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Right ventricular dysfunction is associated with the development of chronic thromboembolic pulmonary hypertension but not with mortality post-acute pulmonary embolism

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH), a late complication of pulmonary embolism (PE), is associated with high mortality. However, whether the right ventricular (RV) echocardiographic parameters can predict – in the short- and long-term – the development of CTEPH and mortality after PE remains unknown. Herein, we aim to investigate the incidence of CTEPH after acute PE and to evaluate the risk factors of CTEPH. In this retrospective cohort, patients with PE were followed for 10 years for the onset of CTEPH. The screening was initially conducted through echocardiography and confirmed by right heart catheterization. Also, transient and permanent risk factors were identified. Among 358 patients with PE, 8 patients (4%) were subsequently diagnosed with CTEPH at a median time of 36 months and 47 died during the follow-up period. Notably, both short- and long-term RV dilatation, hypertrophy, and increased pulmonary pressure increased the incidence of CTEPH. However, RV echocardiographic parameters failed to differentiate survivors from non-survivors. Instead, malignancy, respiratory, or chronic heart failure was strongly associated with post PE mortality in the multivariable analysis. According to our findings, post PE screening of CTEPH may facilitate early diagnosis and intervention for patients at high risk of developing CTEPH. Also, RV echocardiographic parameters are associated with subsequent CTEPH, but mortality is mainly dependent on underlying comorbidities.

Abbreviations: COPD = chronic obstructive pulmonary disease, CTEPH = chronic thromboembolic pulmonary hypertension, PE = pulmonary embolism, RV = right ventricular, VTE = venous thromboembolic events.

Keywords: chronic thromboembolic pulmonary hypertension, pulmonary embolism

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct pulmonary vascular disease caused by chronic obstruction of major pulmonary arteries. CTEPH is a dual vascular disorder, with major-vessel vascular obliteration and a peripheral pulmonary arteriopathy resembling classic pulmonary arterial hypertension (PAH). CTEPH is also considered as a late complication of acute pulmonary embolism (PE).[1,2] While a substantial resolution of the embolus occurs in most patients with PE, in a minority of patients the embolus persists. A residual thrombus that has been in the body for a while can undergo fibrous organization, after which dissolution by endogenous or exogenous fibrinolytics is no longer possible. The organized fibrous thrombus and subsequent pulmonary arterial remodeling can lead to chronic elevation of pulmonary pressure.

CTEPH is characterized by elevated pressure in the artery with persistent pulmonary perfusion defects.[3] The constant, elevated pulmonary pressure is associated with a progressive increase in right ventricle (RV) afterload, resulting in RV dysfunction and eventually heart failure and death.[1] Ideally, patients with PE should be proactively and appropriately managed in the acute phase to prevent progression to CTEPH.

The cumulative incidence of CTEPH within 2 years of asymptomatic PE event has been reported as 0.1% to 9.1%.[4] The actual proportion of patients with PE that progress to CTEPH is still unclear, and also varies relative to how the studied patient population was selected.[5] Early diagnosis of CTEPH remains a

significant clinical challenge, while the first incidence is usually reported within 2 years.[6,7] According to the 2015 ESC/ESR guidelines for the diagnosis and treatment of pulmonary hypertension, requirements for routine screening for CTEPH after PE are currently under debate, as a significant number of CTEPH cases develop without a previous acute PE event.[8] Nevertheless, assessment of the risk factors for CTEPH will be essential to facilitate the early detection of patients at risk after PE.

To date, the incidence of CTEPH after acute PE in the Taiwanese population is not known. Therefore, this study aimed to assess the incidence of CTEPH after acute PE and to evaluate the risk factors associated with CTEPH. Also, we studied the contributing factors to mortality post-acute PE.

2. Methods

2.1. Study design

This is a retrospective chart review that took place at the National Cheng Kung University Hospital between January 1, 2006, and May 31, 2017. The ethics committee of National Cheng Kung University Hospital approved this study (ethics number: B-ER-105–136).

2.2. Patients

Patients with a confirmed diagnosis of acute PE between January 1, 2006, and March 31, 2016, were included in the study. Medical records were retrospectively reviewed, and eligible patients were identified using the ICD-9 and ICD-10 codes for PE. Patients were categorized relative to PE associations with transient and permanent risk factors.[9] Transient risk factors included recent surgery, trauma (with or without bone fracture), prolonged immobilization due to medical reasons (i.e., lasting more than 7 days), deep venous thrombosis, pregnancy or recent childbirth, and the use of oral contraceptives or hormone-replacement therapy. Permanent risk factors included chronic heart or respiratory failure, cerebrovascular disease, thrombophilia, active cancer, obesity, and varicose veins. Patients with PE in the absence of risk factors were considered as having idiopathic (unprovoked) PE. Under the clinical impression of PE, the diagnosis was confirmed by examining CT angiography or ventilation/perfusion (V/Q) scans. Given the echocardiography derived high PAP and RV failure signs, patients with suspected CTEPH were referred for further evaluation. We used an RHC and V/Q scan to arrive at a definite diagnosis of CTEPH.

2.3. Treatment of PE

Anticoagulation agents were initially used to treat hemodynamically stable acute PE using either unfractionated heparin or low molecular weight heparin. Thrombolytic agents, including streptokinase, urokinase, or recombinant tissue plasminogen activator, were initially administered to treat hemodynamically unstable acute PE.[9] After the initial treatment, patients were administered anticoagulant therapy. We assessed the need to extend anticoagulant treatment beyond 6 months using risk stratification of PE recurrence.[10]

2.4. Echocardiography

Echocardiography was initially performed during the admission of acute PE and afterward, depending on patients' clinical symptoms. These symptoms included dyspnea, palpitations, and peripheral edema. The median follow-up duration was 6 months; up to 24 months. Standard imaging was performed (iE33, Philips) with a 3.5-MHz multiphase-array probe per the recommendations of the American Society of Echocardiography.[11] LVEF was measured using the biplane Simpson's method. As described previously,[11] RV dimensions, including mid-cavity diameters and wall thickness, were measured at the mid-cavity in diastole at the parasternal long-axis view. Thickness >5 mm indicates RV hypertrophy and may suggest RV pressure overload. RV dilatation is defined based on the right ventricle appearing larger than the left ventricle. Applying the Bernoulli equation, RV pressure was calculated according to the trans-tricuspid flow velocity. All the analyzed images were acquired in three consecutive cardiac cycles and stored digitally with a frame rate of 50–90 frames per second.

2.5. Follow-up of CTEPH diagnosis and mortality

The primary endpoint of this study was the diagnosis of CTEPH, while the secondary endpoint was mortality. Patients selected from retrospective chart review were checked for a diagnosis of CTEPH within their medical records (before March 31, 2016) and followed up according to ESC guidelines. Patients with signs of pulmonary hypertension were investigated by using echocardiography. CTEPH was considered upon observation of a systolic pulmonary arterial pressure >40 mm Hg, with a lung perfusion scan revealing the perfusion defect.[10] Right heart catheterization was used to confirm the appearance of multiple chronic or organized thromboembolic obstructions. The final diagnosis of CTEPH was determined with the following observations of mean pulmonary arterial pressure ≥25 mm Hg at rest, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance >3 Wood units.[9] Also, during the follow-up period, the subsequent mortality was recorded by the medical record.

2.6. Statistical analysis

Data are presented as means ± SD for continuous variables, and numbers and percentages for categorical variables. To investigate the risk factors for CTEPH and mortality, univariable analysis was carried out by Fisher's exact test for categorical variables when any cell in a contingency table had $n < 5$ or the χ^2 test for all other categorical and Mann–Whitney U test for continuous variables between CTEPH and non-CTEPH groups, survivors and non-survivors, respectively. Given the limited number of CTEPH diagnosis, in the further simple and multiple Cox proportional hazard regression models, we focused on the subsequent mortality post-acute PE. Kaplan–Meier curves were plotted to differentiate the survivals in the sub-group analysis. A P-value of $<.05$ was considered statistically significant throughout the study. SAS software version 9.4 (SAS Inc. Cary, NC) was used for all statistical analyses.

3. Results

3.1. Patients

There were 358 patients diagnosed with PE from January 1, 2006 to March 31, 2016. Fifty-four patients died during the first hospitalization. After discharge, 48 patients were lost to follow-up, and 53 patients did not repeat echocardiography. Thus, the
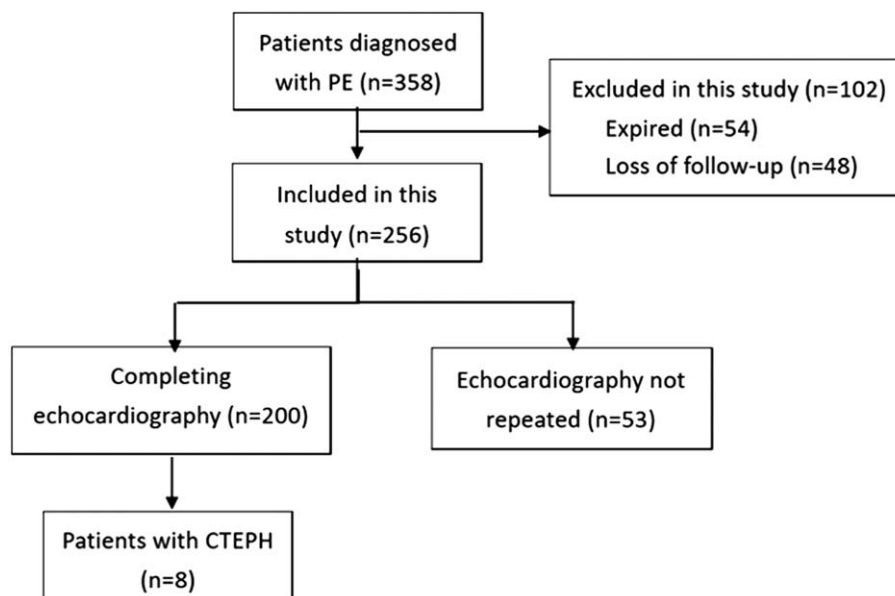
Figure 1. The algorithm of patient enrollment.

final study population consisted of 200 patients, and 8 patients were diagnosed with CTEPH (Fig. 1). Baseline characteristics are shown in Table 1. Mean age at first PE was 63.8 ± 15.9 years old. Of these, 151 (75.5%) patients had encountered an unprovoked PE. The initial treatments at first PE, 87.5% of patient were treated with anticoagulation agents, while 5% were administered thrombolytic therapy.

3.2. Incidence and risk factors of CTEPH

During follow-up, 8 patients (4%) were diagnosed with CTEPH after the first episode of acute PE. The median time from PE to CTEPH is 36 months (range: 3–120 months) (Table 2). The time and cumulative incidence of CTEPH are displayed in Figure 2. Interestingly, despite a higher prevalence of thrombophilia in patients who developed CTEPH, there was only 1 patient with thrombophilia in each group. Also, most of the clinical risk factors, including malignancy, chronic heart or lung disease, obesity, and varicose veins, were not associated with the subsequent diagnosis of CTEPH. In contrast, among echocardiographic risk factors during the acute stage of acute PE, the incidence of RV dilatation, RV hypertrophy, and increased pulmonary artery pressure were significantly higher in patients with CTEPH compared with patients without CTEPH. Furthermore, the follow-up RVD, RV hypertrophy, and PA pressure remained higher in those who developed CTEPH; however, the changes in PA pressure between patients with and without CTEPH were insignificant. The extended uses of anticoagulant at discharge, which implied a relatively higher risk of PE recurrence, were similar between the two groups. Nevertheless, no patients experienced recurrent PE during the follow-up period.

3.3. Incidence and risk factors of mortality

The survival rate of patients post-acute PE in the third and fifth year was 75.89% and 73.49%, respectively. Among the 200 patients

with acute PE, 47 died during the follow-up period. Sixteen patients died of heart failure, 8 died of respiratory failure, 20 died of sepsis, and the causes of death of the three remaining patients were not recorded. The non-survivors tended to be younger and with permanent PE risk factors, including an underlying malignancy, liver disease, and chronic heart and lung failure. Also, the use of anticoagulants was higher in survivors compared with non-survivors. Regarding the echocardiographic parameters, only RV dilatation at the diagnosis of PE and mildly elevated PA pressure during the follow-up period were significantly different between survivors and non-survivors (Table 3).

3.4. The univariate and multivariable analyses of mortality

According to simple Cox regression, the influence of age at first PE, sex, DBP, and permanent PE risks on the prediction of the subsequent mortality was significant (Table 4). Malignancy (HR 6.68; 95% CI 3.01–14.83; $P < .0001$) as well as chronic heart or respiratory failure (HR 3.6; 95% CI 1.57–8.26; $P = .0025$) were permanent PE risk factors that increased the incidence of death. Concerning comorbidities, chronic obstructive pulmonary disease (HR 3.4; 95% CI 1.26–9.17; $P = .0158$), and liver disease (HR 3.43; 95% CI 1.53–7.68; $P = .0027$) were associated with increased mortality. Moreover, previous venous thromboembolic events (VTE) (HR 3.57; 95% CI 1.06–12.04; $P = .0403$) were also potential risk factors that affected mortality. Conversely, all other echocardiographic parameters – except for RV dilatation at the diagnosis of PE – failed to indicate subsequent mortality. Multivariable analysis using multiple Cox regression confirmed that only malignancy (HR 5.43; 95% CI 2.51–11.72; $P < .0001$) and chronic heart or respiratory failure (HR 5.64; 95% CI 2.53–12.54; $P < .0001$) significantly predicted subsequent mortality (Table 5). In patients with malignancies or chronic heart/lung disease, the Kaplan–Meier plot displayed a significantly worse survival compared to patients without malignancies or chronic heart/lung disease (Fig. 3).

Table 1

Baseline characteristics of the studied patients.

Characteristic	N = 200
Clinical parameters	
Age at first PE (yr)	63.8 ± 15.9
Male (%)	83 (41.5%)
BMI (kg/m^2)	25.4 ± 4.7
SBP (mm Hg)	130.7 ± 23.5
DBP (mm Hg)	79.8 ± 15.9
Heart rate (bpm)	94.7 ± 19.3
Respiratory rate (bpm)	20.6 ± 4.1
Smoking status, n (%)	
Non-smoker	170 (85%)
Former smoker	6 (3%)
Smoker	24 (12%)
Unprovoked PE, n (%)	151 (75.5%)
Transient PE risk factor, n (%)	34 (17%)
Concomitant DVT, n (%)	37 (18.5%)
Initial treatment at first PE	
Thrombolysis, n (%)	10 (5%)
Anticoagulation, n (%)	175 (87.5%)
Treatment on discharge of first PE	
Anticoagulation, n (%)	163 (81.5%)
Mortality, n (%)	47 (23.5%)
Permanent PE risk factor, n (%)	
Pre VTE, n (%)	12 (6%)
Malignancy, n (%)	54 (27%)
Chronic heart or respiratory failure, n (%)	29 (14.5%)
Cerebrovascular disease, n (%)	18 (9%)
Thrombophilia, n (%)	2 (1%)
Obesity, n (%)	19 (9.5%)
Varicose veins, n (%)	6 (3%)
Comorbidities	
Hypertension, n (%)	86 (43%)
Diabetes, n (%)	40 (20%)
Hyperlipidemia, n (%)	25 (12.5%)
Coronary artery disease, n (%)	18 (9%)
Atrial fibrillation/flutter, n (%)	22 (11%)
Heart valve pathology, n (%)	30 (15%)
COPD, n (%)	14 (7%)
Gout, n (%)	12 (6%)
Interstitial lung disease, n (%)	4 (2%)
Chronic kidney disease, n (%)	27 (13.5%)
Liver disease, n (%)	42 (21%)
Thyroid disorder/Struma, n (%)	13 (6.5%)
Rheumatism/collagen vascular disease, n (%)	8 (4%)
Family history of CAD, n (%)	22 (11%)
Family history of stroke, n (%)	17 (8.5%)
Echocardiographic parameters	
LVEF (%)	68.4 ± 10.3
RVD (+), n (%)	42 (21%)
RVH (+), n (%)	5 (2.5%)
PA (mm Hg)	40.6 ± 23.2
FU RVD (+), n (%)	16 (8%)
FU RVH (+), n (%)	6 (3%)
FU PA (mm Hg)	30.2 ± 14.2

Data are expressed as mean ± SD or number (%). $P < .05$ as significance.
BMI = body mass index, COPD = chronic obstructive pulmonary disease, DBP = diastolic blood pressure, DVT = deep venous thrombosis, LVEF = left ventricular ejection fraction, PA = pulmonary artery pressure, RVD = RV dilation, RVH = RV hypertrophy, SBP = systolic blood pressure, VTE = venous thromboembolic events. Hyperlipidemia is based on NICE guideline 2014.

Table 2

The comparison of risk factors between patients developing chronic thromboembolic pulmonary hypertension (CTEPH) or not post pulmonary embolism.

Risk factors	CTEPH (n = 8)	Non-CTEPH (n = 192)	P-value
Clinical parameters			
Age at first PE (years)	50.7 ± 15.5	64.3 ± 15.7	.03
Male (%)	2 (25)	81 (42.19)	.33
BMI (kg/m^2)	26.5 ± 5.6	25.4 ± 4.	.37
SBP (mmHg)	130.5 ± 14.2	130.7 ± 23.8	.84
DBP (mmHg)	79.5 ± 11.2	79.8 ± 16.1	.91
Heart rate (bpm)	85 ± 13.1	95.1 ± 19.4	.15
Respiratory rate (bpm)	19.5 ± 2.3	20.6 ± 4.1	.36
Smoking status, n (%)			.27
Non-smoker	6 (75)	164 (85.4)	
Former smoker	1 (12.5)	5 (2.6)	
Smoker	1 (12.5)	23 (11.9)	
Unprovoked PE, n (%)	8 (100)	143 (74.4)	.26
Transient PE risk factor, n (%)	0 (0)	34 (17.7)	.40
Pre_VTE, n (%)	0 (0)	12 (6.25)	.73
Permanent PE risk factor, n (%)	2 (25)	68 (35.4)	.55
Concomitant DVT, n (%)	2 (25)	35 (18.2)	.87
Initial treatment at first PE			
Thrombolysis, n (%)	0 (0)	10 (5.2)	.51
Anticoagulation, n (%)	8 (100)	167 (86.9)	.28
Treatment on discharge of first PE			
Anticoagulation, n (%)	7 (87.5)	156 (81.2)	.66
Permanent PE risk factor, n (%)			
Malignancy, n (%)	0 (0)	54 (28.2)	.19
Chronic heart or respiratory failure, n (%)	1 (12.5)	28 (14.5)	.87
Cerebrovascular disease, n (%)	1 (12.5)	17 (8.8)	.72
Thrombophilia, n (%)	1 (12.5)	1 (0.52)	.001[*]
Obesity, n (%)	2 (25)	17 (8.8)	.13
Varicose veins, n (%)	0 (0)	6 (3.1)	.61
Comorbidities			
Hypertension, n (%)	2 (25)	84 (43.7)	.29
Diabetes, n (%)	1 (12.5)	39 (20.3)	.59
Coronary artery disease, n (%)	0 (0)	18 (9.3)	.36
Atrial fibrillation/flutter, n (%)	0 (0)	22 (11.4)	.31
Heart valve pathology, n (%)	1 (12.5)	29 (15.1)	.84
COPD, n (%)	1 (12.5)	13 (6.7)	.53
Interstitial lung disease, n (%)	0 (0)	4 (2.1)	.68
Chronic kidney disease, n (%)	1 (12.5)	26 (13.5)	.93
Liver disease, n (%)	1 (12.5)	41 (21.3)	.55
Thyroid disorder/Struma, n (%)	0 (0)	13 (6.7)	.45
Rheumatism/collagen vascular disease, n (%)	0 (0)	8 (4.17)	.56
Echocardiographic parameters			
LVEF	71.7 ± 3.2	68.2 ± 10.6	.38
Impaired LV relaxation, n (%)	5 (62.5)	44 (22.9)	.02
RVD (+), n (%)	6 (75)	36 (18.7)	.001[*]
RVH(+), n (%)	3 (37.5)	2 (1)	.001[*]
PA(mmHg)	79.2 ± 38.7	39 ± 21.1	.001[*]
FU RVD(+), n (%)	6 (75)	10 (5.21)	<.0001[*]
FU RVH(+), n (%)	4 (50)	2 (1.04)	<.0001[*]
FU PA(mmHg)	66.2 ± 34	28.7 ± 10.6	<.0001[*]
The change of PA (mmHg)	−13.0 ± 31.9	−10.3 ± 23.0	.79
Duration of follow-up (days ± SD)	1380.3 ± 642.3	1381.8 ± 1465.4	.03[*]

Data are expressed as mean ± SD or number (%).
[*] $P < .05$ as significance.
Abbreviations as Table 1.

4. Discussion

This was the first study to investigate the incidence of CTEPH and mortality in a Taiwanese population after the diagnosis of PE.

The incidence of CTEPH was 4% with the median time was 36 months after the first episode of PE. Previous studies have reported that the incidence of CTEPH after symptomatic acute PE ranges from 0.1% to 9.1%.[4] With regard to the CTEPH

Figure 2. The time and cumulative incidence of chronic thromboembolic pulmonary hypertension (CTEPH).

The comparison of risk factors between non-survivors and survivors post pulmonary embolism.

Risk factors	Non-survivors (n = 47)	Survivors (n = 153)	P-value
Clinical parameters			
Age at first PE (years)	62.1 ± 16.1	69.3 ± 13.9	.01[*]
Male (%)	26 (55.3)	57 (37.2)	.08
BMI (kg/m^2)	25.8 ± 4.9	24.3 ± 3.7	.11
SBP (mmHg)	131.9 ± 23.8	127 ± 22.3	.20
DBP (mmHg)	81 ± 15.2	75.9 ± 17.6	.07
Heart rate (bpm)	95.3 ± 18.5	93.1 ± 22	.45
Respiratory rate (bpm)	20.6 ± 4.3	20.3 ± 3.1	.84
Smoking status, n (%)			.38
Non-smoker	37 (78.7)	133 (86.9)	
Former smoker	2 (4.2)	4 (2.6)	
Smoker	8 (17.)	16 (10.4)	
Unprovoked PE, n (%)	33 (70.2)	118 (77.1)	.49
Transient PE risk factor, n (%)	7 (14.9)	27 (17.6)	.65
Pre_VTE, n (%)	6 (12.7)	6 (3.9)	.05
Permanent PE risk factor, n (%)	29 (61.7)	41 (26.8)	<.0001[*]
Concomitant DVT, n (%)	7 (14.8)	30 (19.6)	.64
Initial treatment at first PE			
Thrombolysis, n (%)	0 (0)	10 (5.2)	.07
Anticoagulation, n (%)	35 (74.4)	140 (91.5)	.002[*]
Treatment on discharge of first PE			
Anticoagulation, n (%)	29 (61.7)	134 (87.5)	<.0001[*]
CTEPH, n (%)	0 (0)	8 (5.2)	.10
Permanent PE risk factor, n (%)			
Malignancy	29 (61.7)	25 (16.3)	<.0001[*]
Chronic heart or respiratory failure	13 (27.6)	16 (10.4)	.001[*]
Cerebrovascular disease	5 (10.6)	13 (8.5)	.65
Thrombophilia	0 (0)	2 (1.31)	.43
Obesity	2 (4.2)	17 (11.1)	.16
Varicose veins	0 (0)	6 (3.9)	.16
Comorbidities			
Hypertension	23 (48.9)	63 (41.1)	.34
Diabetes	11 (23.4)	29 (18.9)	.5
Coronary artery disease	6 (12.7)	12 (7.8)	.3
Atrial fibrillation/flutter	6 (12.7)	16 (10.4)	.65
Heart valve pathology	6 (12.7)	24 (15.7)	.62
COPD	6 (12.7)	8 (5.2)	.07
Interstitial lung disease	2 (4.2)	2 (1.3)	.20
Chronic kidney disease	11 (23.4)	16 (10.4)	.02[*]
Liver disease	19 (40.4)	23 (15)	.0002[*]
Thyroid disorder/Struma	5 (10.6)	8 (5.2)	.18
Rheumatism/collagen vascular disease	2 (4.2)	6 (3.9)	.91
Echocardiographic parameters			
LVEF(%)	68.8 ± 8.7	66.6 ± 15.5	.76
RVD(+), n (%)	4 (8.5)	38 (24.8)	.01[*]
RVH(+), n (%)	0 (0)	5 (3.2)	.20
Impaired_LV relaxation, n (%)	11 (23.4)	38 (24.8)	.84
PA(mmHg)	42.3 ± 24.5	35.1 ± 17.5	.11
FU RVD(+), n (%)	5 (10.6)	11 (7.1)	.44
FU RVH(+), n (%)	1 (2.1)	5 (3.2)	.68
FU PA (mmHg)	29.4 ± 14.1	32.6 ± 14.5	.002[*]

Data are expressed as mean ± SD or number (%).

[*] P < .05 as significance.

Abbreviations as Table 1.

incidence in some Asian countries, 1.7% and 6.1% were reported recently in China and Korea, respectively.[9,12] Several factors may affect the estimation of the incidence of CTEPH, such as selected populations, diagnostic methods, management of acute PE, and follow-up time.[5,9]

According to the current guidelines, patients with a history of venous thromboembolism who present with signs of right-sided heart failure should undergo a diagnostic evaluation for CTEPH.[8,12–14] However, early diagnosis of CTEPH – before the development of right heart failure – should be emphasized to enable early identification and intervention. Screening programs for CTEPH facilitate the detection of PH in specific at-risk populations. Nevertheless, it remains inconclusive whether screening should be conducted after acute PE, given the scant evidence.

Among the various modalities used to detect structural and functional effects of PH on the heart, transthoracic echocardiography is a non-invasive and simple screening tool. However, especially for patients with less-severe disease, false positive and false negative estimates are more frequent during transthoracic echocardiography compared with a right heart catheterization, which is the gold standard for PH diagnosis.[15] Therefore, the ESC guidelines do not support the routine application of echocardiography for acute PE during follow-up.[8] Conversely, it is more cost-efficient to identify patients with PE who have concomitant high risks for CTEPH.

In a recent meta-analysis which enrolled 772 PE-survivors generated a clinical prediction score for the diagnosis of CTEPH after PE.[16] Prediction factors included patients with unprovoked PE, known hypothyroidism, symptom onset weeks before PE diagnosis, right ventricular dysfunction, and diabetes mellitus.[16] In another study, patients who developed CTEPH tended to be older, had previous venous thromboembolic events, and more proximal PE than those without CTEPH.[6] Other reports indicated that medical conditions associated with an increased risk of CTEPH include male gender, a history of splenectomy, cancer, ventriculoatrial shunt, chronic inflammatory disease, and an increased body mass index.[13] Notably, in our study we also found that patients with risk factors such as unprovoked PE tended to develop CTEPH; however, most of the clinical risk factors were not associated with the subsequent diagnosis of

CTEPH. Instead, echocardiographic parameters indicating RV dysfunction significantly predicted the development of CTEPH. Conversely, as we focused on the subsequent mortality post-acute PE, in multivariable Cox regression, the only clinical risk factors that significantly differentiated survivors from non-survivors were malignancy and chronic heart or respiratory failure.

Table 4

The univariate Cox regression analysis of mortality in patients post pulmonary embolism.

Simple Cox regression	Estimate	HR (95% CI)	P
Clinical parameters			
Age at first PE (yr)	0.04	1.04 (1.01–1.07)	.009
Male vs female	1.22	3.4 (1.49–7.75)	.003
BMI (kg/m^2)	−0.09	0.91 (0.81–1.02)	.122
SBP (mm Hg)	−0.01	0.99 (0.97–1.01)	.316
DBP (mm Hg)	−0.04	0.96 (0.93–0.99)	.012
Heart rate (bpm)	−0.01	0.99 (0.97–1.01)	.455
Respiratory rate (bpm)	−0.01	0.99 (0.9–1.1)	.845
Smoking status			
Former smoker vs Non-smoker	0.96	2.6 (0.6–11.32)	.202
Smoker vs Non-smoker	0.77	2.17 (0.8–5.86)	.126
Unprovoked PE	−0.27	0.76 (0.28–2.03)	.585
Transient PE risk factor	−1.28	0.28 (0.04–2.06)	.21
Pre VTE	1.27	3.57 (1.06–12.04)	.04
Permanent PE risk factor	1.35	3.85 (1.73–8.57)	.001
Concomitant DVT	−0.53	0.59 (0.17–1.97)	.388
Initial treatment at first PE			
Thrombolysis	−15.17	0 (0–0)	.991
Anticoagulation	−0.49	0.61 (0.21–1.8)	.373
Treatment on discharge of first PE			
Anticoagulation	−0.85	0.43 (0.17–1.07)	.069
Permanent PE risk factor			
Malignancy	1.90	6.68 (3.01–14.83)	<.0001
Chronic heart or respiratory failure	1.28	3.6 (1.57–8.26)	.002
Cerebrovascular disease	−0.08	0.92 (0.22–3.93)	.914
Thrombophilia	−9.01	0 (0–0)	.993
Obesity	−0.98	0.37 (0.05–2.78)	.336
Varicose veins	−14.08	0 (0–0)	.989
Comorbidities			
Hypertension	0.56	1.76 (0.79–3.91)	.167
Diabetes	0.29	1.33 (0.53–3.34)	.541
Coronary artery disease	0.73	2.07 (0.62–6.97)	.239
Atrial fibrillation/flutter	0.18	1.2 (0.36–4.03)	.767
Heart valve pathology	0.23	1.26 (0.5–3.16)	.619
COPD	1.22	3.4 (1.26–9.17)	.015
Interstitial lung disease	−13.02	0 (0–0)	.992
Chronic kidney disease	1.01	2.75 (0.92–8.21)	.069
Liver disease	1.23	3.43 (1.53–7.68)	.002
Thyroid disorder/Struma	0.86	2.36 (0.55–10.1)	.246
Rheumatism/collagen vascular disease	0.03	1.04 (0.14–7.72)	.973
Echocardiographic parameters			
RVD (+)	−1.07	0.34 (0.12–0.96)	.04
RVH (+)	−13.02	0 (0–0)	.98
Impaired LV relaxation	0.80	2.23 (0.99–5)	.05
LVEE	0.09	1.09 (0.9–1.33)	.37
PA	−0.01	0.99 (0.97–1.01)	.16
FU RVD (+)	0.47	1.59 (0.47–5.38)	.45
FU RVH (+)	−13.04	0 (0–0)	.98
FU PA	0.01	1.01 (0.99–1.03)	.33

$P < .05$ as significance.
Abbreviations as Table 1.

Regarding the impact of low diastolic blood pressure, in the condition of geometric effects of RV enlargement and left ventricle (LV) chamber distortion in patients with CTEPH, the low LV preload, and the relative underfilling may result in the abnormal E/A ratio as well as the diastolic pressure.[17,18] Interestingly, female sex is a risk factor for the development of PAH, but the mortality rate was higher in male patients.[19,20] The sex paradox phenomenon was believed driven by the complex interaction between sex hormones and the pulmonary

Table 5

The multivariable Cox Regression analysis of mortality in patients post pulmonary embolism.

Multivariable Cox Regression	Estimate	HR (95% CI)	P-value
Age at first PE (years)	0.01	1.01 (0.98–1.03)	.5
Male VS Female	0.2	1.22 (0.61–2.44)	.57
DBP (mmHg)	−0.01	0.99 (0.97–1.02)	.63
Malignancy	1.69	5.43 (2.51–11.72)	<.0001[*]
Chronic heart or respiratory failure	1.73	5.64 (2.53–12.54)	<.0001[*]
COPD	0.08	1.08 (0.36–3.3)	.88
Liver disease	0.63	1.88 (0.89–3.96)	.09
Pre_VTE	0.39	1.48 (0.52–4.24)	.46
RVD (+)	−0.62	0.54 (0.17–1.67)	.28

[*] $P < .05$ as significance.
Abbreviations as Table 1.

vasculature as well as RV dysfunction.[20] Correspondingly, we found the same condition in these patients with poor outcomes. Also, in the International Cooperative Pulmonary Embolism Registry, patients with chronic heart failure and chronic obstructive pulmonary disease reportedly demonstrated prognostic factors.[21] In our study, we further identified those risk factors, not only for their negative impact on outcomes of patients with PE, but also because of potential links to subsequent mortality. Similarly, patients with concomitant PE and liver disease may exhibit co-existing RV dysfunction while growing evidence supports the hypothesis that CTEPH is often misclassified as acute PE.[4,8] This reflected our findings that none of the patients diagnosed with CTEPH had a history of acute PE while CTEPH may be under-diagnosed or misclassified as acute PE.[22] Collectively, the early screening of echocardiography may help in predicting the development of CTEPH, but the clinical risk factors decide the subsequent mortality.

4.1. Study limitations

There are some limitations to this study. First, only 4% of patients were finally diagnosed with CTEPH and this small population may attenuate the statistic power. Nevertheless, according to the studies mentioned above, the incidence of CTEPH is not as high as the other types of PH.[4,9,12] Compared with the other major CTEPH registries consisting of hundreds of patients, our study also enrolled 358 patients with PE, which is fewer than others. Notably, in this study, patients with suspected CTEPH were referred for further evaluation, including RHC and V/Q scan. However, only some patients received RHC, while some patients refused RHC. This may have resulted in underestimation of the incidence of CTEPH. Second, as a retrospective study, the echocardiographic parameters may not be measured consistently or in sufficient detail. Given that RV hypertrophy is a marker of long-standing pulmonary hypertension, the dilated and hypertrophic RV observed at baseline may imply a subclinical CTEPH before the diagnosis of PE. Also, the changes in PA pressure between patients with and without CTEPH were insignificant. Thus, we cannot know whether patients diagnosed with acute PE may also have under-diagnosed CTEPH. In addition to RV dimension and PA pressure, other important signs that suggested PH included flattening of the interventricular septum, right ventricular outflow Doppler acceleration time, early diastolic pulmonary regurgitation velocity, and inferior cava diameter.[8] Given the possible under-estimation of echo derived PA pressure in a chamber dilated RV, the gold standard
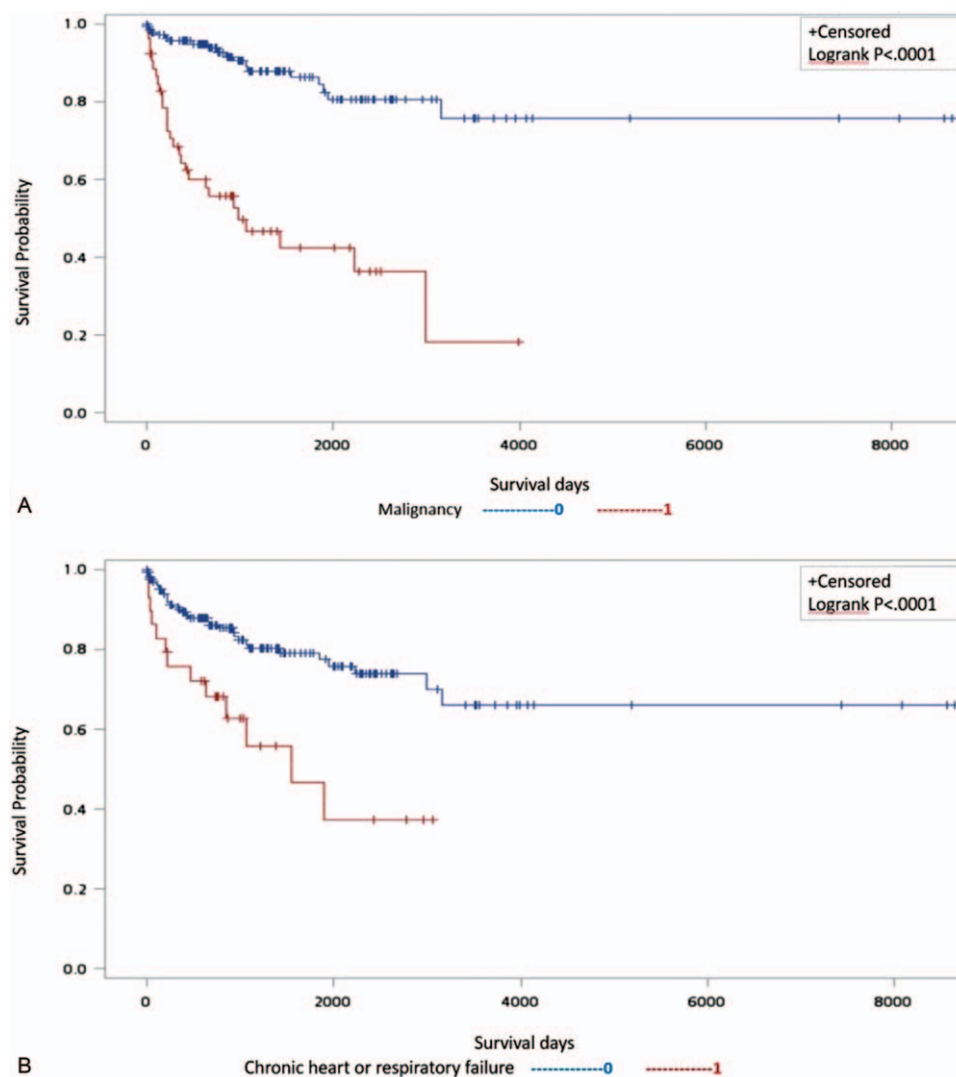
Figure 3. Kaplan–Meier plot representing a significantly worse survival compared with that of patients free from (A) malignancy or (B) chronic heart/lung disease.

test to diagnose CTEPH remains right heart catheterization, which was also performed in our study. In another perspective, using novel techniques, including speckle tracking, may also facilitate in early detection of RV dysfunction in patients post PE beyond the traditional echocardiography.[23,24]

Lastly, some clinical information which may be associated with CTEPH could have been missing from the medical records. Such information could include exercise, alcohol intake, high-sensitivity C-reactive protein, and depression.

4.2. Future directions

Despite the moderate incidence of CTEPH post PE, our finding suggests an urgent need to increase awareness of CTEPH, especially in patients with predisposing factors, to avoid under-diagnosis and under-treatment. Screening echocardiography post PE could be a feasible method for facilitating early diagnosis of subsequent CTEPH. However, larger scale prospective studies are required to further weigh the cost-efficiency of screening programs for early detection of CTEPH.

5. Conclusions

According to our findings, post-acute PE screening of CTEPH may facilitate early diagnosis and intervention, especially for those at high risk for developing CTEPH. Though the subsequent CTEPH is associated with RV echocardiographic parameters, the mortality is mainly dependent on underlying comorbidities. Therefore, optimal risk stratifications and managements of comorbidities are also crucial to improve patients' outcomes.

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