Original Article

# Incidence and risk factors of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a systematic review and meta-analysis of cohort studies

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**Background:** The incidence and risk factors of chronic thromboembolic pulmonary hypertension (CTEPH) after acute pulmonary embolism (PE) were still controversial. A systematic review and meta-analysis was conducted to assess the incidence and risk factors of CTEPH after acute PE.

**Methods:** Embase, Medline, China National Knowledge Infrastructure, Wanfang databases, and various reference lists were searched to identify studies published up to May 2018. Only cohort studies that used right heart catheterization for CTEPH diagnosis were included. The study quality was assessed using the Newcastle-Ottawa Scale (NOS). All analyses were conducted with the meta package in R software (3.2.2).

**Results:** Fifteen studies met the inclusion criteria. The overall incidence of CTEPH after acute PE, with a median follow-up from 6 to 94.3 months, was 3.13% (95% CI: 2.11–4.63%). The incidence of studies from China [4.46% (95% CI: 1.68–11.32%)] was slightly higher than from Europe [2.82% (95% CI: 1.82–4.34%)]. However, there was no significant difference between these two groups (P=0.39). Subgroup analyses of confirmed diagnostic method showed that compared studies using right heart catheterization [3.25% (95% CI: 2.12–4.97%)], studies using right heart catheterization combined with bundled tests tended to yield a similar data [2.40% (95% CI: 0.97–5.81%), P=0.54]. Previous/recurrent PE or previous VTE, idiopathic PE and right heart dysfunction were considered as risk factors of CTEPH in patients with a previous PE.

**Conclusions:** CTEPH is not a rare complication of acute PE. Close follow-up and implementation of a comprehensive screening program are important, especially in patients with independent risk factors.

**Keywords:** Chronic thromboembolic pulmonary hypertension (CTEPH); pulmonary embolism (PE); incidence; meta-analysis

Submitted Dec 07, 2017. Accepted for publication Jul 12, 2018.
doi: 10.21037/jtd.2018.07.106
**View this article at:** http://dx.doi.org/10.21037/jtd.2018.07.106

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## Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition with a considerable morbidity and mortality. It is commonly believed that CTEPH is the result of a long-term complication of pulmonary embolism (PE) which is characterized by the absence of thrombus resolution due to one or more episodes of acute pulmonary embolic events. The actual incidence of CTEPH after an acute PE is still controversial. The incidence of CTEPH has been reported to occur in 4.8% patients with a previous PE in a recent study (1). Another prospective study from Italy in 2004 showed a lower estimate; around 3.8% after 2 years following acute PE (2). According to previous reports, the incidence of CTEPH had been estimated to vary from 0.4% to 14.7% in patients who survive an acute PE (3,4).

To date, potential risk factors regarding CTEPH in patients with previous PE also remain unclear. The risk factors reported in previous studies were highly variable. Younger or older age, idiopathic PE, Previous/recurrent PE or previous venous thromboembolism (VTE), and a higher level of pulmonary artery systole pressure (sPAP) at the presentation were identified as the major risk factors for CTEPH (1,2,5).

In order to better understand the incidence and risk factors of CTEPH in patients with a previous PE, we conducted a systematic review and meta-analysis of the literature.

## Methods

Embase, Medline, China National Knowledge Infrastructure, Wanfang database, and various reference lists were searched to identify studies published up to May 2018. A comprehensive literature search of Embase, Medline, China National Knowledge Infrastructure and Wanfang databases was conducted to identify all studies published up to May 2018. We also manually searched relevant articles from the reference list. The search terms included keywords for CTEPH ("chronic thromboembolic pulmonary hypertension" or "CTEPH") and the outcomes of interest ("incidence", "prevalence", "epidemiology", "morbidity", "predictor", "risk factor", or "prognosis"). The reporting of this meta-analysis and systematic review is conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (6).

Studies that met the following criteria were included: (I) original full articles written in English or Chinese; (II) cohort studies on reporting the incidence or risk factors of CTEPH in patients with acute PE; (III) enrolled patients ≥18 years old; (IV) enrolled patients with PE diagnosed based on computed tomographic pulmonary angiography (CTPA) or ventilation-perfusion scintigraphy (V/Q scan); (V) the diagnosis of CTEPH was confirmed in patients with pre-capillary PH defined as mean pulmonary artery pressure ≥25 mmHg and pulmonary capillary wedge pressure ≤15 mmHg through the right heart catheterization and at least one segmental perfusion defect on CTPA or V/Q scan; (VI) studies with a minimum follow-up of half a year; (VII) the most recent study with the most integral data would be included, if more than one study had been published using the same cohorts.

We excluded studies as follows: (I) abstracts, reviews, and conference proceedings that were not considered eligible; (II) studies with insufficient data for calculation of incidence; (III) low quality studies assessed by the criteria of the Newcastle-Ottawa Scale (NOS).

Data extraction was independently conducted by two investigators with disagreements resolved through discussion, which included the following information: the first author's name, year of publication, sample size and characteristics, study type, follow-up strategy, screening methods of CTEPH, incidence of CTEPH and risk factors related to CTEPH.

The study quality was assessed using the NOS in which the score ranged from 0 to 9 (7). Criteria for the NOS include defined inclusion criteria, diagnostic criteria, quality control, statistical analysis, sample size and its representativeness. Studies with a score >5 were thought to be high-quality studies. Studies with a score ≤5 were thought to be low-quality studies and not included in this systematic review and meta-analysis.

The incidences of CTEPH in patients with a previous PE from various studies were pooled in a meta-analysis. If incidence was not reported, we extracted the incident case numbers and the enrolled patient numbers from the original data. As low incidence of CTEPH, after an acute PE episode, was reported in several articles, the data was transformed into logit proportion. Restricted to a small number of risk factor studies, we didn't pool the data into a meta-analysis. A systematic review of these studies was conducted to identify potential variables.

Heterogeneity was assessed using the Cochran's Q test and $I^2$ statistics. Based on the Q test, a random effect model

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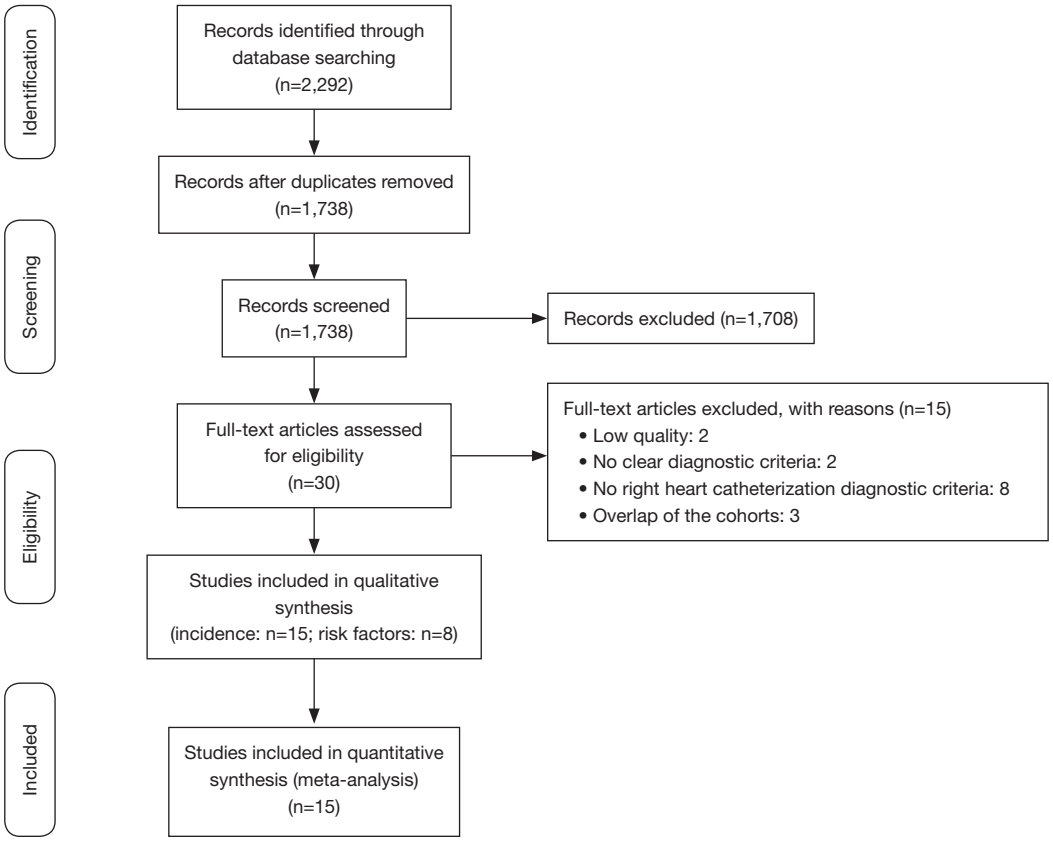


**Figure 1** PRISMA flow diagram of included studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

was utilized when P values <0.1, otherwise a fixed effect model was selected. $I^2$ statistic were utilized to measure the extent of the overall variation due to the heterogeneity; 25%, 50% and 75% of $I^2$ statistic were represented as low, medium, and high heterogeneity, respectively. When substantial heterogeneity was observed ($I^2$ >50%), an investigation of the sources of heterogeneity was conducted using sensitivity and subgroup analyses. During the sensitivity analyses, we excluded each study one by one and recalculated the pooled data to assess whether any one study had a dominant effect on the pooled results. A funnel plot was made to qualitatively demonstrate the publication bias in the studies. Publication bias was quantitatively assessed by the Egger test (P<0.05 was considered statistically significant). All analyses were conducted with the meta package in R software (3.2.2).

## Results

The literature searches yielded 2,292 records. After screening titles and abstracts, 30 full-text articles were assessed for eligibility; 15 articles were excluded after a full review: 2 articles had low quality scores (8,9); 2 articles lacked clear diagnostic criteria; 8 articles lacked right heart catheterization diagnostic criteria; 3 studies had some overlap in the study samples as included patients from Leiden University Medical Center (5,10,11); and 2 studies were based on the same cohort (12,13). We avoided duplicate inclusion of data by selecting only the most complete and more recent article from each cohort (5,13). From a total of 15 studies included in the final analyses (1-3,5,13-23), eight studies reported risk factors of CTEPH among the patients with a previous PE (1,2,5, 14-16,21,23) (*Figure 1*).

The characteristics of included studies are summarized in *Table 1*. The studies were published between 2004 and 2018. Sample sizes varied from 110 to 772. Mean age ranged from 56 to 65 years old. Twelve studies were from Europe, and 3 studies were from China.

As shown in *Figure 2*, in a meta-analysis of 15 independent

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**Table 1** Characteristics of included studies

| Study | Sample size and characteristics | Study type | Follow-up strategy* | Screening methods for CTEPH | Incidence | Risk factors | Quality score |
|---|---|---|---|---|---|---|---|
| Pengo *et al.* 2004, Italy (2) | 223 patients followed up for a median of 94.3 months | Prospective cohort study | Persistent dyspnea | Transthoracic echocardiography | At 6 months: 1.0% (95% CI: 0.0–2.4%); at 1 year: 3.1% (95% CI: 0.7–5.5%); at 2 years: 3.8% (95% CI: 1.1–6.5%) | A previous PE, younger age and a larger perfusion defect | 9 |
| Becattini *et al.* 2006, Italy (19) | 259 patients followed up for an average of 46 months | Prospective cohort study | Persistent dyspnea | Transthoracic echocardiography | 0.8% (95% CI: 0.0–1.9%) | – | 7 |
| Miniati *et al.* 2006, Italy (20) | 320 patients followed up for a median of 2.12 years | Prospective cohort study | Routine follow-up | Transthoracic echocardiography, V/Q scan | 1.3% | – | 7 |
| Poli *et al.* 2010, Italy (3) | 223 patients followed up for a median of 36 months | Prospective cohort study | Persistent dyspnea | Transthoracic echocardiography | 0.4% (95% CI: 0.0–2.7%) | – | 7 |
| Martí *et al.* 2010, Spain (16) | 110 patients followed up for 2 years | Prospective cohort study | Symptoms and/or signs of PH | Transthoracic echocardiography | 9.1% (95% CI: 3.7–14.5%) | Age and previous PE | 8 |
| Surie *et al.* 2010, Dutch (13) | 110 patients followed up for a median of 3 years | Prospective and retrospective cohort study | Symptoms and/or signs of PH | Transthoracic echocardiography | 2.7% (95% CI: 0.6–7.8%) | – | 6 |
| Giuliani *et al.* 2014, Italy (18) | 111 patients followed up for an average of 22 months | retrospective cohort study | Routine follow-up | Transthoracic echocardiography | 4.5% | – | 6 |
| Kayaalp *et al.* 2014, Turkey (17) | 99 patients followed up for a minimum of 1 year | Prospective cohort study | Routine follow-up | Transthoracic echocardiography, V/Q scan, MDCT pulmonary angiography | 5.5% | – | 7 |
| Guérin *et al.* 2014, France (1) | 146 patients followed up for a median of 26 months | Prospective cohort study | Routine follow-up | Transthoracic echocardiography | 4.8% (95% CI: 2.3–9.6%) | Older age, more previous thromboembolic events, more proximal PE and significantly higher level of BNP at PE onset | 8 |

**Table 1** (*continued*)

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**Table 1** (*continued*)

| Study | Sample size and characteristics | Study type | Follow-up strategy* | Screening methods for CTEPH | Incidence | Risk factors | Quality score |
|---|---|---|---|---|---|---|---|
| Yang *et al.* 2015, China (21) | 614 patients followed up for a median of 3.3 years | Prospective cohort study | Routine follow-up | Transthoracic echocardiography | At 1 year: 0.8% (95% CI: 0.0–1.6%); at 2 years: 1.3% (95% CI: 0.3–2.3%); at 3 years: 1.7% (95% CI: 0.7–2.7%) | History of lower-limb varicose veins, sPAP >50 mmHg at initial PE episode, intermediate-risk PE and CT obstruction index over 30% at 3 months after acute PE | 8 |
| Vavera *et al.* 2016, Czech Republic (22) | 97 patients followed up for 2 years | Prospective cohort study | Routine follow-up | Transthoracic echocardiography, V/Q scan | 4.2% | – | 6 |
| Klok *et al.* 2016, Netherlands (5) | 772 patients followed up for a minimum of 6 months | Prospective cohort study | Routine follow-up | Transthoracic echocardiography | 2.8% | Unprovoked PE, known hypothyroidism, symptom onset >2 weeks before PE diagnosis, any right ventricular dysfunction, known diabetes mellitus and thrombolytic therapy or embolectomy | 9 |
| Xi *et al.* 2016, China (15) | 214 patients followed up for an average of 31 months | Prospective cohort study | Symptoms and/or signs of PH | Transthoracic echocardiography, V/Q scan, CTPA | 7.5% | RDW >15%, mean arterial pressure, the duration of symptoms onset to diagnosis, NT-pro-BNP | 9 |
| Xu *et al.* 2016, China (14) | 129 patients followed up for a median of 26 months | Prospective cohort study | Symptoms and/or signs of PH | Transthoracic echocardiography, V/Q scan, CTPA | 6.29% | RDW | 8 |
| Coquoz *et al.* 2018, Switzerland (23) | 508 patients followed up over a median 2 years | Prospective cohort study | Dyspnea | Transthoracic echocardiography | 0.79% (95% CI: 0.31–2.07%) | The presence of antiphospholipid antibodies | 8 |

*, follow-up strategy. Routine follow-up: all patients underwent standard screening examinations of CTEPH during follow-up, such as transthoracic echocardiography; persistent dyspnea/symptoms and/or signs of PH: patients who had otherwise unexplained persistent dyspnea or the presence of symptoms and/or signs of PH during follow-up received the screening examinations of CTEPH. CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension; PE, pulmonary embolism; V/Q scan, ventilation–perfusion scintigraphy; CTPA, computed tomographic pulmonary angiography; MDCT, multidetector computed tomographic; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; sPAP, pulmonary artery systole pressure; RDW, red cell distribution width.

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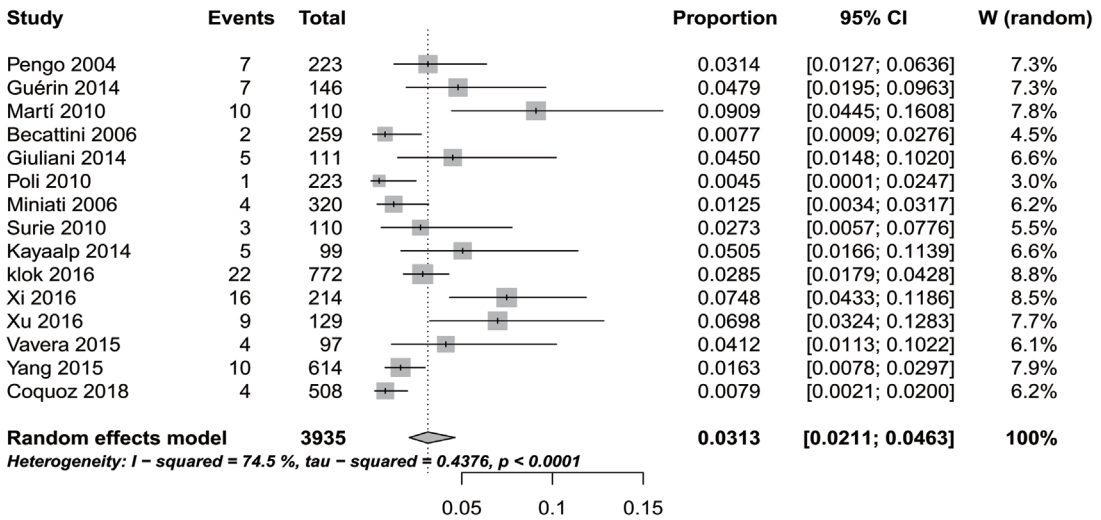


**Figure 2** Meta-analysis of the incidences of CTEPH after acute PE. CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism.

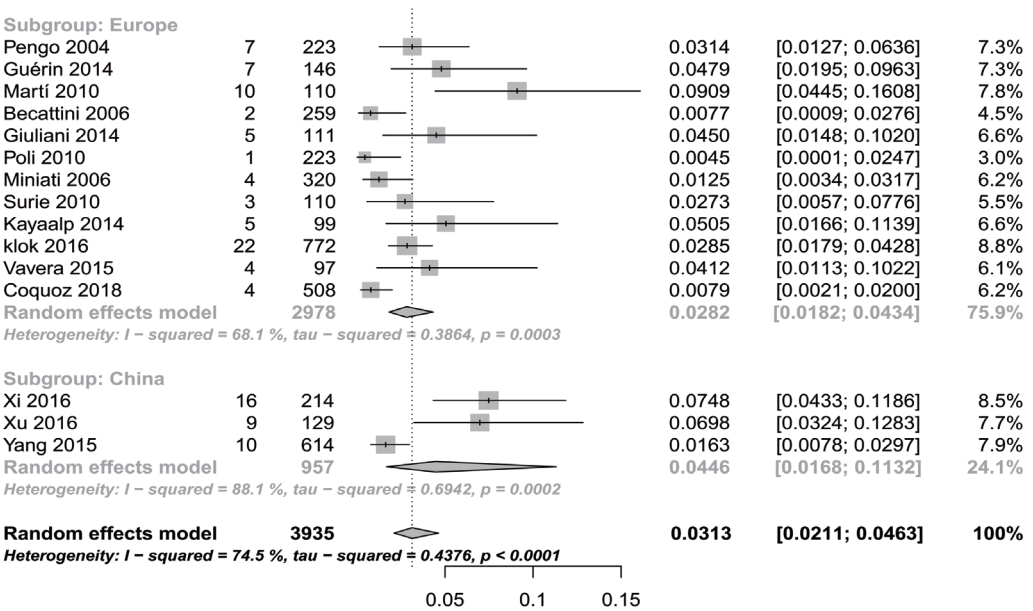


**Figure 3** Subgroup analyses of study locations.

studies, the pooled incidence of CTEPH was 3.13% (95% CI: 2.11–4.63%) with rates in individual studies varying from 0.4% to 9.1%. The highest incidence was in Spain (16), and the lowest incidence was in Italy (5). There was a substantial amount of heterogeneity among the studies ($I^2$=74.5%, P<0.0001; *Figure 2*). To explore the sources of heterogeneity further, we conducted subgroup analyses across key study characteristics. However, subgroup analyses didn't provide clear sources of heterogeneity. The subgroup analyses reported here provide additional insights. The incidence of CTEPH after acute PE was 4.46% (95% CI: 1.68–11.32%) in the Chinese population (14,15,21), higher than the remaining 12 studies from Europe [2.82% (95% CI: 1.82–4.34%), P=0.39] (1-3,5,13,16-20,22,23) (*Figure 3*). Compared studies using right heart catheterization for confirmed diagnosis [3.25% (95% CI: 2.12–4.97%)],

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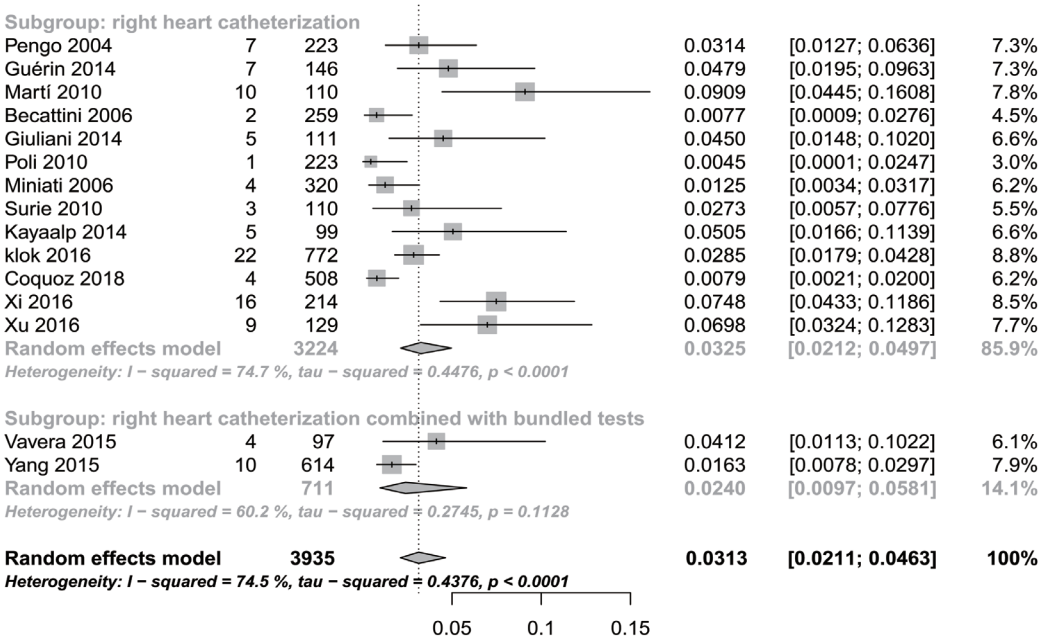


**Figure 4** Subgroup analyses of confirmed diagnostic methods.

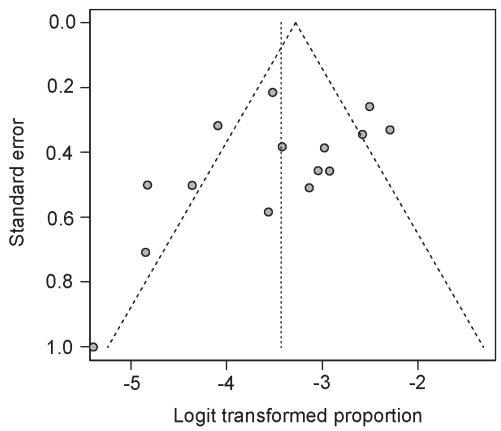


**Figure 5** Funnel plot of included studies for incidence.

studies using right heart catheterization combined with bundled tests (an echocardiography and V/Q scan/CTPA along with clinical features) tended to yield a similar data [2.40% (95% CI: 0.97–5.81%), P=0.54] (*Figure 4*). During the sensitivity analyses, we excluded studies one by one and recalculated the pooled incidence, which was close to 3.13% (95% CI: 2.11–4.63%), varied from 2.90% to 3.47%, with no single study significantly affecting the heterogeneity.

Although the Egger test was not statistically significant (P=0.12), visual inspection of the funnel plot indicated asymmetry (*Figure 5*). By using the trim-and-fill method, which imputes hypothetical negative unpublished studies, the imputed studies produce a symmetrical funnel plot. Two hypothetical missing studies were imputed and the pooled analysis incorporating the hypothetical studies was 3.98% (95% CI: 2.63–5.97%), similar to our results.

Eight studies evaluated risk factors of CTEPH after an acute PE, including a total of 2,716 patients (*Table 2*). Several patient-specific, CTEPH-specific and radiological factors were proved to be relevant to an increased risk of CTEPH. Of the studies that were included, 6 studies performed a multivariate analysis (2,5,14-16,21), and the study by Guérin *et al.* and the study by Coquoz *et al.* just reported unadjusted risk factors (1,23). Previous/recurrent PE or previous VTE (1,2,14,16) and right heart dysfunction at presentation (1,5,14,21) were evaluated as risk factors in more than three studies. The indicators of right heart dysfunction include Initial sPAP, right ventricular (RV) diameter and right ventricle/left ventricle (RV/LV) diameter >1. Idiopathic PE (2,5), older age (1,16), and RDW (14,15) were identified as significant risk factors in two studies. Most risk factors were identified in only one study.

## Discussion

Our meta-analysis suggests that CTEPH is not a rare complication after an episode of PE. The overall incidence of CTEPH was 3.13% (95% CI: 2.11–4.63%). Only one

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**Table 2** Risks factors of CTEPH in patients with an acute PE

| Risk factors | Reference | Unadjusted analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | OR/RR (95% CI) | P | OR/RR/regression coefficient | P |
| Patient-specific variables | | | | | |
| Age | Pengo 2004 (2) | OR: 1.49 (1.15–1.92) | – | OR: 1.79 (1.23–2.56) | – |
| | Guérin 2014 (1) | – | <0.001 | – | – |
| | Martí 2010 (16) | RR: 1.2 (1.0–1.4) | 0.009 | RR: 1.2 (1.0–1.3) | 0.03 |
| Gender (male sex) (%) | Pengo 2004 (2) | OR: 1.39 (0.53–3.61) | – | – | – |
| BMI >30 kg/m$^2$ | Martí 2010 (16) | RR: 5.4 (1.4–21.3) | 0.02 | – | – |
| CTEPH-specific variables | | | | | |
| History | | | | | |
| Previous PE | Pengo 2004 (2) | OR: 16.9 (5.9–48.5) | – | OR: 19.0 (4.5–79.8) | – |
| Recurrent PE | Martí 2010 (16) | RR: 3.1 (1.4–6.7) | 0.03 | RR: 5.7 (1.5–22.0) | 0.01 |
| Previous VTE | Guérin 2014 (1) | – | 0.03 | – | – |
| | Xu 2016 (14) | OR: 4.533 (1.110–18.513) | 0.035 | – | – |
| Idiopathic PE | Pengo 2004 (1) | OR: 2.2 (0.85–5.83) | – | OR: 5.70 (1.41–22.97) | – |
| | Klok 2016 (5) | OR: 20 (2.7 to >100) | – | Regression coefficient: 18 (1.8 to >100) | 0.001 |
| Varicose veins in lower limbs | Yang 2015 (21) | HR: 4.7 (1.3–16.7) | 0.016 | HR: 4.3 (1.2–15.4) | 0.024 |
| Known hypothyroidism | Klok 2016 (5) | OR: 4.3 (1.4–13) | – | Regression coefficient: 8.7 (2.1–34) | 0.002 |
| Known diabetes mellitus | Klok 2016 (5) | OR: Infinitely low | – | Regression coefficient: infinitely low | 0.004 |
| Onset of symptoms >14 days before diagnosis | Klok 2016 (5) | OR: 7.9 (3.3–19) | – | Regression coefficient: 6.9 (2.5–19) | <0.001 |
| The duration of symptom onset to diagnosis | Xi 2016 (15) | OR: 1.002 (1.000–1.004) | 0.044 | OR: 1.002 (1.000–1.004) | 0.034 |
| Clinical presentation | | | | | |
| Chest pain | Martí 2010 (16) | RR: 0.7 (0.5–1.0) | 0.02 | – | – |
| $O_2$ saturation <90% | Martí 2010 (16) | RR: 2.2 (1.3–3.8) | 0.03 | – | – |
| Systemic mean arterial pressure | Xi 2016 (15) | OR: 0.927 (0.882–0.974) | 0.003 | OR: 0.938 (0.886–0.993) | 0.028 |

**Table 2** (*continued*)

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**Table 2** (*continued*)

| Risk factors | Reference | Unadjusted analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | OR/RR (95% CI) | P | OR/RR/regression coefficient | P |
| Radiological variables | | | | | |
| Any right ventricular dysfunction at presentation | Klok 2016 (5) | OR: 4.1 (1.4–12) | – | Regression coefficient: 5.9 (1.8–19) | 0.003 |
| Echocardiography | | | | | |
| sPAP >60 mmHg at diagnosis | Guérin 2014 (1) | – | 0.009 | – | – |
| sPAP >50 mmHg | Yang 2015 (21) | HR: 37.9 (4.8–299.3) | 0.001 | HR: 23.5 (2.7–207.6) | 0.005 |
| sPAP (mmHg) | Xu 2016 (14) | OR: 1.040 (1.008–1.072) | 0.012 | – | – |
| RV/LV diameter >1 | Guérin 2014 (1) | – | <0.001 | – | – |
| | Yang 2015 (21) | HR: 4.3 (1.2–15.3) | 0.024 | HR: 1.0 (0.3–3.6) | 0.946 |
| Right heart diameter | Xu 2016 (14) | OR: 1.125 (1.005–1.260) | 0.041 | – | – |
| Multidetector CT | | | | | |
| Troncular | Guérin 2014 (1) | – | 0.03 | – | – |
| CT obstruction index >30% after 3 months of acute PE | Yang 2015 (21) | HR: 42.5 (4.4–409.8) | 0.001 | | |
| V/Q scan | | | | | |
| Perfusion defect | Pengo 2004 (2) | OR: 2.1 (1.6–2.9) | – | OR: 2.22 (1.49–3.31) | – |
| Biomarkers | | | | | |
| BNP | Guérin 2014 (1) | – | 0.01 | – | – |
| NT-pro-BNP | Xi 2016 (15) | OR: 10.421(3.178~34.177) | 0.009 | OR: 10.657 (2.642–42.991) | 0.001 |
| Uric acid (μmol/L) | Xi 2016 (15) | OR: 1.006 (1.001–1.010) | 0.008 | – | – |
| RDW (%) | Xu 2016 (14) | OR: 1.611 (1.243–2.088) | <0.001 | OR: 1.535 (1.094–2.155) | 0.013 |
| RDW >15% | Xi 2016 (15) | OR: 14.417 (3.203–64.892) | 0.003 | OR: 7.916 (1.474–42.500) | 0.016 |
| Hct (%) | Xi 2016 (15) | OR: 1.115 (1.008–1.234) | 0.035 | – | – |
| Cr (mmol/L) | Xi 2016 (15) | OR: 10.421(3.178~34.177) | 0.006 | – | – |
| The presence of antiphospholipid antibodies | Coquoz 2018 (23) | – | 0.03 | – | – |
| Treatment | | | | | |
| Thrombolytic therapy or embolectomy | Klok 2016 (5) | OR: infinitely low | – | Regression coefficient: infinitely low | 0.003 |

CI, confidence interval; OR, odds ratio; RR, relative risk; BMI, body mass index; PE, pulmonary embolism; sPAP, systole pulmonary arterial pressure; RV/LV, right ventricle/left ventricle; V/Q scan, ventilation-perfusion scintigraphy; BNP, brain natriuretic peptide; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; RDW, red cell distribution width; Hct, hematocrit; Cr, creatinine.

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previous systematic review has examined the incidence of CTEPH after an acute PE (24). Compared with the previous meta-analysis (2.3%), our results suggested a slightly higher estimate, similarly to the results of the study conducted by Pengo and colleagues (At 2 years: 3.8%) (2). Several reasons could explain this discrepancy. First, our analysis didn't include abstracts, reviews, and conference proceedings, because it's difficult to assess quality from incomplete data. Second, our analysis included the latest 4 studies published in 2016 (5,14,15,22) and 1 study published in 2018 (23). Third, the data from China were also included into our meta-analysis (14,15,21). Although our results showed the incidence of CTEPH in Chinese population seems higher than in Europe, no significant difference can be observed between these two groups.

It is not known that using bundled tests that include an echocardiography and V/Q scan/CTPA along with clinical features can accurately diagnose CTEPH in patients not able to undergo right heart catheterization. Our subgroup analyses showed that it is no difference between patients using right heart catheterization and right heart catheterization combined with bundled tests. In Yang *et al.*'s study, if written consent could not be obtained for the right heart catheterization, the diagnostic criteria of CTEPH was sPAP at rest >50 mmHg (echocardiography), with the addition of supportive results from V/Q scan and CTPA (21). Considering it is difficult to use right heart catheterization in every suspected patient, bundled tests including echocardiography and V/Q scan/CTPA along with clinical features appear to be helpful in patients unable to perform right heart catheterization. However, caution is warranted in interpretation, and further studies on the standardization of bundled tests are needed for better medicinal utilization.

Most patients were diagnosed within 2 years after an acute PE. Only one patient who developed CTEPH after 4 years of the occurrence of acute PE was reported in a previous study (3). This tendency might be partly due to the natural process of a thrombus resolution following an acute PE. Residual chronic thrombus was reported in 48% of patients at the 3rd month after the first episode of PE, 27.4% at the 6th month, and 18.2% at 12th month. This result highlighted the importance of close monitoring of patients with PE for an early diagnosis of CTEPH (25). Another explanation is that some of the CTEPH patients were misdiagnosed as acute PE, owing to the fact that the first identified clinical presentation of CTEPH may mimic acute PE (1). This finding suggests more frequent surveillance, throughout the first 2 years after being diagnosed with PE, seems reasonable. As the average follow-up period in most studies was within 2 years, the result needs to be interpreted with caution and more studies are required to confirm this hypothesis.

In recent studies, more CTEPH cases with no symptom or few symptoms have been reported (16,17). Clinical silent CTEPH may be easily missed by the present screening strategies deployed. CTEPH is the only cause of pulmonary hypertension that can be cured by pulmonary endarterectomy. Early detection and diagnosis are crucial for the management of CTEPH. Hence asymptomatic patients warrant attention.

Risk factors of CTEPH after an acute PE were also evaluated in our study. In previous studies, several factors were proven to be closely relevant to the development of CTEPH in patients with an acute PE. Some novel risk factors such as plasma Lp(a) levels, hyperlipidemia, red cell distribution width, known hypothyroidism and known diabetes mellitus have also been considered to be associated with CTEPH in recent studies (14,15,26,27). In view of limited raw data from present studies, more evidence is needed to lend support to these potential associations. Due to inclusion of only 8 studies into our research combined with insufficient raw data, we were unable to report a common statistic for each of the mentioned potential risk factors.

Previous/recurrent PE or previous VTE and idiopathic PE are considered to be associated with an increased risk of CTEPH (24). Previous/recurrent PE or previous VTE is commonly believed to be related to the long-term incomplete resolution, which may result in the presence of pulmonary hypertension. Prevention of recurrent VTE would most likely help prevent CTEPH. Adequate anticoagulant treatment would significantly reduce the appearance of recurrent VTE. Although only two studies identified idiopathic PE as an independent risk factor on multivariate analyses (2, 5), other studies also indicated a similar tendency. In the study by Klok *et al.*, they observed a 0.57% incidence of CTEPH after an acute PE in an unselected large patient series, while a 1.5% incidence of CTEPH in patients with unprovoked PE (10). Becattini *et al.* reported an incidence of symptomatic CTEPH of 0.8%, while the incidence of symptomatic CTEPH in patients with idiopathic PE was 1.5% (19). This is partly because the underlying disease is not treated in patients with idiopathic PE, resulting in continuing thrombus forming. In addition to previous/recurrent PE or previous VTE and idiopathic

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PE, our systematic review indicated that right heart dysfunction at presentation, as reflections of severity of PE, was also associated with the development of CTEPH. However, there is lack of common criteria for clinicians to use these indexes to select potential CTEPH patients.

Although various risk factors have been identified to be associated with CTEPH, it is difficult to apply these risk factors to identify potential CTEPH cases in patients with a previous PE. Klok *et al.* developed a clinical prediction score to identify high-risk CTEPH in patients with previous cases of PE. The results showed this prediction score identified patients at lower (0.38%) or higher (10%) risk of CTEPH (5). This prediction score should be validated in other studies, and further investigations should be designed to develop more effective prediction models.

There were several limitations to this systematic review. Firstly, we detected significant heterogeneity across the studies included in incidence analyses. Although potential sources of heterogeneity were further explored using subgroup analyses, we failed to find sources of heterogeneity through subgroup analyses. Sensitivity analyses used by excluding studies one by one and recalculating the pooled data verified the robustness of results. We postulated potential sources of heterogeneity as follows: (I) different constitution of the final study population might play a role in significant heterogeneity among the studies. Several studies analyzed cohorts of selected patients by excluding patients who died irrelevant of CTEPH and patients with permanent risk factors or previous exertional dyspnea. It is more likely to miss potential CTEPH patients if they have other potential causes for pulmonary hypertension; these patients were excluded from some CTEPH studies (2,16,18); (II) different strategies of follow-up may also result in a wide variation of incidences. In several studies, patients who had otherwise unexplained persistent dyspnea on exertion or at rest during follow-up were considered as suspected CTEPH and received further confirming examinations (1-3,13-15,19,23), while other studies included both symptomatic and asymptomatic patients (5,16-18,20-22); (III) the variations in severity of the initial PE have also been included among the causes of substantial heterogeneity. Based on discussion above, the results need to be interpreted with caution.

Secondly, owing to the paucity of studies and insufficient raw data being reported in the included studies, we didn't pool the original data into a meta-analysis. Most risk factors were identified in only one or two studies, and not all studies conducted rigorous multivariate analyses. Therefore, it is difficult to speculate the predictive ability of these risk factors.

Thirdly, the funnel plot showed the possibility of publication bias. The revised estimate using trim and fill analysis was slightly higher than our results of meta-analysis, suggesting the confidence of the pooled incidence attenuated. Pooled data estimates and results should be interpreted with caution.

Fourthly, NOS was used for the assessment of bias of observational studies, which was not completely applicable in our analysis.

## Conclusions

CTEPH is not a rare complication after acute PE. Close follow-up and implementation of a comprehensive screening program are helpful to select CTEPH patients, especially in patients with the afro mentioned risk factors. Considering it is difficult to use invasive methods in every suspected patient, bundled tests including echocardiography and V/Q scan/CTPA along with clinical features appear to be helpful in patients unable to perform right heart catheterization. Future researches designed to explore other potential risk factors and the use comprehensive statistical adjustments for potential confounders are required.

## Acknowledgements

*Funding*: This study was supported by a grant of the China Key Research Projects of the 12th National Five-Year Development Plan (2012BA105B00, 2013BA109B00) and the fund of National Natural Science Foundation of China (31670928).

## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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**Cite this article as:** Zhang M, Wang N, Zhai Z, Zhang M, Zhou R, Liu Y, Yang Y. Incidence and risk factors of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a systematic review and meta-analysis of cohort studies. J Thorac Dis 2018;10(8):4751-4763. doi: 10.21037/jtd.2018.07.106

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