Clinical profile and outcome of isolated pulmonary embolism: a systematic review and meta-analysis

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eClinicalMedicine 2023;59: 101973
Published Online xxx
https://doi.org/10.1016/j.eclinm.2023.101973

Summary

Background Isolated pulmonary embolism (PE) appears to be associated with a specific clinical profile and sequelae compared to deep vein thrombosis (DVT)-associated PE. The objective of this study was to identify clinical characteristics that discriminate both phenotypes, and to characterize their differences in clinical outcome.

Methods We performed a systematic review and meta-analysis of studies comparing PE phenotypes. A systematic search of the electronic databases PubMed and CENTRAL was conducted, from inception until January 27, 2023. Exclusion criteria were irrelevant content, inability to retrieve the article, language other than English or German, the article comprising a review or case study/series, and inappropriate study design. Data on risk factors, clinical characteristics and clinical endpoints were pooled using random-effects meta-analyses.

Findings Fifty studies with 435,768 PE patients were included. In low risk of bias studies, 30% [95% CI 19–42%, I^2 = 97%] of PE were isolated. The Factor V Leiden [OR: 0.47, 95% CI 0.37–0.58, I^2 = 0%] and prothrombin G20210A mutations [OR: 0.55, 95% CI 0.41–0.75, I^2 = 0%] were significantly less prevalent among patients with isolated PE. Female sex [OR: 1.30, 95% CI 1.17–1.45, I^2 = 79%], recent invasive surgery [OR: 1.31, 95% CI 1.23–1.41, I^2 = 65%], a history of myocardial infarction [OR: 2.07, 95% CI 1.85–2.32, I^2 = 0%], left-sided heart failure [OR: 1.70, 95% CI 1.37–2.10, I^2 = 76%], peripheral artery disease [OR: 1.36, 95% CI 1.31–1.42, I^2 = 0%] and diabetes mellitus [OR: 1.23, 95% CI 1.21–1.25, I^2 = 0%] were significantly more frequently represented among isolated PE patients. In a synthesis of clinical outcome data, the risk of recurrent VTE in isolated PE was half that of DVT-associated PE [RR: 0.55, 95% CI 0.44–0.69, I^2 = 0%], while the risk of arterial thrombosis was nearly 3-fold higher [RR: 2.93, 95% CI 1.43–6.02, I^2 = 0%].

Interpretation Our findings suggest that isolated PE appears to be a specific entity that may signal a long-term risk of arterial thrombosis. Randomised controlled trials are necessary to establish whether alternative treatment regimens are beneficial for this patient subgroup.

Funding None.

Keywords: Pulmonary embolism; Venous thromboembolism; Systematic review; Meta-analysis; Epidemiology

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Research in context

Evidence before this study

Isolated pulmonary embolism (PE) appears to be associated with a different clinical profile and risks than deep vein thrombosis (DVT)-associated PE. It is unclear whether isolated PE should be considered a separate clinical entity that potentially requires alternative therapy. We searched PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) using the search queries *'((((((("isolated pulmonary embolism") OR "isolated PE") OR "PE without DVT" OR "without concomitant deep vein thrombosis") OR "concomitant DVT") OR "without peripheral VTE") OR "DVT-associated PE") OR "concurrent deep vein thrombosis"'* for PubMed and the search query *'isolated pulmonary embolism'* (without apostrophes) for CENTRAL, from inception until respectively November 1st, 2022 and January 27th, 2023.

Added value of this study

This study analysed data of 435,768 patients with pulmonary embolism, providing the first ever synthesis of evidence on differences in clinical profile, molecular profile and clinical outcome between isolated PE and DVT-associated PE. This synthesis demonstrated that prevalent cardiovascular disease is consistently more frequently represented among patients with isolated PE, and that such patients appear to be at increased risk of arterial thrombosis. Simultaneously, a lower risk of recurrent VTE was observed for isolated PE compared to DVT-associated PE, with no difference in all-cause mortality. The majority of patients with isolated PE were women.

Implications of all the available evidence

Isolated PE should be recognised as a separate clinical entity. Randomised controlled trials are required to evaluate whether prioritising the prevention of arterial thrombotic events could result in improved clinical outcome for this patient subgroup.

Introduction

In recent years, studies have increasingly noted differences between isolated pulmonary embolism (PE), a pulmonary thrombus diagnosed without concomitant deep vein thrombosis (DVT), and DVT-associated PE. The first difference highlighted concerned the prevalence of the Factor V Leiden mutation (*F5* G1691A), a missense substitution that renders activated coagulation factor V resistant to inactivation by activated protein C, facilitating excessive thrombin generation. In patients with isolated PE, the prevalence of this common variant (~20% of patients with thromboembolism [VTE][1]) was found to be half that of patients with DVT-associated PE, a finding that became known as the 'Factor V Leiden paradox'.[2] This paradox illustrated for the first time that the natural history of isolated PE may differ from that of DVT-associated PE.

A second notable finding was that cardiac disease appears to be more prevalent among patients with isolated PE than among patients with DVT-associated PE.[3,4] Large cross-sectional studies have provided evidence that atrial fibrillation, coronary artery disease, history of myocardial infarction and stroke, and cardiomyopathy and (left-sided) heart failure are overrepresented in patients with isolated PE.[3–5] Prospective data suggests that the risk of arterial thrombosis remains elevated over time in this group,[6,7] even after adjustment for prevalent comorbidities and medication intake. A recent proteomic investigation of PE phenotypes found that pro-inflammatory proteins were especially upregulated in isolated PE in the acute phase of disease, and that these same proteins were prognostic for the development of a first event a median of 2.9 years in advance in cancer-free individuals from the general population.[8] These findings suggest a chronic inflammatory process in the pathogenesis of isolated PE, which may contribute to the apparent acceleration of atherosclerosis in this subgroup.

A meta-analysis of randomised controlled trials and prospective cohort studies investigating recurrent VTE risk following discontinuation of anticoagulant therapy for a first unprovoked event showed that the recurrence risk associated with DVT-associated PE is 1.5-fold higher than that of isolated PE.[9] To date, no trials with primary endpoints besides venous thromboembolic events or bleeding have been conducted. Moreover, patients with provoked primary events are typically excluded from trials, which may further obscure relevant differences. The body of evidence regarding differences between both PE phenotypes has not yet been summarised, preventing clear conclusions as to whether these may require distinct therapeutic strategies. The objective of this study was to identify those clinical characteristics that discriminate between PE phenotypes, and to characterise the differences in clinical outcome between phenotypes.

Methods

Literature search

A systematic search of the electronic databases PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Cochrane Central Register of Controlled Trials (CENTRAL, https://www.cochranelibrary.com/central) was conducted, using the search queries *'((((((("isolated pulmonary embolism") OR "isolated PE") OR "PE without DVT" OR "without concomitant deep vein thrombosis") OR "concomitant DVT") OR "without peripheral VTE") OR*

"DVT-associated PE") OR "concurrent deep vein thrombosis"' for PubMed and the search query *'isolated pulmonary embolism'* (without apostrophes) for CENTRAL. Databases were searched from inception until respectively November 1st, 2022 and January 27th, 2023.

Study selection

Titles and abstracts of all identified articles were screened for overall eligibility by two individuals (bias and prevalence-adjusted κ for agreement on a random subset of 100 articles: 0.98 [95% CI: 0.89–0.99]), using the Abstrackr screening software (http://abstrackr.cebm.brown.edu).[10] Full text articles were retrieved for all articles for which the title or abstract indicated relevance to the subject matter. In a subsequent step, full text articles were assessed for eligibility for inclusion in the systematic review and meta-analysis. Duplicate articles were removed. Studies were included if they met the following pre-specified criteria, which were agreed upon in interdisciplinary team discussions of up to six individuals, including medical specialists, epidemiologists and biostatisticians: the article had to report quantitative data on both isolated and DVT-associated PE in humans, and present the data stratified by phenotype. Exclusion criteria were irrelevant content, inability to retrieve the full-text article, language other than English or German, the article comprising a review of primary studies, a case study or case series, and inappropriate study design. This latter criterion was met if the study design exhibited a high risk of selection bias, e.g. by only enrolling patients from specific subpopulations (e.g. women, chronic obstructive pulmonary disease, sickle cell disease, trauma, unprovoked VTE, COVID-19), or by employing exclusion criteria that would result in severely diminished representativity of the included patients (e.g. history/active cancer, cardiopulmonary disease, high-risk PE, arterial hypertension). Only for comparative DNA analyses was this criterion slightly relaxed, as their results were considered less susceptible to selection bias, such that studies employing exclusion criteria that would normally lead to exclusion from this review (e.g. active cancer) were also considered. Finally, studies that upon review were identified as having duplicate data with other studies were excluded, unless the non-overlapping data were clearly presented separately. Reasons for considering studies ineligible for inclusion were recorded in an electronic form.

Study quality assessment and data extraction

Information regarding the employed diagnostic protocols and modalities was recorded for the assessment of risk of bias due to diagnostic misclassification. Specifically, we registered whether systematic screening for DVT was performed in all PE patients, whether screening for DVT included assessment of presence of distal (i.e., infrapopliteal) DVT, which modality was used to diagnose DVT, and which modality was used to diagnose PE. Applicable items from two risk of bias tools were used to assess the risk of bias of the included studies: items from the Office of Health Assessment and Translation (OHAT) risk of bias tool,[11] and items from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[12] Two persons assessed risk of bias, with disagreements resolved by discussion. Studies were deemed at low risk of bias if they were evaluated to be at simultaneous low risk of bias due to patient selection, quality of the reference diagnostic protocols and modalities (jointly for PE and DVT), and systematic application of diagnostic protocols and modalities. If any of these criteria were not adequately met, the study was considered at moderate to high risk of bias.

All variables reported in the identified full text articles were recorded in an electronic form. In case of uncertainty regarding the accuracy of data as reported in articles (e.g., due to mismatch of absolute and relative frequencies), the authors of the primary studies were contacted for clarification. For dichotomous variables, unadjusted absolute frequencies (i.e., number of individuals with a given trait) were extracted. For continuous variables, the reported mean and standard deviation, median and interquartile range (IQR), or median and range were recorded, as presented in the article. Data on inherited thrombophilia were only recorded for studies that systematically screened for thrombophilia by performing DNA analysis in all included study participants. To account for potential differences between studies due to ancestry, the study region was also registered.

Statistical analysis

The protocol for the systematic review was not preregistered. Odds ratios and 95% confidence intervals (CI) were computed from dichotomous data, applying the Haldane-Anscombe correction in case of cell counts of zero. Continuous data presented as median and IQR or the range were converted to mean and standard deviation using the Box–Cox method, implemented in the 'estmeans' R package.[13] Dichotomous non-comparative data were pooled as proportions with 95% confidence intervals after transformation by Freeman-Tukey double arcsine transformation. Comparative dichotomous data were pooled as odds ratios with 95% CI. Comparative continuous data were pooled as mean differences with 95% CI. Comparative outcome data were pooled as relative risks with 95% CI. Random-effects meta-analyses using the Paule-Mandel estimator for τ^2 and with Hartung-Knapp adjustment were used for pooling.[14] Variance due to heterogeneity between studies was reported with the I^2 statistic. If no between-study heterogeneity was observed, the results of fixed-effects models were reported. For cross-sectional characteristics, all variables reported in at least 3 separate studies were meta-analysed. All clinical

outcome data were meta-analysed, even if reported in only two studies. Subgroup analysis was performed for low vs moderate to high risk of bias. Meta-regression analyses were performed in cases of residual heterogeneity between studies when the variable was reported in at least five studies to test for moderation of study-level results by mean age difference between phenotypes, by systematic screening for DVT, and by study region in case of observed heterogeneity in genetic comparisons. Funnel plots with Egger regression tests were generated for all variables reported in at least five studies to evaluate funnel plot asymmetry as a potential indicator of publication bias. All meta-analyses and meta-regression models were implemented using the R package 'metafor'.[15] A two-sided p-value below 0.05 was considered statistically significant. Significance was reported at both nominal and Bonferroni-adjusted thresholds. All data pre-processing and analyses were performed in the statistical programming environment R, version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org).

Ethical approval and informed consent

This study used published data from existing studies. The requirement for ethical approval and informed consent was waived for this study.

Role of the funding source

There was no funding source for this study. All authors had full access to all data. All authors take responsibility for the accuracy of the reporting of data and for the decision to submit the manuscript for publication.

Results

Study inclusion

A total of 5568 articles were identified for screening (Fig. 1). After removing duplicates and irrelevant articles, 412 full-text articles were assessed for eligibility. Fifty articles were considered eligible for the final synthesis of evidence in a systematic review and meta-analysis,[3–8,16–58] representing a total of 435,768 patients with PE, of whom 288,258 presented with isolated PE. Systematic DNA analysis was performed in 13 studies. Individual reasons for exclusions of articles, the final selection of 50 studies, and all extracted study data are provided as Supplemental Data. A summary of study characteristics for all included studies is given in Table 1, and the risk of bias assessment is provided in Supplemental Fig. S1.

Prevalence of isolated PE

The proportion of PE described in each article as isolated is shown in Fig. 2. The overall proportion described as isolated was 46% (95% confidence interval, CI: 39–53%), with high between-study heterogeneity (I^2 = 100%). Subgroup analysis by risk of misclassification bias revealed that the proportion of isolated PE was 30% on average (95% CI 19–42%) in studies at low risk of bias (number of studies = 11, I^2 = 97.3%,

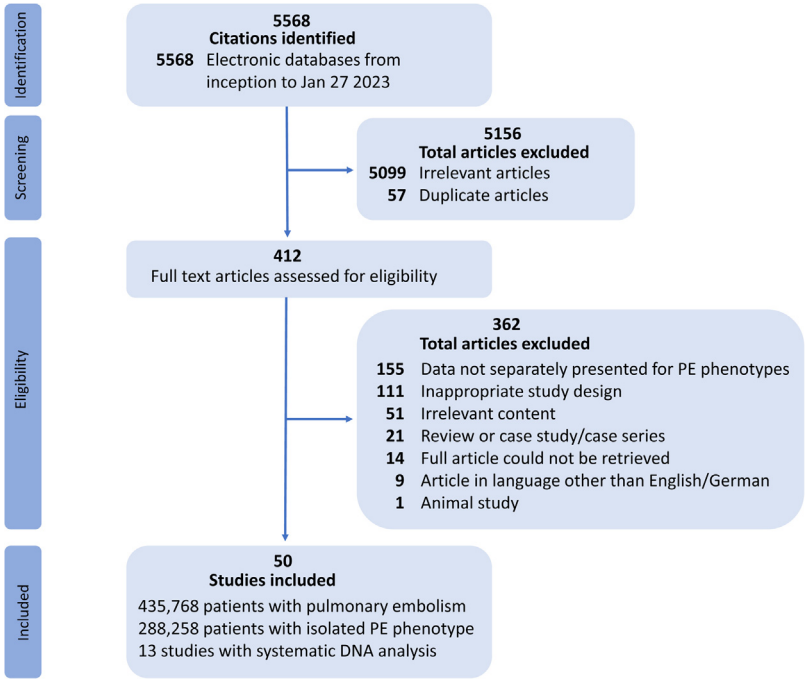

Fig. 1: **Flowchart for the selection of studies for systematic review and meta-analysis.**

First author, year of publication	Study design, observation period	Study country/ region	Setting	N_1 (isolated PE)	N_2 (DVT-associated PE)	Inclusion/exclusion criteria	PE diagnostic modality	DVT diagnostic modality	Systematic DVT screening	Distal DVT included in screening	Systematic DNA analysis
Al Sayegh, 2008	Prospective multi-centre registry, 60-day period in 2003	Gulf region	28 major hospitals and health care centres	35	20	Consecutive acute symptomatic VTE	Lung scan/ blood gases/ D-dimer/ others	US/D-dimer/ venography/ various	Not reported	Not reported	No
Cambron, 2020	Prospective cohort study, 2013–2019	United States of America	Tertiary care centre	550	471	Consecutive acute PE patients treated for at least 3 months with anticoagulation, excluded those without consent (n = 97) and those with <3 months follow-up (n = 70)	CT/MRI	US/CTV	No	Yes	No
Cordeanu, 2019	Prospective cohort study, 2013–2018	France	Tertiary care centre	310	727	Consecutive patients hospitalised with VTE, excluded those with <3 months follow-up (n = 46)	CTPA/V/Q	US	Yes	Yes	No
De Moerloose, 2000	Cross-sectional study of consecutive cases, 1996–1997	Switzerland	Tertiary care centre	57	42	Consecutive outpatients referred for suspected VTE	CTPA/V/Q	US	Yes	No	Yes
Douek, 2020	Retrospective registry of consecutive cases, 2015–2016	Switzerland	Tertiary care centre	81	38	Consecutive patients who underwent CTPA and CTV for suspected PE, excluded age<50	CTPA	CTV	Yes	Yes	No
Erkekol, 2006	Case-control study with unselected cases, period not specified	Turkey	Tertiary care centre	38	26	Unselected in- and outpatients with confirmed PE	CTPA/V/Q	US	Yes	Not reported	Yes
Girard, 1999	Retrospective registry of consecutive cases 1984–1988	France	Tertiary care centre	39	174	Confirmed PE who underwent lower limb venography (213/ 228 consecutive patients)	Pulmonary angiography	Venography	Yes	Yes	No
Goldhaber, 2022	Prospective multi-center observational cohort study of cases (RE-COVERY DVT/PE), 2016–2018	International (34 countries)	229 hospitals reflecting standard of care in each country, not otherwise specified	617	580	Diagnosis of acute DVT and/or PE no more than 6 months ago, ≥18 years old. Excluded those with need for anticoagulation unrelated to VTE (n = 1), participation in other trial for VTE indication.	Not reported	Not reported	Not reported	Not reported	No
Grifoni, 2012	Retrospective registry of consecutive cases 2006–2008	Italy	Tertiary care centre	75	144	Consecutive patients with first VTE event without cancer or antiphospholipid syndrome	CTPA/V/Q	US	Yes	Not reported	Yes
Hirmerova, 2014	Retrospective registry of consecutive cases 2003–2011	Czech republic	Tertiary care centre	196	86	Confirmed VTE, patient >18 years old, 3 weeks after event	CTPA/V/Q	US	No (checked in 95.9% of PE cases)	Not reported	Yes
Hirmerova, 2018	Retrospective registry of consecutive cases 2003–2015	Czech republic	Tertiary care centre	126	302	Confirmed VTE, patient >18 years old, excluded those who did not receive US (n = 10)	CTPA/V/Q	US	Yes	Yes	No

(Table 1 continues on next page)

First author, year of publication	Study design, observation period	Study country/ region	Setting	N_1 (isolated PE)	N_2 (DVT-associated PE)	Inclusion/exclusion criteria	PE diagnostic modality	DVT diagnostic modality	Systematic DVT screening	Distal DVT included in screening	Systematic DNA analysis
(Continued from previous page)											
Imberti, 2017	Epidemiological survey of Italian patients (disseminated by medical specialists), 6 months in 2014	Italy	Electronically administered survey	22	88	Adult patients with suspected VTE receiving rivaroxaban at time of study period	Patient survey	Patient survey	No	Not reported	No
Ivanov, 2007	Case-control study with consecutive cases, period not specified	Bulgaria	Tertiary care centre	27	24	Consecutive patients with confirmed PE. Excluded patients with malignancy, obesity class II/III and recent abdominal or orthopaedic surgery (n not specified)	Chest X-ray/ V/Q	US	Not reported	Not reported	Yes
Jimenez, 2010	Prospective cohort study, 2003–2007	Spain	Tertiary care centre	345	362	Consecutive adult outpatients with confirmed first episode of acute symptomatic PE, excluding patients who did not complete US	CTPA/V/Q	US	Yes	Yes	No
Johnson, 2006	Retrospective registry of consecutive patients, 15-week period in 2003	United States of America	Two community emergency departments	30	10	Consecutive adult patients who underwent CTPA and CTV for suspicion of PE	CTPA	CTV	Yes	Yes	No
Jun, 2006	Case-control study with consecutive cases, 2000–2004	China	Tertiary care centre	54	35	Consecutive patients with symptomatic VTE	Pulmonary angiography/ V/Q	US/venography	No	Not reported	Yes
Kalva, 2008	Retrospective registry of consecutive patients, 2005–2006	United States of America	Tertiary care centre	154	75	Consecutive in- and outpatients who underwent CTPA and CTV for suspicion of PE	CTPA	CTV	Yes	No	No
Kamerkar, 2016	Retrospective multi-centre registry of consecutive patients, 2006–2010	India	3 hospitals	73	124	Consecutive in- and outpatients with confirmed VTE by (CT)PA and/or US	CTPA/V/Q	US	No	Not reported	No
Karimi, 2015	Case-control study with consecutive cases, 2009–2011	Iran	Tertiary care centre	37	23	Consecutive patients with confirmed VTE	V/Q	US	Not reported	Yes	Yes
Keller, 2015	Prospective multi-center cohort study, 2011–2013	Germany	21 hospitals and a coagulation service	91	204	Adult patients with indication for treatment with vitamin K antagonists	Medical records	Medical records	No	Not reported	No
Keller, 2020	Retrospective analysis of nationwide registry of inpatients, 2011–2014	Germany	Nationwide inpatient sample (Federal Statistical Office of Germany)	220,109	126,477	All inpatients diagnosed with PE (ICD-10 code I26)	Medical records	Medical records	Not reported	Not reported	No
Kluge, 2006	Cross-sectional study of consecutive cases, 2002–2005	Germany	Tertiary care centre	11	65	Consecutive inpatients with suspected PE, excluded cardiogenic shock or prolonged low cardiac output and an implanted device (n = 2)	Thorax MRI	MR venography	Yes	Yes	No
Kröger, 2014	Prospective multi-center registry, 2010–2012	Germany	17 specialised practices and hospitals	32	104	Consecutive adult acute VTE patients	Not reported	Not reported	Not reported	Not reported	No
Lee, 2016	Prospective cohort study, 2013–2015	South Korea	Tertiary care centre	77	64	Patients with confirmed PE, diagnosed with CTPA and US/ CTV, excluded those without screening for DVT (n = 36)	CTPA	US/CTV	No	Yes	No

(Table 1 continues on next page)

First author, year of publication	Study design, observation period	Study country/ region	Setting	N_1 (isolated PE)	N_2 (DVT-associated PE)	Inclusion/exclusion criteria	PE diagnostic modality	DVT diagnostic modality	Systematic DVT screening	Distal DVT included in screening	Systematic DNA analysis
(Continued from previous page)											
Lee, 2021	Retrospective cohort study, 2003–2019	South Korea	Tertiary referral centre	322	690	Patients with confirmed PE according to CTPA who also underwent CTV or US for DVT. Excluded patients with CTEPH (n = 21), those without CT (n = 22), and those treated in outpatient setting (n = 38).	CTPA	US/CTV	Yes	Yes	No
Lucena, 2009	Prospective registry of consecutive lethal PE cases, 2003–2006	Spain	Forensic pathology service	9	22	All deaths in which the pathological diagnosis was PE, autopsy performed within 18 h of death	Autopsy	Autopsy	Yes	Yes	No
Margaglione, 2000	Case-control study with consecutive cases, 1996–1999	Italy	5 tertiary care centres	126	175	VTE cases consecutively referred to one of five thrombosis centres. Excluded patients <18 years of age (n = 14).	CTPA/V/Q	US/CTV	Yes	Not reported	Yes
Meyer, 2001	Cross-sectional study with consecutive cases, 1994–1996	France	2 neighbouring hospitals	236	192	Consecutive patients with symptomatic VTE	V/Q	US	No	Not reported	Yes
Monreal, 2006	Prospective multi-centre cohort study (RIETE), 2001–2006	Spain	Spanish hospitals (at time of publication)	3968	2287	Consecutive patients with symptomatic VTE that did not participate in other trials and had at least 3 months of follow-up.	CTPA/V/Q	US/CTV/ impedance plethysmography	Not reported	Not reported	No
Nishiwaki, 2020	Retrospective multi-centre cohort study (COMMAND-VTE), 2010–2014	Japan	29 Japanese hospitals	69	586	Consecutive patients with confirmed symptomatic VTE, excluded patients with thrombus in vena cava (n = 65), upper extremities (n = 12), abdominal vein (n = 8) and right atrium (n = 1), cardiac arrest/collapse at diagnosis (n = 80), and no US at examination (n = 1021)	CTPA/V/Q/ PA/autopsy	US	Yes	Yes	No
Okumus, 2008	Case-control study with consecutive cases, 1998–2008	Turkey	Tertiary care centre	80	74	Consecutively referred patients with confirmed VTE, excluded those with history of VTE (n = 18)	CTPA/V/Q	US/CTV	Yes	Not reported	Yes
Ordonez, 2000	Case-control study with consecutive cases, period not specified	Spain	Tertiary care centre	77	21	Consecutive patients with confirmed VTE	CTPA/V/Q	CTV/US	No	Not reported	Yes
Palareti, 2019	Prospective multi-centre cohort study (START2), 2012–2017	Italy	54 Italian hospitals	693	2880	Consecutively enrolled patients with anticoagulant therapy, excluded if therapy started >30 days before thrombotic event, if life expectancy was <3 months, or if they would leave the study region within six months after enrolment	CTPA/V/Q	US	Yes	Yes	No

(Table 1 continues on next page)

First author, year of publication	Study design, observation period	Study country/ region	Setting	N_1 (isolated PE)	N_2 (DVT-associated PE)	Inclusion/exclusion criteria	PE diagnostic modality	DVT diagnostic modality	Systematic DVT screening	Distal DVT included in screening	Systematic DNA analysis
(Continued from previous page)											
Prandoni, 2009	Retrospective analysis of regional registry of inpatients, 2000–2006	Italy	Electronic database of discharge records from Italian Veneto region	9079	2157	All patients with first inpatient hospital discharge diagnosis of PE (in any of six diagnosis fields), excluded patients <60 years	Medical records	Medical records	No	Not reported	No
Pribish, 2020	Retrospective analysis of consecutive cases using internal billing claims database + prospective registry of patients with pulmonary embolism response team (PERT) consult, 2012–2018	United States of America	Tertiary care centre	562	662	All patients with confirmed acute PE	Medical records	Medical records	Not reported	Yes	No
Sakuma, 2009	Prospective multi-centre cohort study via survey-collected data, 2006	Japan	Japanese hospitals with >100 beds	140	210	All patients with confirmed VTE, excluded data from 17 institutes that had closed or merged	CTPA/V/Q/ MRI/autopsy	US/CTV/MRV/ radioisotope venography	Not reported	Not reported	No
Sanders, 2022	Retrospective, multi-centre observational registry (BBC-VTE), 2012–2014; 2016–2018	United Kingdom	Three Trusts in the Birmingham and Black county area	1222	87	All patients ≥18 years with radiologically proven PE or DVT. Excluded upper limb DVT, portal vein VT, non-pulmonary arterial thrombosis, pregnant patients.	CTPA/V/Q	US	Not reported	Not reported	No
Scheres, 2017	Multi-centre randomised double-blind controlled trial (Hokusai-VTE), 2010–2012	International (35 countries)	436 hospitals	955	388	Adult patients with confirmed acute VTE, excluding pregnant patients, those with thrombectomy, caval filter, or fibrinolytic agent for treatment of index event, more than 48 h pre-treatment with anticoagulation pre-randomisation, creatinine clearance <30 mL/min, significant liver disease, active cancer requiring LMWH, active or high risk of bleeding, chronic treatment with NSAIDs, treatment with aspirin >100 mg/day or dual antiplatelet therapy, concurrent P-gp inhibitor therapy	Not reported	Not reported	No	No	No
Schwartz, 2012	Retrospective analysis of all CTPA with protocol for PE, 2008–2010	United States of America	Tertiary care centre	15	131	Consecutive patients who underwent CTPA with protocol for PE	CTPA	US	Yes	Yes	No
Sevestre, 2010	Prospective multi-centre cohort study (Optimev), 2004–2006	France	359 board-certified vascular medicine specialists evenly distributed geographically throughout France	148	426	Consecutive hemodynamically stable patients with clinical suspicion of VTE, excluding patients <18 years (n = 16) and those not eligible for follow-up due to residence outside France, homelessness or for whom case-report form completion was delayed (n = 75)	CTPA/V/Q	US	Yes	Yes	No

(Table 1 continues on next page)

First author, year of publication	Study design, observation period	Study country/ region	Setting	N_1 (isolated PE)	N_2 (DVT-associated PE)	Inclusion/exclusion criteria	PE diagnostic modality	DVT diagnostic modality	Systematic DVT screening	Distal DVT included in screening	Systematic DNA analysis
(Continued from previous page)											
Singh, 2021	Retrospective observational study of consecutively enrolled VTE patients, 2017–2019	India	Tertiary care centre	58	68	Consecutive VTE patients diagnosed according to standard protocols. Patients with missing data were excluded (n = 27).	Not reported	Not reported	Not reported	Not reported	No
Sivananthan, 2014	Retrospective analysis of all US and CTPA performed within 1 day of each other, period not specified	United States of America	Tertiary care centre	17	18	Consecutive US and CTPA for suspicion of PE performed within 1 day of each other, excluding indeterminate CTPA (n = 6) and CTPA performed in patients without symptoms of PE (n = 7)	CTPA	US	Yes	Yes (until lower calf, excluding anterior tibial veins)	No
Sørensen, 2011	Nested case–control study with consecutive cases, 1980–2007	Denmark	National patient registry (Danish National Patient Registry)	45,282	4680	Inpatients with a first recorded hospitalization for PE or DVT as primary or secondary discharge diagnosis	Medical records	Medical records	Not reported	Not reported	No
Tadlock, 2015	Retrospective analysis of consecutive autopsies, 2002–2010	United States of America	Los Angeles County Forensic Medical Division	86	294	All autopsies with PE as cause of death, excluding those without dissection for origin of PE (n = 111), amniotic embolisms (n = 5), air embolisms (n = 3), fat embolism (n = 1)	Autopsy	Autopsy	Yes	Yes	No
Ten Cate, 2020	Prospective cohort study (VTEval), 2013–2020	Germany	Tertiary care centre	63	210	Consecutive adult patients with suspicion of VTE	CTPA/V/Q	US	Yes	Yes	No
Ten Cate, 2021	Prospective multi-centre cohort study (GMP-VTE), 2013–2020	Germany	8 German hospitals	96	276	Consecutive adult patients with confirmed acute VTE, excluding those with active cancer (n = 80)	CTPA/V/Q	US	Yes	Yes	Yes
Van Stralen, 2008	Population-based case–control study with consecutive cases (MEGA), 1999–2004	The Netherlands	6 anti-coagulation clinics	885	365	Consecutive patients between 18 and 70 years of age with a first episode of VTE, excluding those who could not complete a questionnaire because they died (n = 280) or had end stage disease (n = 82), those who did not give permission to obtain medical records (n = 861) or DNA (n = 250)	CTPA/V/Q	US	Yes	Yes	Yes
Wang, 2020	Retrospective analysis of consecutive cases, 2015–2016	China	Tertiary care centre	88	304	Consecutive patients with confirmed PE, excluding patients with incomplete clinical data (n = 93)	CTPA	US	Yes	Yes	No
Wildberger, 2002	Cross-sectional study of consecutive cases, 2000–2001	Germany	Tertiary care centre	13	47	Consecutive patients with suspicion of PE	CTPA	CTV	Yes	No	No
Yasui, 2007	Cross-sectional study of consecutive cases, 2003–2005	Japan	Tertiary care centre	13	34	Consecutive patients with suspicion of PE	CTPA	CTV	Yes	Yes (until upper calf)	No

Table 1: **Characteristics of studies included in the meta-analysis, alphabetically ordered by first author surname.**

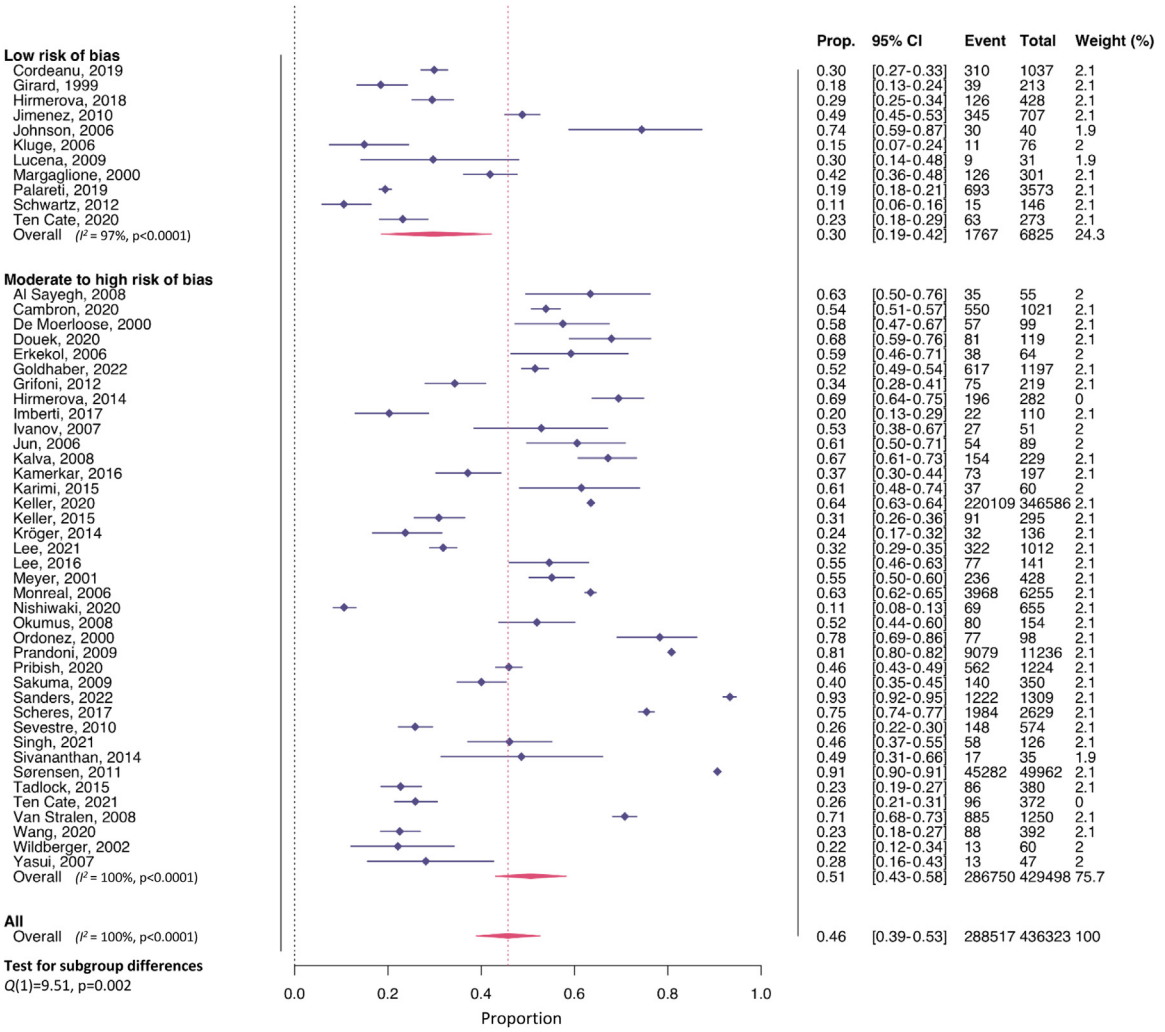

***Fig. 2:* Proportion of isolated pulmonary embolisms, by risk of diagnostic misclassification bias**. A meta-analysis of proportions (isolated PE/all PE), stratified by risk of bias assessment.

between-group Q (1) = 9.5, p = 0.002), but heterogeneity was not resolved by subgrouping. PE was predominantly diagnosed by a combination of computed tomography pulmonary angiography (CTPA) or ventilation/perfusion (V/Q) scintigraphy, with CTPA alone the second most frequently applied modality (Fig. 3A). The majority of studies used ultrasonography to diagnose DVT (Fig. 3B), although venography was also performed in some of the studies. Systematic screening for DVT was done in all PE patients in 54% of studies, with the remainder reporting not having done so (22%), or failing to report whether this was done (Fig. 3C). Nearly half of studies examined the infrapopliteal veins for distal DVT (Fig. 3D). Meta-regression analyses to identify moderators of the meta-analytic prevalence estimate were performed, indicating that studies employing universal screening for DVT had significantly (p = 0.0075) lower estimates of the proportion of isolated PE (Supplemental Table S1). Nevertheless, the residual I^2 statistic remained >99 per cent.

Clinical and molecular profile of isolated PE

There was no relevant age difference between PE phenotypes (0.64 years, 95% CI, −1.00; 2.29, p = 0.42; 22 studies, I^2 = 98.2%; Supplemental Fig. S2). The proportion of isolated PE patients presenting with specific clinical characteristics is shown in Fig. 4. The majority (57%) of patients with isolated PE were women. The prevalence of prothrombotic polymorphisms was low, with 8% (95% CI, 5–11%) being at least heterozygous for the Factor V Leiden (FVL) mutation and 5% (3–7%) for the prothrombin (*F2*) G20210A mutation. Similar low prevalences were observed for antithrombin, protein C and protein S deficiencies. Various comorbidities

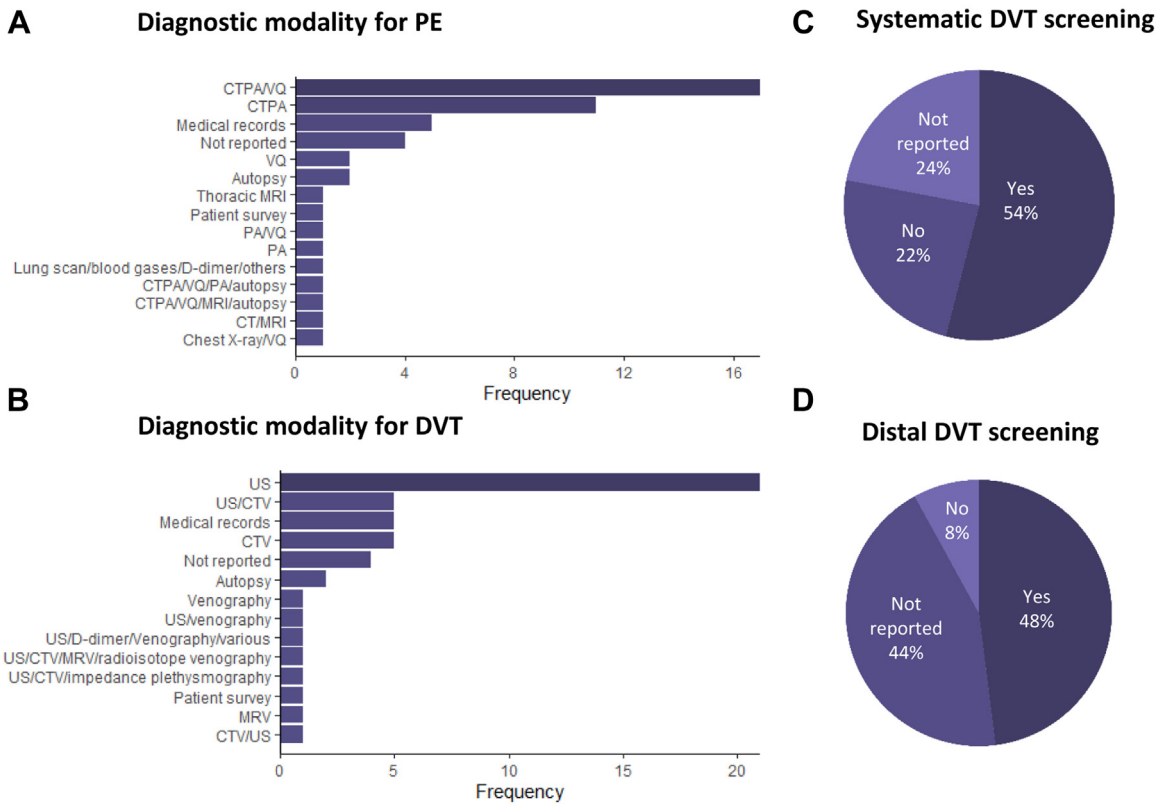

***Fig. 3*: Diagnostic procedures used in the included studies**. Panels A and B denote the frequencies of diagnostic modalities used to diagnose PE and DVT, respectively. Panels C and D summarise the stringency of the diagnostic protocols across studies.

were highly prevalent in patients with isolated PE, although heterogeneity between studies was substantial for all proportions. A direct comparison of patients with isolated PE vs DVT-associated PE (Fig. 5) revealed several significant differences in the clinical profile. Women were more frequently represented in this phenotypic group (28 studies, OR: 1.30, 95% CI 1.17–1.45, $p < 0.0001$; $I^2 = 78.7\%$). Patients with isolated PE less frequently had one of the two main congenital thrombophilias than those with DVT-associated PE (FVL, 13 studies, OR: 0.47, 95% CI 0.37–0.58, $p < 0.0001$; *F2* G20210A, 11 studies, OR: 0.55, 95% CI 0.41–0.75, $p = 0.0001$), with no detectable heterogeneity between studies. Among VTE-provoking risk factors, presence of a central venous catheter and recent (invasive) surgery were positively associated with presentation as isolated PE. Regarding comorbidities, cardiovascular diseases were consistently more frequently represented among patients with isolated PE relative to those with DVT-associated PE: myocardial infarction (MI), (left-sided) heart failure, atrial fibrillation or flutter, coronary artery disease, and peripheral artery disease. Chronic lung disease was also more prevalent in isolated PE patients than among patients with DVT-associated PE. Of traditional cardiovascular risk factors, only diabetes mellitus was associated with presentation as isolated PE over DVT-associated PE (12 studies, OR: 1.23, 95% CI 1.21–1.25, $p < 0.0001$, $I^2 = 0\%$). When applying a Bonferroni correction for 52 tests (corrected $\alpha = 0.0009$) to cover all investigated variables, female sex, FVL genotype, *F2* G20210A genotype, recent surgery, history of MI, heart failure, peripheral artery disease and diabetes mellitus remained significantly different between phenotypes.

Sensitivity analyses and risk of publication bias

In meta-regression models, the observed associations for recent immobilisation, atrial fibrillation or flutter and arterial hypertension were significantly moderated by study-level differences in mean age between participants of both PE phenotypes (Supplemental Table S2; Supplemental Fig. S3). Recent immobilisation was less prevalent among isolated PE after adjustment (OR: 0.83, 95% CI: 0.67–1.02, $p = 0.077$). The adjusted odds ratio for atrial fibrillation or flutter was 1.22 (95% CI 1.06–1.39, $p = 0.012$; 8 studies, residual $I^2 = 0\%$), representing an attenuation compared to the unadjusted relationship. Age-adjustment also resolved heterogeneity for arterial hypertension, resulting in an adjusted odds ratio of 0.80 (95% CI 0.72–0.89, $p = 0.0021$; 9

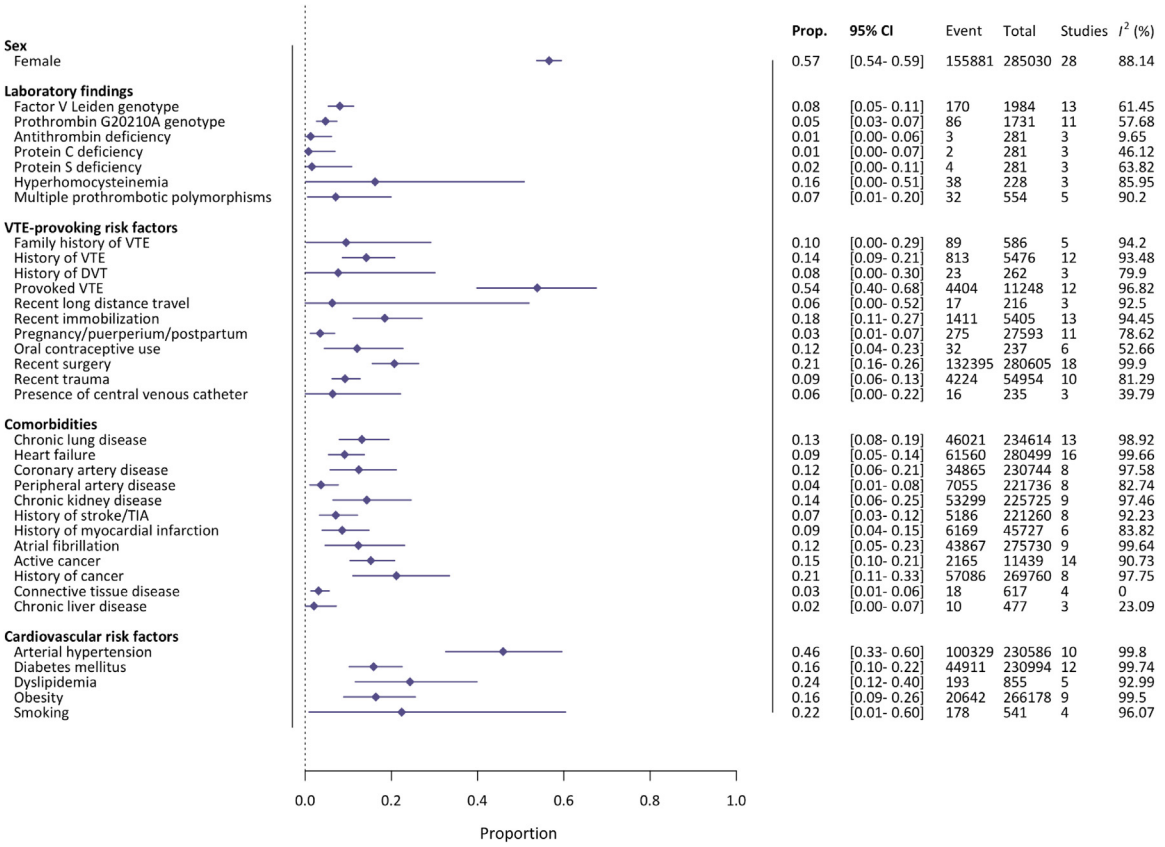

Fig. 4: **Prevalence of risk factors and comorbidities among patients with isolated pulmonary embolism**. Each line represents a separate meta-analysis of proportions, representing the prevalence of a given characteristic within the isolated PE subgroup with a proportion with 95% confidence interval. The number of events (i.e. the characteristic of interest), the total number of isolated PE patients within which the characteristic could be evaluated, the number of studies, and the heterogeneity statistic are reported alongside it.

studies, residual $I^2 = 0\%$), indicating lower prevalence in isolated PE compared to DVT-associated PE. The association between recent trauma and phenotype was significantly moderated by whether systematic DVT screening had been performed (Supplemental Table S3; Supplemental Fig. S4). The adjusted odds ratio for recent trauma was 1.56 (95% CI 1.39–1.77, p < 0.0001; 10 studies, residual I^2 = 0%), indicating significantly higher prevalence among isolated PE patients than those with DVT-associated PE in studies where systematic DVT screening was not performed. All other results remained unchanged by the sensitivity analyses. Egger's tests revealed significant funnel plot asymmetry for the published data for recent trauma, with an underrepresentation of findings with an OR>1 (t = –3.31, df = 8, p = 0.01), potentially indicating publication bias (Supplemental Table S4).

Thrombus localisation and symptoms

A synthesis of evidence regarding thrombus localisation and symptomatology for isolated PE patients is provided in Supplemental Fig. S5. Both categories of traits were highly heterogeneous between studies, and not frequently reported. Isolated PE were more often localised in peripheral (i.e., segmental or subsegmental) pulmonary arteries than DVT-associated PE (4 studies, OR: 1.70, 95% CI 1.33–2.18, p < 0.0001, I^2 = 0%). Dyspnoea (4 studies, OR: 1.37, 95% CI 1.12–1.66, p = 0.0018, I^2 = 0%) and syncope were slightly more common in patients presenting with isolated PE (4 studies, OR: 1.64, 95% CI 1.12–2.42, p = 0.01, I^2 = 0%). Any DVT symptoms (5 studies, OR: 0.03, 95% CI 0.01–0.15, p = 0.003, I^2 = 67.3%) were substantially less prevalent among patients with isolated PE than in those with DVT-associated PE. Peripherally located thrombi remained significantly more prevalent among isolated PE patients after Bonferroni adjustment. Forest plots for all meta-analyses conducted are provided as Supplemental Figs. S6–S16.

Clinical outcome

Clinical outcome data were included in 11 out of 50 studies. Data were heterogeneously reported, using counts, proportions, incidence rates or hazard ratios.

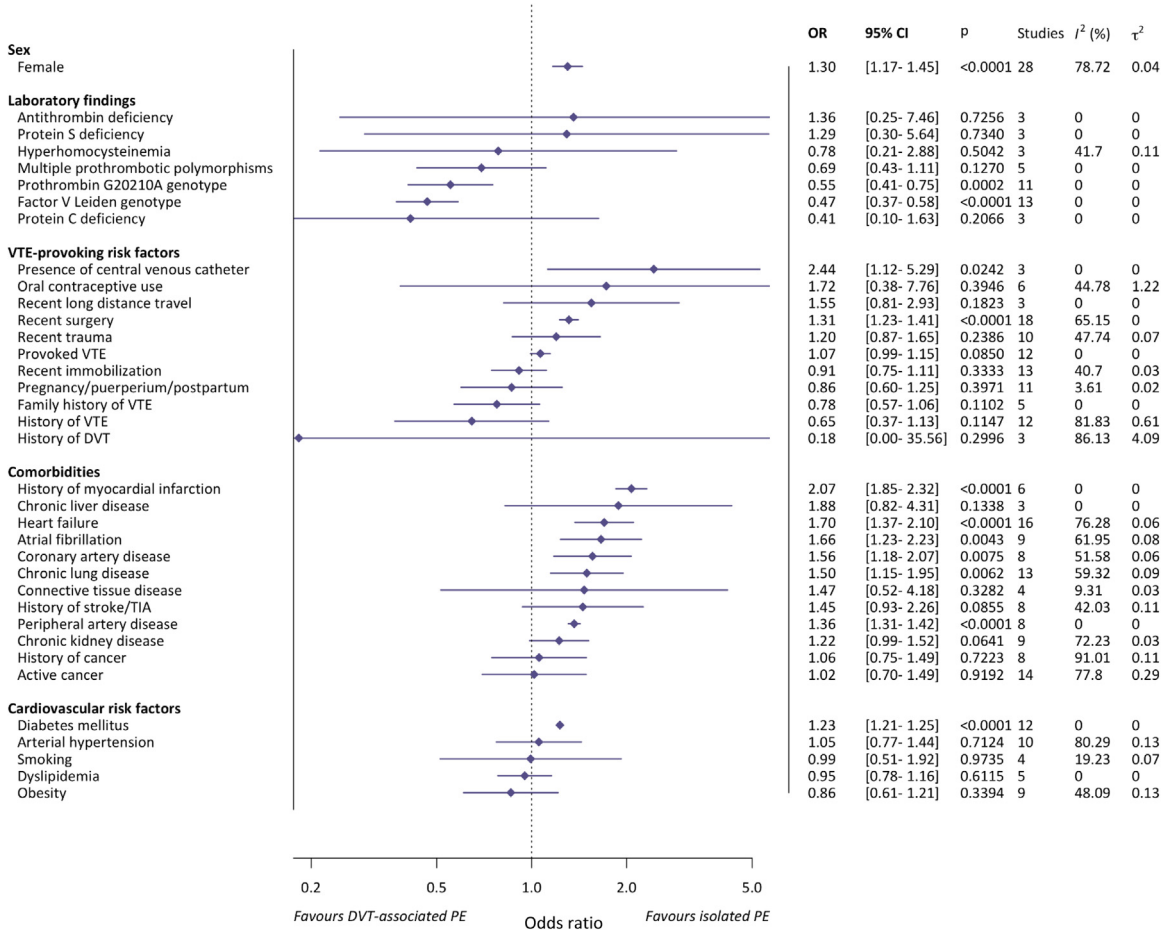

***Fig. 5:* Comparison of clinical profiles of isolated PE vs DVT-associated PE**. Each line represents a separate meta-analysis of comparative dichotomous data, showing the pooled odds ratio, 95% confidence interval and p-value for association of a given characteristic with isolated PE (vs DVT-associated PE). The number of studies and the heterogeneity statistic are reported alongside it.

Follow-up durations were also highly variable. Ten studies reported on (all-cause) death,[5–7,18,32,37,41,42,48,49] 6/11 studies included data on recurrent VTE events (including superficial vein thrombosis),[6,7,18,33,41,42,59] 5/11 studies on fatal, major or clinically relevant non-major bleeding,[5,6,18,41,42] and 2/11 on arterial thrombotic events, an aggregate of acute MI, stroke or TIA.[6,7] Individual and pooled crude relative risks for these endpoints in isolated PE patients compared to DVT-associated PE patients are shown in Supplemental Fig. S17. Significant heterogeneity was observed for all-cause death and bleeding, which did not differ significantly between phenotypes (all-cause death, relative risk [RR]: 1.00, 95% CI 0.62–1.62, p = 1.00; bleeding, RR: 1.12, 95% CI 0.65–1.93, p = 0.61). Recurrent VTE occurred half as often in isolated PE as in DVT-associated PE (RR: 0.55, 95% CI 0.44–0.69, p < 0.0001), although a single study accounted for 65% of the pooled estimate. Conversely, arterial thrombotic events occurred nearly three times as often in isolated PE patients compared to those with DVT-associated PE (2 studies; RR: 2.93, 95% CI 1.32–6.02, p = 0.003). Both endpoints remained significant upon Bonferroni adjustment (corrected α, 0.05/4 = 0.0125). Egger's tests indicated significant funnel plot asymmetry for all-cause death (p = 0.004) and bleeding (p = 0.02), with the study by Keller et al.[5] representing a clear outlier for both endpoints (Supplemental Fig. S18).

Discussion

This systematic review and meta-analysis covering 435,768 unselected patients with PE has provided a comprehensive synthesis of the evidence on the clinical differences between isolated and DVT-associated PE. By recording all reported characteristics of patients of both phenotypes, a large number of risk factors and outcomes could be evaluated. Due to the large number of studies included, power was sufficient to investigate several aspects. While setting-specific differences

resulted in substantial heterogeneity in prevalence estimates, including that of the isolated PE phenotype itself, many ratio estimates reflecting comparative differences between the two phenotypes were homogeneous both in terms of direction and effect size. Meta-regression models indicated that results were robust to differences in study-level characteristics.

The two PE phenotypes appear to differ in several key respects. Firstly, isolated PE appears to be more common in women than DVT-associated PE. More research is necessary to shed light on why this sex difference manifests. Secondly, the genetic background of patients with isolated PE is clearly distinct. Beyond the well-known factor V Leiden (FVL) paradox, the prothrombin G20210A mutation, the polymorphism that confers the second highest risk of venous thrombosis after FVL,[60] is also significantly less prevalent among patients with isolated PE. The FVL paradox has previously been hypothesised to be caused by differences in thrombus organisation and stability between carriers and non-carriers.[19,23,27,52] Under this hypothesis, non-carriers are presumed to have smaller and less organised (i.e., wall-adherent) thrombi, a higher rate of embolisation, and little to no residual thrombus in the deep veins post-embolisation. The recognition of a similar 'prothrombin paradox' in this study rules out that this mechanism would be FV-specific. An alternative, perhaps more parsimonious, explanation of both paradoxes would be that a comparatively large proportion of isolated PE is not driven by genetics, and is rather explained by other risk factors. Consistent with this notion, the provoking risk factor recent surgery (and recent trauma after age-adjustment) was over-represented among patients with isolated PE, which in combination with a lack of clear signal for immobilisation could indicate a relevant contribution of endothelial injury to the pathogenesis of such thrombi. In patients with COVID-19, it has recently become recognized that pulmonary microvascular endotheliopathy induces immunothrombosis in situ, supporting the notion that pulmonary clots need not arise systemically and can also result from local triggers.[61]

One of the most noteworthy findings of this analysis was that cardiovascular disease, especially with an atherosclerotic component, was consistently more frequently represented among patients with isolated PE. Among cardiovascular risk factors, only diabetes mellitus was significantly more prevalent in isolated PE than in DVT-associated PE. Consistently with cross-sectional evidence, studies reporting longitudinal outcomes, although limited in number, also suggested that the risk of arterial thrombosis (i.e. stroke, TIA and myocardial infarction) is persistently higher in patients with isolated PE than in those with DVT-associated PE. Competing explanations for this connection have been offered in the individual studies, which range from a chronic local inflammatory process resulting in both in situ thrombosis as well as accelerated atherogenesis,[5,7] to right-sided cardiac thrombi embolising to the pulmonary arteries.[3–5]

Irrespective of thrombus origin, the results of this study suggest that (i) isolated PE should be recognised as a separate clinical entity, and (ii) a diagnosis of isolated PE should be considered a tentative biomarker for an increased risk for arterial thrombosis. While outcome data are still very limited, ample cross-sectional data suggest that patients diagnosed with isolated PE, even in the face of potential misclassification, are at increased risk of cardiovascular disease. Conversely, the risk of recurrent VTE appears to be much lower for isolated PE patients. Given the large proportion of PE that may be classifiable as isolated, reconsideration of the optimal treatment strategy may be warranted for these patients. Multidisciplinary teams to manage complex PE cases, such as the increasingly proliferating PERTs (pulmonary embolism response teams), may contribute to better care by their more holistic assessment of the patient phenotype.[62,63] Randomised clinical trials should be designed to test whether extending the focus of treatment to include the broader management and long-term secondary/tertiary prevention of cardiovascular disease in these patients could result in improved clinical outcome at an acceptable safety profile. Dual pathway inhibition or other combined treatment approaches that have shown good results in long-term cardiovascular disease management are among the conceivable options.[64]

A primary limitation was that individual patient data were not used, and that syntheses of study level data can suffer from ecological bias. In addition, the majority of studies included in this investigation were observational in nature, which complicates causal inference. Nevertheless, only studies at low risk of selection bias, with the majority employing an unselected enrolment strategy, were included. Moreover, since the estimands of interest in this study were the associations of clinical characteristics with PE phenotypes, and random allocation to risk factors or phenotypes is not possible, no benefit would be obtained by prioritising the inclusion of randomised trials in this study. Third, all meta-analyses of proportions exhibited high between-study heterogeneity. Reasons for such heterogeneity could include differences by study region, healthcare setting, diagnostic protocols, and stringency of medical examination. Large empirical comparisons of ratio measures versus absolute measures (e.g. risk differences, mean differences) for meta-analyses of the same underlying data have previously shown that ratio measures tend to exhibit much less heterogeneity in general, due to their independence of baseline prevalence.[65] A fourth limitation was that few studies reported clinical outcomes, and those that did often followed patients for a limited period of time. Studies with longer follow-up are needed to provide more

reliable insight into the incidence of various outcomes following acute PE.

The available evidence suggests that isolated PE should be recognised as a separate clinical phenotype. The diagnosis of isolated PE may indicate the presence of cardiovascular disease and long-term risk of arterial thrombosis. Randomised controlled trials are needed to determine whether alternative treatment regimens may be beneficial for this common patient subgroup.

Contributors

This study was conceptualised by VTC, JHP and PSW. Inclusion and exclusion criteria for the study were discussed and agreed upon by all authors. VTC and APR performed the screening of studies. VTC and JHP performed the risk of bias assessment. The statistical analysis was performed and verified by VTC, AS and MN. VTC and PSW drafted the first version of the manuscript. The data were discussed and the manuscript was modified based on intellectual contributions from all authors. All authors had full access to all data. All authors take responsibility for the accuracy of the reporting of data and for the decision to submit the manuscript for publication.

Data sharing statement

All data collected for synthesis in this systematic review and meta-analysis are freely available for download as Supplemental Data.

Declaration of interests

None of the authors declare competing interests relevant to the subject matter of this article.

Acknowledgments

VTC is a Virchow Fellow at the Center for Thrombosis and Hemostasis (CTH) of the University Medical Center of the Johannes Gutenberg University Mainz and was funded by internal funds of the Department of Preventive Cardiology and Preventive Medicine. APR received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 813409. PSW is funded by the Federal Ministry of Education and Research (BMBF 01EO1503) and he is PI of the German Center for Vascular Research (DZHK), partner site Rhine-Main. PSW is principal investigator of the DIASyM research core (BMBF 161L0217A). TM is principal investigator of the German Center for Vascular Research (DZHK), partner site Rhine-Main. No specific funding was obtained for this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101973.

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