Capturing venous thromboembolism: imaging and outcomes of venous thromboembolism

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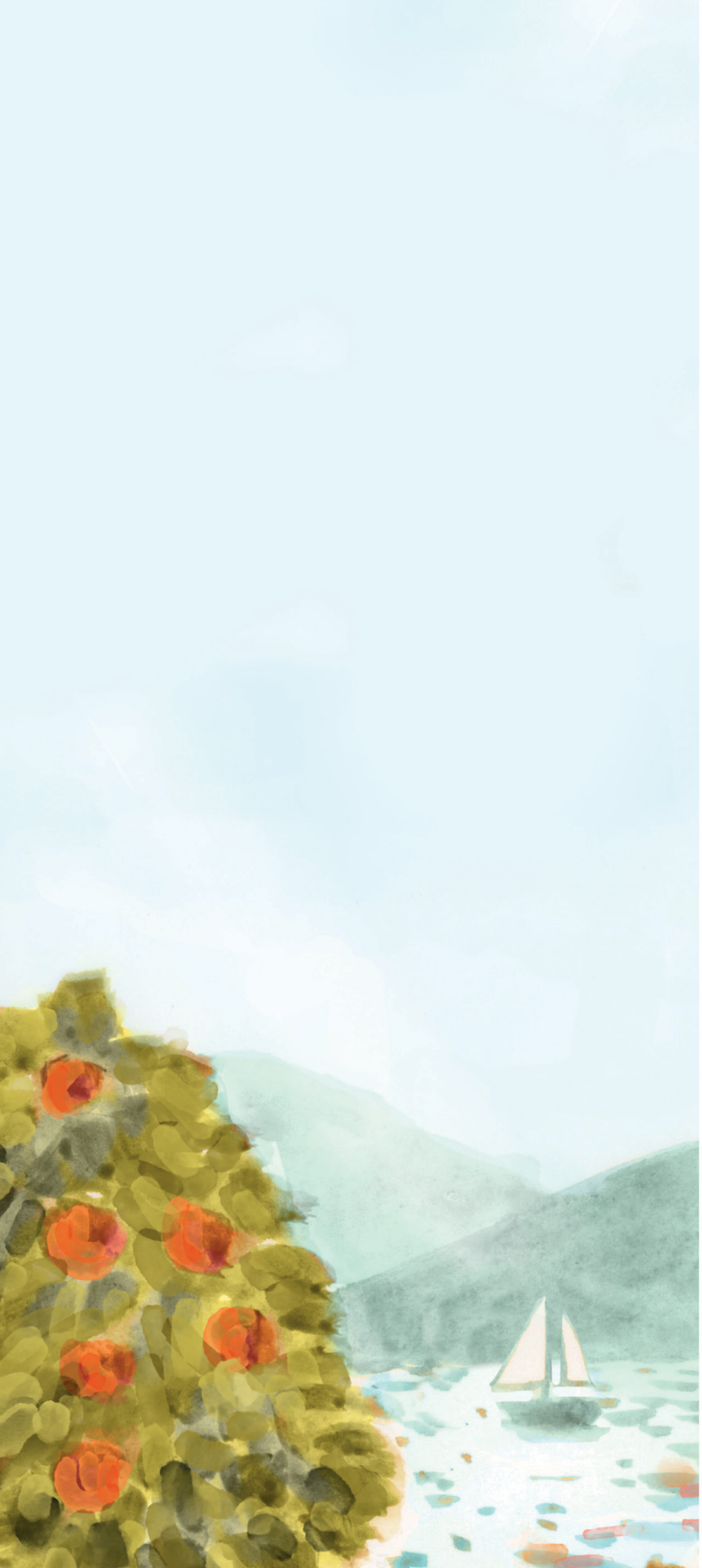

CHAPTER 14

Chronic thromboembolic pulmonary hypertension and clot resolution after COVID-19-associated pulmonary embolism

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Eur Respir J. 2023 Apr 20; 61(4):2300171

Short abstract

The results of our study suggest that CTEPH is not a more common long-term complication after COVID-19-associated PE than after PE in non-COVID-19 patients, and thrombus resolution did not seem to be different from non-COVID-19-associated PE.

To the Editor:

The incidence of chronic thromboembolic pulmonary hypertension (CTEPH) in coronavirus disease 2019 (COVID-19) survivors who were diagnosed with acute pulmonary embolism (PE) is currently unknown. Considering the high PE incidence reported in COVID-19 and its potentially unique pathophysiology, it may be hypothesised that thrombus resolution occurs to a lesser extent after COVID-19-associated PE, and that the prevalence of CTEPH is higher compared to non-COVID-19-associated PE populations. CTEPH could therefore be a treatable cause of long COVID, which captures a broad range of post-acute COVID-19 sequelae, in those with PE during acute COVID-19.[1] In this multicentre cross-sectional study, we aimed to establish the prevalence of CTEPH and recurrent venous thromboembolism (VTE), and evaluate thrombus resolution in COVID-19-associated PE survivors.

Adult hospitalised COVID-19 patients, who had been diagnosed with and treated for acute PE during or after admission, were eligible if they received follow-up procedures aimed at detection of long-term complications after COVID-19-associated PE, including assessment of pulmonary hypertension (PH) or PE resolution, in any of 13 Dutch university and non-university hospitals that are part of the Dutch COVID & Thrombosis Coalition (DC&TC).[2] The study was approved by the institutional review board of the Leiden University Medical Center for observational studies. In each participating site, either informed consent was obtained or an opt-out procedure was applied. Data were extracted from the patients' medical charts.

The primary outcome was the prevalence of CTEPH. CTEPH was defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg and pulmonary capillary wedge pressure ≤15 mmHg in the presence of multiple chronic, organised occlusive thrombi after ≥3 months of anticoagulation. The new definition of pre-capillary PH according to the European Society of Cardiology/European Respiratory Society guideline, i.e. mPAP >20 mmHg and pulmonary vascular resistance >2 Wood Units, was post hoc included in the study protocol.[3] CTEPH was considered ruled out based on ≥1 of the following criteria: 1) low pre-test probability (CTEPH prediction score ≤6 points) without symptoms suggestive of PH after 3-month follow-up; 2) normal electrocardiogram (ECG) and age- and sex-dependent N-terminal-prohormone of brain natriuretic peptide (NT-proBNP) concentration (CTEPH rule-out criteria); 3) low-probability of PH on echocardiography; 4) no persistent perfusion defects on ventilation-perfusion scintigraphy (VQ scan); 5) complete thrombus resolution and/or normal perfusion *and* no signs of PH on computed

tomography pulmonary angiography (CTPA); or 6) right heart catheterization ruling out PH.[3-5] Secondary outcomes were the prevalence of VTE recurrence, and PE resolution based on CTPA performed during follow-up. Two experts adjudicated all suspected recurrent VTE events.

For the primary outcome, the proportion of patients with CTEPH was calculated with corresponding 95% confidence interval (CI), as was the proportion of patients with recurrent VTE and radiographic PE resolution. Missing data were not imputed. Analyses were performed in SPSS version 25.0.

A total of 299 patients who had been diagnosed with COVID-19-associated PE between March 2020 and December 2021 and received follow-up were included. Mean age was 60 years, and 71% (213/299) were male. PE was diagnosed during admission in 265 (89%) patients (257 confirmed by imaging; eight based on high clinical suspicion when imaging could not be obtained due to clinical status) and after discharge in 34 (11%) patients, after a median of 6.5 days (interquartile range [IQR] 3–20 days). All patients were treated with anticoagulation for at least 3 months.

The median follow-up after PE diagnosis was 19 months (IQR 15–22 months). All PEs were considered COVID-19-related with diagnostic delay of less than 14 days, indicating low pre-test probability based on the CTEPH prediction score. After 3 months, 184 (62%) patients did not report any persistent dyspnoea or symptoms compatible with CTEPH of whom 43 were also subjected to the CTEPH rule-out criteria (ECG and NT-proBNP) and 54 to echocardiography, which did not show any signs of CTEPH. CTEPH was considered absent in these 184 patients. Of the 115 (38%) patients who reported persistent dyspnoea or symptoms, CTEPH was considered ruled out in all (prevalence 0%, upper limit of 95% CI 1.3%): by the CTEPH rule-out criteria in 10, by echocardiography in 62, by VQ scan in 26, and by CTPA in 17. Hence, no patients were subjected to right heart catheterization or referred to a CTEPH expertise centre.

Five patients were evaluated for recurrent VTE (three suspected deep vein thrombosis; two suspected PE) after a median follow-up of 117 days (IQR 43–216 days). Recurrent VTE was ruled out in all five with appropriate diagnostic tests (recurrent VTE 0%, upper limit of 95% CI 1.3%).

Residual thrombotic obstruction was observed in six of the 51 patients who were subjected to follow-up CTPA after the first 3 months of follow-up (median 127 days to CTPA; IQR 113–293 days), all within the first 6 months of follow-up. The estimated PE resolution over time is shown in **Figure 1**. After 6 months, an estimated 4.4% (95% CI 1.2–15) of patients had residual thrombotic obstruction.

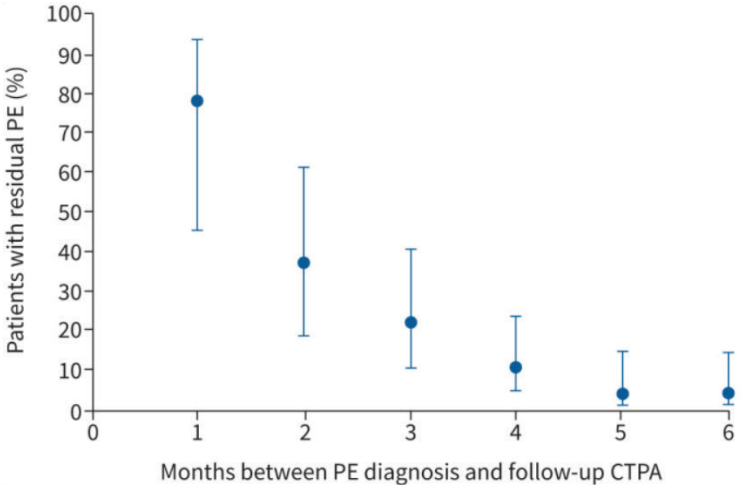
Several previous small studies investigated resolution of COVID-19-associated PE based on repeat imaging, with varying findings: thrombus resolution in 72% of patients after 44±48 days,[6] and 60% after 105 days,[7]; perfusion defects in 57% after 90 days,[8] and 10% after 6 months.[9] In the non-COVID-19-associated PE population, complete resolution occurs in 84% of patients after 6-month follow-up (95% CI 77–89%), which is not higher than observed in the current study.[10]

A higher-than-expected prevalence of PH has been reported in COVID-19 survivors; however, specific data on CTEPH after COVID-19 are very limited. In a series of 77 patients with COVID-19-associated acute PE, three (4%) met the criteria for CTEPH.[11] Data from the CTEPH quaternary centre in the UK, however, showed a decrease in referrals during the pandemic to 228 referred CTEPH cases, of whom none had a history of COVID-19.[12] Our findings are in line with the latter as we did not find any CTEPH cases, which does not suggest that CTEPH cannot occur after COVID-19-associated PE, but rather suggests that the prevalence is likely not higher than the 2–3% observed after non-COVID-19-associated PE.[13,14] As reported in other studies, we observed a low number of patients with (suspected) recurrent VTE.[7,9,15]

Based on a large nationwide population, this study provides data on the occurrence of CTEPH based on long-term follow-up after COVID-19-associated PE: information that was not previously available. One of the limitations is that the findings are based on a selected group of patients who survived COVID-19-associated PE and received follow-up appropriate to detect long-term complications, and may therefore not be fully generalisable to the general COVID-19 population. We did not follow all patients for 2 years, which may have led to an underestimation of the CTEPH prevalence. Of note, in recent (non-COVID-19) PE follow-up studies, most CTEPH cases (69–77%) were identified within 6 months of follow-up.[4,14] Lastly, the follow-up strategies in the participating hospitals were not fully harmonised. As a result, not all patients were subjected to follow-up CTPA and therefore thrombus resolution was not evaluated in the entire study population.

In conclusion, CTEPH was absent in our study population of COVID-19-associated PE survivors, suggesting that CTEPH is not a more common long-term complication after COVID-19-associated PE than after non-COVID-19-associated PE. None of the patients had recurrent symptomatic VTE during median follow-up of 19 months, and thrombus resolution did not seem to be different than after non-COVID-19-associated PE. Hence, typical long-term PE sequelae may not be important determinants of long COVID in COVID-19-associated PE survivors.

Figure 1: Trend of resolution of COVID-19-associated pulmonary embolism over time revealed by follow-up computed tomography pulmonary angiography performed during the first 6 months after diagnosis.



To estimate the proportion of patients with residual PE, based on evaluation of follow-up CTPA, at each timepoint (number of months between PE diagnosis and follow-up CTPA), the patients who were subjected to CTPA at that timepoint were taken into account. The assumption was made that patients with residual thrombosis observed at follow-up CTPA would have residual thrombosis in the months prior to the month in which follow-up CTPA was performed. Patients with resolution of PE, revealed by follow-up CTPA, were assumed to have no signs of residual thrombosis in the months following the month in which their follow-up CTPA was performed.

Abbreviations COVID-19: coronavirus disease, PE: pulmonary embolism, CTPA: computed tomography pulmonary angiography.

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