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ORIGINAL ARTICLE

Epidemiology and management of chronic thromboembolic pulmonary hypertension: experience from two expert centers

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Abstract *Objectives:* Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, distinct pulmonary vascular disease, and therefore, there is a lack of data regarding its clinical presentation, diagnosis, and management at a national basis. We aimed to describe the demographics and management of patients with CTEPH in Northern Greece.
Methods: We conducted a retrospective, observational study by a joint collaboration between two pulmonary hypertension expert centers in Greece, and the study included patients diagnosed with CTEPH. The patient population was divided into two groups depending on their operability.
Results: Overall, 27 consecutive patients were included (59% female, mean age 59.3±15.1 years). Dyspnea and fatigue were the most common presenting symptoms. History of

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pulmonary embolism was present in 82%. Of patients, 18 (67%) were assessed as operable, of whom 10 (55%) finally underwent pulmonary endarterectomy (PEA). There were no differences in symptoms, WHO functional class, 6-min walking test distance, and hemodynamics between the operable and nonoperable groups. At the end of follow-up, all non-operable and operable patients who did not receive surgical treatment were treated with at least one pulmonary hypertension-specific drug.

Conclusion: This is the first report that presents data of patients diagnosed with CTEPH in Greece. The percentage of patients who underwent surgical treatment is lower but approaches the reported rates in large registries. Considering that PEA is a relatively safe and potentially curative surgical procedure, we emphasize the need for establishing a designated PEA center in Greece.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease of the pulmonary vasculature that leads to a poor prognosis if left untreated. Nonresolving thromboemboli obstructing the pulmonary vascular bed and the consequent arterial remodeling are the pathological hallmarks of CTEPH.[1] Therefore, pulmonary vascular resistance (PVR) increases in the arterial component, and progressive right ventricular failure occurs. Acute or recurrent pulmonary embolism and deep venous thrombosis are the main etiologic factors, although roughly 25% of patients diagnosed with CTEPH have no history of clinically evident pulmonary embolism.[2,3]

The main characteristic that differentiates CTEPH from all other causes of pulmonary hypertension (PH) is the possibility of curing PH in patients with CTEPH by surgical intervention (pulmonary endarterectomy, PEA).[4] Yet, a substantial proportion of patients are characterized as nonoperable, and additionally, 10—15% of operable patients develop persistent disease after surgery. These patients have the option of further treatment either medical (riociguat)[5] and/or interventional (balloon pulmonary angioplasty, BPA).[6,7]

Although large international registries from expert centers have shed light on the epidemiology and management options in patients with CTEPH,[3] there may be regional differences regarding patient characteristics, diagnostic workup, and treatment availability.[8] Thus, our main aims were as follows: i) to describe the demographics of consecutive patients with CTEPH in northern Greece and ii) to identify the presentation, diagnosis, and management characteristics of these patients and compare them with those found by other registries.

2. Methods

2.1. Study design and data collection

A retrospective study was conducted, in which adult patients with CTEPH were included from September 2009 until October 2016. Diagnostic procedures and management decisions were performed in two PH expert centers in Thessaloniki, Greece.

Data were collected by reviewing the patients' medical records in each study site and included baseline characteristics, such as symptoms at diagnosis, risk factors for CTEPH, initial baseline diagnostic assessment, and information about medical or surgical treatment. The assessment of patients with CTEPH was performed using the following diagnostic procedures: transthoracic echocardiography; pulmonary function tests, including diffusion capacity for carbon monoxide (DLCO); ventilation-perfusion lung scan; computed tomographic angiography; right heart catheterization; and pulmonary angiography. The date of diagnosis was considered the date of the initial right heart catheterization. The end date of follow-up was considered to be October 1, 2016. The study was conducted according to the Declaration of Helsinki. Institutional ethics approval was obtained, and all patients signed informed consent.

2.2. Definitions

The diagnosis of CTEPH was established after excluding other causes of PH according to the current guidelines.[9] CTEPH was defined by the following observations: (1) a mean pulmonary arterial pressure >25 mmHg with a pulmonary capillary pressure ≤ 15 mmHg, which is measured by right heart catheterization; (2) at least one (segmental) perfusion defect detected by lung scanning, multidetector computed tomographic angiography, or pulmonary angiography; and (3) after at least 3 months of adequate anticoagulation.

Patients were assessed by a team of cardiothoracic surgeons and were classified into two groups according to their operability, considering multiple factors, such as the location of lesions, patients' age, and comorbidities[10,11].

2.3. Statistical Methods

Data are presented as mean$\pm$standard deviation (SD) for continuous variables, following the normal distribution, and as median and range for variables that did not follow the normal distribution. Categorical variables are presented as frequencies and percentages (%). Continuous variables were compared using the t-test for independent samples or the Mann—Whitney *U* test, while the chi-square test or the

Fisher exact test was used to assess categorical variables. For multiple comparisons, ANOVA or the Kruskal–Wallis test was used as appropriate. A p-value <0.05 was considered statistically significant in this study. Data were analyzed using the SPSS version 21.0.

3. Results

3.1. Population characteristics

The study population consisted of 27 consecutive patients (16 women, mean age 59.3±15.1 years) diagnosed with CTEPH from two PH expert centers in Northern Greece (Table 1). The majority of patients (48%) were treated by cardiologists, 30% by pulmonologists, and 22% by both. In presentation, 20 patients (74%) were in WHO functional class III–IV. The most frequently presented symptoms were dyspnea (96%), fatigue (96%), palpitations (37%), and peripheral edema (30%). Only two patients (7%) experienced syncope. At the time of diagnosis, the mean 6-min walking distance was 297.5±134.6 m.

Patients' risk factors for CTEPH are presented in Table 2. Confirmed previous pulmonary embolism was present in 82% of patients, while 22% had a history of deep venous thrombosis prior to CTEPH diagnosis. No patient in our cohort required placement of a venous filter. The most frequent comorbidities were systemic hypertension (52%), obesity (26%), and non-insulin-dependent diabetes mellitus (19%). Overall, 89% of patients reported a medical condition associated with CTEPH and 41% had at least one thrombophilic disorder. Of those, factor V Leiden mutation was the most common thrombophilic risk factor (15%) followed by lupus anticoagulant (7%), protein C deficiency (7%), and prothrombin gene mutation (7%).

3.2. Diagnostic evaluation

Diagnostic evaluation is presented in Table 3. Right heart catheterization was performed on all patients at initial assessment. The mean pulmonary artery pressure was 44.6±8.7 mmHg, right atrial pressure was 8(3-21) mmHg, and pulmonary artery wedge pressure was 10.1±2.3 mmHg; PVR was 8.5±3.3 Wood Units, cardiac index was 2.6 (1.4–5.0) L/min^{-1}/m^{-2}, and O_2 saturation in pulmonary artery was 65.2±8.3%. Echocardiography revealed elevated right ventricular systolic pressure of 78.6±20.9 mmHg, tricuspid regurgitation maximum velocity of 4.10±0.63 m/s, while 92% of patients had right ventricular dilatation (based on measurement of right ventricular inlet in four-chamber view). Ventilation-perfusion scan scintigraphy was performed for 24 out of the 27 (89%) patients. For the three patients who lacked ventilation/perfusion scintigraphy, diagnosis was based on computed tomography pulmonary angiography, which showed proximal thrombi in all three cases. In one third of patients, only lung perfusion but no ventilation scan was performed due to the lack of infrastructure for ventilation scan at that time. Chest radiography and high-resolution computed tomography were used to assess ventilation in these patients. Traditional pulmonary angiography was performed in 21 (78%) patients, which showed proximal lesions in 62% of them. Six patients (22%) did not undergo invasive pulmonary angiography. These patients were mainly elderly and frail and denied the possibility for further operability assessment. Therefore, in these patients, the diagnosis was based on computed tomography pulmonary angiography and ventilation/perfusion scintigraphy. Computed tomography pulmonary angiography scan was performed in 25 (93%) of the patients, which showed proximal lesions in 48% of them.

3.3. Operability

Based on surgical consultation, 18 (67%) patients were considered as candidates for PEA and 9 (33%) were deemed nonoperable. All nonoperable patients in our cohort had distal pulmonary artery obstructions, thereby rendering thrombi surgically inaccessible. For four patients, severe comorbidities including malignancy, severe chronic obstructive pulmonary disease, and respiratory failure were additional prohibitive factors for PEA. One out of the nine nonoperable patients underwent a single BPA session and

Table 1 Basic demographic and clinical characteristics of study population.

Characteristics	Total (n=27)	Operable (n=18)	Nonoperable (n=9)	p-value
Female sex	16(59)	9(50)	7(78)	0.16
Age, years	59.3 ± 15.1	54.1 ± 13.7	70.1 ± 12.5	0.07
BMI, kg/m^2	28.5 ± 5.4	28.1 ± 4.8	29.4 ± 6.6	0.54
Smoking	14(52)	9(50)	5(55)	0.78
NYHA (III/IV)	20(74)	13(72)	7(28)	0.75
6MWD, m	297.5 ± 134.6	306.1 ± 140.5	279.3 ± 128.2	0.65
Dyspnea	26(96)	17(94)	9(100)	1.00
Edema	8(30)	5(27)	3(33)	1.00
Chest pain	3(33)	5(27)	4(44)	0.42
Syncope	2(7)	2(11)	0	-
Fatigue	26(96)	17(94)	9(100)	1.00
Palpitations	10(37)	6(33)	4(44)	0.68

Values represent absolute count (percentage) or mean ± standard deviation.
BMI: Body mass index, NYHA: the New York Heart Association, 6MWD: 6-Min Walk Distance.

Table 2 Risk factors for CTEPH in the study cohort.

Risk factors	Total N=27	Operable N=18	Nonoperable N=9	p-value
History of PE	22(82)	13(72)	9(100)	0.14
Recurrent	5(19)	4(22)	1(11)	0.64
Massive	5(19)	5(28)	0	-
Previous DVT	6(22)	5(28)	1(11)	0.63
Associated conditions at diagnosis	24(89)	15(83)	9(100)	0.52
Thrombophilic disorder	11(41)	10(55)	1(11)	0.04
Lupus anticoagulation	2(7)	2(11)	0	-
Protein C deficiency	2(7)	2(11)	0	-
Factor V Leiden	4(15)	4(22)	0	-
Prothrombin gene mutation	2(7)	1(5)	1(11)	-
Antithrombin III	1(3)	1(5)	0	-
Previous major surgery	4(15)	4(22)	0	-
History of cancer	2(7)	2(11)	0	-
Thyroid disorder	2(7)	1(5)	1(11)	-
Noninsulin DM	5(19)	2(11)	3(33)	0.30
Splenectomy	3(11)	1(5)	2(22)	0.25
Coronary artery disease	3(11)	2(11)	1(11)	-
Varicose veins	4(15)	3(17)	1(11)	-
Obesity	7(26)	4(22)	3(33)	0.65
Chronic venous insufficiency	3(11)	3(17)	0	0.53
Prolonged hospitalization	4(15)	3(17)	1(11)	-
Fracture	1(3)	1(5)	0	-
Family history of DVT/PE	1(3)	1(5)	0	-
Congestive heart failure	1(3)	1(5)	0	-
VA shunt	1(3)	1(5)	0	-
Inflammatory bowel disease	0	0	0	-
Infection of VA shunt /pacemaker	1(3)	1(5)	0	-
History of AF/flutter	2(7)	1(5)	1(11)	-
Other conditions				
Systemic hypertension	14(52)	9(50)	5(55)	1.00
COPD	4(15)	2(11)	2 (22)	-
Sleep apnea	1(3)	0	1(11)	-
Contraceptive pills	1(3)	1(5)	0	-

Values represent absolute count (percentage).
PE: pulmonary embolism, DVT: deep venous thromboembolism, DM: diabetes mellitus, VA: ventriculoarterial, COPD: chronic obstructive pulmonary disease, AF: atrial fibrillation.

was scheduled to undergo further sessions in the future. Only 10 out of the 18 patients, who were assessed as operable, finally underwent PEA, as one patient, with a history of chronic hemolytic anemia and splenectomy, refused surgery and underwent BPA, and 7 patients had no intervention due to unacceptable risk/benefit ratio or socioeconomic factors (Figure 1).

Half of our patients were operated in PEA-specialized centers abroad and half in Greece (Figure 2). None of our patients experienced serious postoperative complications or died soon after PEA. None of the operated patients required postoperative extracorporeal membrane oxygenation. Eight out of the 10 patients who underwent PEA did not have residual PH after the procedure. Two patients had residual disease, as diagnosed by the postoperative right heart catheterization, and received PH-targeted medical treatment with riociguat.

3.4. Conventional treatment at diagnosis and follow-up

Median follow-up period was 23 (IQR 1—79) months. Conventional therapies at diagnosis and follow-up are presented in Table 4. The vast majority (93%) of patients received anticoagulation at the time of diagnosis, and all patients received anticoagulants at the end of follow-up. During the follow-up, 20 patients (75%) were under vitamin K antagonists, 5 (18%) under non-vitamin K oral anticoagulants (NOACs), and 2 (7%) under low-molecular-weight heparin (LMWH). Two out of the five patients in the NOAC group received NOAC after an episode of acute pulmonary embolism and refused to switch to a vitamin K antagonist. For the remaining three patients, NOAC was preferred instead of vitamin K antagonist due to labile INRs

Table 3 Diagnostic evaluation of study cohort.

Diagnostic tests	Total (N=27)	Operable (N=18)	Nonoperable (N=9)	p-value
Right heart catheterization	27(100)	18(100)	9(100)	-
mRAP, mmHg	8.0(3.0-21.0)	8.0(4.0-16.0)	8.0(3.0-21.0)	0.73
mPAP, mmHg	44.6 ± 8.7	45.3 ± 8.4	43.3 ± 9.6	0.58
PCWP, mm Hg	10.0(5.0-14.0)	9.5(5.0-14.0)	10.0(10.0-13.0)	0.24
PVR, Wood Units	8.5 ± 3.3	8.9 ± 3.0	7.7 ± 3.8	0.42
CI, $L/min^{-1}/m^{-2}$	2.6 (1.5-5.0)	2.6(1.7-5.0)	2.6(1.5-4.9)	0.66
SVO_2, %	65.3 ± 8.3	66.5 ± 8.1	62.3 ± 8.8	0.29
Echocardiography	27(100)	18(100)	9(100)	-
RVSP, mmHg	78.6 ± 20.9	76.1 ± 17.3	83.2 ± 26.6	0.42
TR Vmax, m/s	4.10 ± 0.63	4.08 ± 0.45	4.15 ± 0.90	0.83
Abnormal RV contractility	22(81)	15(83)	7(78)	0.53
TAPSE, cm	1.97 ± 0.25	2.00 ± 0.26	1.86 ± 0.22	0.30
Dilated RV	25(92)	16(89)	9(100)	0.43
V/Q scintigraphy	24(89)	16(89)	8(89)	-
Only perfusion scan performed	8(33.3)	6(37.5)	2(25)	0.43
Pulmonary angiography	21(77.7)	15(83)	6(67)	-
Proximal lesions	13(62)	12(80)	1(16.7)	0.01
CT scan	25(93)	17(94)	8(89)	-
Proximal lesions	12(48)	12(70)	0	0.01
Dilation of bronchial arteries,	8(32)	5(29)	3(33.3)	1.00
Mosaic perfusion pattern (HRCT)	11(44)	5(29)	6(67)	0.20
Lung function tests	21(77.7)	13(72.2)	8(88.8)	-
DLCO (% pred)	70.7±10.7	71.0±8.4	70.2±14.2	0.87
FEV1(% pred)	88.6±21.4	92.5±23.3	82.2±11.7	0.29
FVC(% pred)	88.4±18.4	91.5±18.8	83.3±17.8	0.33
FEV1/FVC	1.0±0.1	1.0±0.1	0.9±0.1	0.69
TLC (% pred)	81.3±13	84.5±14.1	75.3±8.7	0.14

Values represent absolute count (percentage), mean ± standard deviation or median (range).
mRAP: mean right atrial pressure, mPAP: mean pulmonary arterial pressure, PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance, CI: cardiac index, SVO_2: oxygen saturation of pulmonary artery, RVSP: right ventricular systolic pressure, TR Vmax: tricuspid regurgitation maximal velocity, RV: right ventricle, TAPSE: tricuspid annular plane systolic excursion, DLCO: diffusing capacity for carbon monoxide, FEV1: forced expiratory volume at 1 s, FVC: forced vital capacity, TLC: total lung capacity.

or noncompliance to regular INR control. Out of the two patients who were treated with LMWH, one had cancer and the other died because of end-stage right heart failure. At initial assessment, 44.4% of the studied population was under ambulatory O_2 treatment, while at the follow-up, this percentage was reduced to half.

3.5. PH advanced treatment at diagnosis and follow-up

Treatment by specific therapies for PH at diagnosis of CTEPH and at the end of the follow-up is shown in Table 5. At diagnosis, 11 patients received phosphodiesterase type 5 (PDE-5) inhibitor, 4 patients were on endothelin receptor antagonists (ERAs), 1 was treated with prostacyclin analogue, and 4 received riociguat. At the end of the follow-up, 1 was on PDE-5 inhibitor, 2 received ERA, 1 received prostacyclin analogue, and 16 received riociguat. Half the patients on riociguat treatment experienced side effects, such as hypotension and gastrointestinal reflux, but only one discontinued the treatment due to side effects (hypotension and generalized weakness).

3.6. Differences among operable PEA patients, operable non-PEA patients, and nonoperable patients

Baseline characteristics and presenting symptoms did not differ between operable and nonoperable patients, although operable patients were younger and more likely to suffer from a thrombophilic disorder (Table 2). Massive pulmonary embolism was present only in the operable PEA group (28%). As expected, the presence of proximal lesions was more frequent in the operable than that in the nonoperable group. There was no difference in lung function tests and hemodynamics between operable and nonoperable patients (Table 3).

Both operable and nonoperable groups received similar conventional treatment for CTEPH (Table 4). At follow-up, 10 (55%) of initially characterized operable patients received PH-specific treatment. Among these, eight did not undergo surgical treatment and two had residual PH after surgery. All patients in the nonoperable group were treated with the PH-specific therapy except the one who died because of right heart failure soon after the diagnosis. At

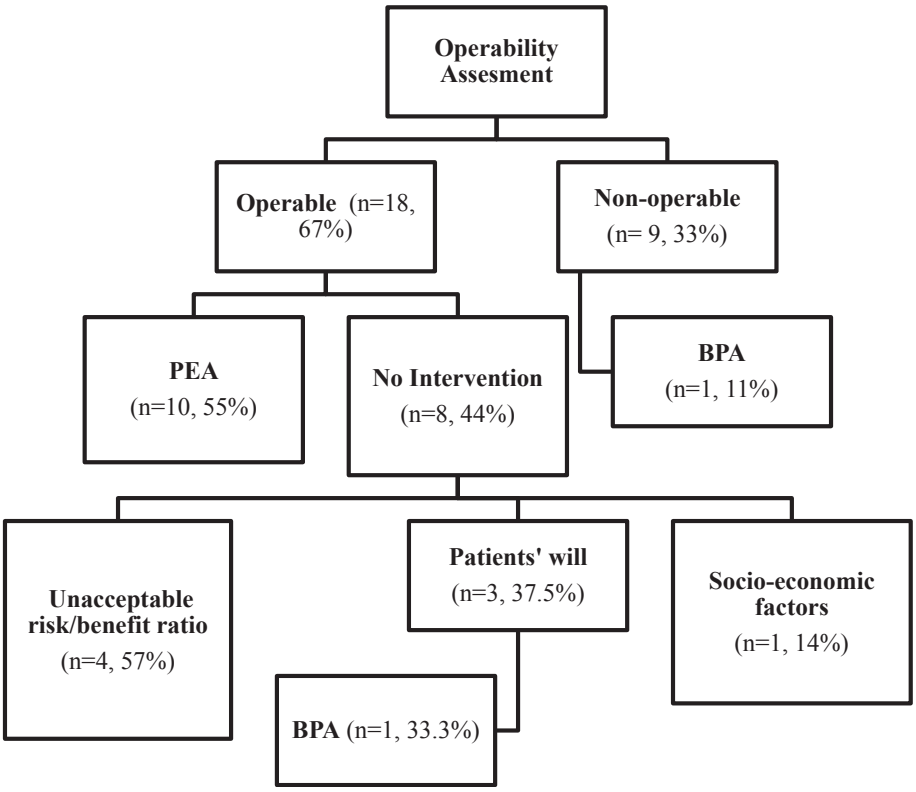

Figure 1 Assessment of operability in patients diagnosed with chronic thromboembolic pulmonary hypertension. PEA: Pulmonary Endarterectomy, BPA: Balloon Pulmonary Angioplasty.

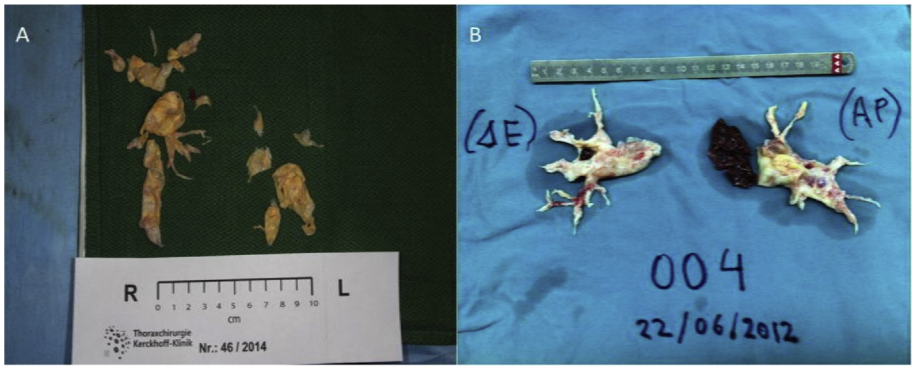

Figure 2 Specimen removed from two patients who underwent pulmonary endarterectomy. A) A 53-year-old, male patient with a history of acute pulmonary embolism who was operated in Germany. B) A 68-year-old male patient with recurrent episodes of acute pulmonary embolism and a history of protein C and antithrombin III deficiency who was operated in Greece.

the end of the follow-up, one patient was under a combination therapy of riociguat, ERA, and prostacyclin analogue, one patient was on ERA due to his own wish not to switch to riociguat, and one patient did not tolerate riociguat due to side effects and switched to monotherapy with PDE-5 inhibitor. The remaining patients from the nonoperable group received treatment with riociguat.

Patients who were assessed as operable were younger than those who were operable but not younger than operated and nonoperable ones (mean age: 47.5±11.3 vs. 62.2±12.3 and 70±12.5 years, respectively, $p=0.04$). There were no differences in the presenting symptoms, WHO functional class, 6-min walking distance, and hemodynamics among these three patient groups.

4. Discussion

This is the first report on the characteristics and management of patients with CTEPH in Greece. In line with the

Table 4 Conventional therapies at diagnosis and follow-up.

Conventional therapies	Total N=27	Operable N=18	Nonoperable N=9	p-value
At diagnosis				
Anticoagulation	25(93)	17(94)	8(88.9)	0.56
VKA	21(77.8)	13(72)	8(88.9)	0.28
NOAC	2(7)	2(11)	0	-
LMWH	2(7)	2(11)	0	-
O_2 therapy	12(44.4)	8(44.4)	4(44.4)	-
Diuretics	13(48.1)	9(50)	4(44.4)	-
At follow-up				
Anticoagulation	27(100)	18(100)	9(100)	-
VKA	20(75)	14(78)	6(66.7)	-
NOAC	5(18)	4(22)	1(11.1)	-
LMWH	2(7)	0	2(22.2)	-
O_2 therapy	6(22.2)	3(16.6)	3(33.3)	0.36
Diuretics	13(48.1)	8(44)	5(55.5)	0.69

Values represent absolute count (percentage).
VKA: Vitamin K antagonist, NOAC: non-vitamin K oral anticoagulant, LMWH: low-molecular-weight heparin.

largest CTEPH registry so far, the patients in our cohort were significantly impaired and the majority presented in the WHO functional class III or IV.[3] The 6-min walking distance was shorter (297 vs. 329 m), and fewer patients experienced syncope (7% vs. 13.7%).

The thromboembolic nature of CTEPH and the association between pulmonary embolism and/or deep vein thrombosis have been well established.[12–14] The Japanese registry revealed a history of deep vein thrombosis and acute pulmonary embolism in 50.4% and 37.2%, respectively. The corresponding percentages were 56.1% and 74.8% in the large European database and 49.2% and 70.6% in the California-San Diego Pulmonary Endarterectomy registry.[1] In our cohort, there was a lower percentage of patients who reported deep venous thrombosis and a higher percentage of patients with a history of acute pulmonary embolism. None of our patients required cava filter placement because they had no absolute contraindication for anticoagulation or recurrent episodes of venous thromboembolism. In addition, massive pulmonary embolism was present only in the operable group in our study. This finding is in line with that reported by Pepke-Zaba et al, who showed that more patients in the operable group had massive pulmonary embolism (47.1% in the operable group vs. 29.4% in the nonoperable group).[3] The proximal localization of the thrombi after massive pulmonary embolism may explain the higher frequency of massive pulmonary embolism in the operable group.

Numerous acquired and inherited coagulopathies have been linked to the development of CTEPH.[12,15] In our study 41% of population reported at least one thrombophilic disorder, and their presence was significantly higher in the operable group, a finding that is in concordance with the International European Database(3). This finding may underlie a correlation between proximal disease and coagulation abnormalities that remains to be elucidated in future studies.

A number of comorbidities are present in patients with CTEPH.[12] In our population, a high percentage of obesity, systemic hypertension, and noninsulin diabetes mellitus was observed, highlighting that traditional cardiovascular risk factors should not be overlooked in these patients.

PEA is the curative treatment option for CTEPH although not all patients are considered the candidates for surgical management.[16] The rate of PEA varies across countries and is highly asymmetric among centers.[17,18] Two thirds of our cohort were assessed as operable, of whom only half underwent PEA. The number of operable patients and the number of patients who finally underwent surgery were less in our cohort, but approached the percentages reported by other groups.[3,19,20] Condliffe et al reported a 68% of operable patients in their cohort out of whom 50% underwent PEA(20). In the large European Registry, 62.9% of patients were considered operable and 56.8% finally underwent PEA(3). However, half of patients in our cohort sought surgical treatment abroad, which may be attributed to the lack of designated PEA centers in the country.

Although riociguat is the only approved therapy for nonoperable CTEPH and for persistent CTEPH after PEA, [21]the majority of our patient population received PH-specific treatment other than riociguat at first assessment because riociguat became commercially available during the early 2015 in Greece. Of note, most patients who

Table 5 Pulmonary hypertension-specific therapy at initiation and follow-up.

PH-specific therapy	Total N=27	Operable N=18	Nonoperable N=9	p-value
At initiation				
Phosphodiesterase type 5 inhibitor	11(40.7)	8(44.4)	3(33.3)	0.69
Endothelin receptor antagonist	4(14.8)	2(11.1)	2(22.2)	0.58
Prostacyclin analogue	1(3)	1(5)	0	-
Riociguat	4(14.8)	2(11.1)	2(22.2)	0.58
At follow-up				
Phosphodiesterase type 5 inhibitor	1(3)	0	1(11.1)	-
Endothelin receptor antagonist	2(7)	0	2(22.2)	-
Prostacyclin analogue	1(3)	0	1(11.1)	-
Riociguat	16(59.3)	10(55)	6(66.7)	0.58

Values represent absolute count (percentage).

required advanced medical treatment for PH were under riociguat at the end of the follow-up.

This is a retrospective analysis, and data have to be interpreted with caution. Another limitation is that some of our patients underwent only lung perfusion scan and not a ventilation-perfusion scan as indicated by the current guidelines. Furthermore, the sample size of this study was small and included patients only from two PH centers in Northern Greece, thus, not representing CTEPH management across the entire country.

5. Conclusions

This is the first report that provides data of patients with CTEPH in Greece. The percentage of patients who finally underwent the surgical treatment, i.e. PEA, was small but close to other registries.

Considering that PEA is a relatively safe and potentially curative surgical procedure, especially when performed at high volume centers with expertise in the disease, we emphasize the need for establishing a PEA center in Greece.

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