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Prevalence of antiphospholipid (aPL) antibodies among patients with chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis

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Abstract
How thrombophilia may contribute to the development of chronic thromboembolic pulmonary hypertension (CTEPH) is unknown. We searched on PubMed and EMBASE (until 15 April 2018), studies on CTEPH reporting data on inherited or acquired thrombophilia. Starting from 367 articles mentioning the search terms, 347 were excluded mainly as duplicate articles or articles not in English. After reading the full text of remaining articles, ten were excluded for being reviews, editorials, letters or case reports, and two were further removed from the analysis because of the potential selection bias. All the eight considered studies provided the proportion of patients positive for antiphospholipid (aPL) antibodies. The crude rate of aPL in CTPEH patients is 11.8% (95% CI 10.09–13.8%). The meta-analysis considering the weighted mean proportion and 95% confidence intervals (CIs) yields a rate of aPL antibody-positive profile of 12.06% (95% CI 8.12–16.65%) among the patients with CTEPH in the random effects model (I^2 76.33%; 95% CI 52.75–88.14%, $p = 0.0001$). The sensibility analysis confirms the result. No predictors of heterogeneity are found in a meta-regression analysis. Our results suggest that aPL antibodies are frequently associated with CTEPH underlining the need to test for aPL antibodies in young patients with "idiopathic" and "provoked" PE caused by mild provoking risk factors.

Keywords Inherited thrombophilia · Antiphospholipid antibodies · Chronic thromboembolic pulmonary hypertension

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is an uncommon disease characterized by intraluminal thrombus organization and fibrous stenosis or complete obliteration of pulmonary arteries [1]. Accepted criteria for the diagnosis of CTEPH are the presence of an elevated mean pulmonary artery pressure (≥ 25 mmHg) and the presence of at least one segmental perfusion defect despite 3 months of anticoagulation therapy [2]. The disease is notoriously underdiagnosed, and the true prevalence is still unclear [3, 4].

CTEPH is caused by the obstruction of pulmonary arteries as a consequence of acute or recurrent pulmonary emboli, in situ thrombosis of pulmonary arteries or small-vessel pulmonary arteriopathy [5]. Clots are yellow, highly adherent to the pulmonary vascular wall, and contain collagen, elastin, inflammatory cells, and recanalized vessels [6]. Risk factors for CTEPH [4] include previous pulmonary embolism (PE), younger age at PE diagnosis, and unprovoked PE. A large prospective international CTEPH registry has reported that 75% of the included patients have a history of acute PE [7]. Other risk factors for the development of CTEPH have also been identified, such as patients with ABO blood groups other than O, human leukocyte antigen polymorphisms, or abnormal endogenous fibrinolysis, chronic inflammatory disorders, myeloproliferative syndromes, the presence of a ventricular-atrial shunt, as well as splenectomy [8].

Thrombophilia is defined as a predisposition to form clots inappropriately due to abnormalities in blood composition, blood flow, or the vascular wall. The predisposition to form

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clots can arise from genetic factors, acquired changes in the clotting mechanism, or an interaction between genetic and acquired factors [9]. Genetic risk factors for venous thromboembolism include deficiency in natural inhibitor of blood coagulation (antithrombin, protein C, and protein S) and variant of factor V and prothrombin (factor V Leiden, prothrombin G20210A). Among acquired risk factors, antiphospholipid antibodies (aPL antibodies) are the most relevant [10]. Known inherited thrombophilias are estimated to explain only a small percentage (~5%) of the genetic risk for VTE [11]. According to limited publication, not all the aforementioned factors have been clearly linked with CTEPH, and the role of thrombophilia is not well recognized [12, 13]. The aim of this study is to ascertain whether thrombophilia may explain at least in part, the development of CTEPH, and if testing for thrombophilia should be encouraged when the discontinuation of anticoagulation is programmed after an episode of PE.

Methods

This systematic review was conducted using a pre-specified protocol and following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [14].

Search strategy

Two investigators (CYC and YXZ) searched PubMed, EMBASE, web of science, and COCHRANE without language restriction for studies reporting thrombophilia results in CTEPH patients until 15 April 2018. We used the following search terms as text words or MeSh: "Pulmonary artery", "Pulmonary Embolism", "Pulmonary Hypertension", "Chronic", and "thrombophilia". Reference lists of included articles and those relevant to the topic were handsearched for the identification of additional, potentially relevant articles.

Study selection and eligibility criteria

Selection criteria were pre-specified before data collection. To assess the effect estimate for a potential association between thrombophilia in CTEPH patients, we selected studies that fulfill the following inclusion criteria: studies that included CTEPH patients (all types) and reported any congenital or any aPL antibody profile. To decrease the risk of bias, case report or non-English studies or unpublished abstracts were excluded. Two authors (CYC and YXZ) extracted data using a standardized spreadsheet. Starting from 367 articles (PubMed = 181, EMBASE = 142, web of science = 38, and COCHRANE = 7) mentioning the search terms, 347 were excluded for reason depicted in Fig. 1. After reading the full text of remaining 20 articles, 12 were excluded for the following reasons: reviews, editorials, letters, case reports, sub-studies, and data with potential selection bias. Finally, eight studies were included in the meta-analysis for aPL and six when assessing the Factor V Leiden and Prothrombin G20210A variant; two Asiatic populations were excluded with these genetic variants almost absent in these populations.

The search strategy, the methodological aspects, and the data presentation comply with the PRISMA statement [15].

Statistics

Available data on hereditary thrombophilia were compiled, and described as percentage of results with confidence intervals. All the eight considered studies reported data on acquired thrombophilia expressed as percentage of positive results. Potential publication bias was assessed with the Egger test, and represented graphically with Begg's funnel plot of the proportion of the outcome event versus its standard error. We assessed heterogeneity among studies with the use of the I^2 statistics. A random effects meta-analysis model was used assuming that the estimated effects in the different studies are not identical. Additional sensitivity analyses were implemented using a "one-study removed analysis." Meta-regression models were formed to explore heterogeneity as a result of changes in practice over time and to evaluate the effect of age and other potential (or reasonable) risk factors (or confounders) on outcomes.

Results

Overall, 367 studies were screened. Of these, 20 were assessed for eligibility and 8 were included in the final analysis (Fig. 1). Patient characteristics and the rate of congenital and acquired thrombophilia are shown in Table 1. The included population consisted of generally young patients, with an equal distribution between genders. Of the eight studies, two did not report data on congenital thrombophilia, one reported partial results, while the rest reported all the relevant data.

Rates of Factor V Leiden and Prothrombin variant are reported in three and two studies, respectively, while all the studies report data on aPL antibodies. The cumulative proportion and 95% confidence intervals of hereditary and acquired thrombophilia are shown in Table 2. The rate of antithrombin, protein C, and protein S deficiencies is higher in CTEPH patients as compared to those with acute PE. On the other hand, the rate of Factor V Leiden mutation and Prothrombin variant is lower in CTEPH with respect to acute PE patients. A crude evaluation of the aPL antibodies in the

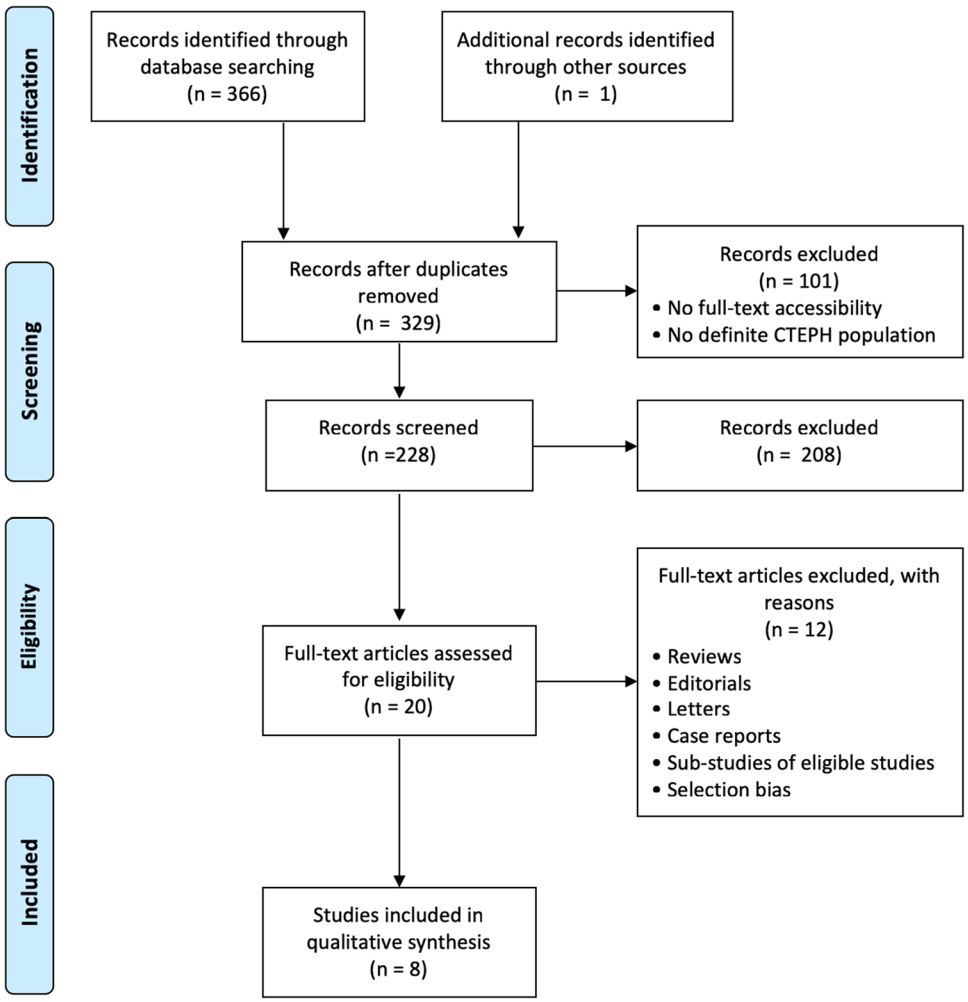


Fig. 1 Search strategy (according to PRISMA statement [15])

Table 1 Characteristics of the included articles

	First author, year (Refs)	N	F	Age	AT	Pr C	Pr S	F V Leiden	PT variant	aPL antibodies
1	So Young Park 2016 [16]	134	58	58 ± 16[†]	9 (6.7%)	8 (6%)	6 (4.5%)	–	–	7/134 (5.2%)[e]
2	Pepke-Zaba 2011 [7]	426	–	63 (51–72)[††]	3 (0.7%)	38 (8.9%)	41 (9.6%)	33 (7.7%)	15/426 (3.5%)	43/426 (10.1%)[a]
3	D'Armini 2010 [17]	204	84	–	–	–	–	–	–	28/184 (15.2%)[e]
4	Wong 2010 [18]	45	–	55 (18–92)[‡]	2 (4.4%)	0	0	9/31 (29%)	3/31 (9.7%)	1/40 (2.5%)[b]
5	Sompradeekul S 2010 [19]	14	9	55 (28–79)[‡]	–	1 (7.1%)	1 (7.1%)	–	–	2/14 (14.3%)[e]
6	Wolf 2000 [20]	116	57	54 ± 14	0/46	1/46 (2.2%)	0/46	3/46 (6.5%)	1/46 (2.2%)	25/116 (21.5%)[c]
7	Auger 1995 [21]	216	–	–	–	–	–	–	–	23/216 (10.6%)[d]
8	Simonneau 1995 [22]	72	54	52 ± 15	1/47 (2.1%)	3/39 (7.7%)	0/39	–	–	9/38 (23.6%)[d]

AT, PrC, and PrS denote antithrombin, protein C, and protein S, respectively

–, not reported

[†]Mean ± SD; [††]range (interquartile range); [‡]range (minimum–maximum)

[a]LAC or aPL; [b]LAC = 0; [c]16/79 were reported positive for LAC, 25/116 positive for aPL; [d]all LAC positive; [e]aPL test type not reported

eight studies shows a higher prevalence among the CTEPH patients (11.8%, 95% CI 10.09–13.8%) as compared to the general population and to the population of patients with PE (Table 2).

To assess the feasibility of a meta-analysis on the studies reporting aPL antibodies, a funnel plot to check for the existence of publication bias was first created. The funnel plot did not show significant publication bias (Fig. 2), thus,

Table 2 The prevalence of thrombophilia among general population, pulmonary embolism, and CTEPH

	General Caucasian population, %	PE, %	CTEPH, % (95% CI)[a]
Antithrombin deficiency	0.02–0.05 [23, 24]	0.66 [25]	1.22 (0.74–2.00)
Protein C deficiency	0.02–0.05 [26]	0.66 [25]	4.54 (3.47–5.92)
Protein S deficiency	0.01–1 [26]	0.33 [25]	4.27 (3.24–5.62)
Factor V Leiden	3–7 [26]	8.6 [26]	5.69 (4.28–7.53)
Prothrombin variant	1–3 [26]	5.3 [26]	0.5 (0.2–1.3)
aPL antibodies	0.04 [27]	8.3 [25]	11.8 (10.09–13.8)

[a]Rates for Factor V Leiden and Prothrombin variant were calculated from six studies (see "Study selection and eligibility criteria"); crude rates are provided for aPL antibodies

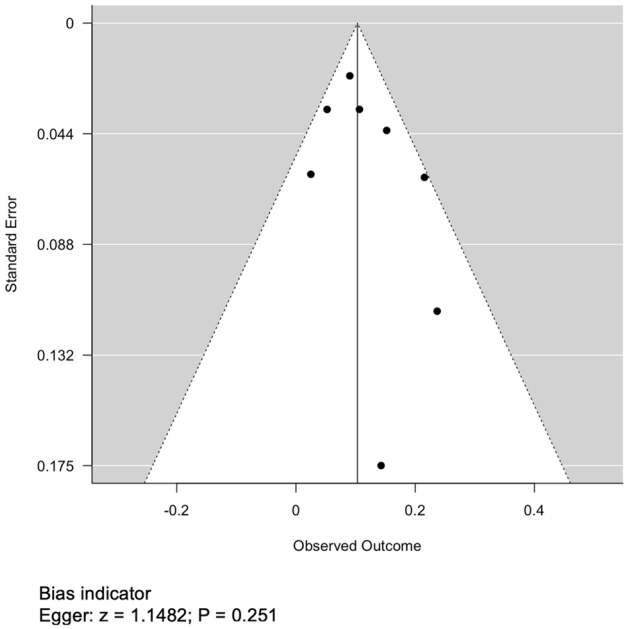
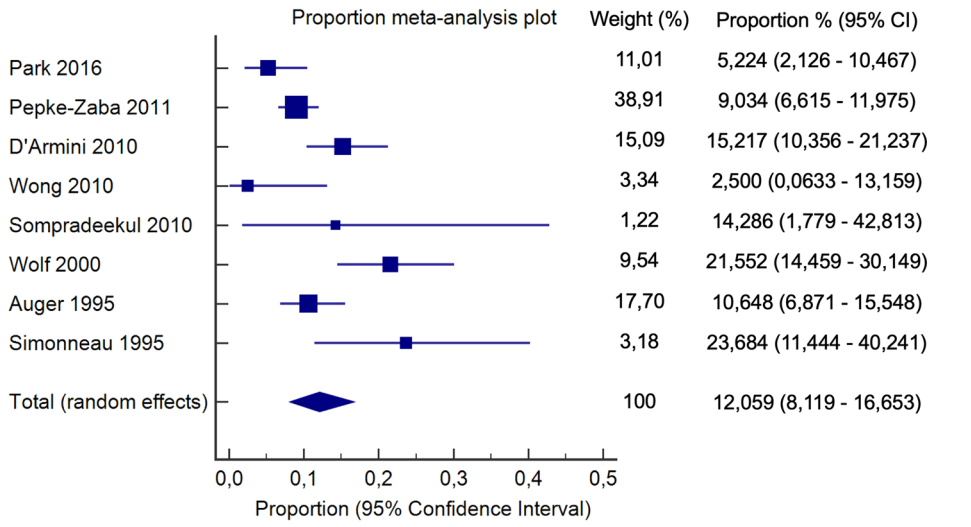


Fig. 2 Bias assessment funnel plot

we proceeded with the meta-analysis of the available data. Results showed a significant heterogeneity among the studies (I^2 76.33%; 95% CI 52.75–88.14%, $p = 0.0001$), consequently a random effect model was chosen. Figure 3 shows the proportion and 95% CI of positive aPL patients in the final analysis (12.06%, 95% CI 8.12–16.65%). The result is not far from that calculated in the crude analysis. The one study removed sensitivity analysis is shown in Fig. 4. This analysis reveals that the relation between aPL and CTEPH is still present when the study with the largest weight (Pepke-Zaba [7]) is removed from the analysis (rate of aPL 12.76%, 95% CI 7.81–18.70%).

A meta-regression analysis was performed to investigate the effects of potential heterogeneity factors on aPL rates in patients with CTEPH. Reasons of heterogeneity weighted by the sample size for each study included the mean age of patients, the year of publication (before and after 2006, year of publication of the latest guidelines on diagnosis of APS [28]), rate of patients undergoing pulmonary thromboarterectomy (PEA), and the type of aPL test performed (LAC versus other tests). Meta-regression shows no statistically

Fig. 3 Forest plot representing the prevalence and 95% CI of aPL in patients with CTEPH in the assessed studies



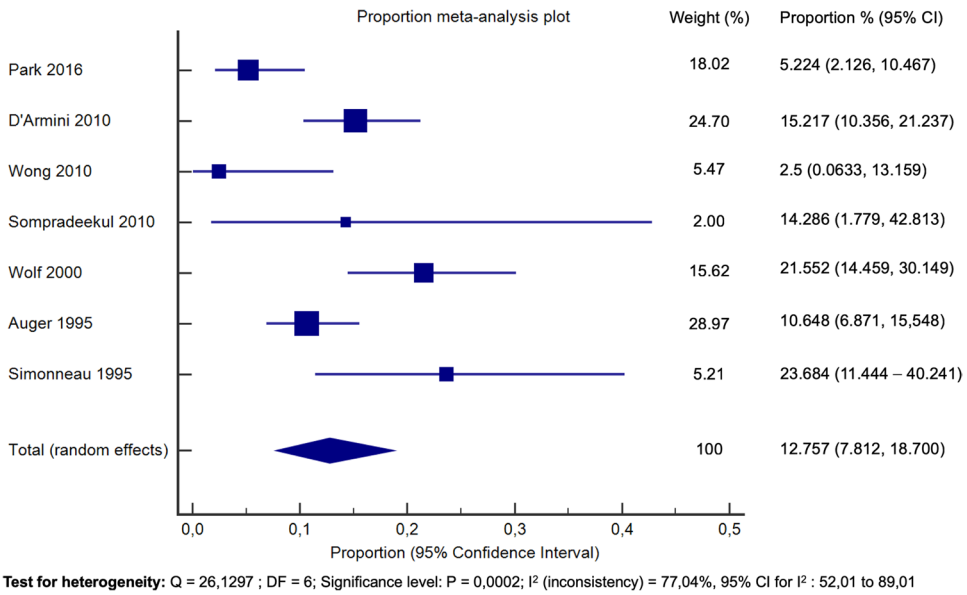


Fig. 4 The one study removed sensitivity analysis (the study with the largest weight [7] was removed)

significant association between the assessed variables (mean age: meta-regression coefficient = − 0.036, $p = 0.927$; year of publication: meta-regression coefficient = 0.322, $p = 0.952$; PEA: meta-regression coefficient = − 1.762, $p = 0.708$; type of aPL test: meta-regression coefficient = 1.1434, $p = 0.696$).

Discussion

In this systematic review, we assess the rate of thrombophilia in patients with CTEPH. The point estimate of all the individual studies reveals a high rate of aPL positivity in patients with CTEPH. This is in line with previous findings that antiphospholipid syndrome (APS) is frequently associated with VTE recurrences [29–32].

A thorough review of the literature suggests that aPL antibodies are associated with pulmonary hypertension [33], and specifically associated with CTEPH [34]. The largest series so far reports that almost 15% of CTEPH patients are positive for at least one thrombophilia factor, with LAC being the most prevalent [35]. The combination of more than one test exploring the presence of aPL antibodies poses the patient at particularly high risk of recurrence. Due to the temporal heterogeneity of the data, none of the studies report results of all three tests exploring aPL antibodies. However, when reported [20], LAC is associated with positivity of another aPL test (mostly aCL antibodies), thus, outlining a group of high-risk patients.

We also find hereditary thrombophilia to be more represented among patients with CTEPH as opposed to those with PE. Specifically, a higher rate of antithrombin and protein C and protein S deficiencies is observed in patients with CTEPH. Previous studies show that antithrombin deficiency is an independent risk factor for VTE recurrence [36], while protein C deficiency increases the risk of CTEPH [37]. However, the figures on the rate of Protein C and Protein S deficiency should be taken with caution, as many of these patients might have been in oral vitamin K antagonist treatment. On the other hand, the rate of Factor V Leiden mutation is lower in CTEPH patients. This is in line with the Factor V Leiden paradox [38, 39], where this mutation is hypothesized to pose a higher risk for deep-vein thrombosis (DVT) than for pulmonary embolism. Lang et al. [40] do not find an increased prevalence of the Factor V Leiden (FVL) mutation in chronic major vessel thromboembolic pulmonary hypertension (CTEPH). Due to the geographic distribution of FVL, in our analysis, we purposely excluded the data from the two Asian studies. Apparently, also the rate of Prothrombin variant is lower in the CTEPH patients, but data are not sufficient to draw any conclusion.

This study has some limitations. Data on thrombophilia are often incomplete in the reported studies. Moreover, the methods for their determination as well as the cutoff values for positivity are either not reported or may differ from the conventional cutoff threshold commonly utilized in traditional assays. Besides, due to temporal extension of the included studies, there are methodological differences in the aPL assays. Another potential drawback on the acquired thrombophilia is that when authors do not report of aPL positivity after 12 weeks to exclude the presence of transient aPL antibodies.

The contribution of thrombophilia as a risk factor for CTEPH is not well established. Clearly, some thrombophilia risk factors pose a higher risk than others do. In this meta-analysis of the data from the literature, we find that APS is possibly the most important thrombophilia risk factor for

CTEPH. Our findings have important clinical implications. Antiphospholipid antibodies should be sought in young patients with "idiopathic" PE and "provoked" PE caused by mild provoking risk factors (e.g., estroprogestinic drugs). Hereditary thrombophilia should only be checked in young patients with family history of VTE. Moreover, the high rate of protein C and S deficiencies may be biased by VKA treatment, therefore, these defects should be sought before the beginning or after stopping the anticoagulant treatment. Additionally, aPL detection during oral anticoagulant treatment should be performed according to the guidelines [41]. The presence of a combination of more than one aPL test (especially triple positivity) might be an important predictor of recurrence, and should raise awareness about anticoagulation prolongation.

In conclusion, present evidence suggests that aPL antibodies seem to be the most prevalent thrombophilia risk factor in patients with CTEPH although their causative role should be evaluated in prospective studies of patients with PE.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statements on human and animal rights The procedures followed in this study are in accordance with the ethical standards and to our knowledge, no unethical study was included in the meta-analysis. Aggregate data (meta-analyses) are likely to have the same objectives as the original studies.

Informed consent There is no particular ethical problem regarding the original informed consent of patients.

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