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Association between splenectomy and chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis

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ABSTRACT

Objective Whether splenectomy increases the risk of chronic thromboembolic pulmonary hypertension (CTEPH) remains unclear. We conducted a systematic review and meta-analysis to explore the association between splenectomy and CTEPH.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase and Cochrane Library databases.

Methods Two authors independently searched and extracted the data. The Newcastle-Ottawa Scale and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used to assess the quality of the included studies, and each quality item was graded as low risk or high risk. A random-effects model was used to calculate different effective values.

Results In total, 8 trials involving 6183 participants fulfilled the inclusion criteria. The overall pooled crude prevalence of splenectomy was 4.0% (95% CI 0.03 to 0.06, I^2=71.5%, p<0.001) in patients with CTEPH. Subgroup analysis showed a statistically significant high incidence of splenectomy in patients with CTEPH (OR=2.94, 95% CI 1.62 to 5.33, I^2=0.0%, p<0.001) compared with patients with pulmonary arterial hypertension. There was a significantly high incidence of splenectomy in patients with CTEPH (OR=5.59, 95% CI 2.12 to 14.74, I^2=0.0%, p<0.001) compared with patients with thromboembolism disease (venous thromboembolism or pulmonary embolism).

Conclusion The prevalence of splenectomy in patients with CTEPH was 4.0% and CTEPH might be associated with splenectomy. However, high-quality prospective trials are needed.

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Strengths and limitations of this study

- This systematic review focuses on the prevalence of splenectomy and also evaluates the association of splenectomy in patients with chronic thromboembolic pulmonary hypertension compared with patients with pulmonary arterial hypertension or thromboembolism disease.
- Absence of evident publication bias increases the reliability of our findings.
- The trials included were not randomised controlled trials and the sample size was small.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease of pulmonary artery obstruction and non-obstructive pulmonary artery remodelling as a consequence of pulmonary artery thromboembolism, which eventually leads to right heart failure and death.[1] CTEPH, a well-known long-lasting complication of acute pulmonary thromboembolism associated with poor thrombus resolution and altered pulmonary artery haemodynamics,[2] is considered a postpulmonary embolism syndrome.[3] In long-term follow-up, the mortality of CTEPH was high, and with increases in pulmonary artery pressure the mortality rate gradually increases.[4] Lupus anticoagulant and antiphospholipid antibodies and coagulation factor VIII have been associated with CTEPH.[5 6]

Splenectomy can also increase the incidence of venous thromboembolism.[7] The 2018 Cologne Consensus Conference mentioned that an interplay between splenectomy and several factors is shown to promote transformation of pulmonary embolism into a fibrotic vascular occlusion.[8] Previous studies reported that 2.1%–8.6% of patients with CTEPH had undergone splenectomy.[9 10] Another study showed that the incidence of splenectomy in patients with CTEPH was similar to that in patients with idiopathic pulmonary arterial hypertension (IPAH).[11] Based on these findings, it is difficult to determine the relationship between splenectomy and CTEPH. Therefore, this systematic review and meta-analysis was conducted to confirm whether splenectomy increased the risk of CTEPH.

METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12–14] AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) was used to assess the methodological quality of this systematic review and meta-analysis.[15 16] This study was registered in PROSPERO (International Prospective Register of Systematic Reviews).

Search strategy

PubMed, Cochrane Library and Embase databases were searched from database inception to 7 April 2019 using the keywords splenectomy, splenectomies, hypertension, pulmonary, pulmonary hypertension and chronic thromboembolic pulmonary hypertension to identify all potentially eligible trials. No language restrictions were imposed. The reference lists of articles relevant to the topic were hand-searched to identify other potentially relevant articles. The specific search strategies are reported in online supplemental appendix 1.

Study selection

Trials that enrolled patients diagnosed with CTEPH and reported any splenectomy profile were selected, as well as trials that reported the prevalence of splenectomy in patients with CTEPH. The exclusion criteria were conference abstracts, reviews, case reports, animal trials, letters and other unrelated topics and trials that contained duplicate data.

Quality assessment

Two authors independently assessed the risk of bias in the non-randomised studies using the Newcastle-Ottawa Scale, which assesses sample representativeness and size, and assessed the representativeness of cases compared with the control group, the comparability between CTEPH and the control group, the ascertainment of splenectomy and the thoroughness of descriptive statistics reporting. Studies with scores of less than 3 points were judged as having a high risk of bias and those with more than 3 points as low risk of bias. The risk of bias in the observational studies was assessed using an adapted version of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[17] Twenty-two items were evaluated to reveal the strengths and weaknesses of the trials to facilitate rational interpretation and application of trial results. The third author resolved disagreements.

Data extraction

Two authors independently extracted the following information from each trial: lead author, publication year, country of origin, study type, sample size, patient characteristics, patient type in the control group, the OR of splenectomy and the prevalence of splenectomy. Disagreements were resolved by the third author.

The primary outcome was the prevalence estimates of splenectomy. The secondary outcome was the ORs of splenectomy. All eight trials reported the prevalence of splenectomy and five trials reported the ORs of splenectomy.

Statistical analysis

A meta-analysis was performed to calculate the OR and 95% CI of the dichotomous outcome data. The prevalence of splenectomy was also calculated. Forest plots showed the individual studies and the meta-analysis estimates.[18] A random-effects model was used to pool the data and evaluate the statistical heterogeneity between the summary data using the I^2 statistics. In this meta-analysis, an I^2 >50% indicated a significant heterogeneity between studies.[19]

Sensitivity analysis was performed to determine the influence of each trial on the association of splenectomy with CTEPH compared with the control group.

To evaluate whether the association between splenectomy and CTEPH was changed when compared with different control groups, subgroup analyses were performed based on different control groups. The control groups were PAH or thromboembolism disease (venous thromboembolism or pulmonary embolism). Publication bias was assessed by examining funnel plots and by Egger test.[20 21]

Review Manager V.5.3 (Nordic Cochrane Centre, The Cochrane Collaboration) and Stata V.13.0 were used to analyse the data. P<0.05 indicated a statistically significant difference.

Patient and public involvement

Patients and the public were not involved in this review.

RESULTS

Study identification and selection

By the search strategy, 422 potentially eligible records were identified when duplicate trials were excluded. The titles and abstracts of the identified records were screened for inclusion. After excluding conference abstracts, reviews, case reports, animal trials, letters and other unrelated topics, the full text of 21 trials was reviewed. Finally, 8 trials[6 9–11 22–25] involving a total of 6183 patients were included in the meta-analysis (figure 1).

Patient characteristics of the included trials are reported in table 1. The included trials were mostly retrospective studies. The majority of patients included were from Europe and there was an equal distribution between genders. All trials reported the prevalence of splenectomy in patients with CTEPH, but three observational studies[23–25] did not report the incidence of splenectomy between the CTEPH group and the PAH or thromboembolism disease (venous thromboembolism or pulmonary embolism) group, so only the prevalence of splenectomy in patients with CTEPH was included. Only two trials reported the causes of splenectomies.[9 23]

The Newcastle-Ottawa Scale score components for the five individual trials are shown in table 1. One trial[22] was of

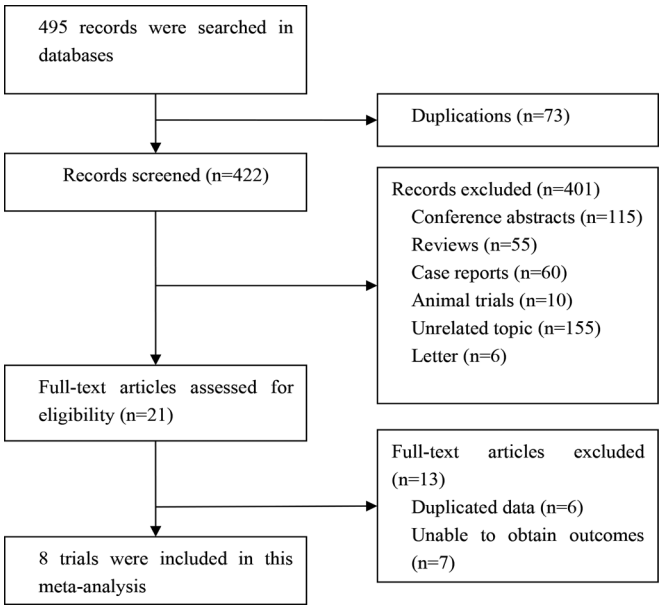

Figure 1 Flow chart of study search and selection process.

low quality and four[6 9–11] were of high quality. The STROBE scores of the three individual trials ranged from 17[23 25] to 18[24] (table 1), but no trials described any efforts to address potential sources of bias. Furthermore, two trials did not clearly define the variables,[23 24] two trials failed to report other analyses such as subgroup or sensitivity analysis,[23 25] and two trials did not report the source of funding.[23 25]

Prevalence of splenectomy in CTEPH

The pooled crude prevalence of splenectomy in patients with CTEPH from the eight trials was 4.0% (95% CI 0.03 to 0.06, I^2=71.5%, p<0.001) (figure 2). The prevalence reported by the individual trials ranged from 2.0% to 9.0%.

Sensitivity analysis of this study excluded each serially repeated trial and showed that no individual trial significantly affected the overall prevalence of splenectomy in patients with CTEPH (online supplemental eTable 1).

Comparison of incidence of splenectomy among patients with CTEPH, PAH and thromboembolism disease

Five trials compared the incidence of splenectomy in patients with CTEPH with that in patients with PAH or thromboembolism disease. As shown in figure 3, the subgroup analysis showed a statistically significant high incidence of splenectomy in patients with CTEPH (OR=2.94, 95% CI 1.62 to 5.33, I^2=0.0%, p<0.001) compared with patients with PAH. There was also a significantly high incidence of splenectomy in patients with CTEPH (OR=5.59, 95% CI 2.12 to 14.74, I^2=0.0%, p<0.001) compared with patients with thromboembolism disease.

A sensitivity analysis was performed to assess the weight of each trial. Sensitivity analysis in this meta-analysis excluded each serially repeated trial and showed that no individual trial significantly affected the overall incidence of splenectomy in patients with CTEPH and patients with PAH or thromboembolism disease (online supplemental eTable 2).

Table 1 Characteristics of included studies

Number	Author	Year	Location	Study type	Patients (n)	Age (years)	Proportion of women (%)	BMI (kg/m^2)		NOS scores	STROBE scores
					CTEPH/control	CTEPH/control	CTEPH/control	CTEPH/control	Control		
1	Jaïs *et al*[9]	2005	France	Case–control study	257/276	51.0/46.0	47.4/60.0	–	IPAH	6	–
2	Bonderman *et al*[6]	2009	Europe	Retrospective cohort study	433/254	58.0/50.5	52.4/65.8	26.0/25.2	PAH	7	–
3	Martinez *et al*[10]	2018	England	Cohort study	283/2356	–	54.1/51.7	–	VTE	6	–
4	Lang *et al*[11]	2013	Europe	Case–control study	436/158	65.0/59.0	49.3/66.5	–	IPAH	6	–
5	Coquoz *et al*[22]	2018	Switzerland	Cohort study	4/504	47.0/61.3	75.0/46.4	33.0/28.0	PE	3	–
6	Pepke-Zaba *et al*[24]	2011	Europe and Canada	Observational study	679/–	63.0/–	49.9/–	–	–	–	18
7	Bohacekova *et al*[25]	2016	Slovakia	Observational study	81/–	60.5/–	37.0/–	27.4/–	–	–	17
8	Condliffe *et al*[23]	2009	UK	Observational study	469/–	–	–	–	–	–	17

BMI, body mass index; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; NOS, Newcastle-Ottawa Scale; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; VTE, venous thromboembolism.

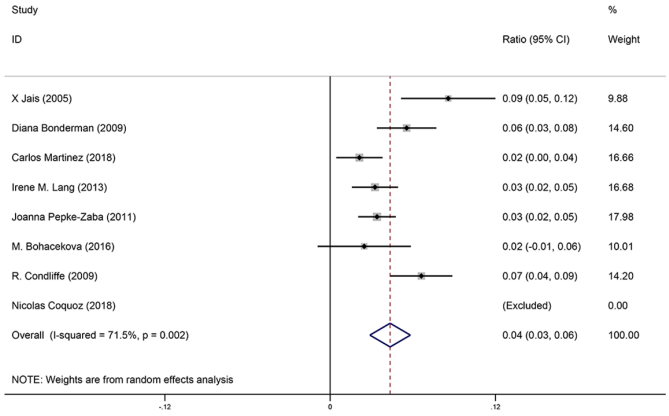

Figure 2 Forest plot with meta-analysis of the prevalence and 95% CI of splenectomy in patients with chronic thromboembolic pulmonary hypertension in the assessed studies.

Publication bias

No significant asymmetry was apparent by visual inspection of the funnel plot of studies reporting on splenectomies (figure 4). The Egger test did not show significant publication bias (p=0.52).

DISCUSSION

The results of this systematic review and meta-analysis showed a statistically significant high incidence of splenectomies in patients with CTEPH compared with patients with PAH or thromboembolism disease. It showed that splenectomy could be significantly associated with CTEPH. The pooled prevalence of patients with CTEPH with splenectomies was 4.0%. Sensitivity analysis showed that no individual trial significantly affected the overall incidence.

The prerequisite for CTEPH may be both in situ thrombosis and embolism.[26] Patients undergoing splenectomy may have significant enrichment of anion phospholipids[26] and platelet-derived microparticles (MP).[27] These MPs contribute to thrombus formation by acting as procoagulants

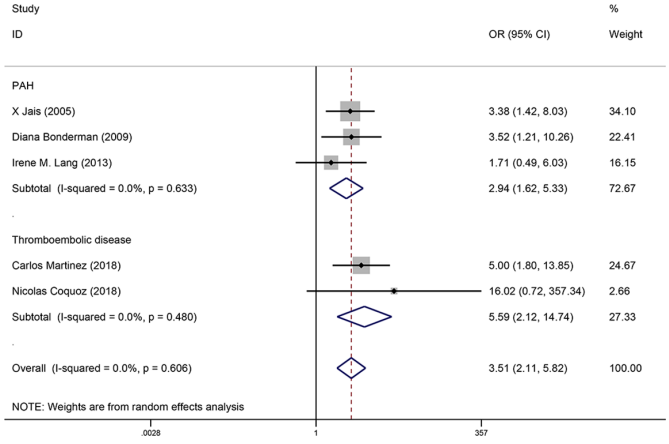

Figure 3 Forest plot with meta-analysis of the association of splenectomy between chronic thromboembolic pulmonary hypertension, pulmonary arterial hypertension (PAH) and thromboembolism disease.

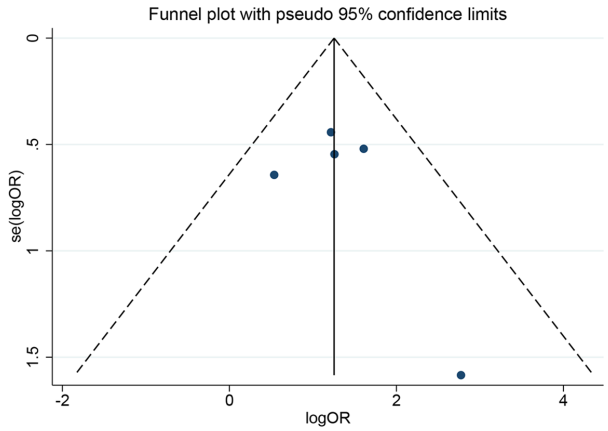

Figure 4 Funnel plot to assess publication bias.

by providing a negatively charged surface for the assembly of coagulation proteases.[28] Erythrocyte membrane components have been reported to have an effect on venous thromboembolic diseases.[29 30] The number of red blood cells with altered phosphatidylserine expression was increased 20-fold after splenectomies in patients with thalassaemia.[29] These cells are also procoagulant phenotypic markers that accelerate thrombin formation. Also, the loss of splenic filtration will result in the retention of abnormal red blood cells in the peripheral circulation after splenectomy, leading to activation of the coagulation cascade, even in the absence of chronic haemolysis.

Therefore, we suggest that the development of thrombotic complications in patients undergoing splenectomy should be monitored closely by routine ECG and/or echocardiography.[31] Splenectomised patients who present with exertional dyspnoea, ECG with right ventricular overload, and right heart enlargement and/or elevated pulmonary arterial pressure by echocardiography should be referred to the centre of pulmonary hypertension for further assessment.[31]

In conclusion, this study found that the prevalence of splenectomy in CTEPH was 4.0% and that CTEPH was associated with splenectomy. High-quality prospective trials are needed to further explore the (causal) relationship between CTEPH and splenectomy.

Limitations

First, the trials included were not randomised controlled trials and had small sample sizes, which might cause bias. Second, trauma is the main indication for splenectomy, and surgery after a traumatic abdominal injury may be a relevant factor in thromboembolism. Therefore, trauma and surgery may have caused substantial heterogeneity in this study. However, there was not enough information to explore these factors further. Third, many haematological disorders responsible for splenectomy are confounding factors for CTEPH, but there was insufficient information for subgroup analysis.

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Contributors LZ and PY analysed patient data and were major contributors to the preparation of the manuscript. SW and KY analysed part of patient data. XZ and YB performed the literature search and extracted the data. XC was responsible for statistical analysis. LL made substantial contributions to the conception of the study. MZ and YC drafted the manuscript. All authors have read and approved the final version of this manuscript.

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