Chapter 7

Healthcare utilisation in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

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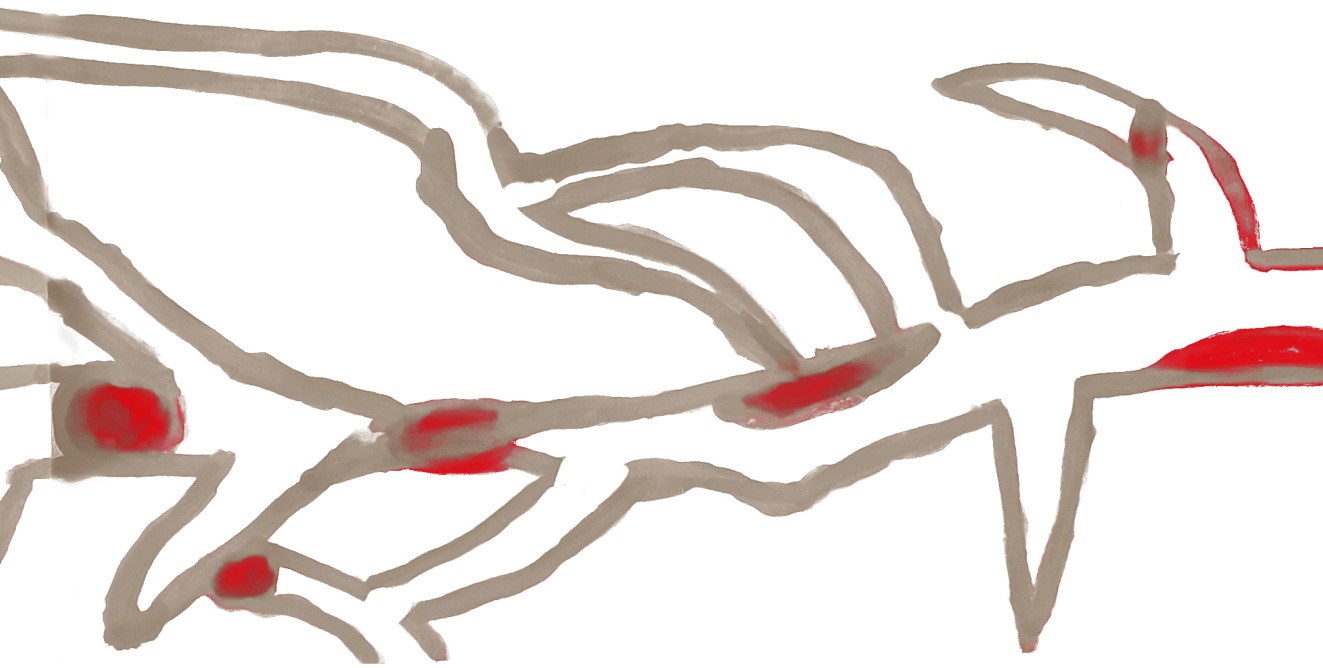

ABSTRACT

Background The median diagnostic delay of chronic thromboembolic pulmonary hypertension (CTEPH) is 14 months, which may affect prognosis. We aimed to explore healthcare utilisation of patients diagnosed with CTEPH after acute pulmonary embolism (PE) and to identify the causes of diagnostic delay.

Methods We collected all data of patient's 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 (inter quartile range [IQR] 10-18) consultations before the correct diagnosis was made. The median diagnostic delay was 21 (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 utilisation 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 remodelling that result in increasing 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 remodelling 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 nonspecific and insidious clinical presentation of CTEPH requires a high level of 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 of 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 even be 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 utilisation, including diagnostic testing and referral patterns, among patients diagnosed with PE with new or persistent dyspnoea would be an important first step in further optimizing the diagnostic process for CTEPH. The aim of this study was to explore the healthcare utilisation 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 be a representative sample for the Dutch situation. CTEPH was diagnosed according

to the most recent guidelines [3], based on the results of right heart catheterisation (RHC) and pulmonary angiography in all patients. Patients with no previous diagnosis of acute PE, those below 18 years of age 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 utilisation 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 (DVT) 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 utilisation 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 health care utilisation for each individual patient from 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 thromboembolic (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

Baseline characteristics of the patients are provided with corresponding frequencies. The median numbers with corresponding inter quartile range (IQRs) of consulted physicians, consultations and diagnostic tests performed were calculated. Three specific forms of delay were considered: 1) patient delay, i.e. the time between the onset of the first symptoms of CTEPH to first contact with a physician; 2) doctor delay, defined as the time between first contact with the first consulted physician to referral to the VUMC; and 3) overall diagnostic delay combining both periods. All three were reported in median number of months with corresponding IQRs.

The association of patient-specific characteristics with the predefined categories of patient, doctor and overall diagnostic delay was 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 statistically significant. All analyses were performed using SPSS software version 23 for Windows IBM Corporation.

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 participation because of lack of time (n=6), lack of detailed memory (n=3), and hearing impairment (n=1), leaving 40 patients signing informed consent. The baseline patient characteristics are presented 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.

Of the 40 patients, 39 patients 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 dyspnoea, seven (18%) persistence of pain, seven (18%) persistence of palpitations and 21 (53%) 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.

Table 1. Patient characteristics.

	Patients (n=40)
Age at CTEPH referral (mean, SD)	65 (15)
Male sex (n, %)	21 (53)
BMI (mean, SD)	26 (4)
Number of patients with 1 VTE event (n,%)*	21 (53)
Number of patients with 2 VTE events (n,%) *	15 (38)
Number of patients with 3 VTE events (n,%) *	4 (10)
Number of patients with a DVT diagnosis concomitant to the index PE (n,%)	4 (10)
Treatment of last PE event	
Vitamin K antagonist (n,%)	38 (95)
DOAC (n,%)	2 (5.0)
Comorbidities at the moment of CTEPH referral	
COPD (n,%)	8 (20)
Pulmonary infection	2 (5.0)
Cardiac ischemia (n,%)	2 (5.0)
Rheumatologic diseases (n,%)	5 (13)
Malignancy (n,%)	5 (13)
Splenectomy (n,%)	0
Prior infected pace maker lead (n,%)	0
Known antiphospholipid syndrome (n,%)	1 (2.5)

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

Health care utilisation

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 presented in **Figure 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 1 GP. Thirty-one patients consulted one cardiologist, and nine consulted more than one cardiologist. Thirty-nine (98%) patients consulted a pulmonologist, and 17 patients consulted more than one pulmonologist. Nine (23%) patients consulted an internist (**Supplement 1**).

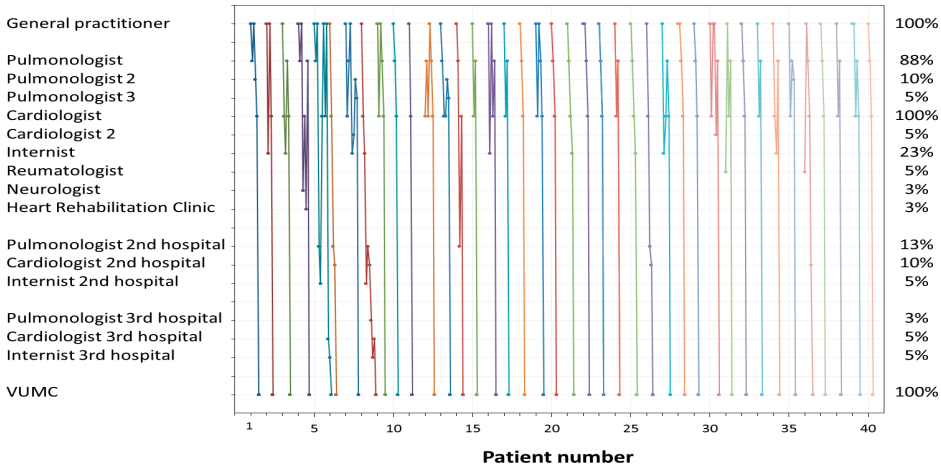

Figure 1. Overview of consulted physicians per patient.
The y-axis represents the number of physicians per specialty and per hospital that were consulted for each individual patient before referral to the VU University Medical Center Amsterdam. The z-axis represents the overall percentage of patients who visited the specific specialist.

Thirty-seven patients were referred to the VUMC by a pulmonologist, two by a cardiologist and one patient 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). In all 40 patients, the median time between the first abnormal echocardiogram and referral to the VUMC was 4 months (IQR 1-12). In 16 (40%) patients, this latter period was longer than 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 (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 (IQR 0.43-3.8) months.

Patient, doctor and overall diagnostic delay

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) (**Table 2**). The median doctor delay, defined as

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-1 month (n,%)	4 (10)
	1-6 months (n,%)	12 (30)
	>6 months (n,%)	14 (35)
Doctors 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)

Note: IQR: inter quartile range.

the moment of first physician contact after symptom onset until referral to the VUMC was 15 months (IQR 7.7-28). The median overall diagnostic delay was 21 months (IQR 12-49). 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 distribution 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 (IQR 3.9-33), the time between first physician contact and the index PE diagnosis was 3.0 months (IQR 0.15-8.7) and the time between the index PE diagnosis and referral to the VUMC was 6.7 months (IQR 4.2-16).

Patient-specific factors associated with delay

The median patient delay of patients in the upper quartile of delay was 33 months (IQR 26-39), and that in patients in the first to third quartile was 1 month (IQR 0.34-3.8). 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), and that in patients in the first to third quartile was 12 months (IQR 5.6-17). Cardiopulmonary comorbidity (odds ratio [OR] 7.5; 95% confidence interval [CI] 1.5-37)

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 >65year	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)
VTE>1 event¥	2.0 (0.47-8.4)	6.9 (1.2-39)†	6.9 (1.2-39)†

Note: OR: Odds ratio; CI: confidence interval; BMI: body mass index; PE: pulmonary embolism; DVT: deep vein thrombosis; VTE: venous thromboembolism;
*25% of patients with the longest patient delay were selected; #25% of patients with the longest doctors delay were selected; ^25% 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 CTEPH).

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 the patients in the upper quartile of delay was 72 months (IQR 62-132) and that in the remaining patients was 16 months (IQR 9.0-26). 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 health care utilisation 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 tests 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 health care utilisation 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), 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) 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) 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 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 for a larger extent then 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 dyspnoea 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 seems 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 as well, with echocardiography being performed in 81-98% of patients but V-Q lung scanning being performed in only 33-54% before CTEPH diagnosis [10]. More-

over, in our study, it took a median of 4 months from the moment PH was suggested on 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 acquisitions. 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 analyse detailed data on performed tests and referrals. Second, the evaluation of the total patient delay is subjective and likely 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 current study, and not patients without a previous acute PE diagnosis or those who remained undiagnosed or were not referred: the diagnostic delay might even 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, health care utilisation in other countries may be different.

In conclusion, we observed a considerable diagnostic delay of 21 months for CTEPH diagnosis, and a 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 health care utilisation and ultimately achieve earlier CTEPH diagnosis. Every PE patient with persistent dyspnoea after three 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.

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Supplement 1. Contacted physicians, number of consultations per physician and number of different physicians before referral to the VUMC.

Total number of contacted physicians (median, IQR)	4 (4-5)
Total number of consultations (median, IQR)	13 (10-18)
Number of patients contacted a GP (N, %)	40 (100)
Number of GP consultations in 40 patients (median, IQR)	3 (1-4)
Number of different consulted GP's in 40 patients (median, IQR)	1 (1-2)
Number of patients consulted >1 GP (n,%)	16 (40)
Number of patients contacted a pulmonologist (N, %)	39 (98)
Number of pulmonologist consultations in 39 patients (median, IQR)	4.5 (3-9)
Number of different consulted pulmonologists in 39 patients (median, IQR)	1 (1-2)
Number of patients consulted >1 pulmonologist (n,%)	17 (44)
Number of patients contacted a cardiologist (N, %)	40 (100)
Number of cardiologist consultations in 40 patients (median, IQR)	3 (2-6)
Number of different consulted cardiologists in 40 patients (median, IQR)	1 (1-1)
Number of patients consulted >1 cardiologist (n,%)	9 (23)
Number of patients contacted an internist (N, %)	9 (23)
Number of internist consultations in 9 patients (median, IQR)	4 (3-6.5)
Number of different consulted internists in 9 patients (median, IQR)	1 (1-2.5)
Number of patients consulted >1 internist (n,%)	3 (33)
Number of patients contacted a rheumatologist (N, %)	2 (5)
Number of rheumatologist consultations in 2 patients (median, IQR))	1 (1-1)
Number of different consulted rheumatologist in 2 patients (median, IQR)	2.5 (2-3)
Number of patients consulted >1 rheumatologist (n,%)	0 (0)

Note: VUMC: VU university Medical Center Amsterdam; IQR: inter quartile range; GP: general physician.