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Risk factors for chronic thromboembolic pulmonary hypertension

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Abstract and Keywords

Aims: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by non-resolving pulmonary thromboemboli that can be treated by surgical pulmonary endarterectomy (PEA). We sought to confirm known and to identify novel CTEPH risk factors in a controlled retrospective cohort study of prevalent CTEPH cases collected in 3 European centers offering PEA.

Methods and Results: Data from CTEPH patients were compared with non-thromboembolic precapillary pulmonary arterial hypertension cohorts at the participating institutions. The study population comprised 687 patients assessed at the time of diagnosis between 1996 and 2007. VA-shunts and infected pacemakers (odds ratio (OR) and 95% confidence interval, 76.40 [7.67-10351], p<0.001), splenectomy (OR 17.87 [1.56-2438], p=0.017), previous venous thromboembolism (VTE) (OR 4.52 [2.35-9.12], p<0.001), recurrent VTE (OR 14.49 [5.40-43.08], p<0.001), blood groups non-0 (OR (OR 2.09 [1.12-3.94], p=0.019), and lupus anticoagulant/anti-phospholipid antibodies (OR 4.20 [1.56-12.21], p=0.004) were more often associated with CTEPH. Thyroid replacement therapy (OR 6.10 [2.73-15.05], p<0.001) and a history of malignancy (OR 3.76 [1.47-10.43], p=0.005) emerged as novel CTEPH risk factors.

Conclusions: This European database confirmed previous knowledge on CTEPH risk factors, and identified thyroid replacement therapy and a history of malignancy as new medical conditions associated with CTEPH.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious and underdiagnosed disorder with significant morbidity and mortality. CTEPH is thought to result from single or recurrent pulmonary thromboemboli arising from sites of venous thrombosis [1]. For reasons still unclear, the lysis of blood clots does not occur in up to 3.8% of survivors of acute pulmonary thromboemboli [2] evolving to organized obstructions inside the pulmonary artery. Increased vascular resistance results in right heart strain and remodeling. In contrast to venous thromboembolism (VTE), classic plasmatic abnormalities have not been found, with the exception of anti-phospholipid antibodies/lupus anticoagulant (APA/LAC) in 10–20% of patients [3], and plasma factor VIII>230IU/dl in 25% of patients [4]. Two recent reports have documented an association of splenectomy [5, 6], ventriculo-atrial (VA-) shunt for the treatment of hydrocephalus, and chronic inflammatory conditions [5] with CTEPH. The aim of the present study was to confirm known and to detect new associated medical conditions (AMCs) in a large database of patients with CTEPH.

Methods

Study Design

This was a controlled retrospective cohort study that used logistic regression modeling. Three large European pulmonary vascular centers contributed prevalent cases between March 1996 and February 2006 (Vienna, Austria and Bratislava, Slovac Republic), between May 1996 and July 2005 (Homburg, Germany), and between January 2001 and June 2007 (Prague, Czech Republic) into the database. An academic pulmonary endarterectomy (PEA) program and yearly follow-up examinations were required for a center to participate, including the presence of at least one PEA surgeon at the institution. Data from consecutive patients with non-thromboembolic precapillary pulmonary arterial hypertension (non-thromboembolic PH) were contributed from participating centers to serve as controls. Viennese patient data were including those patient data previously referred to in other studies [4, 5, 7-9]. The respective ethics committees of the participating institutions approved the study.

Diagnostic criteria

At all institutions, the diagnoses of CTEPH and non-thromboembolic PH were established according to the current clinical classification [10], and the indication for surgery was based on published standards [11]. In brief, CTEPH was defined as invasively measured mean pulmonary-artery pressure ≥ 25 mmHg at rest, or unilateral pulmonary artery occlusion in the presence of normal or elevated pressures at rest, a Pulmonary Wedge Pressure (PWP) ≤15mm Hg, abnormal ventilation-perfusion (V/Q) scan with one or more at least segmental perfusion defects with normal ventilation, an abnormal CT scan and/or abnormal pulmonary angiography showing typical findings

of CTEPH, and ≥ 3 months of efficient anticoagulation prior to these assessments.

A history of malignancy, i.e., past or healed cancer, was confirmed by surgical and pathological reports. The diagnosis of inflammatory bowel disease (IBD) was accepted if the clinical, endoscopic, histological and radiological criteria were fulfilled [12]. Evidence for prior VTE was based on clinical symptoms, and documented phlebography/ultrasound evidence of deep vein thrombosis, or high-probability lung scans at the time of the event. Thyroid hormone substitution therapy was rated only if ongoing at the time of the assessment. All data were extracted from the patients' medical histories at the time of the first diagnostic right heart catheterization.

The diagnosis of non-thromboembolic PH was based on international criteria [10]. The majority of patients were diagnosed as having Venice class I pulmonary hypertension, i.e., PAH (Table 1).

Statistical analysis

For the description of the study population, continuous data are presented as means±standard deviations (SD). Because of their skewed distribution, age, body mass index (BMI) and hemodynamic data are presented as medians, including the lower and upper quartile. Categorical characteristics are described by the number of affected patients. The calculation of percentages ignores missing observations. Exploratory uncorrected p-values of chi-square and Mann-Whitney tests for qualitative and continuous data, respectively, were obtained for the factors listed in Table 2.

Putative risk factors were investigated for their prognostic relevance by logistic regression. Simple analysis with risk factors adjusted for sex, age and expert center (marginal effects) was contrasted with multiple analysis using the full model with risk factors adjusted for sex, age, expert center and all other risk factors as listed in Table

3 (partial effects). Differences between simple and multiple results were investigated by means of Spearman´s partial correlation (adjusted for sex, age, expert center) of the risk factors. Possible departures from main effects models were checked. Starting from a proportion of thyroid (malignancy) patients of 3.5% (4.3%) observed in the control group, this study would have a power of 88% (94%) to detect a marginal odds ratio of 3.0 to a significance level of $\alpha=0.05$. The results are presented as odds ratios and corresponding 95% confidence limits and p-values.

Because of the small number, patients from Bratislava were added to the Vienna cohort. According to recent data demonstrating staphylococcal DNA in the majority of PEA specimens from VA-shunt carriers [7], these were grouped together with infected pacemakers. Blood group analyses could not be included into the main analysis due to the unavailability of blood group determinations in Prague in patients who were not scheduled for a surgical procedure. Therefore, the effect of blood group 0 versus all other blood groups was investigated in a separate multiple logistic model excluding patients from Prague, but adjusting for all risk factors.

Because the occurrence of risk factors was low and the odds ratios were relatively large, the effects were estimated via the penalized likelihood for logistic regression [13]. Confidence limits were obtained by profile penalized likelihood as implemented in a specialized computer program [14], which gives more reliable results than the standard Wald approach.

P-values ≤ 0.05 were considered to be statistically significant. All computations were performed using SAS software, Version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

We retrospectively studied 687 consecutive patients with CTEPH (n=433 (63%)) and non-thromboembolic PH (n=254 (37%)) at the time of their first diagnostic right-heart catheterization. The Medical University of Vienna collected 359 patients, including 9 patients from the Medical University of Bratislava (Slowakia), the Medical University of Prague included 95 patients, and the Medical University of Homburg/Saar contributed 233 patients (Table 1).

Details of the study populations are described in Table 2. Differences in patient characteristics are in part due to the different referral patterns across the participating centers. While the pulmonary vascular centers in Vienna and Prague are both PEA and general pulmonary hypertension referral centers, the PEA program and the strength of the pulmonary and intensive care center are main determinants of the patient population in Homburg.

The median age of CTEPH patients (58.0 years) was on average higher than that of non-thromboembolic precapillary PH patients (50.5 years) (Figure 1). There were 52% females in the CTEPH and 66% in the non-thromboembolic PH diagnostic category. On an average, diagnoses were established two years after the first symptoms, mainly unexplained dyspnea on exertion. The distribution of functional classes was similar in CTEPH and non-thromboembolic PH at the time of diagnosis, with the majority of patients presenting in class III/IV (83% of CTEPH patients versus 78% of non-thromboembolic precapillary PH patients). Six-minute walking distances were assessed in the majority of patients, but could not be reported, as there were too many missing values in the years 1996-1999. Although surgery was offered at each participating center, the rate of PEA varied between 47% (Vienna), 65% (Homburg)

and 72% (Prague, Table 1).

Clinical histories were suggestive of a thromboembolic origin of CTEPH. While almost 70% of patients with CTEPH had a history of VTE, this was reported in only 11% of patients with non-thromboembolic PH. Recurrent VTE was frequent in the CTEPH group (in 225 patients, 52.2%), and a rare finding in the non-thromboembolic precapillary PH group (in 6 patients, 3.2%). Previous leg trauma occurred in 9 CTEPH patients, and in no non-thromboembolic precapillary PH patient. There were 13 cases of arm vein thromboses in the CTEPH group, and one in the non-thromboembolic PH group.

Not a single patient with CTEPH suffered from systemic lupus erythematosus. Abnormal hemoglobins, osteomyelofibrosis and COPD occurred in 2.1%, 1.2% and 1.5% of CTEPH patients, respectively. A history of malignant disease was more frequently observed in CTEPH (12.2% versus 4.7%), mainly breast cancer, gastrointestinal carcinoma, melanoma, prostate cancer and seminoma. The time interval between the diagnosis of cancer and CTEPH was in the order of 5 to 10 years.

While pacemakers in general were equally frequent in both diagnosis groups (1.4% in CTEPH, 1.2% in non-thromboembolic PH), pacemakers with a history of infection were observed in 4 CTEPH patients, but in none of the patients with non-thromboembolic precapillary PH.

Risk factors for CTEPH

Putative risk factors were selected according to current knowledge on CTEPH to enter the logistic regression model. Results from logistic regression analysis apply to 585 patients with complete data sets.

Splenectomy and VA-shunt/infected pacemakers were confirmed as risk factors for CTEPH in the multiple analysis (Table 3). IBD did not reach statistical significance in this multicenter observation, although 12 patients were affected in the CTEPH group, compared with only 3 in the non-thromboembolic PH group. As expected, previous and recurrent VTE were strongly associated with CTEPH. Chronic venous ulcers were shown to be more prevalent in the CTEPH diagnosis group, and borderline significant in the multiple analysis. Ongoing thyroid replacement therapy was strongly associated with the diagnosis of CTEPH.

Differences between results of simple and multiple analyses can be explained by correlations. Previous and recurrent VTE were positively correlated (r = 0.75), and so were abnormal hemoglobins and splenectomy (r = 0.50). The absolute value of the other correlation coefficients was below 0.30. No interactions (effect modifications) of the putative risk factors were assessed due to insignificance.

When blood groups were analyzed, data from Prague had to be excluded because of no entries from this center in the non-thromboembolic PH group. In 495 patients, after adjustment for all other variables in the model, the binary variable blood group non-0 was a predictor for the diagnosis of CTEPH (OR 2.09 [1.12-3.94], p=0.019).

Discussion

This registry represents the largest contemporary population of patients with CTEPH including operable and inoperable cases, thus providing an updated description of this orphan disease in the Western world. Previously, large patient series were derived from medical [15-17] and surgical databases [18, 19], with the most recent representing an in-depth analysis of 1,500 consecutive patients [20]. In the past 20 years it has become recognized that several conditions and diseases could be associated with classical precapillary PH (PAH) [21-23]. Similar to that, recent series of 181 [5, 9] and 257 patients [6] diagnosed with CTEPH have identified distinct medical conditions (associated medical conditions, AMCs) linked to the development of CTEPH. These include splenectomy [5, 6], VA-shunt for the treatment of hydrocephalus, as well as other permanent central intravenous lines, IBD and osteomyelitis [9].

The present investigation was aimed to confirm known and to detect new AMCs in a large database of patients with CTEPH. Overall, CTEPH patients tended to be older and tended to have more comorbidities than non-thromboembolic PH patients. The key findings were that previously reported AMCs were largely confirmed, including information on the prevalence of APA/LAC [3], and the association with splenectomy, VA-shunt [5], and blood groups non-0 [4]. Prevalences were similar regardless of whether patients with PAH [6] or patients with acute VTE not developing CTEPH [5] were regarded as controls. By contrast, IBD and osteomyelitis were not found to be more prevalent in patients with CTEPH. Previous and recurrent VTE, chronic venous ulcers, thyroid hormone replacement therapy and malignancy were associated with CTEPH in 433 patients from several European centers. The greater than commonly reported rate of previous VTE [1, 34] in 69% of patients with CTEPH may have

resulted from the increased awareness for thrombosis in the participating PEA expert centers.

Thyroid disease

The prevalence of subclinical hypothyroidism is 4% to 8% in the general population, and up to 15% to 18% in women who are over 60 years of age [24]. For comparison, the prevalence of recognized thyroid disease (either self-reported history of thyroid disease or current Levothyroxin treatment) in a population aged over 49 years was reported to be 10% [25]. Therefore, the observation of roughly 20% of patients with CTEPH under thyroid hormone replacement is not only statistically different from the non-thromboembolic precapillary PH comparator, but appears biologically meaningful. These data are in contradiction to recent work demonstrating a 24% prevalence of thyroid disorders in patients with non-thromboembolic PH in a 356 patient observation [26]. However, while the authors studied a broad spectrum of serologic thyroid alterations, with only 50-70% of patients having invasively confirmed PH, our data collection was confined to medical thyroid replacement therapy that was ongoing at the time of diagnosis. Based on the available data it cannot be said whether the risk to develop CTEPH is to be attributed to hypothyroidism or thyroid hormone replacement therapy, or both.

It has been shown that patients suffering from moderate hypothyroidism are at an increased risk of thrombosis [27]. In addition, treatment with Levothyroxin increases von Willebrand factor (vWF) levels and shortens in vitro platelet plug formation measured as collagen-epinephrine-induced closure time [28]. We have previously shown that CTEPH patients had higher FVIII/vWF levels than healthy subjects and PAH patients [4]. One year after PEA these levels were unchanged suggesting a role

of elevated FVIII/vWF in disease pathogenesis [4]. In accordance with knowledge on genetic factors determining the variation in plasma concentration of FVIII/vWF [29], blood groups non-0 were more prevalent in CTEPH patients [4], a finding that was confirmed in the registry.

Cancer

Epidemiological studies have identified malignancy as an independent thrombosis risk factor and show that cancer patients are at increased risk of both initial and recurrent venous thromboembolic events. The effects of chemotherapy and other treatments compound the risk due to cancer. The interaction of tissue factor, thrombin and other coagulation factors with protease activated receptor proteins expressed by tumor cells and host vascular cells leads to the induction of genes related to angiogenesis, cell survival and cell adhesion and migration [30]. Findings of the registry support the concept that malignancy is associated with CTEPH. Although there are several kinds of malignancies that are found associated with VTE [31], CTEPH-associated cancers appear to have been survived several years prior to the diagnosis of CTEPH. Whether treatment-related factors, for example adjuvant hormone replacement therapies are also contributory cannot be clarified from this study. Yet, based on the results, pulmonary hypertension in a tumor survivor should be a signal to search for CTEPH, rather than for another etiology of pulmonary hypertension.

Study Limitations

The retrospective study design may favor the inclusion of survivors. Our sensitivity analysis (regression diagnostics according to [32]) showed that the estimates for the covariate effects are stable with exception of the odds ratio for splenectomy which is

highly dependent on a few observations and may be as low as half of its value as reported in Table 3. Furthermore, no follow-ups were obtained in the current investigation, nor medical treatments monitored. While there exists a referral bias based on the fact that participating university hospitals represent PEA centers, diagnoses were made according to international guidelines. The reported odds ratios do not truly describe the risk of CTEPH in patients with a particular medical condition, but the odds ratio of having the medical condition when compared to non-thromboembolic PH patients. Future prospective CTEPH databases are required to gain a full view over this disorder.

Conclusion

The findings of this study underscore previous work on the thromboembolic nature of CTEPH [2] by confirming an association with previous and recurrent VTE, APA/LAC and blood groups non-0. However, recent research has provided evidence suggesting that the mechanistic view of CTEPH as a disease caused by obliteration of central pulmonary arteries due to a classic thrombotic process may have been too simplistic [33, 34]. We speculate that pulmonary embolism may be followed by a pulmonary vascular remodeling process that is modified by infection [7], immune phenomena [3], and possibly by thyroid hormone replacement therapy and malignancy.

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Table 1. Diagnoses by participating centers. *pulmonary endarterectomy †collagen vascular disease; ‡congenital heart disease

Diagnosis	All patients	Vienna	Prague	Homburg
CTEPH (numbers/percentages)	(n=433)	(n=202)	(n=54)	(n=177)
Operable	282 / 65.9	117 / 59.4	39 / 72.2	130 / 73.4
Inoperable	146 / 34.1	80 / 40.6	15 / 27.8	47 / 26.6
Missing (n)	5	5	0	0
PEA* performed	248 / 57.3	94 / 46.5	39 / 72.2	115 / 65.0
PAH (n/%)	(n=254)	(n=157)	(n=41)	(n=56)
Idiopathic	118 / 46.5	79 / 50.3	27 / 65.9	12 / 21.4
Familial	4 / 1.6	2 / 1.3	0 / 0.0	2 / 3.6
Associated with				
CVD†	28 / 11.0	12 / 7.6	6 / 14.6	10 / 17.9
CHD‡	13 / 5.1	10 / 6.4	0 / 0.0	3 / 5.4
Eisenmenger	27 / 10.6	18/ 11.5	3 / 7.3	6 / 10.7
Portal hypertension	19 / 7.5	13 / 8.3	0 / 0.0	6 / 10.7
HIV	5 / 2.0	4 / 2.5	0 / 0.0	1 / 1.8
Appetite suppressants	10 / 3.9	6 / 3.8	1 / 2.4	3 / 5.4
Hereditary hemorrhagic teleangiectasia	3 / 1.1	3 / 1.9	0 / 0.0	0 / 0.0
Other non-thromboembolic precapillary PH (sarcoidosis, histiocytosis X, sleep apnea, veno-occlusive disease, hemolytic anemia)	27 / 10.6	10 / 6.3	4 / 9.8	13 / 23.2

Table 2. Clinical and hemodynamic data by diagnosis.

*mixed venous saturation; †mPAP=mean pulmonary artery pressure; ‡cardiac output; §pulmonary vascular resistance; ||venous thromboembolism; **GI=gastrointestinal

[a] indicates a $p < 0.05$; [b] indicates a $p < 0.05$ for WHO class I/II vs. III/IV

	Thromboembolic PH (n = 433)	Non-thromboembolic PH (n = 254)
Female patients[a] (n/%)	227 / 52.4	167 / 65.8
Age[a], yrs (median and range) missing (n)	58 (46, 67) 2	50.5 (37, 64) 4
Height[a], cm (mean±SD) missing (n)	170.2±9.1 72	166.6±9.2 25
Weight[a], kg (mean±SD) missing (n)	76.3±14.8 72	72.3±17.3 23
Body surface area[a], m^2 (mean±SD) missing (n)	1.89±0.21 74	1.81±0.24 26
Body mass index (median and range) missing (n)	26.0 (23.4, 28.5) 72	25.2 (22.5, 29.0) 25
WHO class[b], I / II / III / IV (n) (%) missing (n)	6 / 66 / 215 / 132 1.4 / 15.8 / 51.3 / 31.5 14	4 / 33 / 99 / 29 2.4 / 20.0 / 60.0 / 17.6 89
Time to diagnosis, months (median and quartiles) missing (n)	24 (12, 48) 170	24 (11, 56) 163
Hemodynamic data at the time of diagnosis (median, range)		
MVS*[a], % missing (n)	59.0 (52.0, 64.0) 112	66.2 (59.6, 71.6) 81
mPAP†[a], mmHg missing (n)	50 (41, 57) 70	69 (50, 94) 89
CO‡[a], L/min missing (n)	3.8 (3.2, 4.5) 55	4.1 (3.3, 5.2) 67
PVR§, $dynes.s.cm^{-5}$ missing (n)	830 (574, 1128) 18	786 (531, 1198) 59
Risk factors (number of affected patients/%) /missing/ (n)		
Previous VTE||[a] Missing (n)	280 / 69.0 27	20 / 10.6 65
Recurrent VTE||[a] Missing (n)	225 / 52.2 2	6 / 3.2 64
Malignancy[a] Breast Cancer	53 / 12.2 12	11 / 4.3 1

GI** carcinoma	9	1
Melanoma	3	0
Prostate cancer	2	3
Sarcoma	2	1
Bronchial carcinoma	3	2
Hepatocellular carcinoma	0	1
Chronic myeloid leukemia	1	1
Renal cell carcinoma	2	1
Uterus carcinoma	3	0
Ovarian cancer	1	0
Seminoma	3	0
Thymoma	1	0
Astrocytoma	1	0
Plasmocytoma	2	1
Other malignancies	8	0
Thyroid hormone replacement[a]	86 / 19.9	9 / 3.5
Ventriculo-atrial shunt[a]	12 / 2.8	0 / 0.0
Pacemaker	6 / 1.4	3 / 1.2
Infected pacemaker	4 / 0.9	0 / 0.0
Splenectomy[a]	24 / 5.5	0 / 0.0
Missing (n)	0 / 0.0	4 / 3.3
Previous leg trauma[a]	9 / 2.1	0 / 0.0
Inflammatory bowel disease	12 / 2.8	3 / 1.2
Chronic venous ulcers[a]	47 / 10.9	6 / 2.4
APA/LAC[a]	43 / 10.0	10 / 4.0
Missing (n)	2 / 0.5	1 / 0.4
Systemic lupus erythematosus[a]	0 / 0.0	8 / 3.2
Missing (n)	1 / 0.2	0 / 0.0
Arm vein thrombosis[a]	13 / 3.0	1 / 0.4
Coronary artery disease	10 / 2.3	1 / 0.4
Hemoglobin abnormalities[a]	9 / 2.1	0 / 0.0
Osteomyelofibrosis	5 / 1.2	1 / 0.4
Klippel Trenaunay syndrome	2 / 0.5	0 / 0.0
Klinefelter syndrome	0 / 0.0	0 / 0.0
Ischemic stroke	19 / 4.4	12 / 4.7
Missing (n)	3 / 0.7	0 / 0.0
COPD	8 / 1.8	8 / 3.2
Sarcoidosis	2 / 0.5	4 / 1.6

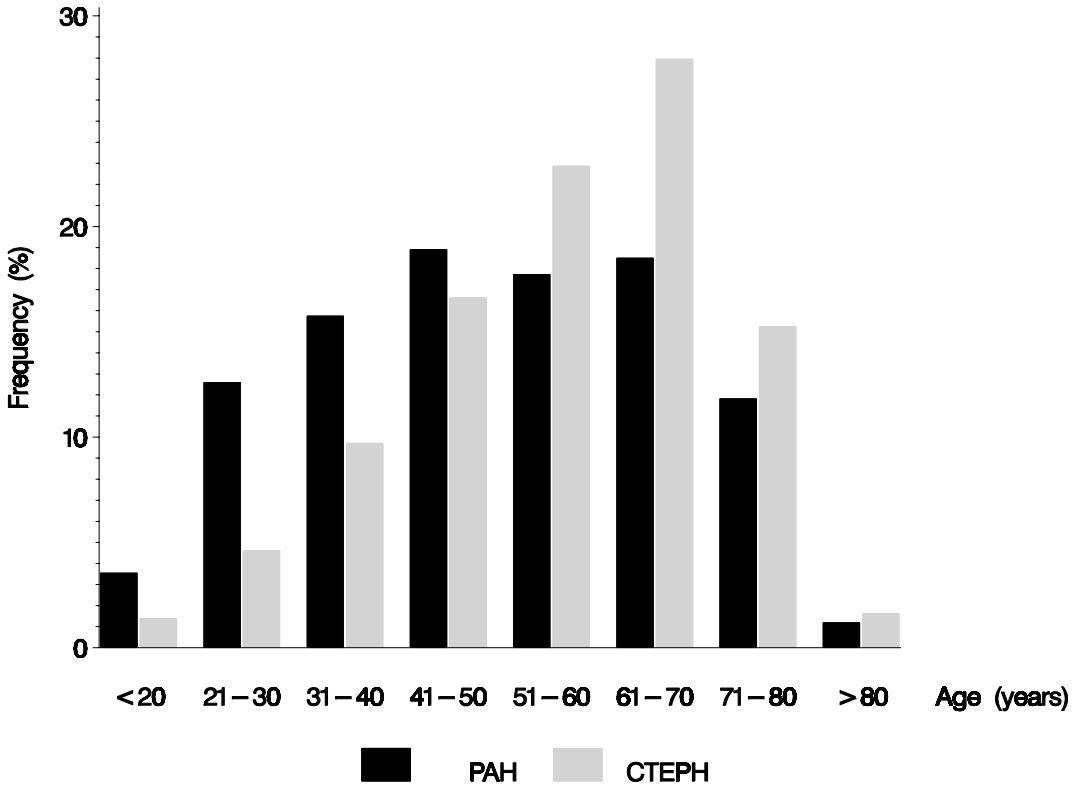
Table 3. Crude and adjusted odds ratios for the risk of CTEPH

*venous thromboembolism, †chronic obstructive pulmonary disease

	Marginal effects		**Partial effects**	
Condition	**Odds Ratios [95% CI]**	**P-Value**	**Odds Ratios [95% CI]**	**P-Value**
Thyroid hormone replacement	5.41 [2.70-12.23]	< 0.001	6.10 [2.73-15.05]	< 0.001
Malignancy	1.99 [1.01-4.26]	0.046	3.76 [1.47-10.43]	0.005
Previous VTE*	19.36 [11.66- 33.79]	< 0.001	4.52 [2.35-9.12]	< 0.001
Recurrent VTE*	45.02 [21.00-114.73]	< 0.001	14.49 [5.40-43.08]	< 0.001
Chronic venous ulcers	3.17 [1.45-8.17]	0.003	2.84 [0.99-9.00]	0.053
APA/LAC	3.28 [1.58-7.50]	0.001	4.20 [1.56-12.21]	0.004
Systemic lupus erythematosus	0.06 [0.00-0.48]	0.005	0.11 [0.00-1.21]	0.076
VA-shunt or infected pacemaker	19.49 [2.47-2520.10]	0.001	76.40 [7.67-10350.62]	< 0.001
Inflammatory bowel disease	2.21 [0.69-9.05]	0.189	3.19 [0.74-16.03]	0.121
Splenectomy	22.09 [2.97-2824.53]	< 0.001	17.87 [1.56-2438.07]	0.017
Abnormal hemoglobins	7.97 [0.98-1035.53]	0.054	0.84 [0.05-122.42]	0.916
COPD†	0.26 [0.09-0.73]	0.012	0.47 [0.12-1.70]	0.251
Osteomyelofibrosis	1.47 [0.28-14.65]	0.673	0.34 [0.02-8.48]	0.519

Figure legend

Figure 1. Age distribution of patients diagnosed with CTEPH and non-thromboembolic precapillary PH. PAH and other diagnoses were summarized as “PAH” according to the Venice classification [10]). Black bars represent PAH, grey bars represent CTEPH diagnoses.


30
20
10
0
Frequency (%)
<20
21–30
31–40
41–50
51–60
61–70
71–80
>80
Age (years)
PAH
CTEPH