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Original research

Symptom-related screening programme for early detection of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: the SYSPPE study

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ABSTRACT

Background Chronic thromboembolic pulmonary hypertension (CTEPH) is the most severe long-term complication of acute pulmonary embolism (PE). We aimed to evaluate the impact of a symptom screening programme to detect CTEPH in PE survivors.

Methods This was a multicentre cohort study of patients diagnosed with acute symptomatic PE between January 2017 and December 2018 in 16 centres in Spain. Patients were contacted by phone 2 years after the index PE diagnosis. Those with dyspnoea corresponding to a New York Heart Association (NYHA)/WHO scale≥II, visited the outpatient clinic for echocardiography and further diagnostic tests including right heart catheterisation (RHC). The primary outcome was the new diagnosis of CTEPH confirmed by RHC.

Results Out of 1077 patients with acute PE, 646 were included in the symptom screening. At 2 years, 21.8% (n=141) reported dyspnoea NYHA/WHO scale≥II. Before symptom screening protocol, five patients were diagnosed with CTEPH following routine care. In patients with NYHA/WHO scale≥II, after symptom screening protocol, the echocardiographic probability of pulmonary hypertension (PH) was low, intermediate and high in 76.6% (n=95), 21.8% (n=27) and 1.6% (n=2), respectively. After performing additional diagnostic test in the latter 2 groups, 12 additional CTEPH cases were confirmed.

Conclusions The implementation of this simple strategy based on symptom evaluation by phone diagnosed more than doubled the number of CTEPH cases. Dedicated follow-up algorithms for PE survivors help diagnosing CTEPH earlier.

Trial registration number NCT03953560.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Guidelines recommend having a high level of suspicion of chronic thromboembolic pulmonary hypertension (CTEPH) in patients with dyspnoea after acute symptomatic pulmonary embolism (PE).

⇒ We aimed to evaluate an easy phone symptom-related screening programme to detect for chronic thromboembolic pulmonary hypertension after acute PE.

WHAT THIS STUDY ADDS

⇒ Through a straightforward and uncomplicated screening process, 12 new cases of CTEPH were identified. When contrasted with the index cohort, the likelihood of detecting CTEPH by symptom screening increased by a factor of 3.44 (95% CI 1.26 to 9.35).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The implementation of this simple strategy based on symptom evaluation by phone more than doubled the number of CTEPH cases in our cohort. Dedicated follow-up algorithms for PE survivors help diagnosing CTEPH earlier.

INTRODUCTION

Pulmonary hypertension (PH) is a serious disease with several possible aetiologies and associations with respiratory and cardiovascular diseases.[1 2] Chronic thromboembolic PH (CTEPH; group 4 of PH) is defined as precapillary PH caused by persistent fibrotic occlusions in the pulmonary arteria tree after at least 3 months of anticoagulant treatment.[1 3] The estimated cumulative incidence of CTEPH is 0.1%–9.1% in the first 2 years after pulmonary embolism (PE), although this wide range depends on the characteristics of the study.[4 5] The prevalence of CTEPH in the general population is difficult to estimate, given the low frequency

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of the disease and reported underdiagnosis. However, this prevalence has increased in recent years from 3.2 per million inhabitants in 2007 to 22.5 in 2018.[6] Interestingly, the prevalence of CTEPH differs in countries. In Spain, the UK, Switzerland and Germany, the prevalence is 1.7, 1.75, 3.7 and 5.7 per million adults, respectively, possibly due to differences in routine care and follow-up of PE patients.[6–9] In 2017, a predictive model for the incidence of CTEPH developed in the USA, Europe and Japan estimated an increase over the next decade and highlights the need to develop effective and cost-effective diagnostic protocols that allow early detection of this disease.[10]

Today, the diagnosis of CTEPH remains a challenge for clinicians because of the high prevalence of the post-PE syndrome with up to 50% of PE survivors reporting dyspnoea despite adequate anticoagulant treatment, mostly caused by deconditioning.[11] The complexity of diagnosing CTEPH lies in the similarity of symptoms with acute PE, less severe presentations of the post-PE syndrome and in the paucity of validated protocols showing the optimal screening approach.[12] Therefore, the average time to diagnosis in specialised centres has reported to be 14 months from the onset of symptoms.[13] Early diagnosis of CTEPH is essential, since a delay can be associated with a worse prognosis, higher perioperative mortality and inoperable states of the disease.[14 15] Indeed, an early detection and treatment of CTEPH is beneficial to achieve favourable clinical results.[16]

Routine screening of PE survivors with imaging tests is not cost-effective given the low incidence of CTEPH, and therefore, not recommended in clinical practice guidelines.[2 4] Focused efforts to identify CTEPH early in those patients with symptoms suggestive of CTEPH is more practical and will avoid a large number of false positive test results. We aimed to evaluate the impact of a symptom-related screening programme to detect CTEPH in long-time PE survivors.

METHODS

Study design and participants

The SYSSPE (Trial registration number: NCT03953560) was a prospective, multicentre study that enrolled consecutive unselected patients with confirmed acute symptomatic PE. This study was performed at 16 centres across Spain. Patients included in the Registro Informatizado de la Enfermedad Tromboembolica (RIETE) registry between 1 January 2017 and 31 December 2018 in the participating hospitals were eligible (ClinicalTrials.gov NCT02832245).[17] The main inclusion criteria were: (1) age >18 year; (2) objectively confirmed diagnosis of acute symptomatic PE with or without symptomatic deep vein thrombosis (DVT), (3) ability of subject to understand the study and (4) informed consent. Exclusion criteria were inability to follow the study procedures, incidental PE, previous confirmed diagnosis of CTEPH or PH. Confirmatory testing for PE consisted of either high probability ventilation-perfusion scintigraphy or positive CT pulmonary angiography for PE.[4]

All study documents were prepared according to Good Clinical Practice guidelines. Individual data elements were purposely obtained for this study, anonymised and protected according to the European Union directive 2016/679 of the European Parliament and the European Council, 27 April 2016. Patients who met all inclusion criteria and none of the exclusion criteria were contacted by phone 2 years after PE. Those patients that reported dyspnoea grade≥II according to the New York Heart Association (NYHA)/WHO classification[18] (online supplemental table 1) were invited for a visit to the outpatient clinical and subjected to echocardiography. In those with intermediate or high probability of PH (online supplemental tables 2 and 3), further diagnostic tests according to guidelines, including V/Q scintigraphy and right heart catheterisation (RHC), were performed[1 19] (online supplemental figure 1). In patients with clinical phenotype suggestive of left heart disease, a fluid challenge was performed to reveal left ventricle diastolic dysfunction. To reach the final diagnosis of CTEPH, all the complementary tests were evaluated, according to the clinical practice guidelines (ie, pulmonary function test, including diffusing capacity of the lungs for carbon monoxide (DLCO) or CT imaging).[1 19]

Data collection and monitoring

Clinical characteristics, baseline demographic data, comorbidities and risk factor for venous thromboembolism (VTE) were collected. Data were recorded onto a computer-based case report form at each participating hospital and submitted to a centralised coordinating centre through a secure web site. Data encoding was used to enhance confidentiality and security. Data quality was regularly monitored and documented electronically to detect inconsistencies or errors, which were solved by the local coordinators. Data quality was also monitored by contracted research organisations that compare the medical records with the data on the web. A data audit was performed at periodic intervals. Patients' identities remain confidential as they were identified only by a number assigned by the study coordinating centre, which was responsible for all data management.

Study outcomes

The primary outcome was a new diagnosis of CTEPH confirmed by RHC. All patients diagnosed of CTEPH were adjudicated after a centralised review of all data provided. Secondary outcomes included evaluation of symptom frequency and burden. During the telephone call, the NYHA/WHO scale was determined by the researcher and three questions about recovering after PE were asked: (1) 'Do you have dyspnoea while doing any activity that you could do without problems before the PE?'; (2) 'Do you consider yourself to be fully recovered from the PE?'; and (3) 'Do you experience palpitations, chest pain or more tiredness than usual and without justification since the PE diagnosis?'. Lastly, we evaluated the reasons for not adhering to the CTEPH diagnostic algorithm proposed by the study protocol.

Since the haemodynamic diagnosis of PH has been changed after the study started,[1] we have analysed the number of new diagnoses of CTEPH with the new definition.

Statistical analysis

The null hypothesis is that usual follow-up of patients with acute symptomatic PE is sufficient to identify all patients with CTEPH and additional follow-up procedures are not necessary. The alternative hypothesis is that routine follow-up of PE is not sufficient to identify all patients with CTEPH and that a symptom-related screening programme will improve CTEPH detection. The sample size calculation was based on the assumption that the incidence of CTEPH in the study group before start of the study would be 0.9%[20–22] and the incidence of CTEPH on the intervention would be 3.1%.[23] With unilateral test, with confidence level of 95%, statistic power of 80% and losses expected of 25%, we calculated a final sample size of 846 to include at least 635 patients.

Continuous variables were expressed as mean±SD and the discrete variables were expressed as numbers and percentages. Proportions and 95% CIs were calculated using Fisher's exact model (Clopper-Pearson). In the calculation of the cumulative

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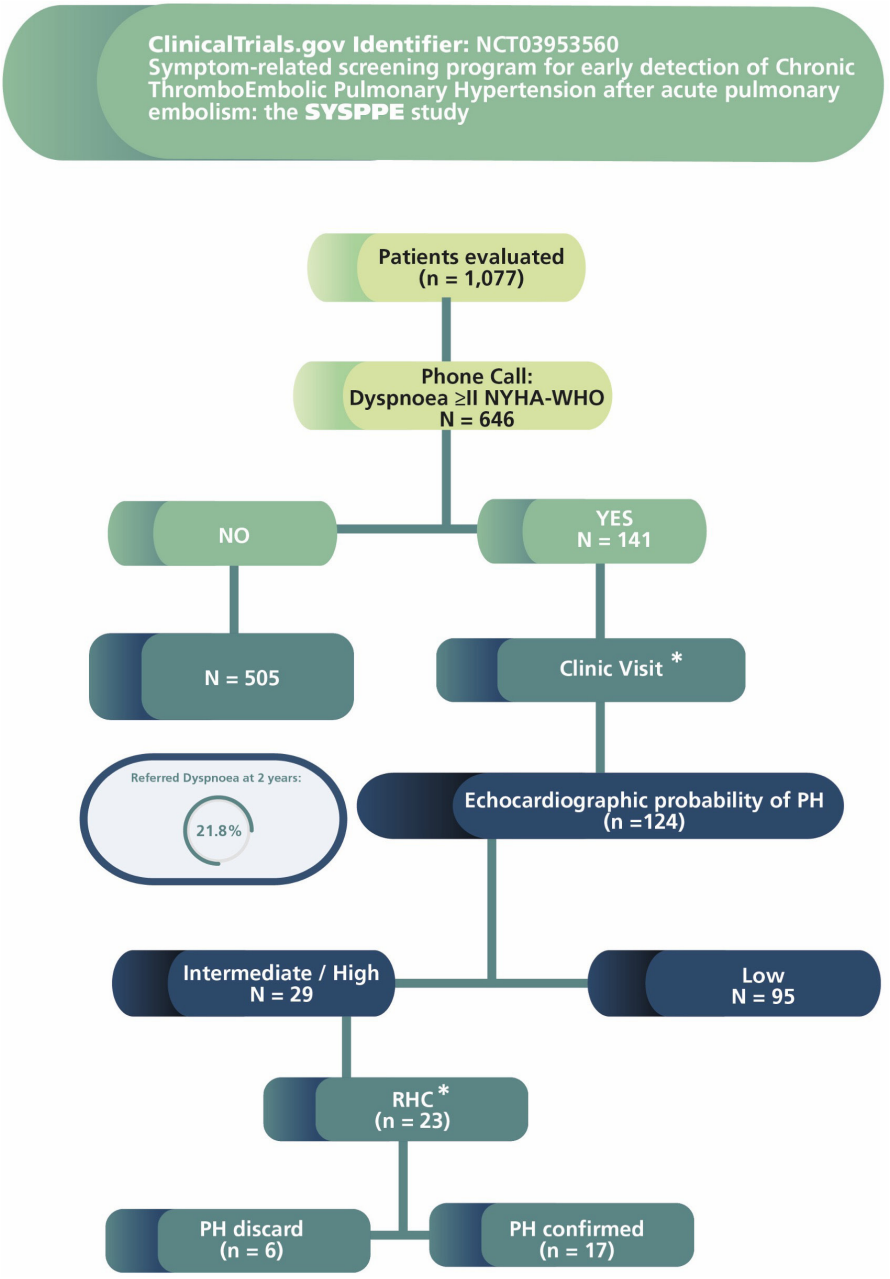

Figure 1 Flow diagram. *Further diagnostic tests according to guidelines were performed to reach the final diagnosis of CTEPH guidelines (ie, pulmonary function test, including DLCO or CT imaging).[1 19] CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusing capacity of the lungs for carbon monoxide; NYHA, New York Heart Association; PH, pulmonary hypertension; RHC, right heart catheterisation.

incidence of CTEPH and PH, we computed the relative risk using the index cohort before symptom screening as the reference group. We calculated the ORs for both comorbidities and risk factors to compare patients who presented with dyspnoea and those who did not. Due to the low prevalence of the disease, adjustments to the models were not feasible, and the models were left unadjusted. IBM SPSS Statistics (V.24) was used for all analyses.

RESULTS

Patients

We identified a total of 1077 consecutive patients with acute symptomatic PE, of whom 646 were included for symptom screening; 431 patients were excluded because they had died (n=238), were lost at follow-up (n=80), refused to participate in the study (n=40), concerned frail elderly (n=31), were unable to participate (n=22), were suspected of PH (n=4), were diagnosed with PH previously (n=8), of whom 5 were diagnosed with CTEPH, or had advanced cancer (n=8) (figure 1). Table 1 shows the characteristics of the index cohort of patients, and online supplemental table 4 display the causes of death according to the death certificates.

An overview of the patients' demographic and baseline clinical characteristics of patients included for symptom screening is provided in table 2. Briefly, mean age was 66±15.7 years and 51.7% were women. The most frequent comorbidities were hypertension (56.5%) and dyslipidaemia (30.1%). Risk factors for VTE were immobilisation (19.2%), active cancer (18.7%), personal history of VTE (13%), surgery in the previous 2 months (10.1%) and the use of hormone replacement therapy (5.8%).

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Table 1 Clinical characteristics of index cohort of patients

	Included for symptom screening (N=646)	Not included for symptom screening (N=431)	Index cohort (N=1077)
Age, mean (SD)	66 (15.7)	72.8 (15)	68.72 (15.8)
Sex, female, n (%)	334 (51.7)	230 (53.4)	564 (52.4)
Weight, mean (SD)	81.6 (16.7)	74.6 (15)	78.8 (16.4)
Height, mean (SD)	165 (10)	162 (10)	164 (10)
BMI, mean (SD)	30.1 (5.9)	28.5 (5.2)	29.5 (5.7)
Smoker, n (%)	95 (14.9)	45 (10.4)	140 (13)
Diabetes mellitus, n (%)	114 (17.9)	91 (21.4)	205 (19.3)
Hypertension, n (%)	362 (56.5)	263 (61.7)	625 (58.6)
Dyslipidaemia, n (%)	192 (30.1)	124 (29.2)	316 (29.5)
Cancer, n (%)	121 (18.7)	167 (38.7)	288 (26.7)
COPD, n (%)	107 (16.6)	86 (20.0)	193 (17.9)
OSA, n (%)	41 (6.3)	19 (4.4)	60 (5.6)
Chronic heart failure, n (%)	58 (9.0)	50 (11.6)	108 (10)
Atrial fibrillation, n (%)	17 (2.6)	24 (5.6)	41 (3.8)
Myocardial infarction, n (%)	28 (4.4)	37 (8.7)	65 (6.1)
Stroke, n (%)	35 (5.5)	55 (12.9)	90 (8.5)
Dementia, n (%)	14 (2.2)	57 (13.2)	71 (6.6)
Depression, n (%)	68 (10.5)	57 (13.2)	125 (11.6)
Bipolar disorder, n (%)	3 (0.5)	4 (0.9)	7 (0.6)
Epilepsy, n (%)	12 (1.9)	10 (2.3)	22 (2.0)
Parkinson's disease, n (%)	10 (1.5)	9 (2.1)	19 (1.8)
Fatty liver disease, n (%)	20 (3.1)	11 (2.6)	31 (2.9)
Crohn's disease, n (%)	4 (0.6)	0 (0.0)	4 (0.4)
Ulcerative colitis, n (%)	4 (0.6)	4 (0.9)	8 (0.7)
Liver cirrhosis, n (%)	4 (0.6)	5 (1.2)	9 (0.8)
Thyroid disease, n (%)	55 (8.5)	34 (7.9)	89 (8.3)
Sarcoidosis, n (%)	2 (0.3)	0 (0.0)	2 (0.2)
HIV infection, n (%)	2 (0.3)	4 (0.9)	6 (0.6)
Systemic lupus erythematosus, n (%)	3 (0.5)	0 (0.0)	3 (0.3)
Antiphospholipid syndrome, n (%)	2 (0.3)	0 (0.0)	2 (0.2)
Organ transplantation, n (%)	6 (0.9)	1 (0.2)	7 (0.6)
Chronic thrombocytopaenia, n (%)	3 (0.5)	2 (0.5)	5 (0.5)
Systolic blood pressure, mean (SD)	131 (23)	128 (23)	129 (23)
Major bleeding last month, n (%)	7 (1.1)	14 (3.2)	21 (1.9)
VTE location, n (%)			
PE alone	422 (65.3%)	320 (74.2%)	742 (68.9%)
PE plus DVT	224 (34.7%)	111 (25.8%)	335 (31.1%)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; OSA, obstructive sleep apnoea; PE, pulmonary embolism; VTE, venous thromboembolism.

Two-thirds of the patients (65.3%) had only PE and one third (34.7%) PE plus DVT.

Initial treatment was low-molecular-weight heparin (LMWH) in 97.5% of patients and unfractionated heparin in 1.7%. Fibrinolysis was performed in 26 patients (4.0%) and inferior vena cava filter was placed in 18 patients (2.8%). Long-term anticoagulation treatment was performed with vitamin K antagonists (58.5%), LMWH (25.2%) or direct oral anticoagulants (16%). During follow-up, 40 patients (6.2%; 95% CI 4.5% to 8.3%) had

Table 2 Baseline characteristics of patients included for symptom screening (N=646)

	Dyspnoea≥II NYHA-WHO No (N=505)	Dyspnoea≥II NYHA-WHO Yes (N=141)	Index cohort (n=646)
Age, mean (SD)	66.2 (15.8)	65.3 (15.1)	66 (15.7)
Sex, female, n (%)	242 (47.9)	92 (65.2)	334 (51.7)
Weight, mean (SD)	81.3 (16.6)	82.6 (17.2)	81.6 (16.7)
BMI, mean (SD)	29.9 (5.8)	31.1 (6.3)	30.1 (5.9)
Smoker, n (%)	70 (14)	25 (18)	95 (14.9)
Diabetes mellitus, n (%)	88 (17.7)	26 (18.6)	114 (17.9)
Hypertension, n (%)	280 (55.9)	82 (58.6)	362 (56.5)
Dyslipidaemia, n (%)	150 (30.1)	42 (30.0)	192 (30.1)
Cancer, n (%)	93 (18.4)	28 (19.9)	121 (18.7)
COPD, n (%)	72 (14.3)	35 (24.8)	107 (16.6)
OSA, n (%)	26 (5.1)	15 (10.6)	41 (6.3)
Chronic heart failure, n (%)	38 (7.5)	20 (14.2)	58 (9.0)
Thyroid disease, n (%)	39 (7.7)	16 (11.3)	55 (8.5)
Atrial fibrillation, n (%)	12 (2.4)	5 (3.5)	17 (2.6)
Myocardial infarction, n (%)	23 (4.6)	5 (3.6)	28 (4.4)
Stroke, n (%)	29 (5.8)	6 (4.4)	35 (5.5)
Dementia, n (%)	10 (2)	4 (2.8)	14 (2.2)
Depression, n (%)	48 (9.5)	20 (14.2)	68 (10.5)
Bipolar disorder, n (%)	1 (0.2)	2 (1.4)	3 (0.5)
Schizophrenia, n (%)	6 (1.2)	0 (0.0)	6 (0.9)
Epilepsy, n (%)	9 (1.8)	3 (2.1)	12 (1.9)
Parkinson's disease, n (%)	9 (1.8)	1 (0.7)	10 (1.5)
Crohn's disease, n (%)	3 (0.6)	1 (0.7)	4 (0.6)
Ulcerative colitis, n (%)	4 (0.8)	0 (0.0)	4 (0.6)
Liver cirrhosis, n (%)	3 (0.6)	1 (0.7)	4 (0.6)
Fatty liver disease, n (%)	16 (3.2)	4 (2.8)	20 (3.1)
Systemic lupus erythematous, n (%)	2 (0.4)	1 (0.7)	3 (0.5)
Antiphospholipid syndrome, n (%)	1 (0.2)	1 (0.7)	2 (0.3)
Chronic thrombocytopaenia, n (%)	3 (0.6)	0 (0.0)	3 (0.5)
Sarcoidosis, n (%)	1 (0.2)	1 (0.7)	2 (0.3)
HIV infection, n (%)	2 (0.4)	0 (0.0)	2 (0.3)
Organ transplantation, n (%)	6 (1.2)	0 (0.0)	6 (0.9)
Major bleeding last month, n (%)	7 (1.4)	0 (0.0)	7 (1.1)
High-risk PE*, n (%)	15 (3)	5 (3.5)	20 (3.1)
VTE location, n (%)			
PE alone	344 (68.1)	78 (55.3)	422 (65.3)
PE plus DVT	161 (31.9)	63 (44.7)	224 (34.7)
Surgery (within previous 2 months), n (%)	53 (10.5)	12 (8.5)	65 (10.1)
Immobility (within previous 2 months), n (%)	91 (18)	33 (23.4)	124 (19.2)
Previous VTE, n (%)	66 (13.1)	18 (12.8)	84 (13.0)
Hormone replacement therapy (within previous 2 months), n (%)	30 (6.2)	6 (4.4)	36 (5.8)
Unprovoked VTE, n (%)	275 (54.5)	77 (54.6)	352 (54.5)
Vena cava filter, n (%)	16 (3.2)	2 (1.4)	18 (2.8)
Laboratory findings			
Haemoglobin (g/L), mean (SD)	13.4 (2)	13.2 (1.9)	13.3 (2)
Leucocyte (x10^9/L), mean (SD)	9.9 (3.8)	9.6 (3.7)	9.8 (3.8)

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Table 2 Continued

	Dyspnoea≥II NYHA-WHO No (N=505)	Dyspnoea≥II NYHA-WHO Yes (N=141)	Index cohort (n=646)
Platelet (x10^9/L), mean (SD)	225 (86)	230 (82)	226 (85)
Creatinine mg/dL, mean (SD)	0.93 (0.3)	0.91 (0.26)	0.9 (0.3)
GPT, mean (SD)	22.8 (14.7)	24.4 (16.3)	23.3 (15.2)
GOT, mean (SD)	22.2 (10)	22.1 (10.3)	22.1 (10)
GGT, mean (SD)	48 (56.6)	48.6 (56.6)	48.2 (65.5)
Alkaline phosphatase, mean (SD)	76.6 (30.3)	81.5 (33.6)	78.1 (31.3)

*High-risk PE defined as systolic blood pressure <90 mm Hg.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; GGT, gamma glutamyl transpeptidase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; NYHA, New York Heart Association; OSA, obstructive sleep apnoea; PE, pulmonary embolism; VTE, venous thromboembolism.

major bleeding under anticoagulant treatment and 28 (4.3%; 95% CI 2.9% to 6.2%) were diagnosed of recurrent VTE.

Follow-up

One hundred and forty-one (21.8%) reported dyspnoea, 20.4% grade II and 1.4% as grade III. Those patients who referred dyspnoea had more chronic obstructive pulmonary disease (24.8% vs 14.3%, OR 1.99, 95%CI 1.26 to 3.13), chronic heart failure (14.2% vs 7.5%, OR 2.03, 95% CI 1.14 to 3.62), OSA (10.6% vs 5.1%, OR 2.19, 95%CI 1.13 to 4.27), PE plus DVT (44.7% vs 31.9%, OR 1.73, 95% CI 1.18 to 2.53) and the proportion of women with dyspnoea was higher (65.2% vs 47.9%, OR 2.0, 95% CI 1.38 to 3). There were no significant differences in other clinical characteristics of patients with vs without dyspnoea (online supplemental table 5).

Transthoracic echocardiography was performed in 124 of 141 with dyspnoea grade≥II. Online supplemental table 6 shows the reasons why the echocardiogram was not performed. The transthoracic echocardiogram showed low, intermediate and high probability of PH in 76.6% (n=95), 21.8% (n=27) and 1.6% (n=2), respectively.

Primary outcome

Of all patients with echocardiographic intermediate/high probability of PH (n=29), RHC was performed in 23 patients. Online supplemental table 7 shows the reasons why RHC was not performed in the remaining six patients. PH was confirmed in 17 patients: 12 were diagnosed with CTEPH, 4 with PH associated with left heart disease and 1 with PH associated with lung disease and/or hypoxaemia. Table 3 shows the clinical characteristics of patients with confirmed PH.

Table 3 Characteristics of the patients with confirmed PH

	Age (yo)	VTE event	Sex	Grade of dyspnoea	Probability of PH	Classification PH	PE to PH diagnosis (months)	Other data
1	50s	DVT/PE	Male	II	Intermediate	GROUP 2 PH associated with left heart disease	24	Diabetes, chronic heart failure, chronic obstructive pulmonary disease.
2	70s	PE	Female	II	Intermediate	GROUP 2 PH associated with left heart disease	30.60	Diabetes, hypertension.
3	80s	PE	Female	III	Intermediate	GROUP 2 PH associated with left heart disease	26	Hypertension, myocardial infarction.
4	80s	PE	Female	III	Intermediate	GROUP 2 PH associated with left heart disease	27.3	Chronic heart failure, chronic obstructive pulmonary disease, cancer.
5	60's	PE	Male	II	Intermediate	GROUP 3 PH associated with lung diseases and/or hypoxia	29.6	Current smoker, diabetes, hypertension, chronic obstructive pulmonary disease.
6	60s	PE	Male	II	Intermediate	GROUP 4 CTEPH combined postcapillary and precapillary PH	28.99	Hypertension.
7	70s	DVT/PE	Female	II	Intermediate	GROUP 4 CTEPH	34.41	Hypertension, chronic heart failure, dyslipidaemia, depression.
8	30's	PE	Male	II	Intermediate	GROUP 4 CTEPH	33.59	
9	70's	DVT/PE	Female	II	Intermediate	GROUP 4 CTEPH	33.44	Hypertension, chronic heart failure, dyslipidaemia.
10	80s	DVT/PE	Female	III	Intermediate	GROUP 4 CTEPH	29.6	Diabetes, hypertension, chronic obstructive pulmonary disease.
11	70s	PE	Male	III	Intermediate	GROUP 4 CTEPH combined postcapillary and precapillary PH	29.19	High-risk PE diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease.
12	80s	PE	Female	II	High	GROUP 4 CTEPH	31.6	Depression.
13	70s	PE	Female	III	Intermediate	GROUP 4 CTEPH	37.60	Hypertension.
14	50's	PE	Male	III	Intermediate	GROUP 4 CTEPH	39.61	Current smoker, hypertension.
15	70s	DVT/PE	Male	II	Intermediate	GROUP 4 CTEPH	35.27	Hypertension, atrial fibrillation, chronic obstructive pulmonary disease.
16	60s	DVT/PE	Female	II	Intermediate	GROUP 4 CTEPH	28.48	Diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, cancer, stroke.
17	70s	PE	Female	II	Intermediate	GROUP 4 CTEPH	30.5	Hypertension.

CTEPH, chronic thromboembolic PH; DVT, deep vein thrombosis; PE, pulmonary embolism; PH, pulmonary hypertension; VTE, venous thromboembolism.

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Table 4 Cumulative incidence of chronic thromboembolic pulmonary hypertension (CTEPH) and PH

Cohort	No patients PH/total patients	Cumulative incidence	95% CI
CTEPH			
Index cohort previous symptom screening	5/1077	0.46%	0.16% to 1.12%
Index cohort after symptom screening	17/1077	1.58%	0.97% to 2.53%
Symptom screening cohort	12/646	1.86%	1.03% to 3.26%
Symptom screening cohort with dyspnoea≥II	12/141	8.51%	4.81% to 14.41%
PH			
Index cohort previous symptom screening	8/1077	0.74%	0.32% to 1.46%
Index cohort after symptom screening	25/1077	2.32%	1.51% to 3.41%
Symptom screening cohort	17/646	2.63%	1.54% to 4.18%
Symptom screening cohort with dyspnoea≥II	17/141	12.06%	7.18% to 18.6%

The incidence of CTEPH in the index cohort based on routine care before the study was initiated was 0.46% (5/1077; 95% CI 0.16% to 1.12%), and the incidence of PH was 0.74% (8/1077; 95% CI 0.32% to 1.46%). After applying the symptom screening protocol, the incidence of CTEPH in the index cohort increased to 1.58% (17/1077; 95% CI 0.97% to 2.53%) and that of PH to 2.32% (25/1077; 95% CI 1.51% to 3.41%). The incidence of CTEPH in the symptom screening cohort was 1.86% (12/646; 95% CI 1.03% to 3.26%) and that of PH 2.63% (17/646; 95% CI 1.54% to 4.18%). The incidence of CTEPH in the symptom screening cohort in patients with dyspnoea grade≥II was 8.51% (12/141; 95% CI 4.81% to 14.41%; table 4), and that of PH 12.06% (17/141; 95% CI 7.18% to 18.6%). The incidence of CTEPH after symptom screening cohort increased 3.44-fold (95% CI 1.26 to 9.35) and the incidence of PH after symptom screening cohort increased 3.13-fold (95% CI 1.42 to 6.9). Characteristics and risk factors for CTEPH in patients with versus without confirmed CTEPH are provided in online supplemental table 8.

With the new haemodynamic criteria to define CTEPH classification, 1 patient more was diagnosed with CTEPH (female, 51 years old, with a mean pulmonary arterial pressure: 22 mm Hg, pulmonary arterial wedge pressure: 10 mm Hg and pulmonary vascular resistance: 2.1 Woods units), with a total of 13 patients diagnosed with CTEPH after the application of the protocol.

Secondary outcome

At 2 years after acute symptomatic PE, 21.8% had dyspnoea class≥II. One hundred and thirty-three (20.6%) reported dyspnoea while doing some activity that they could do without problems before PE, and 21.8% (n=141) considered that they were not fully recovered from PE because of persisting dyspnoea. Moreover, 14.9% (n=96), presented with palpitations, chest pain or more tiredness than before the PE diagnosis (figure 2).

DISCUSSION

In this prospective, multicentre study, a large population of 1077 unselected consecutive patients with acute symptomatic PE were evaluated. Our study confirms the concept that dedicated follow-up algorithms of PE, which can be performed by phone by any clinician, increase the number of CTEPH cases more than threefold compared with routine care. This work also confirms that focusing on symptomatic patients is efficient and reasonable and provides ground to the current proposed follow-up algorithm in the 2019 European Society of Cardiology (ESC) guidelines.[4]

To use a phone call is cheap and easy to implement and especially useful in regions and settings where follow-up at dedicated clinics is not feasible due to long distance or insufficient logistical resources. Moreover, after COVID-19 pandemic, there is a trend to implement telemedicine as an expanding and feasible approach to improve medical care for patients with chronic diseases.[24–26] These advances have the potential to support patients with long-term diseases to manage their health at home, leading a remote healthcare more accessible and efficient.[26] Two earlier studies found usefulness of phone-based patients follow-up,[8 16] although our work analysed the impact of this

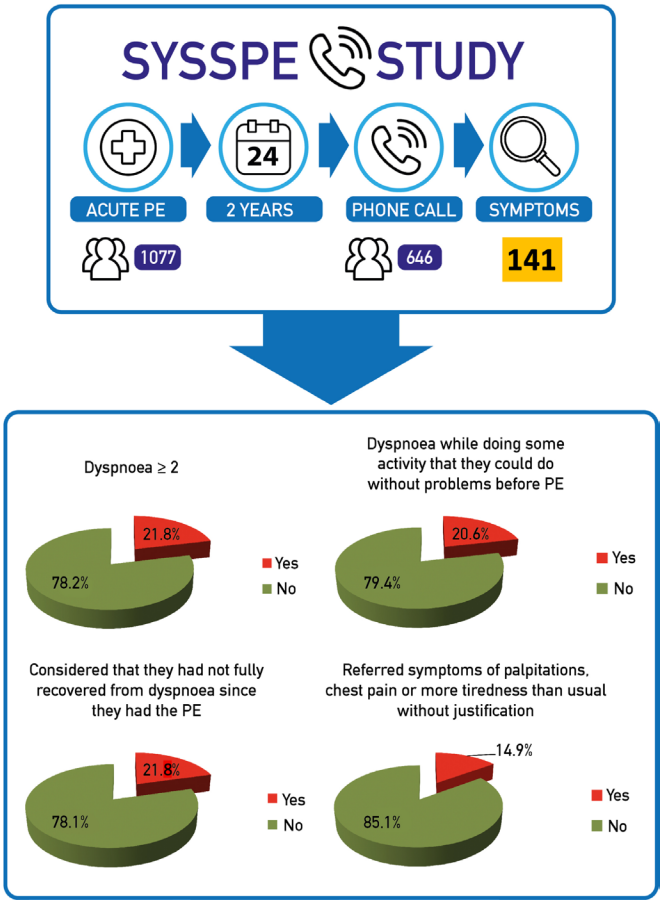

Figure 2 Specific questions about symptom-related after PE. PE, pulmonary embolism.

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strategy comparing patients diagnosed of CTEPH before and after applying the protocol. In 2014, in a prospective cohort of 170 patients, 8 patients were diagnosed with CTEPH.[16] Subsequently, in 2018, a multicentre observational screening survey was conducted for the detection of CTEPH after PE (n=508).[8] At 2 years, the cumulative incidence of CTEPH was 0.79% (95% CI 0.31% to 2.07%), that increased to 4.12% in patients with dyspnoea≥II of NYHA/WHO. Notably, by excluding patients with cancer or those patients with dyspnoea≥III NYHA/WHO, the authors introduced selection bias.

In addition to telephone-guided symptom-based screening, there are other noteworthy strategies for identifying patients with CTEPH. The recently published FOCUS study prospectively examined patients with acute PE by performing echocardiography in all study patients several times during follow-up, revealing an estimated 2-year cumulative incidence of CTEPH and post-PE impairment of 2.3% (95% CI 1.2% to 4.4%) and 16.0% (95% CI 12.8% to 20.8%), respectively.[27] The InShape II study validated the safety of an algorithm for early exclusion of CTEPH following acute PE.[12 28] In patients lacking specific CTEPH symptoms and with a low-risk score, the algorithm effectively ruled out CTEPH, obviating the need for echocardiography in nearly half of the patients. Although certain biomarkers such as brain natriuretic peptide (BNP) and N-terminal pro-BNP have been proposed for pulmonary arterial hypertension, their role in CTEPH screening remains unclear.[29] Nonetheless, a potential strategy involving a combination of symptoms (dyspnoea) and these biomarkers could be considered to enhance screening approaches. We lack studies that directly compare different strategies; however, there are likely approaches that can be complementary. Employing a combined scale alongside the patient's symptoms could optimise supplementary tests for monitoring patients with symptomatic acute PE. Furthermore, findings from prospective studies, when combined with research such as ours that involved consecutive patients from a registry, could potentially facilitate the identification of risk profiles among patients.

The discrepancies in mortality between this study and other prospective studies that have addressed the same topic stem from our inclusion of consecutive patients from a patient registry, while prospective studies employ specific inclusion and exclusion criteria that selectively define the study population. When we analyse 1-year mortality rates in population-based studies or in other registries or databases, we observe how the 1-year mortality among PE patients varies from 19% to 52.3%.[30–32] Among the most relevant factors that could have contributed to higher mortality in our work, compared with other prospective studies that have addressed this issue, are cancer and age. The percentage of patients with cancer in previous studies ranged from 6.15% to 11%,[8 16 27 28] a figure that contrasts with the 26.7% in our series. The mean age in our study was 69 years, whereas in previous prospective studies it ranged from 56 to 65.[8 12 16 27 28 33]

Our study has several strengths. First, this was a well-designed large multicentre study and the first of its kind in Spain. We observed patient characteristics, a dyspnoea incidence of dyspnoea and incidence of CTEPH that were in line with previous studies, demonstrating the external validity of the presented findings.[8 16 27 28] In our cohort, the overall CTEPH incidence was 1.86% (95% CI 1.03% to 3.26%), which is in line with others, with incidence ranged from 0.79% to 4.7%.[8 16 27 28] The presence of persistent dyspnoea has been evaluated differently in studies.[8 16 27 28] While Held *et al* documented that, at 12 months, 29.3% of patients had dyspnoea,[16] Coquoz *et al* found 20% at 2 years.[8] Valerio *et al* included dyspnoea within the criteria of clinically relevant PPEI and found a 2-year cumulative incidence of 16.0% (95% CI 12.8% to 20.8%).[27] Second, our work proposes an easy and cost-effective diagnostic strategy based on a phone evaluation that could be carried out by any clinician and would allow a simple screening and refer patient to an expert centre in the case of suspected PH, as indicated in the clinical practice guidelines.[1 4] Third, the patients included represent consecutive patients obtained from a registry (RIETE), which makes it possible to identify those patients who can benefit from screening, while showing the limitations of some patients when undergoing screening or other complementary tests (echocardiogram or RHC). Fourth, we applied strict and well accepted diagnostic criteria for our primary and secondary outcomes. Lastly, the implementation of a fluid challenge to reveal postcapillary PH in patients with a clinical phenotype suggestive of left heart disease has enabled the identification of patients with PH in group 2.

Our study has some limitations. First, to assess the impact of the screening, we focused on newly diagnosed cases of CTEPH confirmed by RHC as our primary objective and compared them against cases diagnosed with CTEPH in the clinical follow-up of these patients. Conducting screening via telephone calls at 3–6 months after acute PE would have enabled more patients with CTEPH and at an early stage, but it would not have facilitated an analysis of the impact of this strategy against standard clinical practice. Second, implementing telephone screening for patients who have experienced symptomatic acute PE can be complex. However, it is indeed true that the demonstration of a simple question can aid in diagnosing CTEPH patients.[8 16] To achieve early diagnosis of CTEPH, maintaining a high index of suspicion is crucial. If a primary care physician or any other specialist evaluates a patient with dyspnoea, and the patient's medical history includes a history of symptomatic acute PE, suspicion of CTEPH should arise. This should prompt a referral to a specialised clinic for further comprehensive evaluation. Third, it would have been interesting to determine how many patients had chronic thromboembolic pulmonary disease without PH, although this was not the objective of our study. Fourth, the number of patients with CTEPH may have been underestimated for several reasons: (1) Not all the patients included in the study underwent a full diagnostic workup for CTEPH, which could have underestimated the confirmatory diagnosis of CTEPH. This limitation is typical in those studies that include consecutive patients and in which the study cannot be continued due to the patient's clinical situation or due to comorbidities; (2) The number of CTEPH patients may be underestimated as the symptom screening via phone was conducted 2 years after the acute PE episode. Furthermore, even though we have information about the cause of patients' deaths, we lack precise information regarding whether deaths were attributed to right ventricular failure or CTEPH. In the InShape II and FOCUS studies, applying a screening algorithm earlier in the course of disease clearly aided in an early CTEPH detection[27 28]; (3) It is true that focusing on patients with a certain number of symptoms could lead to missing some diagnoses of CTEPH. However, we must consider that in the algorithm for diagnosing CTEPH after a PE, the most important symptom to consider is dyspnoea.[4] The approach of the study was aimed at identifying CTEPH patients in a straightforward and simple manner. In the other hand, we acknowledge that this strategy is not accurate, it is indeed cost-effective; (4) In patients with dyspnoea, the initial test conducted was the echocardiogram. In this context, a meta-analysis was published in 2019 that encompassed 27 studies with 4386 patients, yielding a pooled sensitivity of 85% along with a pooled specificity of 74%.[34] Although the authors found

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a higher sensitivity compared with specificity, it is essential to consider that these sensitivity data are not optimal. Additionally, the heterogeneity of the meta-analysis was high, and in patients with pulmonary diseases, this sensitivity diminishes. However, PH guidelines still suggest that echocardiographic screening is sufficient, even with the adapted definition of PH.[1]

CONCLUSIONS

In conclusion, we showed that applying a dedicated, symptom-based telephonic CTEPH screening intervention in PE survivors is associated with a threefold of the number of confirmed CTEPH cases compared with routine clinical care. Our results help to identify new and simple strategies to detect CTEPH. The timepoint of the screening in clinical practice should probably be in the first 3–6 months after the index PE diagnosis, to facilitate earlier CTEPH diagnosis.

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Contributors LJ-P is the garantor of the study. LJ-P had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. LJ-P, FAK, AM and SM-R contributed to formal analysis, supervision and redaction of the original draft; LJ-P and SM-R contributed to the methodology; LJ-P contributed to the conceptualisation, funding acquisition, resources and software of the study. All authors (SM-R, FAK, LJ-P, AB-Q, PJM-Y, CG-C, PL-M, PJM-Y, ML, MAA-A, IF-A, JBL-S, MP-P, CB-M, AR-M, JAP-L, JC-G, MP-S, TE-H, RO, AM and MB-H) contributed to the data curation, investigation, validation, visualisation, review and edition of the manuscript.

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