**Introduction**

Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating form of pulmonary vascular disease, the pathogenesis of which remains unclear (1). While a history of acute pulmonary embolism (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 they may be distinct but overlapping disease processes. A better understanding of how genetic and environmental risk factors for acute PE and CTEPH differ would shed light on this question.

Most studies that have examined risk factors for CTEPH have compared patients with CTEPH to either healthy controls or patients with non-thromboembolic forms of pulmonary hypertension. In these studies, conditions that associate with venous thromboembolism (VTE)—including malignancy, hypothyroidism, certain inflammatory conditions, intravascular devices, and blood groups other than O—clearly associate with CTEPH (3, 4). However when comparing patients with CTEPH to those with a history of acute PE who did not develop CTEPH, these conditions are equally frequent (5), suggesting that these conditions increase thrombosis risk generally, but do not specifically increase CTEPH risk.

In contrast, a history of splenectomy may predispose to CTEPH risk in excess of the risk conferred on VTE more generally. A history of splenectomy confers a risk for VTE that is increased 2-3 fold compared to non-splenectomized individuals splenectomy (6-8), and evidence suggests that splenectomy is more frequent in patients with CTEPH than those with PE (9) or venous thromboembolism (VTE) more generally (10).

Understanding whether and how splenectomy might confer specific risk for CTEPH may help clarify mechanisms and guide early clinical identification. To better understand the association of splenectomy with CTEPH, we first compared the frequency of splenectomy in patients with CTEPH versus those with acute PE or no history of VTE. We then evaluated clinical features of PE presentations stratified by splenectomy status, theorizing that splenectomy may modify a patient’s PE presentation such that the odds of a subsequent diagnosis of CTEPH are increased.

**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 179 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) 333 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) 326 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) 839 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).

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. This search yielded 134 patients. Among these, we excluded those in whom CTPA images were not available (n=73), since we were unable to objectively confirm splenectomy status and PE diagnosis in these cases. We also excluded 11 patients who were diagnosed with PE on an outpatient basis, leaving 40 subjects with a PE diagnosis linked to an inpatient admission in the context of a prior history of splenectomy.

For the non-splenectomy cohort for substudy 2 we randomly selected 100 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 (16), as well as clot location (peripheral or central). PE was defined as central 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. These analyses were performed by two reviewers (MWD and DW) who independently analyzed subjects' CTPA images. There was high inter-rater agreement between central vs. peripheral assessments (Kappa = 0.71), and excellent agreement in clot burden assessment (Kappa = 0.95 for Qanadli score) between the two reviewers. 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, Pulmonary Artery to Ascending Aorta (PA/AA) ratio, and Right ventricle to left ventricle (RV/LV) ratio were also measured on the index CTPA. PA and AA measurements were performed using methods previously described by our group and others (17). RV to LV ratio were measured (by reviewer DW) using methods described in the American Journal of Roentgenology (18).

   Admit location, hospital length of stay and ICU length of stay were determined through manual chart review. PESI score was determined by review of the admission H&P and/or ED notes and vitals documentation at admission. DVT workup and presence of DVT was determined by review of admission notes and ultrasound results documented in the EMR. DVT workup was considered positive if DVT was found in any extremity by ultrasound and only those patients who had workup were considered for calculating the percentage positive.

Like substudy 1, unadjusted comparisons were also performed using chi-squared test (binary) and Wilcoxen rank-sum tests. Additionally, logistic (for peripheral vs central PE location) and Poisson (for Qanadli score, which represents the proportion of subsegments occluded by clot) regressions were used to summarize the adjusted strength of association with splenectomy after accounting for Age, Sex, and 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:

Add a paragraph on the numbers of patients enrolled in each substudy and reference (Figure 1)

The demographic, clinical, and hemodynamic data for the 179 subjects in the CTEPH group are shown in Table 1. Approximately ¾ of patients in the CTEPH group had been diagnosed with acute PE prior to their diagnosis with CTEPH. The All-PE group was comprised of 333 patients who had a median age at index PE diagnosis of 56 years (IQR 42-69 years), while the Unprovoked-PE group was comprised of 326 patients with a median age at index PE diagnosis of 64 years (IQR 52-79).

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 Data). When comparing the age at splenectomy among the 11 splenectomized CTEPH patients and the 9 splenectomized PE patients (from the two PE groups combined), there was a trend to towards a younger age at splenectomy among CTEPH patients (median 28 years, IQR 19-43 years) compared to PE patients (median 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 Data).

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

Add a paragraph on the numbers of patients enrolled in each substudy and reference (Figure 1) and cover inter-rater agreement. 40 patients with a PE diagnosis linked to an inpatient hospitalization in the context of a prior history of splenectomy and 100 patients hospitalized with PE who had not had a prior splenectomy were identified. Characteristics of these two groups are shown in Table 5. The average age at index PE diagnosis was lower in the splenectomy group, otherwise the groups were similar demographically.

Key clinical characteristics of the two groups are shown in Table 6. 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 PE. Although PA/AA ratio was more frequently abnormal (defined as >0.9) in patients without splenectomy, this may not have biological significance given that PA diameters were not different. 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 6).

Patients with prior splenectomy had higher adjusted odds of peripheral PE than patients without splenectomy (odds ratio 3.1, 95% CI 1.1-8.6; Figure 1) after controlling for age, sex, and BMI However, a statistically significant difference had not been seen in unadjusted analyses (Table 6) despite a trend towards the same result.  Age, sex and BMI did not show independent significant difference in odds ratio of Peripheral PE.   Overall clot burden as assessed by Qanadli score was not different between the two groups (Table 6).

There was no difference in PA diameter, PA:AA ratio or Qanadli score between the two groups when performing similar logistic regression controlling for age, sex and BMI.  (see supplementary materials.)  2 of the 40 (5%) splenectomy patients were eventually diagnosed with CTEPH. 0 of the 100 (0%) non-splenectomy patients have been diagnosed with CTEPH.

**Discussion**

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. Our findings that while splenectomy is an established risk factor for VTE (6-8), it may be a stronger risk factor for CTEPH.

In substudy 2, we analyzed clinical features of PE presentations based on splenectomy status to explore why splenectomy might associate with CTEPH more strongly that it associates with acute PE. Notably, we found that patients with splenectomy were more likely to present with prolonged symptoms (defined as > 2 weeks). PE symptom duration > 2 weeks has been associated with an increased risk of subsequent CTEPH development (11). This may be because patients with prolonged symptoms at PE presentation are actually presenting with CTEPH rather than acute PE, or could reflect that subacute PE which has already been present in the pulmonary arteries for more than 2 weeks prior to initiating anticoagulation has already started to organize and is thus less likely to resolve with anticoagulant therapy.

Patients with PE in the context of prior splenectomy were also less likely to have DVT identified, and more likely to have a more distal clot location Combined with the longer symptom duration at presentation, several hypotheses are suggested. First, patients with PE in the context of splenectomy may have an increased tendency toward multiple small-volume embolic events that accumulate over time (as opposed to one larger embolic event that causes sudden onset symptoms). Second, PEs that occur after splenectomy may be less likely to originate in the deep veins of the extremities, and more likely to originate elsewhere (for example, smaller more superficial veins), which could help predispose to recurrent small volume thromboembolic events to the pulmonary arteries.

***A physiologic reason for the findings we report may have to do with specific prothrombotic effects of splenectomy. Thrombi excised from patients with CTEPH have been found to have increased anionic phospholipids and increased circulating mircroparticles were also been reported following splenectomy in mice models. (14) Anionic phospholipids on circulating microparticles may bind to coagulation factors and also lead to damage to red blood cell membranes causing free hemoglobin release. This free hemoglobin can then scavenge nitric oxide and this may also release arginase I into the bloodstream which competes with endothelial NO synthetase for arginine and reduces arginines availability for NO synthesis. These and other mechanisms were described in a 2016 review (15).***

Our data also suggests a trend towards a younger age at splenectomy among patients with CTEPH compared to those with acute PE who did not develop CTEPH. This suggests that CTEPH risk after splenectomy may increase with accumulated years since the splenectomy. Because a younger age at splenectomy would lead to more post-splenectomy years lived, lifetime risk of CTEPH may be increased. More study into the age at splenectomy and subsequent CTEPH risk is warranted.

Although others have reported that CTEPH patients with a history of splenectomy were less likely to have undergone PTE surgery (2, 12, 13), we found no difference in the frequency of PTE surgery between splenectomized vs non-splenectomized CTEPH patients in our cohort. This discrepancy may reflect the smaller size of the CTEPH cohort in our study compared to prior studies, which left a small number of splenectomized CTEPH patients available for comparison. Indeed, the more distal location of PE in splenectomized subjects in our study would provide biologic rationale for why CTEPH patients with splenectomy may have an increased frequency of inoperability.

Weaknesses of our study is that it was retrospective in nature. Also, due to the nature of reading and measuring from CT scans for each patient, the analysis of splenectomized patient's clot charactersistics could not be blinded as splenectomy status was visible from the imaging.  This may introduce bias to the reviewers regarding clot location, and signs of RV strain. The population studied was predominantly white due to the demographics of the location where the study was performed.  This could theoretically affect generalizability however we are aware of no contribution of race to the dynamics of thrombosis in this situation.  We also had a high number of cases without imaging in the splenectomy group so a large number of patients were not able to be studied. This gave us lower power for our analyses than we had originally predicted.    We also did not have correction for multiple hypothesis testing in our substudy 2 and these results will need to be confirmed in additional cohorts to ensure that random chance is not playing a role.

Future research could include a more prospective evaluation of patients with splenectomy and PE. If differing clinical characteristics were consistently identified relating to the risks for CTEPH and PE in splenectomized patients, then new treatment or prevention avenues might be pursued.   Identification of patients with splenectomy and PE at time of diagnosis could allow for better capture of echocardiographic and laboratory measures as well as further followup screening towards development of CTEPH.  Further understanding the mechanisms in clotting in this group could be useful in understanding and predicting the risks for the development of CTEPH.

In conclusion, this study demonstrated a significantly higher frequency of splenectomy in patients with CTEPH as compared to patients acute PE or no VTE. We also find that patients with splenectomy and PE such as peripheral clot formation, longer duration of symptoms, and lack of associated DVT.  Together, these findings suggest splenectomy may have a particular associated with CTEPH and unique mechanism that predispose to CTEPH development.

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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, PE, and no 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.

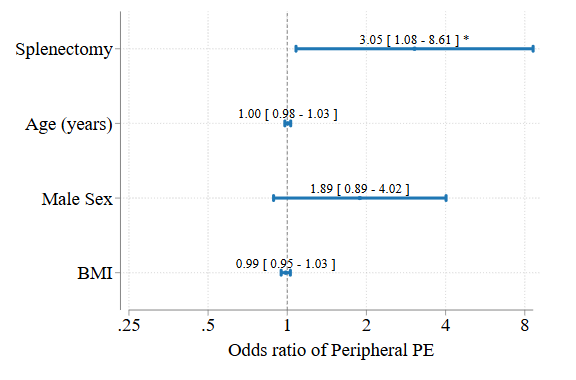
|  |  |  |  |
| --- | --- | --- | --- |
|  | | | |
|  | **No Splenectomy** | **Splenectomy** | **p-value** |
| N | 100 | 40 | - |
| Age at index PE | 61 (52,73) | 56 (41,66) | 0.013 |
| Male Sex | 48% (48) | 35% (14) | 0.16 |
| White Race | 93% (93) | 100% (40) | 0.086 |
| Body Mass Index (BMI) | 31.1 (26.3,36.5) | 28.8 (25.3,37.7) | 0.64 |
| Years between Splenectomy and PE | - | 6.6 (0.2,19.1) | - |
| Admit Location |  |  | 0.54 |
| ICU | 19% (19) | 12% (5) |  |
| Rehab | 1% (1) | 2% (1) |  |
| Ward | 80% (80) | 85% (34) |  |
| Hospital length of stay | 4 (3,6) | 4 (2,7) | 0.74 |
| ICU length of stay | 0 (0,0) | 0 (0,0) | 0.84 |

Data are presented as median (IQR) for continuous measures and %(n) for categorical measures. WIlcoxon Rank-sum used for continuous measures.  Chi-Square for categorical measures.

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) | 97 (75,120) | 89 (66,111) | 0.097 |
| PA Enlargement (CT) | 71% (71) | 68% (27) | 0.68 |
| PA:AA ratio abnormal (> 0.9 CT) | 71% (71) | 52% (21) | **0.037** |
| RV to LV ratio (CT) | 1.07 (0.88,1.31) | 1.07 (0.94,1.35) | 0.31 |
| RV to LV ratio abnormal (>1 by CT) | 55% (55) | 70% (28) | 0.10 |
| Troponin (max) | 0.01 (0.01,0.08) | 0.01 (0.01,0.03) | 0.067 |
| BNP (max) | 62 (18,306) | 49 (24,110) | 0.70 |
| Peripheral PE | 37% (37) | 52% (21) | 0.093 |
| Qanadli Score (Avg) | 0.22 (0.08,0.48) | 0.13 (0.06,0.34) | 0.32 |
| Duration of Symptoms ≥ 2 weeks | 8% (8) | 20% (8) | **0.044** |
| DVT workup (within 2 weeks) | 68% (68) | 57% (23) | 0.24 |
| DVT found | 71% (48) | 35% (8) | **0.002** |

Data are presented as median (IQR) for continuous measures and %(n) for categorical measures.  WIlcoxon Rank-sum used for continuous measures and Chi-Square for categorical measures.  PA enlargement defined as PA measured >27mm in females and > 29mm in males.   RV = Right ventricle.  LV = Left ventricle.  RVSP= Right ventricular systolic pressure.  DVT= Deep venous thrombus.  BNP = Brain natriuretic peptide.

  
Figure 1: Logistic Regression  comparing peripheral and central PE between substudy 2 groups

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