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CHEST

Preexisting Chronic Thromboembolic Pulmonary Hypertension in Acute Pulmonary Embolism

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BACKGROUND: Chronic thromboembolic pulmonary hypertension (CTEPH) is considered a complication of pulmonary embolism (PE). However, signs of CTEPH may exist in patients with a first symptomatic PE.

RESEARCH QUESTION: Which radiologic findings on CT pulmonary angiography (CTPA) at the time of acute PE could indicate the presence of preexisting CTEPH?

STUDY DESIGN AND METHODS: This study included unselected patients with acute PE who were prospectively followed up for 2 years with a structured visit schedule. Two expert radiologists independently assessed patients' baseline CTPAs for preexisting CTEPH; in case of disagreement, a decision was reached by a 2:1 majority with a third expert radiologist. In addition, the radiologists checked for predefined individual parameters suggesting chronic PE and pulmonary hypertension.

RESULTS: Signs of chronic PE or CTEPH at baseline were identified in 46 of 303 included patients (15%). Intravascular webs, arterial narrowing or retraction, dilated bronchial arteries, and right ventricular hypertrophy were the main drivers of the assessment. Five (1.7%) patients were diagnosed with CTEPH during follow-up. All four patients diagnosed with CTEPH early (83-108 days following acute PE) were found in enriched subgroups based on the experts' overall assessment or fulfilling a minimum number of the predefined radiologic criteria at baseline. The specificity of preexisting CTEPH diagnosis and the level of radiologists' agreement improved as the number of required criteria increased.

INTERPRETATION: Searching for predefined radiologic parameters suggesting preexisting CTEPH at the time of acute PE diagnosis may allow for targeted follow-up strategies and risk-adapted CTEPH screening, thus facilitating earlier CTEPH diagnosis.

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KEY WORDS: chronic thromboembolic pulmonary hypertension; CT pulmonary angiography; diagnosis; imaging; pulmonary embolism

ABBREVIATIONS: CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; CTPA = CT pulmonary angiography; PPEI = postpulmonary embolism impairment; Q = quartile

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Take-home Points

Study Question: What is the prevalence of radiologic parameters of chronic pulmonary thromboembolism and pulmonary hypertension at the time of diagnosis of acute PE? Which radiologic findings could indicate preexisting CTEPH?

Results: Radiologic signs of chronic PE or CTEPH at the time of PE diagnosis were identified in 46 of 303 included patients (15%). The most common were intravascular webs, arterial narrowing or retraction, dilated bronchial arteries, and right ventricular hypertrophy. Four of five patients with signs of chronic disease at the time of acute PE were subsequently diagnosed with CTEPH early (83-108 days following an acute PE).

Interpretation: Awareness of radiologic signs suggesting preexisting CTEPH at the time of acute PE may allow for targeted follow-up strategies, risk-adapted screening, and early diagnosis of CTEPH.

Over the past decade, substantial efforts were made to increase our knowledge of the late sequelae of acute pulmonary embolism (PE), contributing to progress in their prevention and timely diagnosis and treatment.[1] It could thus be shown that functional, laboratory, and imaging abnormalities may persist, to a variable extent, in a considerable proportion of patients following acute PE.[2-5] Their combinations define a broad spectrum of clinical symptoms and pathologic conditions, for which the term "post-PE syndrome" has been proposed.[6] Chronic thromboembolic pulmonary hypertension (CTEPH) is considered to represent the far end of the severity spectrum of the post-PE syndrome; if it escapes early detection and is left untreated, it may substantially reduce the life expectancy and quality of life of patients who have survived an acute PE episode.[7,8] We now have a better understanding of the pathogenesis of CTEPH, and a number of concomitant diseases and conditions enhancing the transition from acute to chronic thromboembolism could indeed be identified.[9,10] However, the reported incidence of CTEPH diagnosed following acute PE still varies widely in the literature,[11,12] highlighting the need for further developing and prospectively validating algorithms that will optimize patient follow-up and early detection of CTEPH following acute PE.[1]

Contemporary clinical protocols for the follow-up of survivors of acute PE need to take into account the fact that clinical or functional symptoms and signs as well as imaging findings of CTEPH may already be present at the time of diagnosis of the "first" (index) symptomatic acute PE episode.[13] A number of radiologic parameters and criteria indicating the presence of chronic thromboembolic lung disease and pulmonary hypertension have been identified, particularly on the basis of CT pulmonary angiography (CTPA).[14,15] More recent publications have suggested that such findings can be found (provided that they are explicitly sought) rather frequently in the CTPA performed to diagnose acute PE, and some of them seemed to strongly predict the diagnosis of CTEPH over the long term.[16-18] However, to inform guideline recommendations and clinical practice related to CTPA reporting in acute PE, these data need to be validated and confirmed in cohort studies with prospective clinical follow-up. Our goal, therefore, was to determine the prevalence of radiologic parameters of chronic pulmonary thromboembolism and pulmonary hypertension among unselected consecutive patients with acute PE and no known history of CTEPH. Moreover, we investigated the association between the radiologic assessment at baseline and patient outcomes at the 2-year prospective follow-up.

Study Design and Methods

Study Setting and Patient Population

We prospectively included unselected consecutive patients who presented with acute symptomatic PE at two large tertiary centers and Follow-Up after Acute Pulmonary Embolism (FOCUS) sites (Mainz and Cologne) and who had provided written informed consent. The patients belonged to the population of the FOCUS cohort study.[19,20] Patients were excluded if, among other criteria, they had a known history of diagnosed CTEPH. They were followed up over a 2-year period following the index PE episode, using a standardized assessment plan (patient-reported health status as well as clinical, functional, laboratory, and echocardiographic examinations) at five prespecified visits (upon enrollment, at hospital discharge, and at 3, 12, and 24 months). The visit plan and assessments were part of a harmonized clinical protocol that served as the standard of care at both participating sites.

In addition to the diagnosis of CTEPH during the follow-up period, which was made according to diagnostic criteria available at the time of study design in 2013, the study's primary outcome included post-PE impairment (PPEI), which was prospectively defined according to a combination of echocardiographic, clinical, functional, and laboratory parameters.[19] PPEI was conceived as a warning signal for the possible presence of CTEPH and consequently as a clinical tool for narrowing the target population for advanced CTEPH diagnostic workup among the survivors of acute PE. The study was registered in the German Clinical Trials repository (ID DRKS00005939) and

approved by a central ethics committee and committees of the participating sites.

Study Objectives and Variable Definition

The main goal of the current study was to estimate the prevalence of radiologic parameters of chronic PE or pulmonary hypertension; that is, findings suggestive of preexisting CTEPH, at the time of acute PE diagnosis (index event).

Parameters characterizing the acute and/or chronic phase of PE, and that of CTEPH, were selected for assessment based on current evidence at the time of study design.[14,15,21] These included the following: (1) thrombus morphology typical of acute PE (preserved caliber of the vessel, central ["polo mint" sign if imaged in short axis, or "railway track" sign if imaged in long axis] or eccentric filling defect; (2) vascular/parenchymal findings suggestive of chronic PE (intravascular webs, complete arterial occlusion, arterial narrowing or retraction, poststenotic vascular dilatation, mosaic perfusion, parenchymal bands, and pathologic or dilated bronchial arteries); (3) parameters and signs found both in acute and chronic PE and pulmonary hypertension, including right ventricular dilatation, flattening of the interventricular septum, and pulmonary infarction; and (4) signs of chronic pulmonary hypertension (pulmonary trunk dilatation and right ventricular hypertrophy).

CT pulmonary angiograms for diagnosis of index PE had been performed using scanners with ≥ 64 slices and a reconstructed slice thickness of 1 to 3 mm. Reassessment of the patients' index CTPA was performed in parallel by two independent expert radiologists, who were blinded to each other's assessment and unaware of the patients' baseline characteristics at the time of the index PE event as well as their clinical outcomes and diagnosis of CTEPH or PPEI during follow-up. The radiologists were provided with a charter including a checklist of the predefined radiologic parameters, as well as a file containing representative images of each abnormality. The radiologists performed a parallel independent assessment of the CTPAs by logging into an electronic clinical platform (Castor electronic data capture system), where they were asked to fill a pre-built template. First, they were asked to assess each individual radiologic parameter and anatomically locate the abnormality. Subsequently, they were asked to provide an overall assessment on whether the CTPA was indicative of acute PE alone, or of co-existing chronic pulmonary thromboemboli and/or chronic pulmonary hypertension (ie, acute-on-chronic PE). In case of disagreement concerning the overall assessment, a third blinded expert was asked to assess the CTPA and provide an independent interpretation of the findings. In these latter cases, the CTPA-based diagnosis was ultimately classified into one of the aforementioned categories based on a 2:1 majority opinion. Only following completion of all assessments were the results of the radiologic evaluation merged with each patient's pseudonymized baseline and follow-up clinical data.

Statistical Analysis and Data Transfer

Descriptive statistics were used for summarizing the baseline demographic and clinical characteristics of the included patients. Absolute and relative proportions were computed for categorical variables and medians (quartile 1 [Q1]-Q3) for continuous variables. Comparisons were done by providing ORs and 95% CIs.

CTPA images were transferred between the two centers by using standardized data protection protocols in both institutions. The electronic data capture system was secured according to the most recent standards and is certified for ISO 27001 (Standards for Information Security Assurance).

Results

Baseline Characteristics and Radiologic Parameters of Chronicity

A total of 303 patients were included at the two sites in the current study; their median age was 63 (Q1-Q3, 51-73) years, 135 (44.6%) were female, and 16 patients (5.3%) presented with hemodynamic instability. The prevalence of cancer or myeloproliferative disease was 12.5%, and 30% had a history of VTE. An overview of the demographic and baseline clinical characteristics of the patients is provided in Table 1.

The two radiologists provided an overall assessment of whether the patient's CTPA was suggestive of (preexisting) chronic PE or CTEPH. As shown in Table 2,[14-18,22] expert 1 classified 41 (13.5%) patients as having radiologic signs of chronicity; for expert 2, these totaled 40 (13.2%) patients, however, only partly overlapping with those identified by expert 1. In total, there was an agreement between the two radiologists in 19 cases, and a third expert radiologist was asked to provide an additional blinded assessment in 43 additional cases. Following the third assessment, a total of 46 patients (15.2%) were classified, either by two-expert consensus or by a 2:1 majority, as having chronic PE or CTEPH at baseline (Fig. 1). The median age of these patients was 64 (Q1-Q3, 53-75) years; 21 patients (45.7%) were female, and 22 (47.8%) had a history of VTE.

Table 2 also provides a comparison of the independent blinded assessment by the two radiologists, based on specific predefined parameters in the baseline (index) CTPA of patients with acute PE. Based on thrombus morphology, the two experts confirmed (as expected) that 95% of the patients had acute PE. In addition, however, expert 1 estimated that 195 (64.4%), 92 (30.4%), 42 (13.9%), and 26 (8.6%) of the patients had at least 1, 2, 3, or 4 findings indicating chronic PE or chronic pulmonary hypertension, respectively. In the assessment of expert 2, the corresponding numbers were 269 (88.8%), 205 (67.7%), 128 (42.2%), and 85 (28.1%) patients. A total of 81 (26.7%) patients were classified by expert 1 and 144 (47.5%) by expert 2 as having at least one sign of chronic PE plus at least one sign of chronic pulmonary hypertension.

Table 3 displays the association between individual radiologic signs and each expert's overall assessment of

TABLE 1] Demographic and Baseline Clinical Characteristics of the Study Participants

Variable	Total (N = 303)	Missing
Demographic characteristics		
Female	135 (44.6)	0
Age, median (Q1-Q3), y	63 (51-73)	0
Vital signs and risk classification of pulmonary embolism		
Systolic/diastolic BP, median (Q1-Q3), mm Hg	135 (121-152)/80 (70-90)	42/43
Oxygen saturation, median (Q1-Q3), %	96 (93-97)	70
CTPA or echocardiographic signs of right ventricular dysfunction or dilatation	142 (46.9)	0
Low-risk pulmonary embolism	63 (20.8)	0
Intermediate-risk pulmonary embolism	224 (73.9)	0
High-risk pulmonary embolism	16 (5.3)	0
Risk factors for VTE and comorbidities		
Cancer or myeloproliferative disease	38 (12.5)	0
Hormonal treatment	24 (7.9)	0
Pregnancy	0	0
Recent long-distance travel	28 (9.2)	1
Recent surgery or trauma	50 (16.5)	0
Recent immobilization	82 (27.1)	0
Prior VTE	91 (30.0)	0
Chronic pulmonary disease	35 (11.6)	0
Chronic heart failure	10 (3.3)	0
Chronic liver disease	15 (5.0)	0
Chronic renal disease	19 (6.3)	0

Data are presented as No. (%) unless otherwise indicated. CTPA = CT pulmonary angiography; Q = quartile.

the presence of chronic PE or CTEPH at baseline.[14-18] Intravascular webs, arterial narrowing or retraction, pathologic or dilated bronchial arteries, and right ventricular hypertrophy seemed to be the main drivers of the overall assessment.

Diagnosis of CTEPH During 2-Year Follow-Up and Association With Radiologic Parameters at Baseline

During follow-up, 5 of 303 patients (1.7%; 95% CI, 0.7-3.8) were diagnosed with CTEPH; their key baseline and follow-up data are shown in Table 4. Of these patients, four were among the 46 patients "finally adjudicated," either by two-expert consensus or by a 2:1 majority, as having chronic PE or CTEPH at baseline (Fig. 1). This corresponds to an 8.7% probability of CTEPH confirmation at follow-up, with an OR of 24.4 (95% CI, 2.7-223.5) compared vs patients with no identified signs of preexisting chronicity. Of note, these four patients were assigned to the preexisting CTEPH group by the two first radiologists with no need of further assessment by the third expert. Only one patient, in whom neither radiologist reported signs of chronicity at baseline, was diagnosed with CTEPH during follow-up. In contrast to the other four cases, in which the diagnosis was confirmed as early as 83 to 108 days following acute PE, in this latter patient the CTEPH diagnosis was made much later (ie, following 485 days of follow-up). This observation supports the notion that this particular patient was the only one who developed CTEPH de novo, following the index acute PE event.

We also examined the association between individual predefined radiologic findings at CTPA in the acute phase of PE and the diagnosis of CTEPH during follow-up; the results are displayed in e-Table 1. As the table shows, the ORs calculated separately for each radiologic parameter differed between the two experts. Importantly, however, and as shown in e-Table 2, patients who were diagnosed with CTEPH early at follow-up (within approximately 3 months of the index acute PE event), all could be found in enriched subgroups of patients fulfilling a minimum number of these criteria. For example, CTEPH was confirmed in 11.0% of the patients exhibiting at least two signs of chronic pulmonary PE plus one sign of chronic

TABLE 2] Assessment of Predefined Radiologic Parameters in the Study Population at Baseline (As Performed Post Hoc by Two Independent Experts)

Parameter	Expert 1	Expert 2	Cohen's Kappa Coefficient
Overall assessment of acute vs chronic pulmonary embolism or CTEPH at baseline			
Acute pulmonary embolism	290 (95.7)	283 (93.4)	0.426
Chronic pulmonary embolism or CTEPH	41 (13.5)	40 (13.2)	0.387
Assessment of individual radiologic parameters			
Acute thrombus morphology[a]	290 (95.7)	286 (94.4)	0.477
Intravascular webs	14 (4.6)	25 (8.3)	0.313
Complete arterial occlusion	91 (30.0)	185 (61.1)	0.249
Arterial narrowing or retraction	14 (4.6)	38 (12.5)	0.316
Poststenotic vascular dilatation	1 (0.3)	9 (3.0)	...
Mosaic perfusion	42 (13.9)	35 (11.6)	0.337
Parenchymal bands	5 (1.7)	97 (32.0)	0.066
Pathologic or dilated bronchial arteries	19 (6.3)	38 (12.5)	0.348
RV/LV ratio ≥ 1.0[b]	172 (56.8)	174 (57.4)	0.650
Flattening of the interventricular septum[b]	136 (44.9)	100 (33.0)	0.611
Pulmonary infarction[c]	78 (25.7)	131 (43.2)	0.449
Pulmonary trunk dilatation[d]	147 (48.5)	157 (51.8)	0.697
RV hypertrophy[e]	33 (10.9)	23 (7.6)	0.223

Data are presented as No. (%). The radiologic parameters were selected among those proposed and validated in the literature.[14-18] The two expert radiologists assessed the predefined parameters independently, being blinded both regarding the baseline characteristics of the patients and to their clinical outcome at follow-up. CTEPH = chronic thromboembolic pulmonary hypertension; LV = left ventricular; RV = right ventricular.

[a]Preserved caliber of the vessel; central ("polo mint" sign if imaged in short axis, or "railway track" sign if imaged in long axis); or eccentric filling defect. These findings can also be observed in acute-on-chronic pulmonary embolism.[14]

[b]This finding denotes pressure overload of the right ventricle in acute intermediate-risk or high-risk PE,[1] but it is also encountered in chronic pulmonary hypertension.[22]

[c]Triangular subpleural consolidation.[14]

[d]Pulmonary trunk diameter equal to or above the cutoff of 30 mm for men and 27 mm for women.

[e]Defined as thickness of the RV free wall > 5 mm.

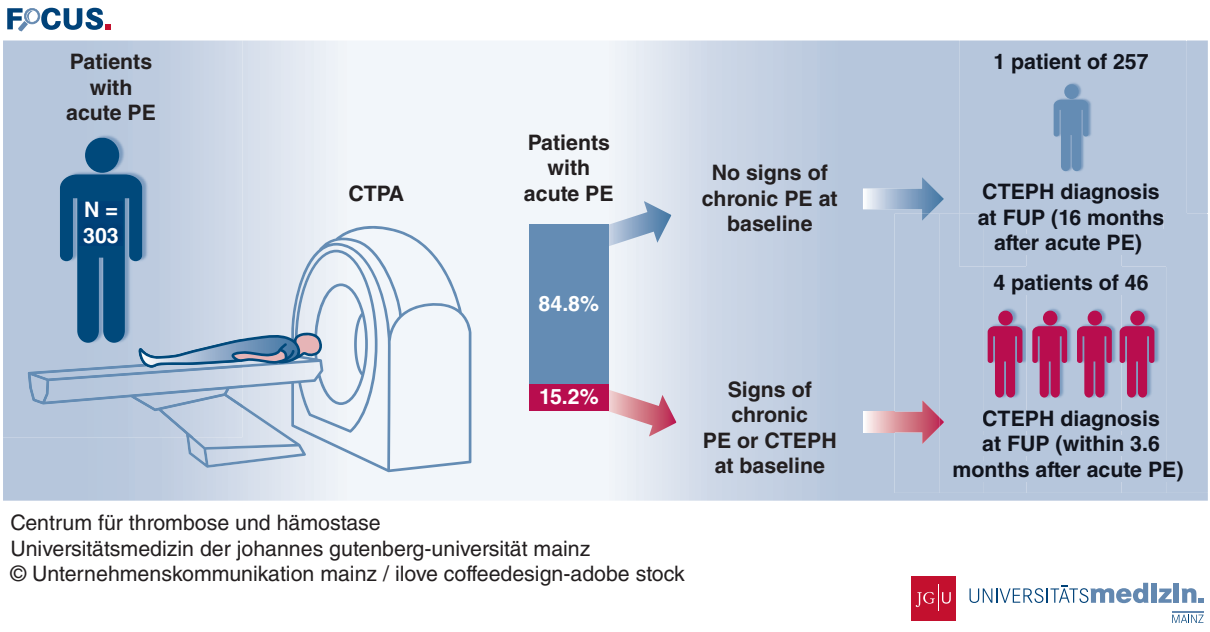

Figure 1 – *Overall assessment for the presence of chronic thrombi or CTEPH among patients with acute symptomatic PE. The overall assessment was based on the overall interpretation of radiologic findings and personal experience: if two expert radiologists disagreed on the interpretation of chronic findings, a third expert radiologist was asked to assess the CTPA independently, and the final judgment was based on the majority opinion. CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = CT pulmonary angiography; FUP = follow-up; PE = pulmonary embolism.*

TABLE 3] Association Between Individual Radiologic Parameters and Overall Assessment of Chronic Pulmonary Embolism or Chronic Thromboembolic Pulmonary Hypertension

Parameter	OR Expert 1 (95%CI)	OR Expert 2 (95%CI)
Acute thrombus morphology[a]	0.20 (0.06-0.68)	0.08 (0.03-0.22)
Intravascular webs	102.78 (13.01-812.02)	48.09 (15.29-151.30)
Complete arterial occlusion	3.41 (1.79-6.49)	2.25 (1.09-4.63)
Arterial narrowing or retraction	46.18 (9.90-215.47)	27.94 (12.21-63.95)
Poststenotic vascular dilatation	infinite [f]	7.71 (1.99-29.92)
Mosaic perfusion	6.24 (3.02-12.90)	6.62 (3.06-14.33)
Parenchymal bands	infinite [f]	1.97 (1.04-3.73)
Pathologic or dilated bronchial arteries	16.99 (6.04-47.84)	11.48 (5.27-25.01)
RV/LV ratio ≥ 1[b]	2.79 (1.36-5.73)	1.65 (0.85-3.20)
Flattening of the interventricular septum[b]	2.99 (1.54-5.82)	2.59 (1.35-4.97)
Pulmonary infarction[c]	1.31 (0.66-2.61)	0.40 (0.20-0.80)
Pulmonary trunk dilatation[d]	2.82 (1.44-5.54)	2.72 (1.37-5.41)
RV hypertrophy[e]	3.95 (1.78-8.75)	26.97 (9.75-74.64)

Cis > 1.0 indicate that the presence of the parameter considered was associated with the assessment of chronic pulmonary embolism or chronic thromboembolic pulmonary hypertension in the same patient. The radiologic parameters were selected among those proposed and validated in the literature.[14-18] The two expert radiologists assessed the predefined parameters independently and were blinded both to the baseline characteristics of the patients and to their clinical outcome at follow-up. LV = left ventricular; RV = right ventricular.

[a]Preserved caliber of the vessel; central ("polo mint" sign if imaged in short axis, or "railway track" sign if imaged in long axis); or eccentric filling defect. These findings can also be observed in acute-on-chronic pulmonary embolism.[14]

[b]This finding denotes pressure overload of the right ventricle in acute intermediate-risk or high-risk PE but is also encountered in chronic pulmonary hypertension.[14]

[c]Triangular subpleural consolidation.[14]

[d]Defined as pulmonary trunk diameter equal to or above the cutoff of 30 mm for men and 27 mm for women.

[e]Defined as thickness of the RV free wall > 5 mm.

[f]OR > 1.00, suggesting an association, but not calculable exactly because of the low number of patients with the parameter in the reference group (no chronic pulmonary embolism or chronic thromboembolic pulmonary hypertension).

pulmonary hypertension as identified by expert 1, or in 4.0% of the patients exhibiting the same number of signs as per expert 2. Of note, these percentages were similar to those (9.8% per expert 1 and 4.5% per expert 2) that would be obtained by selecting patients fulfilling at least three of six recently evaluated radiologic signs

TABLE 4] Baseline and Follow-Up Individual-Level Data of the Patients With Adjudicated Chronic Thromboembolic Pulmonary Hypertension

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
At baseline					
Sex	Female	Female	Female	Female	Male
Age, y	60	77	78	40	38
Prior VTE	Yes	No	No	No	No
Pulmonary embolism risk class	Intermediate	Intermediate	Intermediate	Intermediate	Low
Systemic thrombolysis at baseline	Yes	No	No	No	No
Signs of chronic pulmonary embolism/ CTEPH at baseline	Yes	Yes	Yes	Yes	No
During follow-up					
Persistent or new-onset clinical signs or symptoms of pulmonary hypertension[a]	Yes	Yes	Yes	Yes	Yes
WHO functional class III or IV	Yes	Yes	Yes	Yes	Yes
Time to CTEPH diagnosis, D	95	108	92	83	485

CTEPH = chronic thromboembolic pulmonary hypertension; WHO = World Health Organization.

[a]Dyspnea, dizziness, syncope, chest pain, hemoptysis, cyanosis, distension of the jugular veins, peripheral edema, hepatomegaly, ascites, or other relevant symptoms.

TABLE 5] Long-Term Outcome of Patients With vs Without Signs of Chronic Pulmonary Embolism or CTEPH

Outcome	No Signs of Chronic PE or CTEPH at Baseline (n = 257)	Signs of Chronic PE or CTEPH at Baseline (n = 46)
Death from any cause	15 (5.8%)	3 (6.5%)
Rehospitalization	82 (31.9%)	12 (26.1%)
PPEI[a]	30 (13.9%)	8 (24.2%)
PE recurrence	5 (1.9%)	0
Major bleeding	14 (5.4%)	2 (4.3%)
Stroke	2 (0.8%)	0
EuroQol utility index (3 mo), median (Q1-Q3)	0.91 (0.77-1.00)	0.87 (0.76-0.94)
EuroQol utility index (24 mo), median (Q1-Q3)	0.94 (0.83-1.00)	0.84 (0.58-0.94)
PEmb-Qol global score (3 mo), median (Q1-Q3)	20 (6-49)	26 (12-46)
PEmb-Qol global score (24 mo), median (Q1-Q3)	10 (4-29)	20 (11-35)

The European Quality of Life (EuroQol) utility index ranges from 0 to 1, with lower scores indicating worse quality of life; the Pulmonary Embolism Quality of Life (PEmb-Qol) global score ranges from 0 to 100, with higher scores indicating worse quality of life. CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; PPEI = postpulmonary embolism impairment (defined as in Konstantinides et al[19]); Q = quartile.
[a]Not evaluable for PPEI: 42 of 257 among patients with no signs of chronic thrombi or CTEPH at baseline, 13 of 46 among patients with signs of chronic thrombi or CTEPH at baseline; percentages are calculated out of the nonmissing population in each group.

(e-Table 3).[16,17] Increasing the number of required radiologic criteria increased the specificity of either model.

Table 5 summarizes additional long-term outcomes in patients with vs without radiologic signs of chronic PE or CTEPH at baseline; it also provides information on the temporal course of the patients' quality of life in the two groups during follow-up.[19] In fact, patients with signs of chronicity at baseline had a worse 2-year generic and disease-specific quality of life compared with patients with no such signs. Moreover, they seemed to be at a higher risk of fulfilling the criteria for PPEI over 2-year follow-up.

Discussion

This study analyzed clinical and radiologic data from a cohort of consecutive patients with acute PE. Our results can be summarized as follows: (1) a variable but substantial proportion (between 64% and 89%) of the studied unselected patients with acute PE and no known history of CTEPH were found by either expert to exhibit at least one radiologic sign of chronic PE or chronic pulmonary hypertension on index CTPA; (2) both independent experts correctly identified the same four (of a total of five) patients in whom CTEPH was confirmed at follow-up, and most likely preexisting, irrespective of their agreement on individual parameters; (3) confirmed cases could be found within an enriched population of 40 to 46 patients, in whom re-assessment of the index CTPA by the study radiologists raised the suspicion of chronic PE/CTEPH; (4) the specificity of the diagnosis of preexisting CTEPH improved as the total number of required radiologic criteria increased, with a minimum number of three to four criteria seeming to be a reliable and practicable threshold; and (5) the CTEPH cases suspected following re-assessment of the index CTPA were those that had been confirmed early (83-108 days) following acute PE, whereas the only case not suspected from the baseline examination was diagnosed > 1 year after follow-up, possibly representing the only "true" de novo complication of the index acute PE.

CTEPH is a rare disease,[7,13] and its overall incidence following acute PE is low.[11,12,20] Accordingly, current guidelines and consensus statements do not recommend routine screening for CTEPH in all survivors of acute PE.[1,7,23] Instead, a stepwise approach has been proposed, focusing on patients with persistent symptoms or functional limitations 3 to 6 months following the acute episode as well as on those with conditions known to predispose to the development of CTEPH.[1] In addition, and as proposed in a 2019 study,[17] focused assessment of the CTPA examination performed to confirm acute PE may reveal findings suggestive of preexisting chronic thromboembolic disease and thus possibly contribute to

better defining the target population for CTEPH diagnostic work-up at follow-up. The current study supports the relevance and usefulness of advanced baseline CTPA assessment for early detection of CTEPH in survivors of acute PE, and it provides evidence to improve existing algorithms[1] for post-PE follow-up and care.

The possibility that patients presenting with an acute or recurrent PE episode may (unknowingly) already have chronic thromboembolic disease or CTEPH has repeatedly been highlighted,[7,13] and a number of imaging parameters suggesting chronic pulmonary vascular disease have been identified and proposed.[14,17,18,21,22] At present, however, none of these parameters is requested or reported in CTPAs performed to confirm acute PE in clinical practice. In the current study, independent and blinded evaluation of baseline CTPAs by two (and in case of disagreement, three) expert radiologists revealed that a large proportion (as high as 89%) of the patients seemed to have at least one finding suggestive of chronicity, regardless of whether they had a history of prior symptomatic VTE. In addition to their low specificity, the radiologists interpreted individual parameters, notably the presence of parenchymal bands, differently: consequently, their prevalence largely varied. However, both the level of interobserver agreement and the specificity regarding CTEPH prediction improved as the total number of the fulfilled criteria increased. Our findings in the population of a longitudinal study with prospective clinical follow-up are thus in agreement with previous cross-sectional data.[12,18] The radiologic parameters and criteria tested in the current study partly overlap with those of previous cohorts, although we did place particular focus on distinguishing morphologic parameters of chronic thrombi and those suggesting chronic pulmonary hypertension from those of acute PE; we thus avoided, for example, inclusion of signs such as flattening of the interventricular septum that may be a feature of both acute and chronic PE.[1,24] With only a few patients having had CTEPH in this study, it may be hard, however, to establish an optimal combination of parameters. Irrespective of the strategy used, increasing the number of required radiologic criteria increased the likelihood of having preexisting CTEPH.

Taken together, our results suggest that, instead of seeking the elusive "perfect" radiologic predictor(s), a minimum number of criteria from a predefined list should be required to raise the suspicion of already existing CTEPH in a patient undergoing CTPA for acute PE and inform the follow-up strategy before he or she is discharged from the hospital. Moreover, this approach may, based on the findings of our study, help to identify patients with an expected worse quality of life over the long term and permit quantification of the clinical and functional relevance of this worsening, including PPEI. In the latter cases, targeted appropriate care, including exercise rehabilitation, behavioral education, and modification of risk factors, may be needed to restore the patients' well-being and functional status.

The main strength of the current study is that it included a relatively large population of 303 unselected consecutive patients with acute PE, all of whom underwent prospective, structured follow-up. However, some limitations need to be kept in mind. First, this study was a retrospective focused assessment of CTPAs performed at the time of the index acute PE episode; every care was taken to minimize bias as the expert radiologists went through a standardized list of predefined and previously validated parameters of chronicity,[14,17,21,22] however, and they were blinded to each other's assessment and to the patients' baseline and follow-up data. Second, as was the case in previous reports,[25] radiologists with expertise in CTEPH diagnosis were involved in the CTPA reading for the current study. The accuracy of CTPA reading by less experienced radiologists might have been different. Third, the number (n = 5) of CTEPH cases diagnosed at follow-up was small and confirms CTEPH being overall a rare sequela of acute PE. Consequently, our results and those of others[16] reporting on the number of radiologic parameters required to express an "adequately strong suspicion" of preexisting CTEPH need to undergo further external validation before they can inform training programs for radiologists and future clinical practice guidelines. If this validation is successful, it may eventually be recommended that the reporting of CTPA performed to diagnose acute PE be extended to include signs of chronicity, with possible implications for post-PE follow-up. Clearly, the radiologic criteria we evaluated may indicate the presence of preexisting CTEPH but would not be expected to provide insights into the risk of incident CTEPH. Another potential limitation is that this was an observational cohort study not mandating patient management and specifically screening for CTEPH at follow-up. We can therefore not exclude the possibility that the diagnosis of CTEPH was missed in some cases, and it is unknown what the radiologic findings of these patients might have been. Finally, it must be highlighted that the criteria for

CTEPH diagnosis are evolving, and this analysis necessarily relies on those criteria available at the time of study initiation.

Interpretation

These results from a large multicenter prospective cohort study suggest that a substantial proportion of patients in whom the diagnosis of CTEPH is made following an acute PE event may in fact have preexisting chronic disease that can be detected, or at least suspected, at the time of acute PE. Although no single radiologic finding indicating chronicity seems to be robust and reproducible enough to predict CTEPH diagnosis, fulfilment of an increasing number of criteria from a list of predefined radiologic parameters increases the level of agreement between radiologists and the specificity of predictive models. These findings will help to optimize algorithms for post-PE patient care. In particular, they may contribute to identifying, in the acute phase and prior to discharge from the hospital, a group of patients in whom intensified follow-up and, possibly, early CTEPH screening may be indicated.

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Author contributions: S. B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S. B., S. R., and S. V. K. were responsible for the concept of the study. K.-F. K., A. C. B., R. J. G., and S. L. assessed and adjudicated imaging data. A. C. M. and L. V. were responsible for statistical analysis. All authors contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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