ORIGINAL ARTICLE

Healthcare utilization in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

Y. M. ENDE-VERHAAR,* W. B. VAN DEN HOUT,† H. J. BOGAARD,‡ L. J. MEIJBOOM,§
M. V. HUISMAN,* P. SYMERSKY,¶ A. VONK-NOORDEGRAAF‡ and F. A. KLOK* (iD)

*Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden; †Department of Medical statistics and
Bio-informatics, Leiden University Medical Center, Leiden; ‡Department of Pulmonology, VU University Medical Center, Amsterdam;
§Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam; and ¶Department of Cardiac Surgery, VU
University Medical Center, Amsterdam, the Netherlands

Essentials

- Diagnostic delay of chronic thromboembolic pulmonary hypertension (CTEPH) is long.
- We explored healthcare utilisation of patients diagnosed with CTEPH after pulmonary embolism.
- A large number of physicians were consulted and test results were not always interpreted correctly.
- Better education and higher awareness of CTEPH may lead to faster diagnosis.

Summary. *Background:* The median diagnostic delay of chronic thromboembolic pulmonary hypertension (CTEPH) is 14 months, which may affect prognosis. We aimed to explore the healthcare utilization of patients diagnosed with CTEPH after acute pulmonary embolism (PE), and to identify the causes of diagnostic delay. *Methods:* We collected all data on patient symptoms, medical specialist referrals and ordered diagnostic tests to reconstruct the clinical pathways of 40 patients referred to the VU University Medical Center Amsterdam (VUMC, the Netherlands) for CTEPH treatment. Diagnostic delay was defined as the time between first symptom onset and referral to the VUMC. Correlations of patient-specific characteristics and diagnostic delay were evaluated. *Results:* Patients consulted four (median) different physicians for a median of 13 (interquartile range [IQR] 10–18) consultations before the correct diagnosis was made. The median diagnostic delay was 21 months (IQR 12–49 months). Echocardiographic results suggestive of CTEPH were not always followed by an adequate work-up; most patients were not subjected to ventilation/perfusion scanning. Prior cardiopulmonary comorbidity and recurrent venous thromboembolism were predictors of a longer delay. *Conclusion:* Healthcare utilization in patients before their final CTEPH diagnosis was far from optimal, contributing to a considerable diagnostic delay. Better education and higher awareness of CTEPH among PE caretakers may lead to faster diagnosis.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially curable long-term complication of acute pulmonary embolism (PE), occurring in ~ 3.2% of PE survivors [1]. CTEPH is caused by persistent obstruction of the pulmonary arteries by major vessel thromboembolism and vascular remodeling, resulting in increased vascular resistance and progressive right heart failure [2]. CTEPH can be cured by surgical removal of these chronic thrombi by pulmonary endarterectomy (PEA) [2,3]. However, when PEA is not feasible, owing to advanced distal pulmonary artery remodeling or the patient's performance status, the prognosis is poor [3–5]. Therefore, early CTEPH diagnosis and referral to an expert center are both crucial for optimal treatment [2,3,6]. Notably, the often non-specific and insidious clinical presentation of CTEPH requires a high level of

Correspondence: Y. M. Ende-Verhaar, Department of Thrombosis and Hemostasis, LUMC (C7Q-68), Albinusdreef 2, Postbus 9600, 2300 RC Leiden, the Netherlands
Tel.: +31 71 529 8096
E-mail: y.m.ende-verhaar@lumc.nl

suspicion in patients presenting with unexplained new or persisting symptoms suggestive of CTEPH in the clinical course of acute PE [7]. Early CTEPH diagnosis has already been proven to be a major clinical challenge, as demonstrated by a median diagnostic delay of 14 months in the International CTEPH registry [8].

In clinical practice, the diagnostic process for CTEPH after a PE diagnosis may take some time, and often involves multiple healthcare providers from different clinical specialties [2,3,8,9]. This diagnostic process may be even longer in patients without a previous acute PE diagnosis. Prior research has consistently identified a gap between what is identified as 'best practice' by scientific evidence and recommended by the guidelines, and patterns of clinical practice [3,10,11]. It was shown that only 33–54% of 1748 patients diagnosed with CTEPH underwent a ventilation/perfusion (V/Q) lung scan during diagnostic work-up, and that only 25–44% were referred to a dedicated multidisciplinary CTEPH team [10], although both are indicated [3].

An improved understanding of healthcare utilization, including diagnostic testing and referral patterns, among patients diagnosed with PE with new or persistent dyspnea would be an important first step in further optimizing the diagnostic process for CTEPH. The aim of this study was to explore the healthcare utilization of PE patients who were diagnosed with CTEPH, and to identify causes of diagnostic delay.

Methods

Study population

Consecutive patients diagnosed at the VU University Medical Center Amsterdam (VUMC) with CTEPH between 2014 and 2016 were eligible for inclusion. Because the VUMC is the primary referral center for CTEPH in the Netherlands, we consider the patients studied to constitute a representative sample for the Dutch situation. CTEPH was diagnosed according to the most recent guidelines [3], based on the results of right heart catheterization (RHC) and pulmonary angiography in all patients. Patients with no previous diagnosis of acute PE, those aged < 18 years or those with any psychological condition that would preclude completion of the study were excluded from participation. This study was approved by the institutional review board of the VUMC, and all patients provided informed consent.

Study procedures

To evaluate healthcare utilization from first symptom onset to referral to the CTEPH expertise center, all patients were subjected to an extensive and structured interview by one of the investigators (Y.E.-V.). Moreover, original medical charts were scrutinized. During the

interview, patients were questioned on their medical history, including the number of previous PE and deep vein thrombosis events, the moment of symptom onset, the course of symptoms before and after the diagnosis of acute PE, the clinical course of symptoms related to CTEPH, the first physician visited for these symptoms, the diagnostic tests performed, and the number and type of clinical referrals.

On the basis of the information provided by the patients, all relevant medical charts from relevant departments and hospitals were collected and scrutinized for the number and type of physicians consulted, the dates when they were consulted, the date of PE diagnosis, and the dates and results of imaging and/or functional tests performed, including echocardiography and V/Q lung scans. Data from the charts and the interview were correlated and combined in the study database, and the healthcare utilization from the moment of symptom onset up to the moment of referral to the VUMC was reconstructed.

Study outcome and definitions

The primary aim of this study was to assess the healthcare utilization for each individual patient from the moment of first symptom onset to referral to the VUMC for CTEPH diagnosis. We also aimed to evaluate whether the following patient-specific characteristics were associated with diagnostic delay: age, sex, body mass index (BMI), number of prior venous thromboembolism (VTE) events, and the presence of cardiopulmonary comorbidities, including chronic obstructive pulmonary disease (COPD), pulmonary infections, cardiac ischemia, and left-sided heart failure. To assess the potential presence of CTEPH at the moment of the index PE diagnosis, we also evaluated the presence of chronic PE or pulmonary hypertension (PH) on the computed tomography pulmonary angiogram (CTPA) performed for PE diagnosis. This evaluation was based on the original CTPA report and – if the original scan images were available – on a retrospective evaluation of the CTPA scan by an expert radiologist (L.J.M.).

Statistical analysis

The baseline characteristics of the patients are provided with corresponding frequencies. The median numbers with corresponding interquartile range (IQRs) of consulted physicians, consultations and diagnostic tests performed were calculated. Three specific forms of delay were considered: (i) patient delay, i.e. the time between the onset of the first symptoms of CTEPH to the first contact with a physician; (ii) doctor delay, defined as the time between first contact with the first consulted physician to referral to the VUMC; and (iii) overall diagnostic delay combining both periods. All three were reported as median numbers of months with corresponding IQRs.

The associations of patient-specific characteristics with the predefined categories of patient, doctor and overall diagnostic delay were assessed with univariate logistic regression analyses. For this analysis, the 25% of patients with the longest delay were compared with the remaining patients. A *P*-value of < 0.05 was considered to be statistically significant. All analyses were performed with SPSS version 23 for Windows (IBM Corporation; Armonk, NY, USA).

Results

Patients

A total of 64 patients were diagnosed with CTEPH in the VUMC between 2014 and 2016. Of these 64 patients, 12 had no documented previous acute PE event and two could not be reached. Ten patients refused to participate, because of lack of time (*n* = 6), lack of detailed memory (*n* = 3), and hearing impairment (*n* = 1), leaving 40 patients providing signed informed consent. The baseline patient characteristics are shown in Table 1. The mean age at the moment of referral to the VUMC was 65 ± 15 years, and 21 (53%) of the patients were male. A total of 16 (40%) patients were diagnosed with recurrent VTE before the CTEPH diagnosis. Anticoagulation treatment for the acute PE consisted of vitamin K antagonists in 38 (95%) patients. Two (5.0%) patients were treated with direct oral anticoagulants.

Table 1 Patient characteristics

Characteristic	Patients (*N* = 40)
Mean age (years) at CTEPH referral (SD)	65 (15)
Male sex, *n* (%)	21 (53)
BMI, mean (SD)	26 (4)
Number of patients with one VTE event (%)*	21 (53)
Number of patients with two VTE events (%)*	15 (38)
Number of patients with three VTE events (%)*	4 (10)
Number of patients with a DVT diagnosis concomitant with the index PE (%)	4 (10)
Treatment of last PE event, *n* (%)	
Vitamin K antagonist	38 (95)
DOAC	2 (5.0)
Comorbidities at the moment of CTEPH referral, *n* (%)	
COPD	8 (20)
Pulmonary infection	2 (5.0)
Cardiac ischemia	2 (5.0)
Rheumatological diseases	5 (13)
Malignancy	5 (13)
Splenectomy	0
Prior infected pacemaker lead	0
Known antiphospholipid syndrome	1 (2.5)

COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; BMI, body mass index; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism. *Number of VTE events at the time of symptom onset.

Of the 40 patients, 39 reported that the onset of CTEPH symptoms preceded the diagnosis of acute PE, and none of these patients completely recovered, despite anticoagulant treatment: 36 (90%) patients reported persistence of dyspnea, seven (18%) reported persistence of pain, seven (18%) reported persistence of palpitations and 21 (53%) reported persistence of fatigue following the index PE diagnosis.

In nine of the 40 patients, the presence of chronic PE had already been suggested by the radiologist on the original report of CTPA performed for acute PE diagnosis. After re-evaluation of the CTPA scans, signs of chronic PE and/or PH were identified in an additional 23 patients. One CTPA scan could not be assessed for this purpose, owing to inadequate contrast timing, and the remaining seven scans were unavailable for re-evaluation.

Healthcare utilization

The first physician that the patient consulted after symptom onset was the general practitioner (GP) for 37 (93%) patients, a rheumatologist for two (5.0%) patients, and a cardiologist for one patient (2.5%). A complete overview of the order of consulted physicians per specialty and per hospital is shown in Fig. 1. Six patients consulted physicians in two or more different hospitals before referral to the VUMC.

Before referral to the VUMC, patients consulted a median number of four (IQR 4–5) different physicians for a median number of 13 (IQR 10–18) consultations. All 40 patients were evaluated by at least a GP and a cardiologist during the diagnostic process. Of the 40 patients, 24 consulted one GP and 16 patients consulted more than one GP. Thirty-one patients consulted one cardiologist, and nine consulted more than one cardiologist. Thirty-nine 39 (98%) patients consulted a pulmonologist, and 17 patients consulted more than one pulmonologist. Nine (23%) patients consulted an internist (Table S1). Thirty-seven patients were referred to the VUMC by a pulmonologist, two by a cardiologist, and one by an internist.

During the diagnostic process, all 40 patients underwent echocardiography; 13 had one echocardiogram, and 11 patients had three or more echocardiograms. PH was concluded not to be present in nine patients on the first echocardiogram. However, in retrospect, some of these latter patients had subtle signs of PH on the echocardiogram, such as an enlarged right ventricle, a short acceleration time over the pulmonary valve, or a slightly elevated mean pulmonary arterial pressure. Therefore, it is quite possible that these patients already had CTEPH at that specific moment. For these nine patients, the median time between the first normal echocardiogram and the first echocardiogram with PH was 8 months (IQR 2–59 months). In all 40 patients, the median time between the first abnormal echocardiogram and referral to the
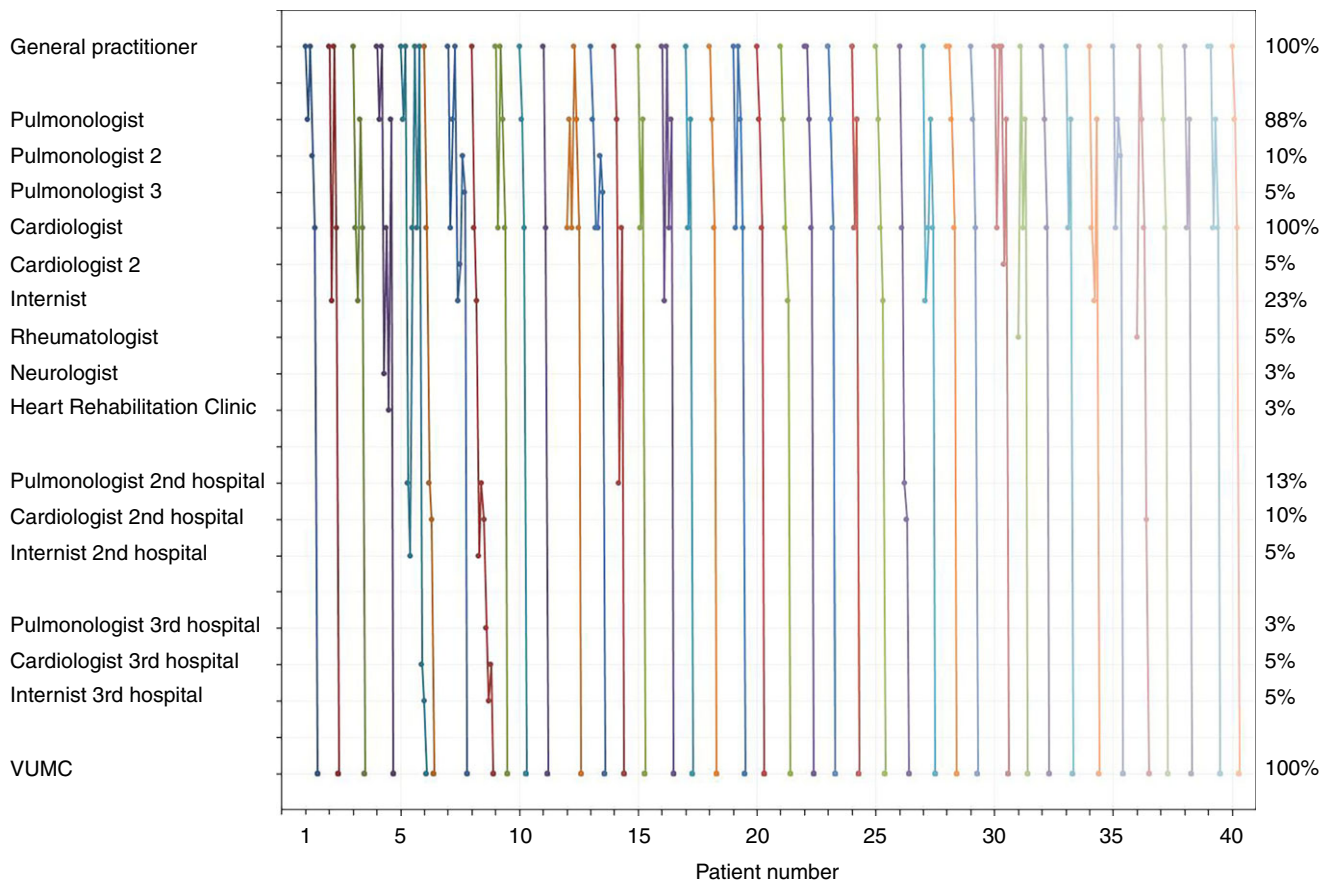
Fig. 1. Overview of consulted physicians per patient. The *y*-axis represents the number of physicians per specialty and per hospital that were consulted for each individual patient before referral to the VU University Medical Center Amsterdam (VUMC). The *z*-axis represents the overall percentage of patients who visited the specific specialist. [Color figure can be viewed at wileyonlinelibrary.com]

VUMC was 4 months (IQR 1–12 months). In 16 (40%) patients, this latter period was >6 months.

A V/Q lung scan was performed in 26 (52%) patients before referral to the VUMC, and showed perfusion defects in all. The median time between an abnormal V/Q lung scan and referral to the VUMC was 0.63 months (IQR 0.23–5.5 months). RHC was performed in 11 (22%) patients before referral to the VUMC. The median time between an abnormal RHC and referral to the VUMC was 1.7 months (IQR 0.43–3.8 months).

Patient, doctor and overall diagnostic delays

The median patient delay, from the first symptoms of CTEPH to the first contact with a physician, was 3.3 months (IQR 0.47–8.9 months) (Table 2). The median doctor delay, defined as the moment of first physician contact after symptom onset until referral to the VUMC, was 15 months (IQR 7.7–28 months). The median overall diagnostic delay was 21 months (IQR 12–49 months). This evident longer median overall diagnostic delay than the combined medians of each delay is caused by considerable individual differences in patient and doctor delay per patient, with skewed distributions of both doctor and patient delays.

In the 39 patients with persistent functional limitation or pain after the acute PE, the median time between first symptoms and the index PE diagnosis was 9.5 months

Table 2 Patient, doctor and overall diagnostic delays; the evident longer median overall diagnostic delay than the combined median patient delay and doctor delay was caused by large individual differences in patient and doctor delay per patient

	Patients ($N = 40$)
Patient delay (months), median (IQR)	3.3 (0.47–8.9)
< 14 days, *n* (%)	10 (25)
14 days to 1 month, *n* (%)	4 (10)
1–6 months, *n* (%)	12 (30)
> 6 months, *n* (%)	14 (35)
Doctor delay (months), median (IQR)	15 (7.7–28)
< 6 months, *n* (%)	8 (20)
6–12 months, *n* (%)	7 (17)
12–24 months, *n* (%)	14 (35)
> 24 months, *n* (%)	11 (28)
Total diagnostic delay (months), median (IQR)	21 (12–49)
< 6 months, *n* (%)	2 (5.0)
6–12 months, *n* (%)	7 (16)
12–24 months, *n* (%)	12 (30)
> 24 months, *n* (%)	19 (48)

IQR, interquartile range.

(IQR 3.9–33 months), the time between first physician contact and the index PE diagnosis was 3.0 months (IQR 0.15–8.7 months), and the time between the index PE diagnosis and referral to the VUMC was 6.7 months (IQR 4.2–16 months).

Patient-specific factors associated with delay

The median patient delay of patients in the upper quartile of delay was 33 months (IQR 26–39 months), and that in patients in the first to third quartile was 1 month (IQR 0.34–3.8 months). None of the studied patient characteristics showed a correlation with longer patient delay (Table 3).

The median doctor delay of patients in the upper quartile of delay was 69 months (IQR 44–109 months), and that in patients in the first to third quartile was 12 months (IQR 5.6–17 months). Cardiopulmonary comorbidity (odds ratio [OR] 7.5; 95% confidence interval [CI] 1.5–37) and a recurrent VTE event (OR 6.9; 95% CI 1.2–39) were significantly associated with a longer doctor delay.

The median overall diagnostic delay of patients in the upper quartile of delay was 72 months (IQR 62–132 months), and that in the remaining patients was 16 months (IQR 9.0–26 months). A recurrent VTE event (OR 6.9; 95% CI 1.2–39) was the only predictor of a longer overall diagnostic delay.

Discussion

In this study, we evaluated the healthcare utilization in obtaining the correct diagnosis of 40 patients with CTEPH after a diagnosis of acute PE. Our main finding was that patients consulted a large number of different physicians for many consultations before the correct diagnosis was made. The median overall diagnostic delay was 21 months, and consisted mostly of doctor delay. Moreover, abnormal diagnostic test results suggestive of CTEPH were not always followed by further evaluation, as recommended by current guidelines. Prior cardiopulmonary comorbidity and recurrent VTE were associated

with longer delay, but age, sex and BMI were not. Finally, radiological signs of CTEPH were already present on the first available CTPA of the index PE diagnosis in the majority of patients, and many patients reported symptoms compatible with CTEPH long before the index PE diagnosis. This probably indicates that they already had CTEPH at the moment of the index diagnosis of PE, which was misclassified as an acute PE. Although recall bias may limit the validity of this observation, similar findings from a French study support this hypothesis [12]. In this study, a retrospective evaluation of the initial CTPA scan for signs of CTEPH at the moment of PE diagnosis showed that all seven patients diagnosed with CTEPH already had several clear radiological signs of CTEPH at the moment of the PE diagnosis. Moreover, we speculate that the fact that recurrent VTE was associated with longer overall diagnostic delay may also be explained by diagnostic misclassification of CTEPH.

By reconstructing the healthcare utilization of the 40 patients diagnosed with CTEPH and included in this study, we demonstrated an overall median diagnostic delay of 21 months (IQR 12–49 months), which is even longer than the 14 months reported in the International registry, although IQRs do overlap [8]. Patients experienced symptoms for a median of 3.3 months (IQR 0.47–8.9 months) before they contacted a physician. In comparison, patients diagnosed with idiopathic pulmonary hypertension were found to have a median diagnostic delay of 44 months (IQR 21–65 months) from first symptom onset to diagnosis [13]. In this particular study, patients consulted their GP a mean number of 5.3 ± 3.8 times and were seen by 3.0 ± 2.1 specialists before referral to a PH expertise center.

Recurrent VTE was an independent predictor of longer delay. One possible explanation for this is that, as we outlined above, the VTE recurrence was not an actual recurrence but a misclassified CTEPH. Unfortunately, we did not have all original radiological images available to confirm this hypothesis. In addition to recurrent VTE, prior cardiopulmonary comorbidity was identified as a relevant predictor of a longer doctor delay. A possible explanation

Table 3 Univariate regression analysis of patient-specific factors associated with longer delay

	Patient delay OR* (95% CI)	Doctor delay OR† (95% CI)	Overall diagnostic delay OR‡ (95% CI)
Age > 65 years	2.7 (0.57–12.3)	0.85 (0.21–3.7)	0.88 (0.21–3.7)
Male sex	3.5 (0.75–16.3)	0.38 (0.08–1.7)	1.1 (0.27–4.8)
BMI > 30	0.56 (0.06–5.4)	1.6 (0.25–10.6)	1.6 (0.25–10.6)
Cardiopulmonary comorbidity	2.2 (0.48–10.0)	7.5 (1.5–36.7)§	4.0 (0.87–18.4)
More than one VTE event¶	2.0 (0.47–8.4)	6.9 (1.2–39)§	6.9 (1.2–39)§

BMI, body mass index; CI, confidence interval; OR, odds ratio; VTE, venous thromboembolism. *Twenty-five per cent of patients with the longest patient delay were selected. †Twenty-five per cent of patients with the longest doctor delay were selected. ‡Twenty-five per cent of patients with the longest diagnostic delay were selected. §Statistically significant at $P < 0.05$. ¶One or more recurrent VTEs (regardless of when the patient developed symptoms of chronic thromboembolic pulmonary hypertension).

for this may be the clinical assumption that the reported signs and symptoms were caused by these cardiopulmonary comorbidities, so that CTEPH was not considered immediately. From the International CTEPH registry, it is known that many patients with CTEPH have a concomitant diagnosis of coronary disease (12% of patients) and COPD (9.5% of patients) [8]. Hence, a CTEPH diagnosis should be considered in all patients who do not completely recover after an acute PE event, even in the presence of other conditions that may explain the presentation of the patient.

Doctor delay contributed to a larger extent than patient delay to the overall diagnostic delay. It took a median of 13 consultations by four different physicians to reach the correct diagnosis. We have two explanations for this phenomenon. First, CTEPH has a low incidence and often has an insidious presentation. The number of patients reporting persisting symptoms such as dyspnea after an acute PE largely exceeds the number of patients who have or develop CTEPH [7,14–18]. Second, both CTEPH awareness and knowledge of the diagnostic work-up among PE caretakers seem to be suboptimal, as diagnostic clues from abnormal echocardiograms were not followed by adequate further diagnostic work-up by V/Q lung scan and direct referral to a CTEPH expertise center. A recent large retrospective international study evaluating the diagnostic management of CTEPH in both non-PH and PH centers showed poor adherence to the guideline recommendations, with echocardiography being performed in 81–98% of patients but V/Q lung scanning being performed in only 33–54% before CTEPH diagnosis [10]. Moreover, in our study, it took a median of 4 months from the moment when PH was suggested on an echocardiogram to the moment of actual referral to a CTEPH expertise center.

An important limitation of this study is the retrospective nature of the data acquisition. With this study design, we were not able to reconstruct the actual diagnostic reasoning of the involved physicians, which could have introduced bias. Even so, we were able to find and analyze detailed data on tests performed and referrals. Second, the evaluation of total patient delay is subjective and probably suffers from recall bias. Third, echocardiography or other hemodynamic data obtained at the moment of the acute PE diagnosis were not available, and could have provided a better indication of the presence of CTEPH at that moment. Fourth, only patients referred to the VUMC for CTEPH diagnosis after a previous acute PE diagnosis were included in the current study, and not patients without a previous acute PE diagnosis or those who remained undiagnosed or were not referred: the diagnostic delay might be much longer in these patients. This challenges the external validity of our findings. Fifth, as we did not adjudicate the VTE recurrences reported in our study, or the other comorbid conditions included in the multivariate analysis,

we cannot exclude biases in this part of our study. Finally, as only patients referred to the VUMC in the Netherlands were evaluated, healthcare utilization in other countries may be different.

In conclusion, we observed a considerable diagnostic delay of 21 months for CTEPH diagnosis, and far from optimal use and interpretation of diagnostic tests performed in the clinical course after the acute PE diagnosis. In many patients, CTEPH was probably already present at the moment of the index PE diagnosis but was not recognized. In line with this observation, we found that most of the diagnostic delay was attributable to doctor delay. Specifically, patients with prior cardiopulmonary comorbidity and recurrent VTE had the longest doctor delay. On the basis of these findings, we underline the need for better knowledge and higher awareness of CTEPH among PE caretakers. This may be the best way to improve healthcare utilization and ultimately achieve earlier CTEPH diagnosis. Every PE patient with persistent dyspnea after 3 months of follow-up should be evaluated for the presence of CTEPH according to the guidelines, and correct interpretation of the diagnostic test results suggestive of CTEPH is essential. Particular vigilance is required in patients with signs of chronic PE or PH on the initial CTPA performed to confirm the diagnosis of acute PE.

Addendum

Acknowledgements

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Contacted physicians, number of consultations per physician and number of different physicians before referral to the VUMC.

References

1 Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, Delcroix M, Pruszczyk P, Mairuhu AT, Huisman MV, Klok FA. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J* 2017; **49**: 1601792.

2 Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. *Circulation* 2014; **130**: 508–18.

3 Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, *et al*. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2015; **2015**: 67–119.

4 Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barbera JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jais X, Ambroz D, *et al*. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an International Prospective Registry. *Circulation* 2016; **133**: 859–71.

5 Escribano-Subias P, Del Pozo R, Roman-Broto A, Domingo Morera JA, Lara-Padron A, Elias Hernandez T, Molina-Ferragut L, Blanco I, Cortina J, Barbera JA. Management and outcomes in chronic thromboembolic pulmonary hypertension: from expert centers to a nationwide perspective. *Int J Cardiol* 2016; **203**: 938–44.

6 Ende-Verhaar YM, Huisman MV, Klok FA. To screen or not to screen for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *Thromb Res* 2017; **151**: 1–7.

7 Sista AK, Klok FA. Late outcomes of pulmonary embolism: the post-PE syndrome. *Thromb Res* 2017; **164**: 157–62.

8 Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barbera JA, de Perrot M, Hoeper MM, Gaine S, Speich R, *et al*. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation* 2011; **124**: 1973–81.

9 Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. *Eur Respir J* 2013; **41**: 462–8.

10 Gall H, Preston IR, Hinzmann B, Heinz S, Jenkins D, Kim NH, Lang I. An international physician survey of chronic thromboembolic pulmonary hypertension management. *Pulm Circ* 2016; **6**: 472–82.

11 Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, Gibbs JS, Huisman MV, Humbert M, Kucher N, Lang I, Lankeit M, Lekakis J, Maack C, Mayer E, Meneveau N, Perrier A, Pruszczyk P, Rasmussen LH, Schindler TH, *et al*. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; **35**: 3069a–k.

12 Guerin L, Couturaud F, Parent F, Revel MP, Gillaizeau F, Planquette B, Pontal D, Guegan M, Simonneau G, Meyer G, Sanchez O. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. *Thromb Haemost* 2014; **112**: 598–605.

13 Strange G, Gabbay E, Kermeen F, Williams T, Carrington M, Stewart S, Keogh A. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: the delay study. *Pulm Circ* 2013; **3**: 89–94.

14 Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Kaptein AA, Huisman MV. Quality of life in long-term survivors of acute pulmonary embolism. *Chest* 2010; **138**: 1432–40.

15 Klok FA, van Kralingen KW, van Dijk AP, Heyning FH, Vliegen HW, Huisman MV. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. *Respir Med* 2010; **104**: 1744–9.

16 Klok FA, Tijmensen JE, Haeck ML, van Kralingen KW, Huisman MV. Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire. *Eur J Intern Med* 2008; **19**: 625–9.

17 Kahn SR, Hirsch AM, Akaberi A, Hernandez P, Anderson DR, Wells PS, Rodger MA, Solymoss S, Kovacs MJ, Rudski L, Shimony A, Dennie C, Rush C, Geerts WH, Aaron SD, Granton JT. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. *Chest* 2017; **151**: 1058–68.

18 Kahn SR, Akaberi A, Granton JT, Anderson DR, Wells PS, Rodger MA, Solymoss S, Kovacs MJ, Rudski L, Shimony A, Dennie C, Rush C, Hernandez P, Aaron SD, Hirsch AM. Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study. *Am J Med* 2017; **130**: 990.e9–e21.