DOI: 10.1002/pul2.12306

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Long-term sequelae following acute pulmonary embolism: A nationwide follow-up study regarding the incidence of CTEPH, dyspnea, echocardiographic and V/Q scan abnormalities

Therese Andersson[1] | **Lars Nilsson**[1] | **Flemming Larsen**[2,3] | **Bo Carlberg**[1] | **Stefan Söderberg**[1]

[1]Department of Public Health and Clinical Medicine, Unit of Medicine, Umeå University, Umeå, Sweden

[2]Department of Molecular Medicine and Surgery, Section of Clinical Physiology, Karolinska Institute, Stockholm, Sweden

[3]Department of Clinical Physiology, Karolinska University Hospital, Stockholm, Sweden

Correspondence
Therese Andersson, Department of Public Health and Clinical Medicine, Unit of Medicine, Umeå University, Umeå, Sweden.
Email: therese.m.andersson@umu.se

Funding information
Actelion Pharmaceuticals

Abstract

We aimed to follow a nationwide cohort of patients with pulmonary embolism (PE) without any exclusions to generate information regarding long-term symptoms, investigational findings and to determine the prevalence of chronic thromboembolic pulmonary hypertension (CTEPH). We hypothesized that this approach would yield generalizable estimates of CTEPH prevalence and incidence. All individuals diagnosed with acute PE in Sweden in 2005 were identified using the National Patient Register. In 2007, survivors were asked to complete a questionnaire regarding current symptoms. Those with dyspnea were referred for further examinations with laboratory tests, electrocardiogram (ECG), and a ventilation/perfusion scan (V/Q scan). If CTEPH was suspected, a referral to the nearest pulmonary arterial hypertension-center was recommended. Of 5793 unique individuals with PE diagnosis in 2005, 3510 were alive at the beginning of 2007. Altogether 53% reported dyspnea at some degree whereof a large proportion had V/Q scans indicating mismatched defects. Further investigation revealed 6 cases of CTEPH and in parallel 18 cases were diagnosed outside this study. The overall prevalence of CTEPH was 0.4% (95% confidence interval [CI]: 0.2%–0.6%) and 0.7% (95% CI: 0.4%–1.0%) among the survivors. The cumulative incidence of CTEPH in the group of patients who underwent a V/Q scan was 1.1% (95% CI: 0.2%–2.0%). There was a high mortality following an acute PE, a high proportion of persistent dyspnea among survivors, whereof several had pathological findings on V/Q scans and echocardiography. Only a minority developed CTEPH, indicating that CTEPH is the tip of the iceberg of post-PE disturbances.

KEYWORDS
chronic thromboembolic pulmonary hypertension, dyspnea, pulmonary embolism, V/Q scan

INTRODUCTION

Acute pulmonary embolism (PE) is a common condition with substantial morbidity and mortality and is often associated with multiple comorbidities. Despite recent improvements in diagnostic and treatment regimes, survival after an acute PE is still poor. Many studies have focused on the short-term consequences after PE, but less attention has been directed to the long-term effects.

Our research group has previously published a nationwide study covering all patients (i.e., unselected patients with a wide range of comorbidities) diagnosed with acute PE in 2005. We found that the 5-year mortality was more than doubled (50% vs. 22%) in this group compared with age- and sex-matched controls.[1]

In addition to increased mortality in the post-PE population, acute PE may trigger the development of other and sometimes serious late complications. The most feared complication is chronic thromboembolic pulmonary hypertension (CTEPH), which is associated with severe functional impairment and high mortality,[2,3] with incidence rates ranging from 0.6% to 4.8% after an acute PE.

Even though CTEPH is a rare complication after PE, dyspnea and functional impairment are common complaints.[4–7] We have previously demonstrated that post-PE patients, compared with a control population, significantly more often report exertional (53% vs. 17.3%) and wake-up dyspnea (12% vs. 1.7%), independently of other comorbidities.[8] These findings are in line with those of previous studies showing a high prevalence of dyspnea in the post-PE population.[6,7,9,10]

Despite adequate anticoagulation, thrombus resolution may not be complete after an acute PE, and 20%–50% of patients have residual pulmonary thrombi at 6 months.[5,11–15] Furthermore, the long-term prevalence of persistent right ventricular (RV) dysfunction after an acute PE exceeds the prevalence expected with CTEPH alone.[7,9,10,16]

In 2014, Klok et al. proposed the concept of "post-PE syndrome," characterized by dyspnea, exercise limitations, and fatigue and associated with findings of chronic changes in the pulmonary circulation, gas exchange, and/or cardiac function.[17,18] However, many patients do not have hemodynamic findings that fulfill the CTEPH criteria at rest, and it has been proposed that CTEPH should be viewed as the ultimate manifestation of post-PE syndrome. In addition, the term "chronic thromboembolic disease" (CTED) has been used for radiological findings suggestive of CTEPH but not fulfilling the hemodynamic criteria for pulmonary hypertension at rest.[19] Lately, the term chronic thromboembolic pulmonary disease (CTEPD) has been proposed to clarify that this is a disease of the pulmonary vessels.[20]

The aim of this study was to prospectively follow a large nationwide cohort of post-PE patients and to gather information regarding the presence of dyspnea, as well as findings on ventilation/perfusion scans (V/Q scans) and echocardiography after a PE event. In addition to following the clinical course after a PE, we aimed to determine the prevalence and cumulative incidence of CTEPH. We hypothesized that using this large, national cohort would yield widely generalizable estimates of CTEPH prevalence and incidence.

MATERIALS AND METHODS

This study was initiated in 2007 and a previous study had then reported a high cumulative incidence of CTEPH 2 years after an acute PE.[21] Therefore, we chose to identify all individuals registered in the Swedish National Patient Register (NPR) diagnosed with acute PE in 2005 according to the ICD-10-SE system (I26.0 and I26.9), together with information about the department and hospital responsible for the PE-related admission.

Baseline characteristics have previously been reported.[1] In summary, altogether 5793 unique individuals were identified, and the age range was 1–103 years (mean age 70.4 years ± 15.1 SD), 48% were men (mean age 72.1 years ± 15.3 SD), and 52% were women (mean age of 68.7 years ± 14.6 SD). The majority (80%) had admissions due to cardiovascular diseases, injuries, malignancies, infectious, and gastrointestinal diseases before the PE, whereas 20% did not have any registered in-patient care between 1998 until the index event in 2005. During the first 3 months after the PE, 1204 (21%) died and until April 2010, altogether 2841 (50%) died. Unfortunately, causes of death are not available.

In 2007, a letter of information was sent to all heads of the departments, and written approval for continued care of any individual who needed further investigation and follow-up was obtained. Thereafter, all surviving individuals 18 years and older were invited by letter to participate.

The letter contained written information about the study, a consent form and a study-specific questionnaire (see Supporting Information) to allow gathering of information regarding symptoms and risk factors for long-term sequelae including CTEPH.[8] One of the authors (S. S.) manually reviewed all self-reported risk factors to determine which individuals were considered to be at risk for CTEPH development.

Individuals who reported dyspnea that had either worsened or remained unchanged after the acute PE

event, as well as those with known risk factors for CTEPH or with other chronic medical conditions, were considered to be at risk and in need of further follow-up. All remaining individuals were sent a second letter with the information that they had not been identified as being at risk for CTEPH and were considered to be healthy with regard to their previous PE. The evaluation of self-reported symptoms and risk factors for CTEPH has been described in detail previously.[8]

Individuals considered to be at risk were contacted by letter with information about a further examination at the nearest health center, including blood sampling, and two sodium heparin tubes were provided. After sampling, the tubes were sent overnight to Umeå, where samples were aliquoted for analysis of N-terminal prohormone brain natriuretic peptide (NT-pro-BNP). The analysis was performed at the clinical chemistry laboratory at Skellefteå Hospital according to standard clinical practice using an Immulite machine and the reagent IMMULITE® from Diagnostic Products Corporation.

Individuals who had risk factors for CTEPH or had other chronic conditions but no dyspnea and with normal NT-pro-BNP values (<100 ng/L) were considered to need no further investigation and were released from the study. All others were referred to their nearest local hospital for further follow-up, including a recommendation to perform a pulmonary V/Q scan. These scans are considered the first-line imaging modality for CTEPH, with a 96%–97% sensitivity and 90%–95% specificity for CTEPH.[19]

V/Q scans were performed at 26 examining units, according to clinical practice. The majority used planar imaging with the recommendation to obtain eight standard projections with a maximum pixel size of 5 mm. Those using single-photon emission computed tomography were recommended to collect 60–64 projections over 360° with a maximum pixel size of 5 mm. Patients were investigated in the supine position. For ventilation, inhaled 99mTc-labeled aerosol of diethylenetriamine pentaacetate, 99mTc-labeled carbon microparticles (Technegas), or 133Xe gas was used. For perfusion, an intravenous bolus of 99mTc-labeled macroaggregates of albumin was generally used.

At least one segmental perfusion defect with adequate ventilation or adjacent subsegmental perfusion defects (of segmental equivalent size) with adequate ventilation was considered indicative of PE of unknown duration.[2,22–25] Radiologists at each examining unit interpreted the V/Q scans and reported results back to the responsible local physician. If any perfusion defects were detected, the local hospitals were asked to perform echocardiography to identify direct or indirect signs of pulmonary hypertension. Echocardiography was performed at each local hospital using standard clinical practice. If a V/Q scan or echocardiography already had been performed after the PE event in 2005, a copy of these results was obtained. For validation of the V/Q scan interpretation, a second review was performed by two additional independent investigators, demonstrating high inter-rater reliability ($\kappa = 0.77$).

In cases where the local hospital did not perform a V/Q scan, with no reason declared, the patients received a referral letter to their nearest primary health care physician to establish an alternative follow-up strategy.

After referral for V/Q scan, the research group had limited control over the patient flow and how the investigations and follow-up proceeded. However, the research group continued to collect data, and in many cases, worked in close contact with the local hospitals to provide patients with the best possible care.

In summary, the study contained the following consecutive elements:

1. Questionnaire regarding the presence of dyspnea and related comorbidities. Individuals reporting no dyspnea and without any chronic comorbidities were excluded.
2. If questionnaire indicated dyspnea and/or risk factors, a letter was sent with test tubes for blood sampling, and NT-pro-BNP was analyzed. Individuals with NT-pro-BNP values < 100 ng/L and without any risk factors for CTEPH were excluded.
3. Referral for follow-up including the recommendation to perform a V/Q scan.
4. Referral for echocardiography if the V/Q scan showed any perfusion defect or was not interpretable.
5. Referral to primary care if the local hospital did not follow up individuals identified with symptoms.

This study was conducted in compliance with the Declaration of Helsinki and was approved by the Regional Ethics Review Board in Umeå, Sweden (07-074). The Ethics Board at the Swedish National Board of Health and Welfare reviewed and approved the extraction of data from the Swedish NPR.

Statistical methods

All data were analyzed using IBM SPSS statistics software version 27. Categorical variables are expressed as frequencies and continuous variables as means with 95% confidence intervals (95% CIs) or as medians with interquartile ranges (IQRs) when appropriate. Formal tests of significance between those developing CTEPH

and those who did not was deemed not appropriate since the CTEPH patients were in clear minority to the non-CTEPH patients.

Based on suggested criteria for post-PE-impairment,[10] a modified calculation was performed as data from the questionnaire and from the echocardiography did not allow evaluation of deterioration.

RESULTS

Figures 1 and 2 illustrate the flow of patients and examinations performed in this study. Altogether, 5793 unique individuals were admitted in 2005 with a PE diagnosis according to the NPR. Of those, 3510 were still alive at the beginning of 2007, and 3226 individuals were contacted and asked to complete the questionnaire after consenting. A total of 2105 (65%) individuals returned the questionnaire. Of these, 48% were women, with a median age (IQR) of 74 (20) years, and 52% were men, with a median age of 67 (21) years. A total of 53% reported dyspnea and 15% were asymptomatic but had known risk factors for CTEPH or reported other chronic medical conditions. Among those who were asked to do further follow-up, 72% returned blood samples, and 1029 NT-pro-BNP analyses were performed. Finally, a total of 944 individuals were referred to their nearest hospital for further follow-up, including a recommendation to undergo a V/Q scan.

Altogether, 530 V/Q scans were performed from January 2010 to April 2017. Of these, 224 (42%) showed mismatched perfusion defects, 6 (1%) showed matched defects, 4 (1%) were not interpretable, and 296 (56%) were normal.

Of the 196 echocardiographic examinations done in the group with mismatched perfusion defects (88%), 72 showed signs of pulmonary hypertension (estimated RV pressure > 30 mmHg), and one examination was not interpretable. An additional 35 echocardiography exams were done in the remaining groups, of which 16 showed signs of pulmonary hypertension and three were not interpretable.

Altogether seven right heart catheterizations (RHCs) were performed within the study protocol. Of these, six had hemodynamic findings that met the criteria for pulmonary hypertension suggestive of CTEPH.

In all cases in which the patient or the treating doctor had stated that the patient already had been diagnosed with CTEPH, a thorough review of the medical record (including the RHC protocol if available) was performed. Ultimately, 10 patients had a confirmed diagnosis of CTEPH before 2005, and eight patients were diagnosed with CTEPH after 2005, but outside this study.

Based on the clinical information received and the data obtained during this study, 24 of the entire cohort of 5793 patients had CTEPH, indicating an overall CTEPH prevalence of 0.4% (95% CI: 0.2%–0.6%). Among patients who survived until the beginning of 2007 ($n = 3510$), CTEPH prevalence was 0.7% (95% CI: 0.4%–1.0%), and among the survivors who reported being symptomatic on their questionnaire, CTEPH prevalence was 1.2% (95% CI: 0.6%–1.9%). The clinical characteristics of patients diagnosed with CTEPH are presented in Table 1.

The cumulative incidence of CTEPH in the group of patients who underwent a V/Q scan within the study protocol ($n = 530$) was 1.1% (95% CI: 0.2%–2.0%). Among patients who underwent a V/Q scan with perfusion defects and echocardiography with an estimated RV pressure > 30 mmHg ($n = 72$), the cumulative incidence was 6.9% (95% CI: 0.9%–13.0%).

To assess selection bias, an analysis of the six regions that referred all symptomatic survivors for V/Q scans was performed. The results indicated no major differences in the percentage of V/Q scans with perfusion defects (47% vs. 42%) but somewhat lower CTEPH prevalence [0.3% (95% CI: 0.04%–0.6%) vs. 0.7% [95% CI: 0.4%–1.0%)], suggesting that some selection bias might have affected the final results.

CTEPH versus non-CTEPH

After exclusion of 10 patients with CTEPH diagnosed before 2005, a total of 14 patients with CTEPH diagnosed from 2005 onward remained: 10 women (71%; median age, 75 [13] years) and four men (29%; median age, 64 [9] years). According to the Swedish NPR, three (21%) had at least one episode of acute PE before the index event in 2005.

In the non-CTEPH group (3486 survivors in 2007), 1782 were women (51%; median age, 74 [20] years), and 1704 were men (49%; median age, 67 [21] years). A total of 416 (12%) had had at least one previous PE.

Dyspnea

In the subgroup without a CTEPH diagnosis ($n = 2090$), 1410 (67%) reported some degree of dyspnea, among whom 115 (6%) reported dyspnea at rest, 498 (35%) had dyspnea at a low level of physical activity, and 797 (57%) had dyspnea at a high level of physical activity. In 98 cases, the answers regarding dyspnea were inconclusive or left blank.

In the subgroup of patients with a CTEPH diagnosis after 2005, a total of 11 (100%) reported having had some

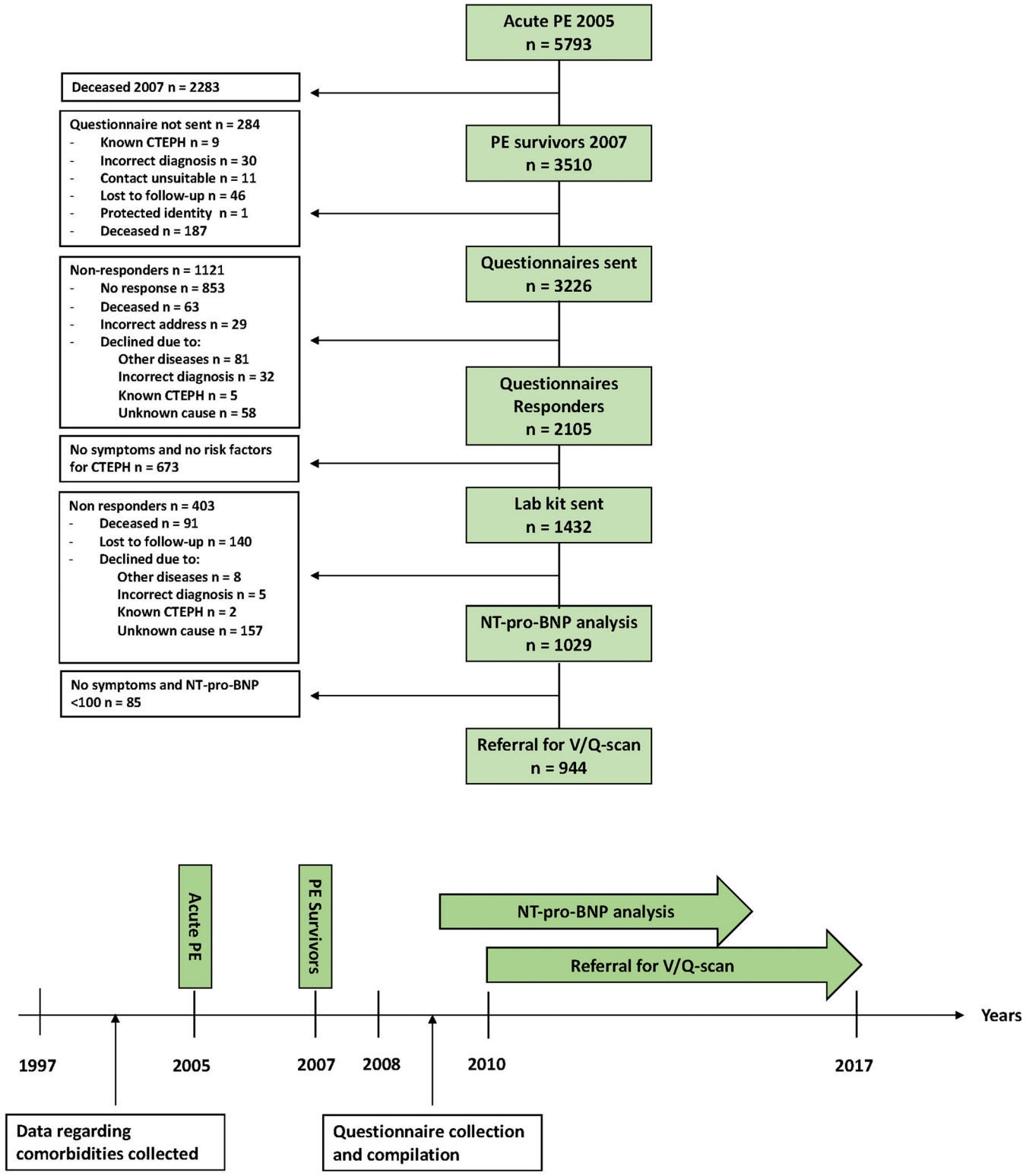

FIGURE 1 Flowchart and timeline from the acute pulmonary embolism (PE) diagnosis to referral for ventilation/perfusion scan. CTEPH, chronic thromboembolic pulmonary hypertension; NT-pro-BNP, N-terminal prohormone brain natriuretic peptide; V/Q, ventilation/perfusion.

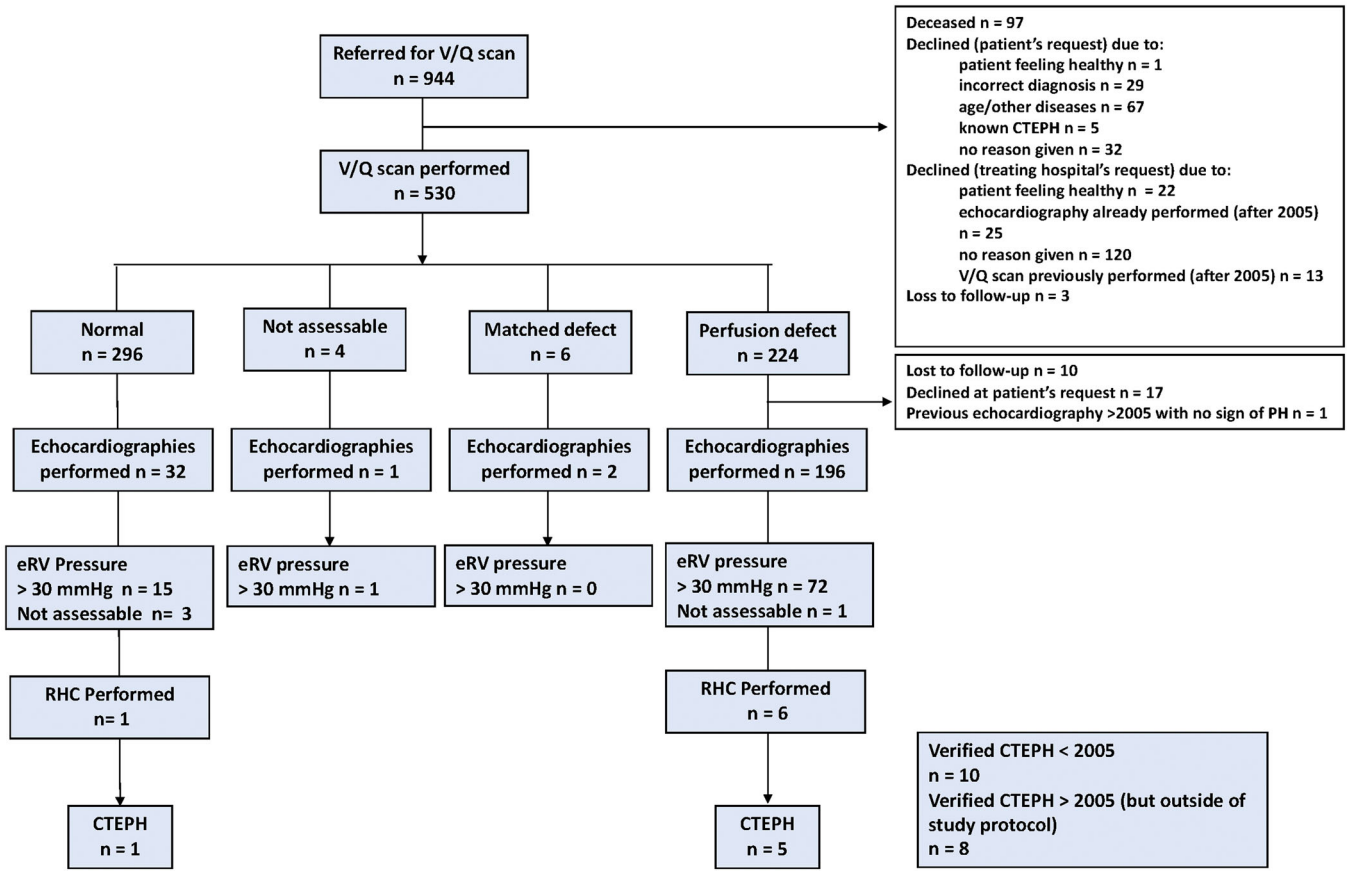

FIGURE 2 Flowchart demonstrating results and investigational findings after referral for a V/Q scan. CTEPH, chronic thromboembolic pulmonary hypertension; eRV, estimated right ventricular; PH, pulmonary hypertension; RHC, right heart catheterization; V/Q, ventilation/perfusion.

degree of dyspnea. Overall, 10 (91%) had dyspnea with easy physical activity and 1 (9%) with vigorous physical activity. In three cases, the question regarding dyspnea was unanswered.

NT-pro-BNP

Of the 1017 tested in the non-CTEPH group, the mean NT-pro-BNP level was 540 ng/L (95% CI: 449–627), and the median was 177 (344) ng/L. The mean NT-pro-BNP level in the CTEPH group was 657 ng/L (95% CI: 188–1066) and the median was 504 (591) ng/L. In the CTEPH group, all 14 were tested.

V/Q scintigraphy

In total, 538 V/Q scans were performed in the non-CTEPH group, 524 of them within the study protocol and 14 outside of it. When the referrals for a V/Q scan were sent, 14 patients had already undergone a scan, and the local hospitals provided copies of the results. Of the 538 V/Q scans performed in the non-CTEPH group, 302 were normal, 226 demonstrated mismatched perfusion defect (s), six demonstrated a matched V/Q defect, and 4 were inconclusive.

In the CTEPH group, six V/Q scans were performed within the study protocol and two outside of it. Of these eight scans, one was normal and seven demonstrated perfusion defects.

Echocardiography

In the non-CTEPH group, 289 echocardiography studies were performed, 225 within the study protocol and 64 outside of it. Of the 289, a total of 93 (32%) demonstrated indirect signs of pulmonary hypertension (RVRV pressure > 30 mmHg), four were inconclusive, and the remaining 192 showed no signs of pulmonary hypertension.

Nine echocardiography studies were performed in the CTEPH group, six of them within the study protocol and

TABLE 1 Clinical characteristics of patients diagnosed with CTEPH.

	Age[a]	Sex F/M	CTEPH-diagnosis year	Recurrent PE[b] Y/N	PEA performed Y/N	CTEPH confirmed by RHC Y/N
1	50	F	2012	N	N	Y
2	59	M	2005	Y	N	Y
3	60	M	1998	Y	N	Y
4	60	F	n/a	Y	Y	n/a
5	61	M	n/a	N	N	Y
6	61	M	2011	N	N	n/a
7	65	F	2005	N	N	Y
8	65	F	2012	N	N	Y
9	65	F	2008	N	Y	N
10	65	M	2004	N	N	Y
11	66	M	2011	Y	N	Y
12	67	F	2003	Y	N	Y
13	69	F	2006	Y	N	Y
14	69	F	2004	Y	N	Y
15	70	M	1992	Y	N	Y
16	71	M	2006	N	N	Y
17	71	M	2012	Y	N	Y
18	72	F	2005	N	N	Y
19	72	M	2012	Y	Y	Y
20	77	F	2005	N	N	N
21	79	F	2012	N	N	N
22	80	F	2006	N	N	Y
23	80	F	2008	N	N	Y
24	86	F	2012	N	N	Y

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; F, female; M, male; PE, pulmonary embolism; PEA, pulmonary endarterectomy; RHC, right heart catheterization.

[a]Age at PE diagnosis in 2005.

[b]Previous PE before the index event in 2005.

the other three outside of it. Of the echocardiograhies performed in this group, eight demonstrated signs of pulmonary hypertension (RV pressure > 30 mmHg), and one was inconclusive.

Post-hoc analysis of post-PE-impairment

Based on the presence of persistent or worsening dyspnea in combination of estimated RV pressure > 30 mmHg on echocardiography at follow-up, the prevalence of post-PE-impairment was 2.7%.

DISCUSSION

In this study, we used real-world data to track the clinical course after PE, following a national cohort of 5931 patients diagnosed with acute PE for over 10 years. We report the prevalence and cumulative incidence of CTEPH, as well as the magnitude of symptoms and investigational findings.

First, all 14 patients diagnosed with CTEPH after the PE event in 2005 had dyspnea to some degree, and almost all (8/9) CTEPH demonstrated signs of pulmonary hypertension on echocardiography. This finding supports

previous evidence that echocardiography and symptom-taking are good screening methods for follow-up after PE and supports recommendations in the current guidelines.[19,26,27]

We found a substantial proportion of patients with remaining or worsening dyspnea in the years following a PE event. This prevalence of dyspnea is somewhat higher than previously reported, probably because of differences in study designs.[6,9] However, dyspnea is a nonspecific symptom with multiple possible underlying factors. We recently showed that the prevalence of dyspnea in the post-PE population is significantly higher compared with age- and gender-matched control participants. In addition, after adjustment for comorbidities, we found that a PE event was independently associated with the risk of dyspnea.[8]

Brain natriuretic peptide is released from the stretched myocardium and is predictive of mortality in CTEPH patients because an elevated level is associated with more advanced disease. The mean NT-pro-BNP levels in this study did not differ obviously between the CTEPH and non-CTEPH groups, although the median NT-pro-BNP was numerically higher in the CTEPH group. CTEPH patients were few compared with those tested in the non-CTEPH group, so we did not perform statistical evaluation of the between-group differences. We analyzed NT-pro-BNP because of an earlier suggestion that electrocardiography and NT-pro-BNP could represent a noninvasive approach to ruling out CTEPH.[28] If this approach is safe is still not clear, and it was not recommended in previous guidelines.[19,26] In 2021, Boon et al. recommended a modified approach based on NT-pro-BNP and echocardiography with a failure rate of 0.29%.[29] However, this approach has not yet been endorsed by the latest guidelines.[27]

Of the V/Q scans performed, approximately half demonstrated signs of perfusion defects, which is somewhat higher than previously reported.[5] Many studies have shown incomplete thrombus resolution even though most used computed tomography pulmonary angiography for imaging.[12–15]

Of note, one in six CTEPH patients diagnosed within the study protocol had a normal V/Q scan, and the final diagnosis was probably pulmonary arterial hypertension.

In the group of PE patients with persistent dyspnea and a V/Q scan demonstrating perfusion defects, 37% (72/196) had an indirect sign of pulmonary hypertension on echocardiography. These numbers contrast with those of the minority of patients diagnosed with CTEPH. Because all V/Q scans and echocardiography studies performed in this investigation were administered in symptomatic patients, these findings may indicate the presence of CTEPD, which needs to be assessed in future work. The prevalence of CTEPD in this cohort among the patients with dyspnea, perfusion defects, and indirect signs of pulmonary hypertension on echocardiography is unclear and merits further study.

Previous reports have described a broad variation in CTEPH prevalence following acute PE, partly because of differences in the diagnostic process of selecting patients for RHC, and in inclusion and exclusion criteria. In addition, many CTEPH studies have included a mixture of prevalent and incident cases, which is further complicated by the risk of misclassifying CTEPH as acute PE.

The overall prevalence of CTEPH in this study is in line with previously published data but in the lower range of the scale. We suggest that the prevalence reported here should be regarded as a minimum because as noted, it was not possible to perform a V/Q scan in all patients with symptoms. It is therefore not unlikely that there are undiagnosed cases of CTEPH in the group of symptomatic individuals who did not receive a V/Q scan. In addition, there may have been undiagnosed cases of CTEPH within the group of individuals who died during the study as well as within the group of individuals that were asymptomatic at the time of the questionnaire.

The fact that some CTEPH patients were diagnosed outside the study protocol is not considered a weakness but rather reflects well on the Swedish health care system. There were 10 cases of acute PE diagnoses in patients who already were diagnosed with CTEPH. Because there was no review of medical records of acute PE episodes in this study, information was insufficient with regard to whether these patients were correctly diagnosed (i.e., acute PE on top of CTEPH), were misdiagnosed as having acute PE, or were subject to an ICD coding error. We have recently demonstrated a high positive predictive value for acute PE diagnosis in the Swedish NPR, but some cases of misclassification also were identified.[30]

Only three CTEPH patients had performed a PEA, which is noteworthy since PEA is a well-established therapy that has the potential to improve both hemodynamics and survival.[31] However, the reason for this low frequency of PEA procedures in this cohort is beyond the scope for this manuscript.

To our knowledge, no previous prospective follow-up studies of this magnitude have contributed findings based on real-life data related to the clinical course after acute PE. However, we recognize that there are limitations of this study. First, since we aimed to follow a complete national cohort of PE patients, this resulted in an elderly cohort, as the incidence of PE increases with age.[26] A prospective follow-up of an elderly cohort for more than 10 years may be complicated by a high risk for

death and other medical events; therefore, it is not surprising that in some cases, patients or their treating doctors refrained from further investigations.

Furthermore, we had only limited influence over the investigations performed in the later part of the study. There were the significant number of losses to follow-up at the stage of referral to the local hospitals with the recommendation to perform a V/Q scan, which most likely have influenced the prevalence of CTEPH. The limited influence in this phase is also a contributing factor to the fact that some V/Q scans were performed as late as 2017. In addition, there was a risk of selection bias because the different local hospitals had different approaches to selection for a V/Q scan referral. However, we took full responsibility for all patients, and when the local hospitals refrained from follow-up, and alternative follow-up at a primary health care center was established.

In conclusion, we report a high mortality following an acute PE, a high proportion of persistent dyspnea among survivors, and substantial proportions of pathological findings on V/Q scans and echocardiography in the post-PE population. A minority of patients developed CTEPH, which highlights a gap in knowledge regarding survivors of PE. Even though this study answers many questions about the clinical course during long-term follow-up after a PE event, more questions emerge from our results. Among them is determining the prevalence of CTEPD and how to find and select CTEPD patients who will benefit from pulmonary endarterectomy and/or balloon angioplasty. This patient population clearly needs proper follow-up, as the latest guidelines state, and we hope this study will inspire further research on this topic to ensure appropriate care for the post-PE population.

AUTHOR CONTRIBUTIONS

Stefan Söderberg had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Therese Andersson, Lars Nilsson, Flemming Larsen, and Stefan Söderberg contributed substantially to the study design, data analysis, and interpretation. Therese Andersson drafted the manuscript, and all authors critically revived the final manuscript.

ACKNOWLEDGMENTS

We are grateful to Owe Luhr, Yvette Palm Jensen, and Kristian Broms at Actelion Pharmaceuticals, Sweden, for practical and financial support; and to Camilla Ring, research nurse, for incredible work with questionnaires and contacting the authorities, clinics, and hundreds of patients with PE. We also thank Per Liv and Kurt Boman for their expertise and assistance during this study. We also express our gratitude to all local hospitals, all primary health care centers, and especially all local pulmonary arterial hypertension centers that made this study possible. This study was supported by an unrestricted research grant from Actelion Pharmaceuticals, Sweden. S. S. received grants from the Swedish Heart and Lung Foundation, Västerbotten County Council (ALF), and Umeå University. The sponsors did not have any role in analysis and interpretation of data and in writing the manuscript.

CONFLICTS OF INTEREST STATEMENT

T. A. received speaker's honoraria from Actelion Ltd., Vifor Pharma, Astra Zeneca, and Pharmacosmos. F. L. participated in research advisory boards within the field and received speaker's honoraria from Actelion Ltd and from Schering AG (BayerHealth Care). S. S. is an advisory board member and received speaker's honoraria from Actelion Ltd. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets included in this analysis contains identifiable personal data, and Swedish law prohibits free sharing of such data. But can be discussed after individual and reasonable request.

ETHICS STATEMENT

This study was conducted in compliance with the Declaration of Helsinki and was approved by the Regional Ethics Review Board in Umeå, Sweden (07-074). The Ethics Board at the Swedish National Board of Health and Welfare reviewed and approved the extraction of data from the Swedish NPR.

ORCID

Therese Andersson http://orcid.org/0000-0002-5119-8411
Lars Nilsson http://orcid.org/0000-0003-4574-9448
Stefan Söderberg http://orcid.org/0000-0001-9225-1306

REFERENCES

1. Andersson T, Söderberg S. Incidence of acute pulmonary embolism, related comorbidities and survival; analysis of a Swedish national cohort. BMC Cardiovasc Disord. 2017;17(1):155.
2. Fedullo P, Kerr KM, Kim NH, Auger WR. Chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2011;183(12):1605–13.
3. McNeil K, Dunning J. Chronic thromboembolic pulmonary hypertension (CTEPH). Heart. 2007;93(9):1152–8.
4. Klok FA, Tijmensen JE, Haeck MLA, 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(8):625–9.
5. Sanchez O, Helley D, Couchon S, Roux A, Delaval A, Trinquart L, Collignon MA, Fischer AM, Meyer G. Perfusion defects after pulmonary embolism: risk factors and clinical significance. J Thromb Haemostasis. 2010;8(6):1248–55.
6. Klok FA, van Kralingen KW, van Dijk APJ, Heyning FH, Vliegen HW, Huisman MV. Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. Respir Med. 2010;104(11):1744–9.
7. Stevinson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J. 2007;28(20):2517–24.
8. Nilsson LT, Andersson T, Larsen F, Lang IM, Liv P, Söderberg S. Dyspnea after pulmonary embolism: a nationwide population-based case-control study. Pulm Circ. 2021;11(4):1–9.
9. Konstantinides SV, Vicaut E, Danays T, Becattini C, Bertoletti L, Beyer-Westendorf J, Bouvaist H, Couturaud F, Dellas C, Duerschmied D, Empen K, Ferrari E, Galiè N, Jiménez D, Kostrubiec M, Kozak M, Kupatt C, Lang IM, Lankeit M, Meneveau N, Palazzini M, Pruszczyk P, Rugolotto M, Salvi A, Sanchez O, Schellong S, Sobkowicz B, Meyer G. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol. 2017;69(12):1536–44.
10. Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism. Chest. 2009;136(5):1202–10.
11. Nijkeuter M, Hovens MMC, Davidson BL, Huisman MV. Resolution of thromboemboli in patients with acute pulmonary embolism. Chest. 2006;129(1):192–7.
12. Alonso-Martínez JL, Anniccherico-Sánchez FJ, Urbieta-Echezarreta MA, García-Sanchotena JL, Herrero HG. Residual pulmonary thromboemboli after acute pulmonary embolism. Eur J Intern Med. 2012;23(4):379–83.
13. Cosmi B, Nijkeuter M, Valentino M, Huisman MV, Barozzi L, Palareti G. Residual emboli on lung perfusion scan or multidetector computed tomography after a first episode of acute pulmonary embolism. Intern Emerg Med. 2011;6(6):521–8.
14. Golpe R, de Llano LAP, Castro-Añón O, Vázquez-Caruncho M, González-Juanatey C, Fariñas MC. Long-term outcome of patients with persistent vascular obstruction on computed tomography pulmonary angiography 6 months after acute pulmonary embolism. Acta Radiol. 2012;53(7):728–31.
15. Korkmaz A, Ozlu T, Ozsu S, Kazaz Z, Bulbul Y. Long-term outcomes in acute pulmonary thromboembolism: the incidence of chronic thromboembolic pulmonary hypertension and associated risk factors. Clin Appl Thromb Hemost. 2012;18(3):281–8.
16. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. Circulation. 1999;99(10):1325–30.
17. Sista AK, Klok FA. Late outcomes of pulmonary embolism: the post-PE syndrome. Thromb Res. 2018;164:157–62.
18. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev. 2014;28(6):221–6.
19. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Noordegraaf AV, Beghetti M, Ghofrani A, Sanchez MAG, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, ESC Scientific Document Group. 2015 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. 2016;37(1):67–119.
20. Delcroix M, Torbicki A, Gopalan D, Sitbon O, Klok FA, Lang I, Jenkins D, Kim NH, Humbert M, Jais X, Vonk Noordegraaf A, Pepke-Zaba J, Brénot P, Dorfmuller P, Fadel E, Ghofrani HA, Hoeper MM, Jansa P, Madani M, Matsubara H, Ogo T, Grünig E, D'Armini A, Galie N, Meyer B, Corkery P, Meszaros G, Mayer E, Simonneau G. ERS statement on chronic thromboembolic pulmonary hypertension. Eur Respir J. 2021;57(6):2002828.
21. Pengo V, Lensing AWA, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, Prandoni P. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350(22):2257–64.
22. Tunariu N, Gibbs SJR, Win Z, Gin-Sing W, Graham A, Gishen P, AL-Nahhas A. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48(5):680–4.
23. Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, Lang E, Stiell I, Kovacs G, Dreyer J, Dennie C, Cartier Y, Barnes D, Burton E, Pleasance S, Skedgel C, O'Rouke K, Wells PS. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA. 2007;298(23):2743–53.
24. Glaser JE, Chamarthy M, Haramati LB, Esses D, Freeman LM. Successful and safe implementation of a trinary interpretation and reporting strategy for V/Q lung scintigraphy. J Nucl Med. 2011;52(10):1508–12.
25. Dournes G, Verdier D, Montaudon M, Bullier E, Rivière A, Dromer C, Picard F, Billes MA, Corneloup O, Laurent F, Lederlin M. Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. Eur Radiol. 2014;24(1):42–51.
26. Konstantinides SV, Meyer G. The 2019 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2019;40(42):3453–5.
27. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK,

Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Noordegraaf AV, Delcroix M, Rosenkranz S, ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731.

28. Klok FA, Surie S, Kempf T, Eikenboom J, van Straalen JP, van Kralingen KW, van Dijk APJ, Vliegen HW, Bresser P, Wollert KC, Huisman MV. A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Thromb Res. 2011;128(1):21–6.
29. Boon GJAM, Ende-Verhaar YM, Bavalia R, El Bouazzaoui LH, Delcroix M, Dzikowska-Diduch O, Huisman MV, Kurnicka K, Mairuhu ATA, Middeldorp S, Pruszczyk P, Ruigrok D, Verhamme P, Vliegen HW, Vonk Noordegraaf A, Vriend JWJ, Klok FA. Non-invasive early exclusion of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the InShape II study. Thorax. 2021;76(10):1002–9.
30. Andersson T, Isaksson A, Khalil H, Lapidus L, Carlberg B, Söderberg S. Validation of the Swedish National Inpatient Register for the diagnosis of pulmonary embolism in 2005. Pulm Circ. 2022;12(1):e12037.
31. Sandqvist A, Kylhammar D, Bartfay SE, Hesselstrand R, Hjalmarsson C, Kavianipour M, Nisell M, Rådegran G, Wikström G, Kjellström B, Söderberg S. Risk stratification in chronic thromboembolic pulmonary hypertension predicts survival. Scand Cardiovasc J. 2021;55(1):43–9.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Andersson T, Nilsson L, Larsen F, Carlberg B, Söderberg S. Long-term sequelae following acute pulmonary embolism: a nationwide follow-up study regarding the incidence of CTEPH, dyspnea, echocardiographic and V/Q scan abnormalities. Pulm Circ. 2023;13:e12306. https://doi.org/10.1002/pul2.12306