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RISK STRATIFICATION OF PATIENTS WITH ACUTE SYMPTOMATIC PULMONARY EMBOLISM BASED ON PRESENCE OR ABSENCE OF LOWER EXTREMITY DEEP VEIN THROMBOSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

Authors:

Cecilia Becattini¹, Alexander T. Cohen², Giancarlo Agnelli¹, Luke Howard³, Borja Castejón⁴, Javier Trujillo-Santos⁵, Manuel Monreal⁶, Arnaud Perrier⁷, Roger D. Yusen⁸ and David Jiménez⁹

Affiliation:

¹*Internal and Cardiovascular Medicine, University of Perugia, Perugia, Italy*

²*Department of Haematological Medicine, Guys and St Thomas' NHS Foundation Trust, London, UK*

³*National Pulmonary Hypertension Service, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK*

⁴*Vascular Department, Ramón y Cajal Hospital, IRYCIS, Madrid, Spain*

⁵*Medicine Department, Santa Lucía Hospital, Cartagena, Murcia, Spain*

⁶*Medicine Department, Germans Trias i Pujol Hospital, Badalona, Spain*

⁷*Division of General Internal Medicine, Department of Internal Medicine, Rehabilitation and Geriatrics, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland*

⁸*Divisions of Pulmonary and Critical Care Medicine and General Medical Sciences, Washington University School of Medicine, St. Louis, Missouri, USA*

⁹*Respiratory Department, Ramón y Cajal Hospital and Alcala de Henares University, IRYCIS, Madrid, Spain*

Correspondence and reprints:

David Jiménez Castro

Respiratory Department and Medicine Department

Ramón y Cajal Hospital, IRYCIS and Alcala de Henares University

28034 Madrid, SPAIN

Phone: 34 913368314

e-mail: djimenez.hrc@gmail.com

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ABBREVIATION LIST

CUS, compression ultrasound

CI, confidence interval

DVT, deep vein thrombosis

LR, likelihood ratio

NPV, negative predictive value

OR, odds ratio

PPV, positive predictive value

PESI, Pulmonary Embolism Severity Index

PE, pulmonary embolism

QUIPS, Quality in Prognosis Studies

RV, right ventricular

sPESI, simplified Pulmonary Embolism Severity Index

TTE, transthoracic echocardiography

VTE, venous thromboembolism

ABSTRACT

Background: For patients diagnosed with acute pulmonary embolism (**PE**), the prognostic significance of concomitant deep vein thrombosis (**DVT**) lacks clarity.

Methods: We performed a meta-analysis of studies that enrolled patients with acute PE to assess the prognostic value of concomitant DVT for the primary outcome of 30-day all-cause mortality, and the secondary outcome of 90-day PE-related adverse events. We conducted unrestricted searches of Pubmed and Embase from 1980 through September 30, 2014 and used the terms “deep vein thrombosis”, “pulmonary embolism”, and “prognos*”. We used a random-effects model to pool study results; Begg rank correlation method to evaluate for publication bias; and I^2 testing to assess for heterogeneity.

Results: The meta-analysis included a total of 9 studies (10 cohorts, as one study had 2 cohorts) with 8,859 patients. Of the 7 cohorts with 7,868 participants that had PE and provided results on the primary outcome, 4,379 (56%) had concomitant DVT; 272 of 4,379 (6.2%) patients with concomitant DVT died 30-days after the diagnosis of PE compared with 133 of 3,489 (3.8%) without DVT. Concomitant DVT had a significant association with 30-day all-cause mortality in all patients (7 cohorts; odds ratio [**OR**], 1.9; 95% CI, 1.5 to 2.4; $I^2 = 0\%$). Concomitant DVT was not significantly associated with 90-day PE-related adverse outcomes (5 cohorts; OR, 1.6; 95% CI, 0.8 to 3.4; $I^2 = 75\%$).

Conclusions: In patients diagnosed with acute symptomatic PE, concomitant DVT was significantly associated with an increased risk of death within 30 days of PE diagnosis.

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INTRODUCTION

Pulmonary embolism (**PE**) is a leading cause of death in the Western world (1). For patients with acute symptomatic PE, subgroup risk stratification may assist with decision-making regarding PE therapy (2). For example, patients at low risk for early complications (i.e., death, recurrent venous thromboembolism [**VTE**], and major bleeding) might be considered for partial or complete outpatient PE treatment (3). Alternatively, normotensive patients at high risk of early death may benefit from more intensive surveillance or aggressive therapy (i.e., intermediate-risk group) (4, 5).

Studies have validated clinical prognostic models (e.g., Pulmonary Embolism Severity Index [**PESI**], simplified PESI [**sPESI**]) for identification of low-risk patients with PE who might safely undergo outpatient PE therapy (6-8). For prognosticating PE-related short-term adverse events (i.e., intermediate-risk PE), studies of patients with acute PE yielded equivocal findings regarding performance of test combinations (e.g., lower extremity compression ultrasound [**CUS**] testing for deep vein thrombosis (**DVT**), cardiac troponin testing for myocardial injury, transthoracic echocardiography [**TTE**] testing for right ventricular [**RV**] dysfunction) (9-11).

A study of patients with a first, objectively confirmed episode of acute symptomatic PE supported the hypothesis that increased thrombus burden has a poor prognosis by demonstrating that those with evidence of concomitant DVT had, compared to those without DVT, an increased risk of all-cause death, PE-related death, and recurrent VTE over 3-months of follow-up (12). However, other studies have shown conflicting data regarding the association between concomitant DVT at the time of PE diagnosis and VTE event rates (13-15). While one study found the presence of proximal DVT on compression ultrasonography to be an independent predictor of adverse patient outcomes (i.e., death, recurrent VTE, and major bleeding) (14), two other studies did not confirm these findings (13, 15). To clarify the prognostic potential of concomitant DVT among patients with acute symptomatic PE and its usefulness

for treatment decision-making, this study aimed to review the literature systematically and perform an updated meta-analysis.

METHODS

The authors used methods for this meta-analysis recommended in “Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting” (16).

Study Objectives

The *primary* aim of the study was to look for an association between concomitant DVT and 30-day mortality in patients with acute symptomatic PE. The *secondary* aim was to examine the potential association between concomitant DVT and 90-day PE-related complications (i.e., PE-related death or non fatal venous thromboembolic recurrences).

Data sources and searches

A computerized search of Pubmed and Embase from 1980 through September 30, 2014 used the terms “pulmonary embolism”; “deep vein thrombosis”; and “prognos*” to identify eligible studies (17, 18). Full articles of all potentially appropriate abstracts were reviewed. Hand searching of cited bibliographies and investigator files complemented the literature search.

Inclusion and exclusion criteria

Pre-specified study inclusion criteria were prospective or retrospective studies with 1) an objective diagnosis of PE; and 2) CUS testing performed around the time of PE diagnosis. Studies were included if they reported all-cause mortality, PE-related mortality, or a composite endpoint encompassing all-cause or PE-related mortality and other adverse events. Studies were excluded if their outcome parameters omitted mortality. For duplicate publications, the most recent was considered.

Study selection

Two investigators (B.C. and D.J.) independently assessed identified articles to determine study eligibility. Based on title and abstract review, the reviewers excluded non-relevant studies. For relevant studies, the reviewers independently carried out data extraction using a pre-piloted, standardized form. Consensus or discussion with a third reviewer (J.T-S.) resolved eligibility and data extraction discrepancies or uncertainties.

Data extraction and quality assessment

For each study, investigators abstracted data regarding patient characteristics, lower limb ultrasound testing results and outcomes. Two investigators (B.C. and D.J.) used the Quality in Prognosis Studies (**QUIPS**) tool to independently assess the quality of the eligible studies (19).

Data synthesis and analysis

For each study, we determined the incidence of 30-day all-cause mortality, and 90-day PE-related complications for the positive and negative DVT groups, and we calculated an odds ratio (**OR**) and its 95% confidence interval (**CI**). We pooled odds ratios across studies by using a random-effects model approach. Statistical heterogeneity between groups was measured using the Cochran's Q statistic and the Higgins I^2 statistic (20). The Begg rank correlation method assessed for publication bias. We planned separate analyses for: 1) prospective studies; 2) retrospective studies; and 3) cohorts of haemodynamically stable patients. All analyses were carried out using Review Manager 5.2 (The Cochrane Collaboration, Oxford, England) and MetaDisc version 1.4 (21).

RESULTS

Description of studies

Of the 165 articles screened, 9 appeared potentially eligible and underwent an in depth review (12, 15, 22-28). Four of the 9 studies were deemed ineligible (22-25). Hand searching found 5 additional studies (3, 13, 29-31), therefore 10 studies met the eligibility criteria (3, 12, 13, 15, 26-31) (**Figure 1**). For 3 of these

studies (27, 28, 30), the numbers of patients who experienced an adverse outcome event were obtained by contacting the authors. One of the studies was excluded because we were not able to obtain the necessary data from the authors (13). For one study, the derivation and validation cohorts were analyzed separately (12). Overall, a total of 9 studies (10 cohorts) with 8,859 patients with acute PE who underwent bilateral lower limb ultrasound testing were included in the analysis.

Six cohorts had a prospective design (3, 12, 26, 27, 29, 30) and 4 cohorts had a retrospective design (12, 15, 28, 31). Demographic features of study populations (age, gender) were similar across the studies, and all the included patients had an objective diagnosis of PE (**Table 1**). Seven cohorts provided results on the primary outcome (3, 12, 26, 27, 29, 31). Four studies only included hemodynamically stable patients (3, 15, 26, 28). For the survival analyses (performed in 7 studies), 2 studies (12, 27) used the Cox proportional-hazards regression, and 5 studies (3, 15, 26, 29, 30) used logistic regression.

Length of follow-up ranged from 5 days (29) to 3 months after PE diagnosis (12, 15, 28, 30). The prevalence of ultrasound-detectable concomitant DVT varied from 39% (3) to 63% (12).

Outcomes

Two studies used all-cause mortality as the primary outcome (12, 31), 1 study used PE-related death (3), and 6 studies reported combined adverse clinical events as an outcome (15, 26-30). Vedovati et al (27) defined clinical deterioration as the occurrence of one or more of the following events: shock (systemic systolic blood pressure < 90 mm Hg or a drop by ≥ 40 mm Hg for > 15 min with signs of peripheral hypoperfusion), need for rescue thrombolysis, endotracheal intubation, catecholamine infusion, or cardiopulmonary resuscitation. Kabrhel et al (29) defined clinical deterioration as an inherently unstable condition or advanced intervention/therapy. Jimenez et al (26) defined a “complicated course” as death from any cause, haemodynamic collapse (defined as need for cardiopulmonary resuscitation, systolic blood pressure <90

mm Hg for at least 15 min, need for catecholamine administration or need for thrombolysis) or adjudicated recurrent PE within 30 days of follow-up.

Quality assessment of included studies

Regarding study quality assessment criteria (**Table 2**), the study participation was adequate and the baseline study sample was adequately described in all the studies (3, 12, 15, 26-31). Eight studies (3, 12, 26-31) provided adequate information about patients lost to follow-up, whereas the other study did not. Bilateral complete CUS testing was performed in the 4 studies that adequately described methods for the assessment of concomitant DVT (3, 12, 15, 26). An independent blinded committee assessed the outcome criteria in 4 studies (3, 12, 15, 26). Most studies accounted for important potential confounders (3, 12, 15, 26, 27, 29, 30). The use of appropriate statistical analyses in 6 studies (3, 12, 15, 26, 27, 29, 30) limited the potential for the incorporation of and presentation of invalid results, whereas 2 studies did not perform any predictive statistics (28, 31).

Endpoints

Of the 7 cohorts with 7,868 PE patients that provided results on the primary outcome, 4,379 (56%; 95% CI, 55 to 57%) had concomitant DVT and 3,489 (44%; 95% CI, 43 to 45%) did not. Two hundred seventy two of 4,379 patients with concomitant DVT died (6.2%; 95% CI, 5.5 to 7.0%) compared with 133 of 3,489 without DVT (3.8%; 95% CI, 3.2 to 4.5%). Pooled results from these 7 cohorts showed that concomitant DVT was associated with 1.9-fold increased odds of 30-day all-cause mortality [95% CI, 1.5 to 2.4, heterogeneity $\chi^2 = 4.9$, $df = 6$, $P = 0.56$] (**Figure 2A**). The pooled estimate was dominated by the 2 larger studies (3, 12), which together provided about two-thirds of the total patients. Four of the 7 cohorts (26, 27, 29, 31) did not have statistically significant findings, though all studies showed the same trend. There was no evidence of publication bias using the Begg rank correlation method. The predictive value of concomitant DVT with respect to death was confirmed when the analysis was limited to 5 studies (2,793 patients) that used a prospective design (OR 1.9; 95% CI, 1.4 to 2.6), with no evidence for heterogeneity (heterogeneity $\chi^2 = 2.2$, $df = 4$, $P = 0.70$, $I^2 = 0\%$) (**Figure 2B**). The retrospective (OR 1.7; 95% CI, 1.0

to 3.1, heterogeneity $\chi = 2.7$, $df = 1$, $P = 0.10$, $I^2 = 63\%$) studies showed similar trends, though they did not achieve statistical significance (**Figure 2C**).

The pooled estimated negative predictive value (**NPV**) for concomitant DVT was 96% (95% CI, 95 to 97%) and the positive predictive value (**PPV**) was 6.2% (95% CI, 5.5 to 7.0%). The meta-analysis showed (1) a slight increase in the rate of ultrasound-detectable concomitant DVT in patients who died, compared to the rate of DVT in patients who survived (positive likelihood ratio [**LR**] 1.27; 95% CI, 1.19 to 1.36), and (2) a slight decrease in the rate of negative ultrasound assessment for concomitant DVT in patients that died, compared to the rate of negative ultrasound assessment for DVT in patients that survived (negative LR 0.73; 95% CI, 0.62 to 0.86) during the short-term follow-up.

Five cohorts (2 prospective, 3 retrospective; 5,982 patients) evaluated the occurrence of 90-day PE-related complications (12, 15, 28, 30). The incidence of PE-related complications was 7.2% (256 of 3,573 patients; 95% CI, 6.3 to 8.0%) and 5.5% (132 of 2,409 patients; 95% CI, 4.6 to 6.4%) in patients with and without concomitant DVT, respectively. The pooled analysis of these studies did not show a significant association between concomitant DVT and 90-day PE-related complications (OR, 1.6; 95% CI, 0.8 to 3.4), with evidence for heterogeneity (heterogeneity $\chi = 15.9$, $df = 4$, $P = 0.003$, $I^2 = 75\%$) (**Figure 3**).

Two prospective studies (1,409 patients) only included hemodynamically stable patients (3, 26), whereas the other studies did not specify the hemodynamic status of the patients. In this subgroup, concomitant DVT was associated with an increased risk of 30-day all-cause death (OR, 1.8; 95% CI, 1.2 to 2.8).

Testing did not detect heterogeneity (heterogeneity $\chi = 0.01$, $df = 1$, $P = 0.92$, $I^2 = 0\%$).

DISCUSSION

In this meta-analysis of ten cohorts that included 7,868 patients with acute symptomatic PE, patients with concomitant ultrasound-detectable DVT had a 1.9-fold increased risk of short-term death compared to patients without DVT. Regardless of the length of follow-up, haemodynamic status, and study design, the studies showed relatively consistent results.

Very few published studies allow the estimation of the prevalence of concomitant DVT in patients with proven PE, and studies have reported prevalences that range from 13 to 93% (32, 33). The heterogeneity of the diagnostic criteria for DVT both between and within these studies may explain some of the discrepancies in the prevalence estimates. The prevalence of ultrasound-detectable concomitant DVT in this meta-analysis (55%) was similar to that in a previous meta-analysis in which 45% of patients with ventilation/perfusion scan-proven PE had concurrent DVT (34). Furthermore, the results of several studies included in this review suggest that CUS diagnoses DVT in only about half of the patients that have symptoms or clinical signs of DVT (12, 15, 35).

For patients with acute symptomatic PE, this study shows that the absence of concomitant DVT has a high negative predictive value for death during short-term follow-up of 96%. Predictive clinical models (e.g., sPESI, PESI) that do not utilize CUS have also repeatedly shown a high negative predictive value for all-cause mortality, and they may accurately identify low-risk patients with confirmed PE who might be candidates for partial or complete outpatient treatment (36). The design of this meta-analysis did not allow to test whether or not venous CUS of the lower extremities (i.e., to exclude concomitant DVT) could potentially improve the accuracy of clinical prediction rules for the identification of low-risk patients for outpatient management. In the PROTECT study of 848 normotensive patients with PE, the sPESI accurately identified those at low-risk for a complicated course (26). Incorporation of ultrasound-detected concomitant DVT into the sPESI did not significantly improve prognostication (26).

For patients with acute symptomatic PE, this study shows that concomitant DVT has a low positive predictive value for death during short-term follow-up of 6.2%. This finding is similar to those obtained with echocardiography and biomarkers (37, 38). Thus, individual clinical variables, single markers of RV dysfunction, myocardial injury or clot burden (e.g., CUS), have an insufficiently low positive predictive value for PE-specific complications to drive decision-making toward primary reperfusion (e.g., thrombolytic therapy). Whether CUS testing could improve the positive predictive value of echocardiography and cardiac biomarkers for death is currently undefined. Two studies suggested that the combination of CUS testing with prognostic tools that detect myocardial injury or right ventricular dysfunction might offer an advantage compared with each test alone with regard to the identification of patients with acute PE at high-risk of PE-associated mortality (3, 26). Future studies might address the potential survival benefit associated with inferior vena cava filter use in these high-risk patients.

For the present meta-analysis, the large total sample size, the proportion of patients with ultrasound-detectable DVT, and the death rate all allowed for reasonable estimates of risk. Moreover, the varied settings and patient characteristics improved the generalizability of the study results. Despite the significant association between concomitant DVT and death, it does not follow that the presence of DVT in association with acute symptomatic PE provides a basis for an effective prediction rule for individual patients.

Regarding the limitations of this meta-analysis of aggregate data, we did not have sufficient information that would allow us to adjust for confounding variables. Meta-analyses of individual patient data could have potentially allowed for such adjustments. Limitations of each of the included studies (e.g., not every patient underwent CUS testing) may have introduced significant biases into this meta-analysis's estimates of the prognostic value of concomitant DVT. Some of the studies did not clearly describe the referral patterns, and they may have not included consecutive patients. Also, some studies did not report whether or not an independent blinded committee

assessed the outcome data. Finally, we were not able to detect an association between concomitant DVT and 90-day PE-related complications.

In conclusion, this systematic review showed that concomitant DVT had an association with increased risk of mortality in patients with acute symptomatic PE. Future studies should assess if the combination of bilateral lower limb ultrasound testing (complete vs. limited) with clinical scores (e.g., PESI, sPESI) or prognostic tools indicating myocardial injury or RV dysfunction (i.e., cardiac troponin, and transthoracic echocardiography, respectively) might offer advantages compared with each test alone with regard to enhanced risk stratification of low- and intermediate-risk patients with an objectively confirmed episode of acute symptomatic PE.

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Conflict of interest statement

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Becattini, Agnelli, Perrier, Yusen and Jimenez authored studies assessed by this meta-analysis.

Author contributions

Study concept and design: Becattini, Cohen, Agnelli, Howard, Perrier, Yusen, Jimenez.

Acquisition of data; analysis and interpretation of data; statistical analysis: Becattini, Cohen, Agnelli, Howard, Castejon, Trujillo-Santos, Monreal, Perrier, Yusen, Jimenez.

Drafting of the manuscript: Becattini, Cohen, Perrier, Yusen, Jimenez.

Critical revision of the manuscript for important intellectual content: Becattini, Cohen, Agnelli, Howard, Castejon, Trujillo-Santos, Monreal, Perrier, Yusen, Jimenez.

Study supervision: Becattini, Jimenez

The corresponding author, David Jiménez, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Figure 1. Flow chart of the study selection process

Figure 2. Odds ratio of 30-day all-cause mortality based on the presence or absence of concomitant DVT in patients with acute PE: random-effects meta-analysis of 7 cohorts (with results on the primary outcome)

A) All 7 PE cohorts

B) Prospective subset of PE cohorts

C) Retrospective subset of PE cohorts

Figure 3. Odds ratio of 90-day PE-related adverse outcomes based on the presence or absence of concomitant DVT in patients with acute PE: random-effects meta-analysis of 5 cohorts (with results on the secondary outcome)

Table 1. Characteristics of the studies included

<i>Author</i>	<i>Year</i>	<i>Study design</i>	<i>Outcome event</i>	<i>Concomitant DVT</i>	<i>Population, n</i>	<i>Sex</i>	<i>Age, Mean (SD) or Range, y</i>	<i>Follow-up</i>	<i>Study results</i>
Wicki et al (30)	2000	Prospective	Deaths, VTE events and major bleeding	50%	Outpatients, 296	52% female	67 (17)	3-months	16% adverse outcome rate for positive DVT group vs 4.7% for negative DVT group
Nendaz et al (28)	2004	Retrospective	Deaths, VTE events and major bleeding	43%	Nonsevere outpatients, 212	55% female	66 (18)	3-months	3.3% complication rate for positive DVT group vs 7.7% for negative DVT group
Girard et al (15)	2005	Retrospective	Death or non fatal VTE recurrences	60%	Nonsevere patients, 281	55% female	-	90-days	Risk of complications was not significantly different among patients with and without DVT (6.5% vs 2.7%, P = 0.15).
Jimenez et al (31)	2007	Retrospective	All-cause death	44%	Outpatients, 599	55% female	-	30-days	7.9% mortality rate for positive DVT group vs 6.6% for negative DVT group
Jimenez et al (derivation cohort) (12)	2010	Prospective	All-cause death	51%	Outpatients, 707	55%, female	68 (16)	3-months	Crude all-cause mortality rate was 2.5-fold (95% CI, 1.5-4.1) greater in patients with concomitant DVT
Jimenez et al (validation cohort) (12)	2010	Retrospective	All-cause death	63%	Outpatients, 4,476	55%, female	67 (16)	3-months	Adjusted all-cause mortality rate was 1.7-fold (95% CI, 1.3-2.1) greater in patients with concomitant DVT

Jimenez et al (4)	2011	Prospective	Death due to PE	39%	Normotensive patients, 591	57% female	65-82	30-days	10% PE-related mortality rate for positive DVT group vs 4% for negative DVT group
Vedovati et al (27)	2012	Prospective	All-cause death or clinical deterioration	47%	Outpatients and inpatients, 579	52% female	68 (16)	30-days	Mortality or clinical deterioration was significantly higher in patients with concomitant DVT
Kabhrel et al (29)	2014	Prospective	Clinical deterioration	25%	Outpatients, 298	49% female	59 (17)	5-days	47% deterioration rate for positive DVT group vs 29% for negative DVT group
Jimenez et al (26)	2014	Prospective	All-cause death, hemodynamic collapse or recurrent PE	46%	Normotensive outpatients, 820	51% females	59-80	30-days	Concomitant DVT was predictive of complicated course (OR, 2.08; P = 0.01) after adjustment

Table 2. Quality assessment of studies included in the systematic review

<i>Study</i>	<i>Study participation</i>	<i>Follow-up described and adequate</i>	<i>Description of diagnosis of DVT</i>	<i>Outcome defined and described appropriately</i>	<i>Control of confounding*</i>	<i>Analysis described appropriately</i>
Wicki et al (30), 2000	Adequate	Yes	Unclear	Yes	Good	Yes
Nendaz et al (28), 2004	Adequate	Yes	Unclear	Yes	Poor	Yes
Girard et al (15), 2005	Adequate	Unclear	Adequate	Yes	Good	Yes
Jimenez et al (31), 2007	Adequate	Yes	Unclear	Yes	Poor	Yes
Jimenez et al (derivation cohort) (12), 2010	Adequate	Yes	Adequate	Yes	Good	Yes
Jimenez et al (validation cohort) (12), 2010	Adequate	Yes	Unclear	Yes	Good	Yes
Jimenez et al (4), 2011	Adequate	Yes	Adequate	Yes	Good	Yes
Vedovati et al (27), 2012	Adequate	Yes	Unclear	Yes	Good	Yes
Kabhrel et al (29), 2014	Adequate	Yes	Unclear	Yes	Good	Yes
Jimenez et al (26), 2014	Adequate	Yes	Adequate	Yes	Good	Yes

* Control of confounding was classified as poor if little or no attempt was made to measure or control for known basic confounders. Adequate control considered at least age and comorbidities, and good control considered the majority of the confounders.

Abbreviations: DVT, deep vein thrombosis.

Figure 1.

Abbreviations: PE, pulmonary embolism; CUS, compression ultrasound.

*One study (12) had 2 cohorts.

Figure 2.**A) All 7 PE cohorts** **B) Prospective subset of PE cohorts** **C) Retrospective subset of PE cohorts**

Figure 3.