**Title**

Splenectomy increases CTEPH risk and modifies clinical features of acute pulmonary embolism

**Running title**

Splenectomy in CTEPH and PE

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**Abstract**

Chronic thromboembolic pulmonary hypertension (CTEPH) is due to unresolved pulmonary embolism (PE), however why and how PE evolves into CTEPH remains unclear. Study of acute PE patients at particularly high risk of developing CTEPH may provide insight into this process. Prior studies have suggested that a history of splenectomy is a risk factor for developing CTEPH. Thus, we performed two substudies to evaluate this connection. In the first, we compared the frequency of splenectomy among groups of patients with CTEPH, PE, and no PE. In the second, we compared clinical features of PE presentation in patients hospitalized with acute PE either with or without a prior splenectomy. We find that a history of splenectomy is significantly more frequent in patients with CTEPH than in patients with PE (Odds ratio (OR) 4.3, 95% CI 1.5-12.6), and this remained when comparing to PE patients without an environmental risk factor for PE (OR for splenectomy 5.3, 95% CI 1.7-16.9), a population that is at increased risk of developing CTEPH. Patients with acute PE who had a prior splenectomy were more likely to present with subacute symptoms, and were more likely to have a distal location of PE and less likely to have deep venous thrombosis (DVT) than were non-splenectomized acute PE patients. Thus, splenectomy modifies the clinical features of acute PE. We hypothesize that the difference in clinical features of PE that are observed in the context of prior splenectomy are relevant to the increased risk of CTEPH observed in this population.

**Introduction**

Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating form of pulmonary vascular disease that results from unresolved thromboembolic material in the pulmonary arteries.1 How acute pulmonary embolism (PE) evolves into CTEPH remains unclear, impairing our ability to prevent the disease. Moreover, even though a history of PE is an important risk factor for CTEPH, approximately 25% of patients diagnosed with CTEPH have not had a previously recognized acute PE.2 This challenges the assumption that acute PE progresses to CTEPH, raising the possibility that the two conditions may represent distinct but overlapping disease processes.

Study of patients with acute PE who are at particularly high risk of developing CTEPH may inform how PE evolves to CTEPH, potentially allowing for improved treatment and preventative strategies. To that end, identification of risk factors for CTEPH is crucial. Several risk factors for CTEPH have been reported—including malignancy, hypothyroidism, certain inflammatory conditions, intravascular devices, and blood groups other than O3, 4 –however these appear to increase venous thromboembolism (VTE) risk more generally rather than being specific risk factors for CTEPH.5 However, a prior history of splenectomy may be an example of a condition that specifically associates with CTEPH risk. While ample data suggests that splenectomy increases VTE risk, 6-8 a prior cohort study and a nested case control study both suggest that splenectomy is more common among patients with CTEPH than among patients with either PE or VTE more generally.9, 10

Understanding whether and how splenectomy might confer specific risk for CTEPH may help clarify mechanisms and guide early clinical identification. In this work, we performed two separate substudies. The first was a case-control study designed to assess the association of splenectomy status with CTEPH compared to all comers with PE, a specific subpopulation of patients with PE not provoked by an environmental risk factor (which is associated with significantly increased CTEPH risk11), and controls without PE. The second substudy was designed to evaluate whether splenectomy status modifies the clinical features of a patient’s acute PE presentation.

**Methods**

Study design:

We performed two substudies. The first was a retrospective, 4-arm case-control study designed to determine the frequency of splenectomy in groups of patients with CTEPH, acute PE, acute unprovoked PE, and healthy controls. The second was a two-arm matched cohort study designed to compare clinical features of patients hospitalized with PE who either had a prior history of splenectomy or did not.

Patient selection:

In substudy 1, we defined four groups of subjects based on outcome: 1) a historical cohort of patients diagnosed with CTEPH at Intermountain Medical Center (IMC) from January 1993 to March 2022 who had a computed tomography pulmonary angiogram (CTPA) available for analysis (“CTEPH group”), 2) consecutive individuals diagnosed with acute PE by CTPA during an emergency department (ED) visit at one of two Intermountain Health hospitals (IMC and LDS Hospital) between 1/1/2009-12/31/2010 (“All PE” group), 3) consecutive patients who were hospitalized at IMC between 4/1/2014 and 4/1/2016 with acute PE, and in whom no provoking factor for acute PE could be identified on retrospective chart review (“Unprovoked PE” group), and 4) consecutive patients with no lifetime history of VTE (defined by a negative index CTPA and no historical diagnosis code for DVT or PE) who underwent CTPA in the ED at IMC or LDS Hospital between 1/1/2009 and 12/31/2010 and in whom the CTPA was read as negative for PE (“No PE” group). We included the “Unprovoked PE” group because PE that is not associated with a provoking risk factor is specifically associated with CTEPH.11 The following conditions were considered environmental risk factors for PE, and the absence of all of these defined unprovoked PE: malignancy (either active at the time of the PE or diagnosed within 6 months after PE diagnosis), estrogen or testosterone therapy, pregnancy up to three months post-partum, surgery requiring general anesthesia in the three months prior to PE diagnosis, or trauma or medical illness requiring immobilization for ≥ 3 days in the 3 months prior to PE diagnosis.

In substudy 2, we defined two groups of subjects who were diagnosed with acute PE (based on ICD code) and had an associated inpatient hospitalization at IMC based on whether or not they had a history of splenectomy preceding the PE diagnosis. The splenectomy group was identified via an enterprise data warehouse (EDW) search of patients with a diagnosis code for acute PE and the occurrence of the term “splenectomy” (identified by natural language processing) in their chart prior to first use of the PE ICD code, from the years 2003-2021. For the non-splenectomy cohort for substudy 2 we randomly selected subjects from the above-mentioned group of patients who were admitted to IMC with a PE diagnosis between 4/1/2014 and 3/31/2016, and in whom the presence of a spleen could be confirmed on review of CTPA images.

Statistics:

In substudy 1, the unadjusted association of the binary exposure (splenectomy), with the outcome (group membership) was evaluated with the Chi-square test and strength of association was summarized using the odds ratio. No adjusted analysis was performed due to insufficient power given low rates of splenectomy in each arm. Within the CTEPH group, characteristics of patients with and without splenectomy were compared by chi-square test (for binary variables) and Wilcoxen rank-sum test (for continuous variables). No correction for multiple hypothesis testing was performed in this exploratory analysis and a p-value < 0.05 was considered statistically significant.

In substudy 2, we compared clinical features of PE presentation between the groups of subjects hospitalized for PE based on splenectomy status. We analyzed clot burden using the Qanadli scoring system,12 as well as clot location (proximal versus distal). These analyses were performed by two reviewers (MWD and DW) who independently analyzed subjects' CTPA images. Inter-rater agreement was assessed using Cohen’s Kappa. PE was defined as proximal if either reviewer identified the most proximal portion of clot in a lobar or more central pulmonary artery (PA), and distal if both reviewers identified the most proximal portion of clot in a segmental or subsegmental vessel. Because the presence or absence of the spleen can be easily determined by review of CTPA images, the reviewers were not blinded to splenectomy status. Pulmonary artery (PA) diameter and right ventricle to left ventricle (RV/LV) ratio were also measured on the index CTPA (by DW) using previously described methods.13, 14 PA enlargement was defined by PA diameter >27mm in females and > 29mm in males. Admit location, hospital length of stay (LOS) and ICU LOS were determined through manual chart review. PESI score was determined by review of the admission H&P and/or ED notes and vitals documented at admission. DVT workup within two weeks of PE diagnosis and presence of DVT was determined by review of admission notes and ultrasound results documented in the EMR.

As in substudy 1, unadjusted comparisons were performed using chi-squared test (binary) and Wilcoxen rank-sum tests. Additionally, logistic (for proximal versus distal PE location) and Poisson (for Qanadli score) regressions were used to summarize the adjusted strength of association with splenectomy after accounting for age, sex, and body mass index (BMI), which were a-priori hypothesized to be confounders.

Ethics:

This retrospective study was approved by the Institutional Review Board (IRB) at IMC under a waiver of informed consent.

**Results**

Substudy 1: Frequency of splenectomy in CTEPH and control subjects

The CTEPH group comprised 179 patients, the “All PE” group 333 patients, the “Unprovoked PE” group 326 patients, and the “No PE” group 839 patients (Figure 1). The demographic, clinical, and hemodynamic data for subjects in the CTEPH group are shown in Table 1. The median age at CTEPH diagnosis was 66 years (IQR 53-72 years). Approximately ¾ of patients in the CTEPH group had been diagnosed with acute PE prior to their diagnosis with CTEPH. The median age at PE diagnosis was 56 years (IQR 42-69 years) in the “All PE” group and 64 years (IQR 52-79 years) in the “Unprovoked PE” group.

A higher frequency of splenectomy was observed in the CTEPH group (6.1%) than in the “No PE” group (0.8%, p<0.00001), the “All PE” group (1.5%, p=0.004), or the “Unprovoked PE” group (1.2%, p=0.002). The odds ratio for splenectomy for patients in the CTEPH group relative to the “No PE” group was 7.8 (95% CI 3.0-20.4), and relative to the “All PE” and “Unprovoked PE” groups was 4.3 (95% CI 1.5-12.6) and 5.3 (1.7-16.9), respectively (Table 2).

In the CTEPH, “All PE”, and “Unprovoked PE” groups most splenectomies were performed due to trauma or were performed incidentally during other abdominal surgical procedures (Supplementary Table S1). When comparing the age at splenectomy among the 11 splenectomized CTEPH patients and the 9 splenectomized PE patients (from the two PE groups combined), CTEPH patients were numerically younger (median age 28 years, IQR 19-43 years) at the time of splenectomy than were PE patients (median age 44 years, IQR 37-49), however this did not reach statistical significance (p=0.13). Among splenectomized CTEPH patients, the median elapsed time from splenectomy to CTEPH diagnosis was 28 years (IQR 12-42 years), whereas among PE patients the medial elapsed time from splenectomy to index PE diagnosis was 13 years (IQR 10-24 years).

In an exploratory analysis, clinical and hemodynamic parameters were compared between CTEPH subjects with versus without a history of splenectomy. No significant differences were observed between these two subgroups in any of the parameters studied, aside from there being a significantly higher cardiac output in CTEPH patients with a history of splenectomy than those without (Supplementary Table S2).

Substudy 2: Clinical features of PE in patients with and without prior splenectomy

The search for patients with a diagnosis code for PE in the context of prior splenectomy yielded 134 potential subjects. Among these, 73 were excluded because CTPA images were not available (and thus splenectomy status and PE diagnosis could not be confirmed), and 11 were excluded because their PE diagnosis was not in the context of an inpatient admission. This left 40 subjects with a PE diagnosis linked to an inpatient admission in the context of a prior history of splenectomy. As a comparison group, we randomly selected 100 patients from the parent group from which the “Unprovoked PE” group in substudy 1 was drawn, who had an inpatient admission for PE without a prior history of splenectomy. Demographic characteristics of these two groups are shown in Table 3. The average age at index PE diagnosis was lower in the splenectomy group, otherwise the groups were similar demographically.

Key clinical characteristics of the PE with and without prior splenectomy groups are shown in Table 4. There were no significant differences in PE severity index (PESI) scores, biomarker (troponin, BNP) levels, PA diameter, or RV/LV ratio in patients hospitalized with PE with or without prior splenectomy. Patients with splenectomy were more likely to present with longer symptom duration (defined as symptoms for ≥ 2 weeks at the time of presentation) and were less likely to have DVT identified during their PE presentation (Table 4).

After adjusting for age, sex, and BMI, patients with prior splenectomy were more likely to have distal PE (Figure 2), although the association was not seen in the unadjusted analysis (Table 4). Clot burden as assessed by Qanadli score was similar in both groups (Table 4). There was high inter-rater agreement between proximal vs. distal assessments (Kappa = 0.71), and excellent agreement in clot burden assessment (Kappa = 0.95 for Qanadli score) between the two reviewers. Two of 40 (5%) subjects in the splenectomy group were subsequently diagnosed with CTEPH, vs. 0 of 100 (0%) in the no splenectomy group.

**Discussion**

In this pair of substudies, we show that the odds of a prior splenectomy are higher in patients with CTEPH than in patients with acute PE, and that patients with splenectomy often have unique features of their PE presentations (prolonged symptoms prior to PE diagnosis, less DVT, more distal PE location). Together, these findings suggest that a prior history of splenectomy may predispose to CTEPH through separate mechanisms than solely raising clot risk.

In substudy 1, we demonstrate that a history of splenectomy is observed more frequently in patients with CTEPH than in comparable patients with a history of acute PE—whether all comers with acute PE, or the subset of acute PE patients with PE not provoked by an environmental risk factor, who appear to be at a particularly increased risk of developing CTEPH.11 While prior work has shown that splenectomy is a risk factor for VTE,6-8 our results suggest that splenectomy increases the risk of CTEPH beyond the risk conferred on VTE. Our work corroborates and extends findings from earlier studies. Several studies have reported an increased frequency of splenectomy in patients with CTEPH compared to patients with non-thromboembolic forms of pulmonary hypertension,4, 15 or acute PE.9 Our work demonstrates that even compared to patients with unprovoked PE, splenectomy is much more common in patients with CTEPH. This is an important finding given that a history of unprovoked PE is an important risk factor for CTEPH,11 and that a significant majority of patients with CTEPH have a history of unprovoked PE.5

In substudy 2, we have demonstrated for the first time that splenectomy modifies the PE phenotype. Patients with a prior history of splenectomy are more likely to present with subacute PE symptoms, less likely to have DVT present, and are more likely to have a distal location of PE. We speculate that these features may be relevant for the development of CTEPH. Symptom duration >2 weeks at the time of PE presentation has independently been identified as a risk factor for subsequent development of CTEPH.11 This could be explained by data suggesting that many patients with acute PE who are subsequently diagnosed with CTEPH already had features of CTEPH present at the time of their acute PE presentation.16 Thus, splenectomy may increase the likelihood that CTEPH was already present at the patient’s index PE presentation. Alternatively, splenectomy may contribute to subacute PE presentations via different mechanisms. The decreased frequency of DVT among splenectomized patients with PE suggests that VTE might originate in sites distinct from the deep veins of the extremities in some patients with splenectomy. Perhaps this predisposes to recurrent small volume VTE events, or even in situ thrombosis in the pulmonary arteries, which may lead to subclinical symptoms that accumulate over time and thus predispose to a subacute presentation. It is notable that we have found that although splenectomized patients with PE are more likely to have distally located PE, the overall clot burden (based on the Qanadli score, which measures the total number of segmental PAs that are affected by clot) is similar between splenectomized and non-splenectomized patients with PE. Perhaps recurrent small volume VTE events only become symptomatic once a threshold of PA involvement is surpassed.

Several prior registry studies have consistently reported that CTEPH patients with a history of splenectomy are less likely to have operable disease than those without a history of splenectomy.2, 17, 18 Although these studies did not report specifically whether inoperable disease in CTEPH patients with splenectomy was due to chronic thromboembolic disease being located in more distal pulmonary arteries, distal disease is overall the most common reason for a patient to be judged inoperable.2 Thus, it is likely that CTEPH patients with splenectomy have more distal disease than non-splenectomized comparators. Our results demonstrate that the same is observed with acute PE. Thus, splenectomy status appears to promote more distal disease both in the setting of acute PE and in CTEPH.

Prior work has demonstrated that patients who have undergone splenectomy demonstrate an increase in circulating platelet-derived microparticles.19-21 These particles exert a strong prothrombotic effect22 mediated in part by their enrichment with the anionic phospholipid phosphatidylserine.23 Interestingly, chronic thromboembolic lesions removed during pulmonary thromboendarterectomy surgery in patients with CTEPH who have had a prior splenectomy are likewise enriched in phosphatidylserine.24 This suggests that the increase in circulating platelet-derived microparticles may contribute to the unresolved thromboembolism that occurs in splenectomized CTEPH patients, providing one potential mechanism for how splenectomy might contribute directly to CTEPH risk.

The main weaknesses of our study include the racial homogeneity of the population, which may limit the generalizability of the findings. CT reviewers also could not be blinded to splenectomy status when assessing clot location and burden in substudy 2, since the spleen is easily visualized on the upper abdominal images from a standard CTPA. Additionally, our subject groups were drawn from slightly different base populations for logistical purposes, which may affect the comparability of the groups. We also had limitations to the data available to us in for the subjects in substudy 1, which limited our ability to characterize the groups (for example, we did not have access to age or BMI for the “No PE” group in substudy 1, so could not control for these variables in analyzing the frequency of splenectomy.

In conclusion, this study demonstrates a significantly higher frequency of splenectomy in patients with CTEPH as compared to patients with acute PE or no VTE and also establishes that there are important phenotypic differences between patients with PE who have had a prior splenectomy versus those who have not. We propose that the unique features of PE presentation in splenectomized patients contribute to CTEPH risk, suggesting that splenectomy influences CTEPH risk beyond its effect on increasing VTE risk. This work establishes that splenectomized patients are a subpopulation of particular interest, further study of which may better inform how PE evolves into CTEPH, paving the way for better treatment and preventative strategies.

Figure 1. Consort diagram outlining the patient groups identified for the two substudies.

A screenshot of a diagram

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Table 1. Clinical and hemodynamic data for patients in the CTEPH group.

|  |  |
| --- | --- |
|  |  |
|  | **CTEPH group** |
| N | 179 |
| Age in years at diagnosis with CTEPH, median (IQR) | 66 (53-72) |
| PE diagnosis preceding diagnosis with CTEPH (%) | 76.5 |
| Female (%) | 48.3 |
| Caucasian (%) | 94.4 |
| WHO functional class at diagnosis with CTEPH, median (IQR) | 3 (2-3) |
| 6 minute walk distance at diagnosis with CTEPH in meters, median (IQR) | 393 (307-459) |
| Hemodynamics at diagnosis with CTEPH   * mPAP in mmHg, median (IQR) * PCWP in mmHg, median (IQR) * Cardiac output in L/min, median (IQR) * PVR in Wood units, median (IQR) | 41 (34-51)  11 (9-15)  4.4 (3.8-5.3)  6.9 (4.1-9.8) |
| Status post PTE surgery (%) | 56.7 |
| Status post BPA (%) | 2.2 |

Table 2. Frequency of splenectomy in the CTEPH, no PE, All PE, and Unprovoked PE groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  | **CTEPH** | **No PE** | **All PE** | **Unprovoked PE** |
| Total n in cohort | 179 | 839 | 333 | 326 |
| N with splenectomy | 11 | 7 | 5 | 4 |
| % with splenectomy | 6.1 | 0.8 | 1.5 | 1.2 |
| Odds ratios (95% CI)     - relative to no PE group     - relative to all PE group     - relative to unprovoked PE group | 7.8 (3.0-20.4)  4.3 (1.5-12.6)  5.3 (1.7-16.9) | 1  0.6 (0.2-1.8)  0.7 (0.2-2.3) | 1.8 (0.6-5.8)  1  1.2 (0.3-4.6) | 1.5 (0.4-5.1)  0.8 (0.2-3.1)  1 |

Table 3. Demographics and clinical characteristics of patients with and without prior splenectomy hospitalized for PE.

|  |  |  |  |
| --- | --- | --- | --- |
|  | | | |
|  | **No Splenectomy** | **Splenectomy** | **p-value** |
| N | 100 | 40 | - |
| Age in years at index PE, median (IQR) | 61 (52-73) | 56 (41-66) | 0.013 |
| Female (%) | 52 | 65 | 0.16 |
| Caucasian (%) | 93 | 100 | 0.086 |
| Body Mass Index (BMI), median (IQR) | 31.1 (26.3-36.5) | 28.8 (25.3-37.7) | 0.64 |
| Time from splenectomy to PE in years, median (IQR) | - | 6.6 (0.2-19.1) | - |
| Admit Location |  |  | 0.54 |
| ICU (%) | 19 | 12 |  |
| Rehab (%) | 1 | 2 |  |
| Ward (%) | 80 | 85 |  |
| Hospital length of stay in days, median (IQR) | 4 (3-6) | 4 (2-7) | 0.74 |
| ICU length of stay in days, median (IQR) | 0 (0-0) | 0 (0-0) | 0.84 |

Table 4. Key clinical characteristics of PE presentation between the splenectomy and no splenectomy groups.

|  |  |  |  |
| --- | --- | --- | --- |
|  | No Splenectomy | Splenectomy | p-value |
| N | 100 | 40 |  |
| PE severity index (PESI) score, median (IQR) | 97 (75-120) | 89 (66-111) | 0.097 |
| PA Enlargement (%) | 71 | 68 | 0.68 |
| RV/LV ratio, median (IQR) | 1.07 (0.88-1.31) | 1.07 (0.94-1.35) | 0.31 |
| RV/LV ratio > 1 (%) | 55 | 70 | 0.10 |
| Highest troponin, median (IQR) | 0.01 (0.01-0.08) | 0.01 (0.01-0.03) | 0.067 |
| Highest BNP, median (IQR) | 62 (18-306) | 49 (24-110) | 0.70 |
| Distal PE (%) | 37 | 52 | 0.093 |
| Qanadli Score, average (IQR) | 0.22 (0.08-0.48) | 0.13 (0.06-0.34) | 0.32 |
| Duration of Symptoms ≥ 2 weeks (%) | 8 | 20 | **0.044** |
| DVT workup performed (%) | 68 | 57 | 0.24 |
| DVT identified (%) | 71 | 35 | **0.002** |

Figure 2: Logistic regression comparing odds of distal PE (defined as located in segmental or more distal pulmonary arteries) based on clinical risk factors.

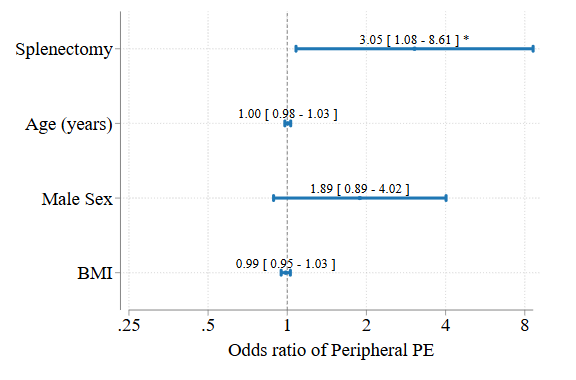


Table S1. Indication for splenectomy in all splenectomized patients in the CTEPH and PE groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient | Indication for splenectomy | Age at splenectomy | Age at diagnosis with CTEPH/index PE/index CTPA1 | Age at first PE diagnosis |
| CTEPH group | |  |  |  |
| 1  2  3  4  5  6  7  8  9  10  11 | Splenic vein thrombosis  Trauma  ITP  Trauma  Trauma  Resected with ovarian tumor  Benign tumor  ITP  Trauma  Benign splenomegaly  Trauma | 53  18  73  22  12  31  28  12  19  45  40 | 60  63  78  68  41  49  45  40  68  49  78 | na2  61  60  65  40  46  45  na2  68  40  74 |
| All PE group | |  |  |  |
| 1  2  3  4  5 | Resected with pancreatic tumor  ITP  Trauma  Trauma  Resected with liposarcoma | 44  33  40  44  56 | 52  43  64  89  59 | 52  41  64  89  59 |
| Unprovoked PE group | |  |  |  |
| 1  2  3  4 | During hiatal hernia repair  During staging laparotomy  Trauma  Autoimmune hemolytic anemia | 76  22  37  49 | 86  61  57  62 | 86  57  57  62 |

1 Age at initial CTEPH diagnosis for patients in the CTEPH group and age at index PE diagnosis for patients in the all PE and unprovoked PE groups. 2 Patient was not diagnosed with acute PE prior to CTEPH diagnosis.

Table S2. Comparison of clinical and hemodynamic parameters for CTEPH patients with and without a history of splenectomy.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
|  | **No splenectomy** | **History of splenectomy** | **p-value** |
| N | 168 | 11 |  |
| Age in years at diagnosis with CTEPH, median (IQR) | 66 (53-72) | 60 (47-68) | 0.51 |
| Female (%) | 48.8 | 36.4 | 0.42 |
| PE diagnosis preceding diagnosis with CTEPH (%) | 76.2 | 81.8 | 0.67 |
| History of DVT (%) | 53.0 | 54.5 | 0.92 |
| WHO functional, median (IQR) | 3 (2-3) | 2 (2-3) | 0.25 |
| 6 minute walk distance in meters, median (IQR) | 391 (306-460) | 404 (335-454) | 0.87 |
| Hemodynamics at diagnosis with CTEPH   * mPAP in mmHg, median (IQR) * PCWP in mmHg, median (IQR) * Cardiac output in L/min, median (IQR) * PVR in Wood units, median (IQR) | 41 (34-51)  11 (9-15)  4.4 (3.7-5.2)  7.0 (4.3-9.9) | 38 (33-43)  10 (10-14)  5.3 (4.4-6.3)  4.7 (3.6-7.5) | 0.36  0.87  0.02  0.18 |
| Status post PTE surgery (%) | 56.5 | 54.5 | 0.90 |

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