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Chronic thromboembolic pulmonary hypertension in acute pulmonary embolism: a risk factor evaluation study

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ABSTRACT*

Aims: Pulmonary thromboembolism (PTE) is a highly mortal disease, defined by presence of a thrombus partially or completely obstructing pulmonary arteries and/or veins, commonly originating from deep venous system. Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of PTE with high mortality if not treated properly. In recent studies, the incidence of CTEPH was found between 0.4-9.1%. Due to clinically silent PTE in roughly 50% of patients, it is difficult to pinpoint the exact incidence of CTEPH. This study aims to investigate PTE patients during their long-term follow up to observe CTEPH presence and evaluate CTEPH risk factors.

Methods: Patients who had been evaluated in emergency service and/or admitted to the pulmonary medicine ward between January 2014 and January 2017 with PTE diagnosis confirmed by computed tomography pulmonary angiogram (CTPA) were accepted retrospectively into the study. Their echocardiography, CTPA and lower extremity venous Doppler ultrasonography at 3rd, 6th and 12th months follow up were also included. In the patient group with pulmonary arterial pressure (PAP) above 50 mmHg and residual thrombosis at CTPA, ventilation-perfusion scintigraphy was performed and was added to the study. Among those suitable for CTEPH, right cardiac catheterization was done to confirm the diagnosis and accepted as CTEPH. In addition to this group, patients who were not found suitable for right cardiac catheterization but were clinically suitable for CTEPH are also included in the CTEPH group.

Results: The average age of patients included into the study was 62 (±16.5), with 71 (39%) being male and 111 (61%) female. As for risk factors, 130 (71.4%) had acquired, 16 (8.8%) had genetic and the rest 36 (19.8%) did not have any prominent risk factors. At the time of diagnosis, 10 patients were accepted as massive, 26 as sub massive and the rest 139 were considered non-massive PTE. Due to hemodynamic instability, 7 (3.8%) patients were given thrombolytic therapy. During 1 year follow-up, 5 (2.7%) patients were diagnosed with CTPH. When further investigation was performed on these 5 patients, atrial fibrillation (AF) and persistent thrombosis at 12-month follow up CTPA and PAP above 55 mmHg upon time of diagnosis were found significant risk factors (p being 0.001/0.023/0.009 respectively). In multivariate analysis, no independent predictive factors were found in regards to CTEPH diagnosis.

Conclusion: CTEPH is a preventable complication of PTE with severe mortality and morbidity if not properly treated. It might prove useful to utilize echocardiography and CTPA together, especially in high risk groups, to diagnose patients in the early stage of CTEPH with no evident signs or symptoms.

Keywords: Pulmonary thromboembolism, chronic thromboembolic pulmonary hypertension, right cardiac catheterization

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INTRODUCTION

Pulmonary thromboembolism (PTE), a highly fatal disease that develops as a result of complete or partial occlusion of the pulmonary artery and/or its branches by a thrombus that breaks away from the deep venous system and reaches the pulmonary bed, occurs frequently but is difficult to diagnose.[1] Chronic thromboembolic pulmonary hypertension (CTEPH) develops when recurrent and organized PTE or in situ thrombosis occludes the pulmonary vascular bed and causes structural changes. CTEPH is diagnosed by visualizing residual perfusion defects in ventilation-perfusion (V/P) scintigraphy despite using anticoagulants at effective doses for at least three months after an acute pulmonary embolism

episode, detecting a mean pulmonary artery pressure of 20 mmHg or above, a pulmonary capillary wedge pressure (PCWP) of 15 mmHg or below and excluding other conditions that may cause pulmonary hypertension (PHT).[2] Although its true incidence remains unknown, its incidence after acute PTE has been found to range between 1% and 9%.[3] CTEPH is characterized by the presence of occlusive fibrotic thromboembolic material in large pulmonary vessels and accompanying microvascular arteriopathy.[4] Although PTE is the initiating event in CTEPH, vascular remodeling that develops in small vessels with the effect of the mediators released from cells found in thrombus has an important role in the pathogenesis.[5,6] These changes cause an increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) over time. Pulmonary hypertension (PHT) is a severe medical condition characterized by increased pulmonary artery pressure (PAP) which may frequently result in progressive right ventricular (RV) failure and death.[4] CTEPH is included in class 4 pulmonary hypertension, and is the only pulmonary hypertension subgroup that may be cured by pulmonary endarterectomy (PEA), a surgical treatment method.[7]

In this study we aimed to investigate the incidence of CTEPH development over long follow-up periods in patients with acute PTE, to define factors that predispose patients to CTEPH, which patients develop CTEPH, patients' profile, type of admission, clinical presentation, diagnostic methods applied, and treatment approaches, and to contribute to the literature on CTEPH.

METHODS

The ethical approval of the study was received from the ethics committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, where the study was conducted, on 19.02.2018 with the decision number of 46/12. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The medical records of patients who were admitted to University of Health Sciences Ankara Dışkapı Yıldırım Beyazıt Health Application and Research Center chest diseases outpatient clinic and diagnosed with acute PTE using thoracic computerized tomographic angiography (CTPA) between January 2014 and January 2017 were retrospectively reviewed. The files were scanned with the "I-26=Pulmonary Embolism" ICD diagnostic code using the Alpdata Medical Information System from the hospital information management system. Laboratory results, and radiology reports of patients diagnosed with PTE were reviewed. Patients with missing medical records, those who were younger than 16 years of age, and those who did not attend their follow-up appointments at 3rd, 6th, and 12th months after discharge due to any reason were excluded. A total of 182 patients with a minimal follow-up duration of 2 years were enrolled.

The patients' demographic characteristics, PTE-related risk factors, comorbidities, D-dimer (quantitative-PCR), troponin I, clinical probability scores (Wells, Modified Genova), site and diffuseness of PTE involvement in ECHO and CTPA, treatment methods and treatment durations were recorded.

The CTPA and ECHO results of the patients with PTE, both at admission and at 3rd, 6th, and 12th months of follow-up were recorded. Pulmonary hypertension was considered to have a low probability when PAP was below 36 mmHg; moderate probability when PAP was between 37 mmHg and 50 mmHg; and high probability when PAP was above 50 mmHg.[8] In patients with PAP above 36 mmHg despite effective anticoagulant use for more than 3 months, a V/P scan was performed to evaluate CTEPH when there were signs of chronic thrombus in pulmonary arteries on CTPA. Patients whose V/P could not be performed for any reason were evaluated for CTEPH using the CTPA result.

Patients with suspected CTEPH were evaluated further if residual thrombus persisted on CTPA at 3rd, 6th, and 12th month follow-up appointments despite effective anticoagulant use for more than three months. If residual thrombus were reported on CTPA, a V/P scan was performed in patients with a PAP over 36 mmHg on ECHO.

In patients who refused to give written consent for right heart catheterization or for whom invasive intervention was not considered appropriate due to hemodynamic disorders or comorbidities, CTEPH was diagnosed if PAP was >50 mmHg after anticoagulant use for at least three months and there were findings compatible with CTEPH on CTPA or V/P scintigraphy.[2]

IBM SPSS (Statistics Program for Social Scientists) 20 (USA) software was used for statistical analyses. Continuous data were reported as mean ± standard deviation. Categorical data were presented as percentage (%). Normality of data was tested with Kolmogorov Smirnov test. Mann Whitney U test and Student's t test were used to compare two independent groups with respect to non-normally and normally distributed data, respectively. Chi-square or Fisher's exact test was used to compare independent categorical variables; Cochrane's Q test was used for the comparison of dependent categorical variables. A ROC analysis was performed to determine the cut-off values of the tests that could be used to diagnose CTEPH. A p value of less than 0.05 was considered statistically significant.

RESULTS

The patients who were included in the study had a mean age of 62 (±16.5) years; 71 (39%) patients were male and 111 (61%) were female. As for the cause of pulmonary hypertension, 130 (71.4%) patients had acquired pulmonary hypertension and 16 (8.8%) had genetic risk factors while 36 (19.8%) patients had idiopathic PTE with no identifiable risk factor.

The ECHO findings and CTPA results of patients with acute pulmonary embolism included in the study were evaluated at control visits at 3rd, 6th, and 12th months. Forty-one patients were found to have residual pulmonary embolism on ECHO evaluation. Because there were mismatch defects compatible with CTEPH on V/P scintigraphy, the patients were evaluated with right heart catheterization. CTEPH was confirmed by detecting a mean PAP of 25 mmHg on right heart catheterization in one of the patients, and 50 mmHg in another patient. In two of the other three patients, invasive catheterization was not deemed appropriate by the

cardiology department due to comorbidities; one patient did not undergo catheterization because he did not give written consent.

The patients were considered to have CTEPH based on the ECHO results, imaging techniques, and clinical presentation. To conclude, residual pulmonary thrombus persisted despite effective anticoagulant therapy for 3 months in 41 of 182 patients with acute pulmonary embolism included in the study. Five of those 41 patients were diagnosed with CTEPH. In our strategy, the incidence of CTEPH after acute pulmonary embolism was calculated 2.7% (5 of 182 patients). The characteristics of the patients diagnosed with CTEPH are shown on Table 1.

Table 1. Characteristics of patients with CTEPH

	Sex	Age	Diagnosis sPAP (mmHg)	PTE clinical evaluation	Diagnostic method	RHC mPAP (mmHg)
Patient 1	Female	47	100	submassive	RHC	50
Patient 2	Male	75	85	submassive	RHC	25
Patient 3	Male	74	85	Non- massive	V/P scintigraphy	-
Patient 4	Female	68	70	Non-massive	V/P scintigraphy	-
Patient 5	Female	86	60	Non-massive	V/P scintigraphy	-

(sPAP: Systolic pulmonary artery pressure, RHC: Right heart catheterization, mPAP: Mean pulmonary artery pressure)

Five patients with CTEPH antd 36 patients without CTEPH but residual pulmonary thrombus despite anticoagulant therapy for 3 months after acute pulmonary embolism were compared with regard to the risk factors of CTEPH. The groups with and without CTEPH were not significantly different with respect to age, sex, Wells and Modified Genova scores, D-dimer, and troponin level. The median CRP level of the patients with CTEPH was significantly higher than the median CRP level of the patients who did not develop CTEPH (p:0.042).

No significant difference was found between the patients with and without CTEPH with respect to the rates of diabetes mellitus, hypertension, coronary artery disease, chronic pulmonary disease, and malignancy (p 0.066/1.00/1.00/0.299/1.00, respectively). All patients with AF were in the CTEPH group. The diagnosis of CTEPH was more frequent in patients with AF than those without (p:0.001).

An analysis of the patients by the presence of residual thrombus on CTPA showed that all patients with CTEPH had residual thrombus whereas 21% of patients without CTEPH had residual thrombus on 12th-month CTPA (p:0.023). No significant difference was found between the patients with and without CTEPH regarding the presence of residual thrombus on CTPA (p:0.579) Table 2.

The patients with CTEPH had a significantly higher mean PAP value both at the time of diagnosis and at 3rd, 6th, and 12th months than patients without CTEPH (p<0.001/0.043/<0.001/<0.001, respectively) (Table 3). A ROC analysis was done to determine the cut-off value of PAPs at the time of diagnosis, which was shown in Figure. The AUC value was 0.897, cut-off 55 mmHg, sensitivity 80, and specificity 83.3 Table 3.

Table 2. Comparison of patients with and without CTEPH by comorbidities

	CTEPH (+) n:5	CTEPH (-) n:36	p
Age, years (sd)	71 (±14.7)	63 (±15.5)	0.273
Sex			1.00
Female	3 (60)	23 (63.9)	
Male	2 (40)	13 (36.1)	
D-Dimer	869 (609-892)	1920 (153-17887)	0.222
CRP	31 (12-65)	15 (5-58)	0.042
Diabetes mellitus	2 (40)	2 (5.6)	0.066
Hypertension	1 (20)	10 (27.8)	1.00
Coronary artery disease	1 (20)	8 (22.2)	1.00
Chronic pulmonary disease	2 (40)	7 (19.4)	0.299
Atrial fibrillation	3 (60)	0 (0)	0.001
Presence of residual thrombus on CTPA thrombus on CTPA thrombus on CTPA			
6th month	1 (33.3)	17 (56.7)	0.579
12th month	0 (0)	15 (78.9)	0.023
sPAP levels at ECHO follow-ups (%)(mean±SD)			
sPAP at the time of diagnosis	77 (±23.6)	41 (±14.3)	<0.001
sPAP 3rd month	55 (±13.2)	38 (±12.8)	0.043
sPAP 6th month	71 (±19.4)	33 (±10.9)	<0.001
sPAP 12th month	71 (±11.1)	35 (±14.5)	<0.001

CRP: C-Reactive protein, CTPA: Computed tomography pulmonary angiogram, sPAP: Systolic pulmonary artery pressure, sd: Standard deviation

Table 3. Results of the ROC analysis of sPAP level at the time of diagnosis for the diagnosis of CTEPH

AUC	Cut-off	Sensitivity	Specificity	p
.897	55	80	83.3	0.004

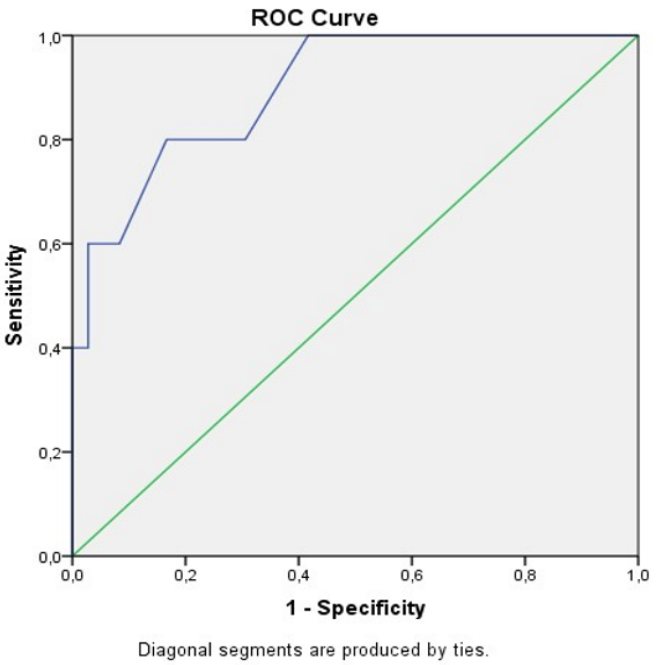

Figure. ROC curve for the PAPs value at the time of diagnosis for use in the diagnosis of CTEPH

A univariate analysis was performed to determine the risk factors for developing CTEPH, and its results are shown on Table 4. The statistically significant risk factors were AF, residual thrombus on CTPA taken at 12th month and the PAPs measured at the time of diagnosis (p 0.001/0.023/0.009, respectively). A multivariate analysis, however, failed to detect any independent predictive factor for CTEPH.

Table 4. Results of the univariate analysis for the risk factors of CTEPH

		CI		
	p	OR	Lower limit	Upper limit
Age	0.636	2.5	0.25	25.17
Gender (Male/Female)	1.00	1.2	0.17	7.99
Diyabetes mellitus	0.066	0.09	0.01	0.87
Hypertension	1.00	1.5	0.15	15.49
Coronary artery disease	1.00	1.1	0.11	11.72
Atrial fibrillation	0.001	-	-	-
Chronic pulmonary disease	0.299	0.36	0.05	2.59
Malignancy	1.00	-	-	-
Thrombophilia	1.00	-	-	-
Presence of residual thrombus on CTPA 6th month	0.579	0.38	0.03	4.68
Presence of residual thrombus on CTPA 12th month	0.023	-	-	-
Concomitant DVT	0.373	1.14	0.91	1.42
sPAP (at the time of diagnosis) ≥55	0.009	20	1.88	211.84

(CTPA: Computed tomography pulmonary angiogram, sPAP: Systolic pulmonary artery pressure)

DISCUSSION

Chronic thromboembolic pulmonary hypertension (CTEPH), which develops as a result of fibrous remodelling, is a long-term complication of acute pulmonary embolism that is uncommon but has high morbidity and mortality. In the present study we primarily aimed to determine the incidence of CTEPH in patients diagnosed with acute pulmonary embolism after long-term follow-up; our secondary aim was to determine the factors associated with CTEPH development. In that context, we calculated the incidence of CTEPH as 2.7% after a minimum follow-up of 12 months and a maximum follow-up of 24 months in 182 patients with acute pulmonary embolism. Our study determined that the presence of AF, residual thrombus on CTPA taken at the 12th-month follow-up, and an elevated sPAP measured at the time of diagnosis (55 mmHg or above) as risk factors for developing CTEPH.

The exact incidence after acute PTE is unclear; it was previously thought to be between 0.1% and 0.5%. However, recent studies have reported higher figures. In a study conducted with 91 patients, Dentali et al.[9] found an incidence of 8.8% over a follow-up of 6-12 months. In a study by Marti et al.,[10] which followed 110 patients for 2 years, the incidence was found 9.1%. A review of contemporary studies indicates that the incidence of CTEPH following acute pulmonary embolism ranges between 0.4% and 9.1%, with an average figure around 4%.[11-13] This variation on the incidence figures stems from the differing population sizes of the studies, diagnostic methods, cut-off levels used for the diagnosis, and follow-up durations. Some of the studies on the incidence of CTEPH after acute PTE have been prospectively conducted while some of them have been retrospectively conducted. While an echocardiographic study has been performed in all enrolled patients in some studies, some others have enrolled patients with symptoms compatible with CTEPH. It was found out that only symptomatic patients with persistent dyspnea are screened for pulmonary hypertension by ECHO in most studies.[11,12,14,15] In a study conducted by Surie et al.[16] with 110 patients, a questionnaire about the possible symptoms of CTEPH (new-onset dyspnea or dyspnea that worsened after PTE, which affects daily life activities etc.) was applied to the patients with a history of PTE 2-4 years after the acute event. Patients with suspected CTEPH were subjected to further evaluation using ECHO and V/P scintigraphy. After a mean follow-up duration of 3 years, the incidence was found to be 2.7%. All of our patients, whether symptomatic or not, regularly underwent echocardiographic evaluation. Although excluding asymptomatic patients is a cost-effective approach, it can be considered to cause finding a lower CTEPH incidence.

CTEPH is diagnosed by showing PAPm≥20 mmHg and PCWP≤15mmHg on right heart catheterization, at least one segmental perfusion defect on perfusion scintigraphy, or pulmonary artery obstruction on CTPA/conventional angiography after receiving effective anticoagulant treatment for at least 3 months. While the diagnosis of CTEPH was confirmed by catheterization in some studies, it was diagnosed by ECHO and V/P scintigraphy in most. Pengo et al. followed 223 patients with acute PTE for a mean period of 94.3 months (1-10 years); they examined patients with symptoms suggesting CTEPH with transthoracic echocardiography, and when there were ECHO signs compatible with CTEPH, they confirmed the diagnosis with V/P scintigraphy and pulmonary angiography.

Using these tests and examinations, they calculated a cumulative CTEPH incidence of 1% at 6 months after acute PTE, 3.1% at 1 year, and 3.8% at 2 years.[16] In a domestic study where 99 patients were followed for 2 years, the researchers applied right heart catheterization to patients with PAPs>30 mmHg or signs suggestive of CTEPH on CTPA or V/P scintigraphy. They found a CTEPH incidence of 5.5%.[17] In a study by Dentali et al.[9] with a small cohort consisting of 91 patients, the patients were examined with ECHO 6 and 12 months after acute PTE. CTEPH was diagnosed in patients with a PAPs>40 mmHg on ECHO and residual perfusion defects on perfusion scintigraphy, but the diagnosis was not confirmed by invasive diagnostic methods. That study found an incidence as high as 8.8%. Also in our study, the diagnosis of CTEPH was confirmed by right heart catheterization performed in our hospital in 2 patients. Catheterization could not be performed in a patient because he was taking high-intensity anticoagulant therapy due to a high CVA risk while two other patients refused to provide written informed consent for the invasive catheterization procedure. Those three patients were diagnosed with CTEPH because they had PAPs>50 mmHg and residual perfusion defects on V/P scintigraphy.

Pulmonary embolism is mostly considered an acute and reversible disease and the patients are considered to be cured altogether by appropriate anticoagulant therapy. However, studies have reported residual perfusion defects at 6th month follow-up scans after acute PTE in more than half of patients.[18] Failure in thrombus resolution or slow thrombus resolution after acute PTE brings about remodelling in the affected vessels. A proximal obstruction results in secondary vasculopathy and pulmonary hypertension.[19] Therefore, large perfusion defects and incompletely resolved PTE are considered risk factors for developing CTEPH. In a previous study, partial or unresolved PTE was observed in 35% of patients, most of whom were followed with an inferior vena cava filter without anticoagulant treatment, after 1 to 7 years of follow-up.[20] In a study from our country, conducted by Korkmaz et al.,[12] it was shown that residual chronic thrombi persisted on CTPA in 48%, 27.4%, and 18.2% of PTE patients on anticoagulant therapy at 3, 6, and 12 months after the acute event, respectively. It was reported that pulmonary hypertension was detected at the end of the first year in 19 of 29 patients with persistent residual thrombi on the CTPA taken at 12th month.

Yang et al.[21] found that an obstruction index of more than 30% three months after acute pulmonary embolism was significant. In our study, an evaluation of the patients for residual thrombus in the pulmonary arteries revealed that thrombus persisted on CTPA in 22.8%, 16.3% and 8.6% of the patients at the 3rd, 6th, and 12th months, respectively, after acute PTE. Five of 16 patients with persisting residual thrombus on CTPA at 12th month were found to have pulmonary hypertension. While residual thrombus was present on the CTPA at 12th month in all patients with CTEPH, residual thrombus existed in 21% of patients who were free of CTEPH. The univariate analysis in our analysis indicated that the presence of residual thrombus at 12th month was a risk factor for developing CTEPH (p=0.023).

One of the important risk factors for developing CTEPH are elevated PAP and right ventricular dysfunction, which are observed in approximately half of all patients with PTE and related to early mortality.[12,22-24] Studies have demonstrated that a sPAP of more than 50 mmHg during acute PTE is associated with the development of persistent PHT in the long term.[22,23] Korkmaz et al.[12] found high PAPs (>35 mmHg) and right ventricular dysfunction in 57% of patients with acute PTE; they also added that sPAP was higher in patients who developed CTEPH than those who did not. In a study by Yang et al.,[21] basal sPAP above 50 mmHg after acute PTE and a history of DVT were significantly related to CTEPH development. Our study showed a significantly higher basal PAPs level in patients who developed CTEPH than those who did not. In the ROC analysis to determine a cut-off level for sPAP to diagnose CTEPH, the cut-off level was found to be 55 mmHg (sensitivity 80, specificity 83.3). The mean sPAP at the time of diagnosis of the group that developed CTEPH was 77 (±23,6) mmHg; hence, a univariate analysis determined a high sPAP (sPAP≥55 mmHg) at the time of diagnosis was an important risk factor for developing CTEPH (p=0.009).

In a cohort study by Martinez et al.[25] from the UK it was reported that the presence of COPD, AF, and left heart failure may predict CTEPH in patients with a history of VTE. AF was considered to develop as a result of thrombus formation inside the atrium due to inadequate anticoagulant therapy after pulmonary embolism. Klok et al.[26] reported that the presence of DM as a comorbidity is associated hypercoagulability and comes forth as a risk factor for CTEPH. Three (60%) patients who developed CTEPH in our study had AF; a univariate analysis showed that AF caused statistically significant risk for CTEPH development (p=0.001).

Limitations

Our study has some limitations. The most important limitations are the inadequate number of patients with CTEPH for performing any statistical analysis and the single-centre nature of our study. Studies with greater sample size are thought to obtain more clear results about the incidence and risk factors of CTEPH.

CONCLUSION

Our single-centre retrospective study determined a CTEPH incidence of 2.7% after acute PTE. The presence of AF, residual thrombus on CTPA taken at the 12th-month follow-up, and elevated sPAP (55 mmHg or above) at the time of diagnosis after acute PTE were determined as the risk factors for developing CTEPH after acute PTE (0.001/0.023/0.009, respectively). A multivariate analysis, however, failed to determine any independent predictor of CTEPH. The diagnostic algorithms used in our study were consistent with the current publications.

CTEPH developed in a considerable number of patients with pulmonary embolism during follow-up. We therefore do not consider CTEPH a rare complication of acute PTE. Unlike other pulmonary hypertension groups, patients with CTEPH have a higher potential to improve with medical and surgical therapies. Thus, early diagnosis and treatment are extremely important in CTEPH. Regular and long-term screening of symptomatic and asymptomatic patients with ECHO and CTPA after acute PTE is important for early diagnosis and treatment of CTEPH; it will reduce mortality and morbidity rates and also provide a significant decrease in the financial burden of the disease. Additionally, increasing clinical awareness of CTEPH and directing patients to surgical treatment will contribute to efforts for improving their quality of life and extending their life expectancy.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethics Committe of Dışkapı Yıldırım Beyazıt Training and Research Hospital (*Date:19.02.2018, Decision No: 46/12*).

Informed Consentw

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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