPH beyond the first two years from the acute PE event.

How can our findings be useful for clinical practice? It seems clear that specific radiological findings on CTPA may accurately predict CTEPH diagnosis, or the concurrent presence of CTEPH. Several considerations need however to be taken into account. The control patients were selected based on RV dilatation to force the radiologist to focus on the subtle aspects of thrombus remnants and to prevent bias towards overestimation of our primary endpoint. The results of this study are therefore only applicable to PE patients with signs of RV overload. Nevertheless, it is not likely that PE patients without RV overload have CTEPH. Also, the interobserver agreement between the expert thoracic radiologists was mostly good. The performance for less specialized radiologists may be less, and additional training may be needed for them.

Strong points of this study are the blind assessment of the CTPA scans by three independent expert radiologists, the relative large number of patients with CTEPH and the selection of the controls based on RV dysfunction. Also, the fact that not all CTPA scans were of excellent technical quality underlines the fact that our study truly represents daily practice rather than trial circumstances, favouring external validity of our findings.

The main study limitation is that we studied clear-cut cases of patients with CTEPH and PE patients with right ventricular overload who did not develop CTEPH after 2 years of follow-up, while in clinical practice, the presentation of CTEPH is heterogeneous and the diagnosis is often challenging, for instance considering other conditions that may cause PH such as left sided heart failure and/or chronic obstructive pulmonary disease

[24, 25]. Moreover, the prevalence of CTEPH in the cohort was 50%, while this number is much lower in clinical practice. This may have influenced the predictive value of the identified radiological parameters.

In conclusion, we showed that expert radiologists are able to accurately identify patients who were later on diagnosed with CTEPH based on careful reading of the CTPA scan performed in the setting of suspected acute PE. We identified six radiological parameters that proved to be independent predictors of definite CTEPH diagnosis in the clinical course of acute PE. The presence of three or more of these radiological parameters was associated with a 56-fold higher incidence of CTEPH, with a sensitivity of 70% and a specificity of 96%. Our findings support the hypothesis that dedicated CTPA reading in patients with acute PE with integral focus on signs of chronic thrombus remnants and PH may help to detect CTEPH earlier, which may improve the prognosis of these patients with CTEPH [26].

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Supplement 1. Patient characteristics of the cases identified versus those not identified.

	Cases identified as CTEPH (n=36)	Cases not identified as CTEPH (n=14)	Difference
Age at moment of PE diagnosis (mean, SD)	62 (15)	64 (16)	0.79[#]
Male sex (n, %)	17 (47)	6 (43)	0.83 (0.24-2.9)[^]
Unprovoked PE (n, %)	31 (86)	12 (86)	0.97 (0.16-5.7)[^]
Recurrent VTE (n, %)	14 (39)	6 (43)	1.2 (0.34-4.1)[^]
Duration between PE diagnosis and referral to VUMC (month; median, IQR)	6.7 (4.5-16)	10.5 (4.9-19)	0.13[‡]
Malignancy (n, %)	4 (11)	3 (21)	2.2 (0.42-11)[^]
Cardiopulmonary comorbidity (n, %)	10 (28)	4 (29)	1.0 (0.26-4.1)[^]

Note: PE: pulmonary embolism; VTE: venous thromboembolism; VUMC: VU university medical Center Amsterdam.

[#] Independent sample t-test; [^]OR with corresponding 95% confidence interval; [‡]Mann Whitney U test.