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Sex as a prognostic factor for mortality in adults with acute symptomatic pulmonary embolism (Review)

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[Prognosis Review]

Sex as a prognostic factor for mortality in adults with acute symptomatic pulmonary embolism

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ABSTRACT

Background

Pulmonary embolism (PE) is relatively common worldwide. It is a serious condition that can be life-threatening. Studies on the relationship between adverse outcomes of this condition and whether a patient is male or female have yielded inconsistent results. Determining whether there is an association between sex and short-term mortality in patients with acute PE is important as this information may help guide different approaches to PE monitoring and treatment.

Objectives

To determine whether sex (i.e. being a male or a female patient) is an independent prognostic factor for predicting mortality in adults with acute symptomatic pulmonary embolism.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases, and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials register up to 17 February 2023. We scanned conference abstracts and reference lists of included studies and systematic reviews. We also contacted experts to identify additional studies. There were no restrictions with respect to language or date of publication.

Selection criteria

We included phase 2-confirmatory prognostic studies, that is, any longitudinal study (prospective or retrospective) evaluating the independent association between sex (male or female) and mortality in adults with acute PE.

Data collection and analysis

We followed the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of prognostic factor studies (CHARMS-PF) and the Cochrane Prognosis Methods Group template for prognosis reviews. Two review authors independently screened the studies, extracted data, assessed the risk of bias according to the Quality in Prognosis Studies (QUIPS) tool, and assessed the certainty of the evidence (GRADE). Meta-analyses were performed by pooling adjusted estimates. When meta-analysis was not possible, we reported the main results narratively.

Main results

We included seven studies (726,293 participants), all of which were retrospective cohort studies with participants recruited and managed in hospitals between 2000 and 2018. Studies took place in the USA, Spain, and Japan. Most studies were multicentre. None were conducted in low- or middle-income countries. The participants' mean age ranged from 62 to 69 years, and the proportion of females was higher in six of the seven studies, ranging from 46% to 60%. Sex and gender terms were used inconsistently. Participants received different PE treatments: reperfusion, inferior vena cava filter, anticoagulation, and haemodynamic/respiratory support.

The prognostication time (the point from which the outcome was predicted) was frequently omitted. The included studies provided data for three of our outcomes of interest. We did not consider any of the studies to be at an overall low risk of bias for any of the outcomes analysed. We judged the certainty of the evidence as moderate to low due to imprecision and risk of bias.

We found moderate-certainty evidence (due to imprecision) that for female patients there is likely a small but clinically important reduction in **all-cause mortality at 30 days** (odds ratio (OR) 0.81, 95% confidence interval (CI) 0.72 to 0.92; I^2 = 0%; absolute risk difference (ARD) 24 fewer deaths in women per 1000 participants, 95% CI 35 to 10 fewer; 2 studies, 17,627 participants). However, the remaining review outcomes do not indicate lower mortality in female patients.

There is low-certainty evidence (due to serious risk of bias and imprecision) indicating that for females with PE, there may be a small but clinically important increase in **all-cause hospital mortality** (OR 1.11, 95% CI 1.00 to 1.22; I^2 = 21.7%; 95% prediction interval (PI) 0.76 to 1.61; ARD 13 more deaths in women per 1000 participants, 95% CI 0 to 26 more; 3 studies, 611,210 participants).

There is also low-certainty evidence (due to very serious imprecision) indicating that there may be little to no difference between males and females in **PE-related mortality at 30 days** (OR 1.08, 95% CI 0.55 to 2.12; I^2 = 0%; ARD 4 more deaths in women per 1000 participants, 95% CI 22 fewer to 50 more; 2 studies, 3524 participants).

No study data was found for the other outcomes, including sex-specific mortality data at one year. Moreover, due to insufficient studies, many of our planned methods were not implemented. In particular, we were unable to conduct assessments of heterogeneity or publication bias or subgroup and sensitivity analyses.

Authors' conclusions

The evidence is uncertain about sex (being male or female) as an independent prognostic factor for predicting mortality in adults with PE. We found that, for female patients with PE, there is likely a small but clinically important reduction in all-cause mortality at 30 days relative to male patients. However, this result should be interpreted cautiously, as the remaining review outcomes do not point to an association between being female and having a lower risk of death. In fact, the evidence in the review also suggested that, in female patients, there may be a small but clinically important increase in all-cause hospital mortality. It also showed that there may be little to no difference in PE-related mortality at 30 days between male and female patients. There is currently no study evidence from longitudinal studies for our other review outcomes.

Although the available evidence is conflicting and therefore cannot support a recommendation for or against routinely considering sex to quantify prognosis or to guide personalised therapeutic approaches for patients with PE, this Cochrane review offers information to guide future primary research and systematic reviews.

PLAIN LANGUAGE SUMMARY

Does the risk of death differ between female and male adult patients with pulmonary embolism (a blood clot in the lungs)?

Key messages

- We concluded that it is uncertain if sex (whether a patient is male or female) is an independent predictor of the risk of death in people with pulmonary embolism (a blood clot in the lungs), as our review found contradictory results.

- We found a small but important reduction in death from any cause by 30 days after pulmonary embolism in female compared to male patients. However, in female patients, there may be a small but important increase in death occurring in hospital from any cause. We found little to no difference between male and female patients in death specifically related to pulmonary embolism by 30 days. We have moderate to low confidence in these results.

- There is a need for further research of good quality to clarify whether there is a difference between males and females in the likelihood of death after PE. Our review makes suggestions about how this research should be carried out.

What is pulmonary embolism?

A blood clot is a mass of blood cells that form in the blood vessels. Blood clots can protect from bleeding, but they can also cause problems. Pulmonary embolism occurs when blood clots dislodge from where they originate and move to the lungs, where they can cause a blockage in blood circulation.

Pulmonary embolism can be life-threatening. It is the third most frequent cause of cardiovascular death (after heart attack and stroke), and it is the leading preventable cause of death in hospitalised patients.

What did we want to find out?

This Cochrane Review aimed to determine if sex (being a female or a male patient), by itself, can predict the risk of death in adults with pulmonary embolism.

What did we do?

We searched for studies that evaluated whether there is an association (independent of other factors) between sex and mortality in adults with pulmonary embolism. We compared and summarised the results of the studies we identified, and we rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found seven relevant studies involving 726,293 participants. The studies informed three review outcomes: death in hospital for any reason ('all-cause hospital mortality'); death occurring for any reason from the time of diagnosis of pulmonary embolism or starting treatment until 30 days later ('all-cause mortality at 30 days'); and death due to pulmonary embolism (PE) occurring between the time of PR diagnosis or starting treatment and 30 days later ('PE-related mortality at 30 days'). No study measured our other outcomes of interest (e.g. death by the one-year time point).

Main results

The studies looked at past medical records of patients who were treated in hospitals between 2000 and 2018, either in the USA, Spain, or Japan. Most studies were carried out in multiple hospitals. No studies were conducted in low- or middle-income countries. The participants in each study had an average age of over 60 years, and most participants had symptomatic PE.

We found that, in female patients with PE, there is likely a small but important reduction in all-cause mortality at 30 days (2 studies, 17,627 participants) when compared to male patients. On the other hand, we also found that, for female patients, there may be a small but important increase in all-cause hospital mortality (3 studies, 611,210 participants), and there may be little to no difference between the sexes in PE-related mortality at 30 days (2 studies, 3524 participants). Due to the mixed results and gaps in information (e.g. many of our outcomes were not measured), it is not possible for us to reach reliable conclusions about whether the risk of death after a pulmonary embolism can be predicted based on whether a patient is male or female.

What are the limitations of the evidence?

The evidence is limited by the small number of studies, the poor descriptions of how they were conducted, and our inclusion of studies that gathered patient information from administrative databases, such as hospital or insurance records. In the future, when more studies have been conducted and included in an update of this review, our findings may differ from the results presented here.

How up-to-date is this evidence?

The evidence is based on searches carried out until 17 February 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings - can mortality be predicted for adults with acute symptomatic pulmonary embolism based on whether the patient is female or male?

Can mortality be predicted for adults with acute symptomatic pulmonary embolism based on whether the patient is female or male?

Patient or population: adults with acute symptomatic PE (confirmed by objective testing)

Setting: any

Index prognostic factor: being female

Comparator prognostic factors: age, history of cancer, current cancer, history of chronic cardiopulmonary disease, current chronic cardiopulmonary disease, heart rate, systolic blood pressure, and oxygen saturation

Outcome; follow-up; participants; studies	Relative effect (95% CI)	Anticipate absolute effects* (95% CI)			Certainty of the evidence	Comments**
		Risk in male study participants	Corresponding risk in female study participants	Absolute risk difference		
All-cause hospital mortality Follow-up: median, range 4 to 9 days Number of participants: 611,210 3 retrospective cohort studies; the pooled overall rates in each study were 32‰ (Marshall 2017), 34‰ (Agarwal 2015), and 309‰ (Sedhom 2022).[a,b]	**OR 1.11** (95% CI 1.00 to 1.22) 95% PI 0.76 to 1.61	**Low risk**			⨁⨁◯◯ **Low**[f,g,h]	Female participants may present a small (clinically important) increase in all-cause hospital mortality.
		31 per 1000[c]	34 per 1000 (31 to 38)	3 more per 1000 (95% CI 0 fewer to 7 more)		
		Intermediate risk				
		140 per 1000[d]	153 per 1000 (140 to 166)	**13 more per 1000** **(95% CI 0 fewer to 26 more)**		
		High risk				
		293 per 1000[e]	315 per 1000 (293 to 336)	22 more per 1000 (95% CI 0 fewer to 43 more)		

Early all-cause hospital mortality (during the first 48 hours)	Not reported					
All-cause hospital mortality at 30 days	Not reported					
All-cause mortality at 30 days Follow-up: not reported Number of participants: 17,627 2 retrospective cohort studies; the pooled overall rates in each study were 67‰ (Barrios 2017) and 93‰ (Borrero 2007).	**OR 0.81** (95% CI 0.72 to 0.92)	**Low risk**			⊕⊕⊕○ **Moderate**[i,j]	Female participants likely present a small (clinically important) reduction in all-cause mortality at 30 days.
		31 per 1000[c]	25 per 1000 (23 to 29)	6 fewer per 1000 (95% CI 8 fewer to 2 fewer)		
		Intermediate risk				
		140 per 1000[d]	116 per 1000 (105 to 130)	**24 fewer per 1000** **(95% CI 35 fewer to 10 fewer)**		
		High risk				
		293 per 1000[e]	251 per 1000 (230 to 276)	42 fewer per 1000 (95% CI 63 fewer to 17 fewer)		
All-cause mortality at 90 days	Not reported					
All-cause mortality at 1 year	Not reported					
PE-related hospital mortality	Not reported					
Early PE-related hospital mortality (during the first 48 hours)	Not reported					
PE-related hospital mortality at 30 days	Not reported					
PE-related mortality at 30 days Follow-up: not reported Number of participants: 3524 2 retrospective cohort studies; pooled overall rates were 30‰ (Barrios 2017) and 40‰ (Tanabe 2018).	**OR 1.08** (95% CI 0.55 to 2.12)	**Low risk**			⊕⊕○○ **Low**[n,o]	Female participants may present little to no difference in PE-related mortality at 30 days.
		27 per 1000[k]	29 per 1000 (15 to 56)	2 more per 1000 (95% CI 12 fewer to 29 more)		
		Intermediate risk				

50 per 1000[l]	54 per 1000 (28 to 100)	**4 more per 1000 (95% CI 22 fewer to 50 more)**
High risk		
94 per 1000[m]	101 per 1000 (54 to 180)	7 more per 1000 (95% CI 40 fewer to 86 more)

*__The risk in female study participants__ (and its 95% confidence interval) is based on the assumed risk in the comparison group (male participants) and the **relative prognostic effect** of sex (and its 95% CI).

**The review findings for each outcome effect estimate are expressed following GRADE wording (Santesso 2020). This approach integrates the certainty of the evidence and association size. We defined the size by considering the central estimate of the ARD in the intermediate risk scenario as follows (‰ = per 1000 participants): no association: 0‰; small association (not important): less than 5‰; small association (clinically important): less than 25‰; moderate association: less than 50‰; large association: at least 50‰.

Abbreviations: ARD: absolute risk difference; CI: confidence interval; DL: DerSimonian-Laird; FE: fixed effect; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HKSJ: Hartung-Knapp-Sidik-Jonkman; IV: inverse variance; MID: minimal important difference; OR: odds ratio; PE: pulmonary embolism; PESI: Pulmonary Embolism Severity Index; PI: prediction interval; REML: Restricted Maximum Likelihood; RIETE: Registro Informatizado de la Enfermedad TromboEmbólica (Spanish registry for thromboembolic disease)

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect**.**

Explanations

[a]Two studies reported the median follow-up (Marshall 2017; Sedhom 2022).

[b]Pribish 2020 could not be pooled due to insufficient information for estimating the OR. This study did not find evidence of differences in all-cause hospital mortality between sexes (ARD −2.2‰, 95% CI − 42.1 to 37.4 more).

[c]We defined the low-risk scenario for all-cause hospital mortality in male participants based on Marshall 2017: a cohort of 146,505 male participants treated for acute PE.

[d]We defined the intermediate-risk scenario for all-cause hospital mortality in male participants based on Jiménez 2018: RIETE registry, including 1207 haemodynamically unstable participants (males and females) treated for acute PE embolism.

[e]We defined the high-risk scenario for all-cause hospital mortality in male participants based on Sedhom 2022: a cohort of 15,920 male participants treated for acute PE.

[f]We downgraded one level for risk of bias: the proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

[g]We downgraded one level for imprecision. The point estimate of the ARD in the moderate risk scenario meets our predefined MID of at least 5 deaths per 1000 participants. However, although the 95% CI excludes a lower risk in women, it crosses the MID and is also compatible with a trivial increase in mortality. Furthermore, the primary analysis (REML + HKSJ meta-analysis) lacks robustness when subjected to sensitivity analyses: IV, FE model meta-analysis yielded an OR of 1.11 (95% CI 1.06 to 1.15), and REML + DL yielded an OR of 1.11 (95% CI 1.05 to 1.16). Consequently, due to these uncertainties, we downgraded the certainty rating by one level for imprecision.

[h]Although the 95% PI indicating the factor's potential true prognostic effects in the population ranged from OR 0.76 to 1.61, we decided not to downgrade an additional level for inconsistency: PIs tend to be too wide when the number of included studies is low.

[i]We did not downgrade the evidence for risk of bias. The information is from studies at moderate risk of bias (Barrios 2017; Borrero 2007), but it is unclear if the potential limitations are likely to lower the confidence in the estimate.

[j]We downgraded one level for imprecision. The point estimate of the ARD in the moderate risk scenario meets our predefined MID of at least 5 deaths per 1000 participants. The 95% CI does not cross the null and is always compatible with a relevant reduction in mortality in women. However, the primary analysis (IV FE model meta-analysis) lacks robustness when subjected to sensitivity analyses: REML + HKSJ meta-analysis: OR 0.81 (95% CI 0.39 to 1.69).

[k]We defined the low-risk scenario for PE-related mortality in male participants based on Jiménez 2018: RIETE registry, including 33,173 haemodynamically stable participants (males and females) treated for acute PE.

[l]We defined the intermediate-risk scenario for PE-related mortality in male participants based on PESI class III moderate mortality risk, which ranges from 3.2% to 7.1%.

[m]We defined the high-risk scenario for PE-related mortality in male participants based on Jiménez 2018: RIETE registry, including 1207 haemodynamically unstable participants (men and women) treated for acute PE.

[n]We did not downgrade the certainty of the evidence for risk of bias: most of the information is from one study at low risk of bias (Barrios 2017).

[o]We downgraded two levels for imprecision. The point estimate of the ARD in the moderate-risk scenario does not reach our predefined MID of at least 5 deaths per 1000 participants (trivial association between being a female patient and mortality). However, the 95% CI crosses the null and is also compatible with a small (clinically relevant) decrease and a large increase in mortality in female participants.

BACKGROUND

Description of the health condition and context

Venous thromboembolism (VTE) is a common cardiovascular disease that involves the formation of a blood clot (thrombus) in a vein (Bartholomew 2017). VTE can manifest as pulmonary embolism (PE) or deep vein thrombosis (DVT). Pulmonary embolism (PE), the targeted health condition in this review, occurs when venous thrombi dislodge from their formation sites and travel to the pulmonary artery circulation system (Konstantinides 2014). About 90% of pulmonary emboli originate from the lower extremities, most involving the proximal veins (Lee 2016). Moreover, about half of patients with pelvic vein thrombosis or proximal leg DVT develop PE, which is often asymptomatic (Kearon 2012). Acute PE is the most severe VTE clinical presentation (Konstantinides 2014). The moment of prognostication in this review was at the diagnosis of PE.

According to its short-term prognosis, PE can be classified as low-risk, intermediate-risk, or high-risk (Merli 2017). High-risk PE is an acute PE with obstructive shock or systolic blood pressure (SBP) lower than 90 mmHg. Intermediate-risk PE is an acute PE without systemic hypotension but with either right ventricle dysfunction or myocardial necrosis (Murphy 2018). If a PE has none of these severe features, it is called low-risk PE.

Epidemiology and predisposing factors for pulmonary embolism

PE is relatively common worldwide. The incidence of PE is estimated to be 60 to 120 cases per 100,000 population per year in Western countries (Keller 2020; Lehnert 2018; Virani 2020). Incidence increases with age; specifically, individuals aged under 50 years have an incidence rate of less than 50 per 100,000 population annually, whereas those aged over 75 years experience a significantly higher rate, approximately 350 per 100,000 (Sonne-Holm 2022).

PE incidence has been increasing, at least in high-income countries (Alotaibi 2016; Barco 2021b; Belohlavek 2013). For example, PE incidence nearly doubled in the US from 1998 to 2006 without relevant changes in mortality (Murphy 2017). This rise in cases could be explained by longer life expectancy and the availability of better technology that detects previously missed pulmonary emboli that are not clinically relevant (Doherty 2017; Wiener 2013). However, no exact worldwide epidemiological data are available (Barco 2021b), and most PE cases are undiagnosed and, thus, untreated (Cohen 2007). Moreover, many countries, especially low-income countries, lack population-based estimates for thrombotic conditions (Wendelboe 2016).

Estimates derived from the World Health Organization (WHO) Mortality Database and the US Centers for Disease Control and Prevention (CDC) Multiple Cause of Death Database indicate that the age-standardised mortality rate (ASMR) for PE in the USA is approximately four deaths per 100,000 population annually, with similar numbers in Canada and the European region (Barco 2020; Barco 2021a). Thus, PE-related ASMR is generally lower than the ASMR for other cardiovascular diseases. For instance, the current ASMR for stroke in the US is reported to be 41.1 deaths per 100,000 individuals (Martin 2024). This figure underscores the relative rarity of PE as a cause of death when compared to other cardiovascular conditions.

Still, PE is a serious condition that can be life-threatening. There are between 60,000 and 100,000 deaths from PE per year in the USA (CDC 2022), which represents 0.4% of all deaths in the country per year (Murphy 2017). The mortality data from Australia and the UK show a similar frequency to the USA, at 0.2% and 0.4% of all deaths, respectively (Australian Bureau of Statistics 2017; Office for National Statistics 2022). Worldwide, 86,930 (0.46%) of the deaths registered in 2019 in the WHO mortality database (123 countries) were attributed to PE (Barco 2021b). The differences in the number of reported PE-attributed deaths across regions are likely explained by differences in the accuracy of cause-of-death reporting systems (Barco 2021b).

Mortality rates related to PE have generally declined over time. These downward trends may be attributed to advancements in disease management, the lack of a consistent definition for PE cases, and alterations in coding protocols and autopsy practices (Barco 2021a). Nevertheless, PE continues to be a significant health and social concern, a relevance that has increased following the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This is because PE may play a role in the morbidity associated with COVID-19 (Klok 2020).

PE is a multifactorial disease that involves genetic, clinical, and environmental factors. Secondary PE is associated with precipitating risk factors, such as surgery, cancer, trauma, immobilisation, pregnancy and the postpartum period, oral contraceptives, and hormone replacement therapy (Bukhari 2022; Cushman 2004; James 2006; Konstantinides 2020; Marik 2008; Morris 2010, Peragallo Urrutia 2013; Stegeman 2013; Vinogradova 2019). Idiopathic PE presents no known precipitating factors (Kearon 2016).

Description of the index and comparator prognostic factors

This is a prognostic factor systematic review. A prognostic factor is a characteristic in people with a given health condition that is associated with a subsequent clinical outcome (an endpoint) (Hemingway 2013; Riley 2019). Therefore, prognostic factors distinguish groups of people with different average prognoses (Riley 2019). The relevance of prognosis research is increasingly recognised because chronic health conditions are common and costly.

Health equity is the absence of avoidable and unfair differences in healthcare (Welch 2020). Sex, gender, and sexual orientation may contribute to health inequalities and inequities (Evans 2003; Welch 2020). Sex refers to the biological, genetic, and physiological processes that generally distinguish females from males. On the other hand, gender refers to the roles, relationships, behaviours, and other traits that societies typically ascribe to women, men, and people of diverse gender identities (e.g. transgender) (CIHR 2012; Heidari 2016).

This review aimed to assess the potential role of sex (i.e. being a female patient compared to being a male patient) as a prognostic factor in people with acute symptomatic PE. As indicated in our protocol (López-Alcalde 2021), we did not set out to evaluate the association between gender or sexual orientation and the

outcomes of patients with PE. Our review focused on biological sex rather than gender orientation because, at the protocol stage, we considered that the data sources would be primarily categorised and reported based on sex. This approach would allow us to use metrics commonly employed in clinical settings and readily available in medical records. However, we recognise that gender orientation might influence health outcomes through direct biological mechanisms, such as hormonal therapies in transgender individuals, and indirect factors, such as disparities in healthcare access, treatment biases, and social determinants of health. By not evaluating gender orientation, we acknowledge the potential oversight of complex interactions that could impact outcomes. Recognising this, exploring gender orientation in future studies could enhance the understanding of personalised treatment strategies and contribute to addressing broader health inequities. This more inclusive approach would provide deeper insights into the nuances affecting treatment efficacy and patient care.

Health outcomes

We will assess the association between sex and mortality in patients with PE. We will evaluate all-cause mortality and PE-related mortality after PE diagnosis in different settings (in-hospital and after discharge) and at different time points up to one year (short term). We define all-cause mortality as death from any cause following the diagnosis of PE. We define PE-related mortality as death due to PE confirmed by autopsy or death following a clinically severe PE in the absence of any alternative diagnosis (Muriel 2014).

Why it is important to do this review

Global awareness campaigns highlight the significant burden of thrombosis and promote the implementation of management strategies. The effective management of PE is a priority for improving survival in patients with thromboembolic disorders (Barco 2021b; World Thrombosis Day 2022).

Prognostic factor research aims to identify factors associated with clinical outcomes in people with a particular disease or health condition (Hemingway 2013; Riley 2019). There can be different uses of the evidence on individual prognostic factors, such as identifying modifiable targets for interventions, generating building blocks for prognostic models, and determining predictors of differential treatment response (Riley 2013). Prognostic factors are relevant to patient management as they help to stratify patients into different risk groups, thus potentially helping to reduce morbidity and mortality (Riley 2013). Identifying prognostic factors is a crucial step in the current drive towards personalised medicine (Riley 2013; Trusheim 2007), which aims to find patient-specific effect estimates to support more individualised clinical decision-making (Kent 2018).

Biological differences between the sexes can result in differential health risks, disease incidence, and health service needs (O'Neill 2014). Sex differences in the presentation and clinical course of conditions may dictate different approaches to detection and management. Although sex differences in arterial disease have received substantial attention, very few studies have explored sex differences within VTE (Blanco-Molina 2014). Studies about the relationship between sex and adverse outcomes in studies of patients with proven acute PE have shown inconsistent results. For example, female patients had higher in-hospital mortality than males in a study analysing 266,446 acute PE patients (Agarwal 2015). However, in other studies, the risk of all-cause mortality at 30 days was lower in females (Aujesky 2005; Borrero 2007). Moreover, three other studies found no evidence of any association between sex and prognosis (Jimenez 2010; Keller 2019a; Panigada 2016).

We believe there is a need for a rigorous systematic review assessing the association between sex and mortality in patients with PE. Although a systematic review by Thachil 2022 consulted PubMed and Embase until 1 April 2022 to identify published studies that explored the role of sex as a prognostic factor for mortality in patients with PE, the review did not assess the risk of bias or the certainty of the evidence, and meta-analyses were not performed.

It is important to know if there are differences between the sexes in mortality rates of patients treated for PE and to quantify any such differences. Identifying clinically relevant differences will influence the development of different PE monitoring and management approaches for males and females. This is particularly important for supporting decisions when the benefit-risk balance of an intervention is unclear. Moreover, this information is also important for drug discovery and development and for regulatory authorities.

Exploring the influence of sex on PE outcomes is essential, even if any differences in mortality are small. Such knowledge deepens our understanding of PE, providing insights into how biological factors like hormones or genetics may affect disease progression. Moreover, this information can refine risk stratification models, enhancing their accuracy. Overall, investigating even minor sex-related differences in PE-related mortality is important for advancing personalised medicine.

OBJECTIVES

To determine whether sex (i.e. being a male or female patient) is an independent prognostic factor for predicting mortality in adults with acute symptomatic pulmonary embolism.

METHODS

We followed the CHARMS Checklist for prognostic factors (CHARMS-PF) (Riley 2019), the Cochrane Prognosis Methods Group template for prognosis reviews (PMG 2020), the PRISMA Statement (Page 2021), and other Cochrane prognosis reviews (Hayden 2014; Skoetz 2017; Westby 2018). In the Differences between protocol and review section, we have described any changes that we have made since the published protocol and any methods we planned in the protocol that we have been unable to implement in the full review.

Criteria for considering studies for this review

See Table 1 for a formulation of the review question in PICOTS (population, index prognostic factor, comparator prognostic factor, outcome(s), timing, and setting) format. This format is based on the CHARMS-PF checklist and informs the review objectives and eligibility criteria (Debray 2017; Moons 2014; Riley 2019).

Types of studies

We included longitudinal studies, randomised or non-randomised, that investigated the prognostic significance of sex in adults with PE for predicting mortality. In particular, the following study designs were eligible (Foroutan 2020): (i) observational studies (e.g. cohort or database linkage studies) and (ii) secondary analyses of experimental studies (randomised or non-randomised) providing

evidence regarding prognosis. For an experimental study to be eligible, it must have used either the intervention group alone or the entire study cohort adjusted for the intervention.

We included phase 2-confirmatory studies, that is, explanatory research that aimed to confirm an independent association between a potential prognostic factor (sex) and the outcome of interest. A phase-2 study seeks to measure the independent effect of a prognostic factor while controlling for other factors (Hayden 2008; Hayden 2014) and is recognisable by its having a statement of the study objective that outlines a specific prognostic factor of interest (Hayden 2008). We excluded the following study designs, but studies that met the remaining eligibility criteria were reported in the Characteristics of excluded studies table.

- **Descriptive studies describing the course of the condition/ disease**
- **Phase-1 exploratory prognostic studies ('exploratory studies'):** studies aimed at investigating all associations, usually in univariate analyses, of potential prognostic factors and outcomes. These studies are necessary to identify new prognostic factors. Still, they were not eligible for our review because they provide the least conclusive information regarding the independence of a variable as a valid prognostic factor. Moreover, due to the many factors explored, exploratory studies often have widely varying results with common spurious associations, which may overstate their conclusions (Hayden 2008; Hayden 2014).
- **Other studies reporting univariate associations**
- **Phase-3 prognostic studies:** studies to understand prognostic pathways. We excluded these studies because our primary objective is to determine the prognostic role of sex, independent of other factors, such as interventions. Phase-3 prognostic studies focus on validating markers that predict disease outcomes and enable tailored patient therapeutic approaches. Consequently, the interventions in phase-3 studies may confound the prognostic value of sex on mortality by altering the natural course of the disease.
- **Cross-sectional studies**
- **Prognostic model studies**
  - Studies to develop a prediction model (independently, if it reports any association of sex with any of our review outcomes)
  - Studies to validate a prediction model (that is, to validate the model in patients' data not used in the development process)
  - Studies to evaluate the impact of a prognostic model on clinical practice and outcomes
- **Studies evaluating only the interactions between intervention and prognostic factors**, such as a randomised controlled trial (RCT) or another study that reported only treatment effect modification data.

We did not exclude any study based on sample size, duration of follow-up, publication status, publication year, or language. We excluded studies that fulfilled all our review eligibility criteria but did not assess or report our outcomes of interest. To be included, the study should have informed at least one mortality outcome (see 'Selection of studies' below).

Appendix 1 details the study design features we used to determine study design eligibility.

Targeted population

We included adults, regardless of hospitalisation status, who were treated for acute symptomatic PE confirmed by objective testing.

- **Adult:** person aged 16 years or older (in many settings, age 16 is when patients leave paediatric care and enter adult care).

Children and adults differ significantly in physiological parameters such as cardiovascular function, lung development, and haemostatic balance. These differences affect the development and progression of PE and responses to treatment (Navanandan 2019; Zaidi 2017). By focusing on sex as a variable and avoiding division into age subgroups, we ensure that our review provides specific insights into how sex alone influences mortality in adult patients with PE, making our findings more straightforward and applicable for clinical use and policymaking.

- **PE:** the dislodgement of venous thrombi from their site of formation and their embolisation to the pulmonary artery circulation system (Konstantinides 2014).
- **Acute**: the study follow-up should start no later than 15 days after diagnosis.
- **Symptomatic:** at a minimum, chest symptoms must be present, for example, dyspnoea or chest pain.
- **Objective testing confirmation:** we considered the following valid examples of objective testing: high probability ventilation-perfusion scintigraphy; positive contrast-enhanced PE protocol; helical chest computerised tomography for PE; or lower limb compression ultrasonography, positive for proximal DVT. We assumed objective testing if the PE was classified according to an internationally recognised system, such as the ICD-9 or ICD-10 coding (WHO 2004).

We included studies involving participants treated for PE independently if the treatment was explicitly described. In practical terms, we assumed that all patients with PE had received treatment unless it was explicitly stated that they had not.

We excluded studies of the following types of participants.

- Animals, cadavers, or in vitro
- Females or males only (the role of sex cannot be evaluated)
- Healthy volunteers
- More than half of the participants were children or adolescents (younger than 16 years of age);
- Participants with no PE confirmation.

Studies that had only a subset of participants relevant to our review question (e.g. people with different thrombotic events) were eligible if we could extract relevant stratified data. Otherwise, we excluded them from the review and listed them in the Characteristics of excluded studies table.

Types of prognostic factors

Index prognostic factor

We included studies assessing the role of sex - being a female participant - as a prognostic factor. Sex, categorised as female or male, relates to biological attributes in humans and animals (Heidari 2016). In particular, sex refers to the biological, genetic, and physiological processes that generally distinguish females from males, and is associated with features including chromosomes,

gene expression, hormone function, and reproductive/sexual anatomy (Heidari 2016). We accepted any assessment of sex as reported by the study authors.

Sex and gender are distinct and interrelated concepts (Doull 2010). For this review, we did not assess gender. Gender refers to the roles, relationships, behaviours, relative power, and other traits that societies generally ascribe to women and men, as well as people of diverse gender identities (e.g. transgender persons) (Heidari 2016). We acknowledge that 'sex' and 'gender' are poorly reported in published articles (Doull 2010; Lopez-Alcalde 2019; Runnels 2014; Welch 2017). In the case of unclear or incorrect reporting, we assumed the study considered sex unless the authors explicitly stated that they had evaluated gender.

Comparator prognostic factors

Our review focused on the adjusted prognostic value of sex, that is, its prognostic effect after adjusting for other covariates. We considered the following factors as key covariates for adjustment in each study, most taken from the scale of the Simplified PESI (sPESI) (Jimenez 2010) for mortality in patients with PE: age, history of cancer, current cancer, history of chronic cardiopulmonary disease, current chronic cardiopulmonary disease, heart rate, systolic blood pressure, and oxygen saturation. The adjustment for these covariates was not an inclusion criterion for the review. We considered the variables on this list to assess the adjustment domain in the risk of bias tool (see below).

We acknowledge that selecting key covariates was somewhat arbitrary and challenging for our review team. We have outlined this process in Appendix 2. Our focus was primarily on clinically measurable factors within the hospital setting and those commonly reported in the studies. However, we recognise that additional factors may not be included in our list that could be relevant to our clinical question. For instance, other commonly used prognostic factors in many studies—such as race, socioeconomic status, access to care, and the time between symptoms and diagnosis—might explain differences in mortality rates between sexes, potentially influencing our findings (Barco 2021a; Barco 2021b). We may modify our list of key covariates in future updates of this review if we find compelling evidence that justifies such changes.

Type of outcomes to be predicted

We considered all-cause mortality and PE-related mortality measured at or outwith the hospital at different short-term time points up to one year. We defined each outcome by adapting the five outcome elements from Saldanha 2014: domain or outcome title, specific measurement, specific metric, method of aggregation, time points. The time point we used for the analysis (the period over which the outcome is predicted) was from PE diagnosis to 48 hours, 30 days, 90 days, or one year. For example, we calculated all-cause mortality at 30 days, counting events during the hospital stay and after discharge. We used the start of the PE diagnosis as the inception point where possible. If this information was unavailable, we used the inception point provided by the study authors, such as the start of PE treatment.

Outcome	Definition	Specific measurement[a]	Specific metric[b]	Type of data[c]	Method of aggregation[d]	Timing		
						Prognostication time[e]	Period over which the outcome is predicted[f,g]	Minimum follow-up duration to be considered
1. All-cause hospital mortality	Death from any cause occurring in hospital	Any, as reported by the study authors	Value at a time point	Dichotomous Event of interest: death	Proportion	•Index prognostic factor (sex): to be measured at the start of PE diagnosis •Other covariates: preferably measured at the start of PE diagnosis[g]	The longest follow-up provided by the study authors	None
2. Early all-cause hospital mortality (during the first 48 hours)	Death from any cause occurring in hospital during the 48 hours following the start of PE diagnosis	Any, as reported by the study authors	Value at a time point	Dichotomous Event of interest: death	Proportion		48 hours from PE diagnosis	All participants must be followed for at least 48 hours after PE diagnosis[h] and outcome data reported for that specific time interval (or similar).
3. All-cause hospital mortality at 30 days	Death from any cause occurring in hospital during the first 30 days following the start of PE diagnosis	Any, as reported by the study authors	Value at a time point	Dichotomous Event of interest: death	Proportion		30 days from PE diagnosis	All participants must be followed for at least 30 days after PE diagnosisand outcome data reported for that specific time interval (or similar).
4. All-cause mortality at 30 days	Death from any cause occurring in hospital or after discharge during the first 30 days following the start of PE diagnosis	Any, as reported by the study authors	Value at a time point	Dichotomous Event of interest: death	Proportion		30 days from PE diagnosis	All participants must be followed for at least 30 days after PE diagnosis[i] and outcome data reported for that specific time interval (or similar).
5. All-cause mortality at 90 days	Death from any cause occurring in hospital or after discharge during the first 90 days following the start of PE diagnosis	Any, as reported by the study authors	Value at a time point	Dichotomous Event of interest: death	Proportion		90 days from PE diagnosis	All participants must be followed for at least 90 days after PE diagnosisand outcome data reported for that specific time interval (or similar).
6. All-cause mortality at 1 year	Death from any cause occurring in hospital or after discharge during	Any, as reported by the study authors	Value at a time point	Dichotomous	Proportion		1 year from PE diagnosis	All participants must be followed for at least one year after PE

	the first year following the start of PE diagnosis			Event of interest: death			diagnosis[i] and outcome data reported for that specific time interval (or similar).
7. PE-related hospital mortality	Death due to PE occurring in hospital	We admitted any definition of death provided by the authors.	Value at a time point	Dichotomous Event of interest: death	Proportion	The longest follow-up provided by the study authors	None
8. Early PE-related hospital mortality (during the first 48 hours)	Death due to PE occurring in hospital during the 48 hours following the start of PE diagnosis		Value at a time point	Dichotomous Event of interest: death	Proportion	48 hours from PE diagnosis	All participants must be followed for at least 48 hours after PE diagnosis[h] and outcome data reported for that specific time interval (or similar).
9. PE-related hospital mortality at 30 days	Death due to PE occurring in hospital during the first 30 days following the start of PE diagnosis		Value at a time point	Dichotomous Event of interest: death	Proportion	30 days from PE diagnosis	All participants must be followed for at least 30 days after PE diagnosis[h] and outcome data reported for that specific time interval (or similar).
10. PE-related mortality at 30 days	Death due to PE occurring in hospital or after discharge during the first 30 days following the start of PE diagnosis					30 days from PE diagnosis	All participants must be followed for at least 30 days after PE diagnosis[i] and outcome data reported for that specific time interval (or similar).

Footnotes

[a]The specific measurement or technique/instrument used to make the measurement (Saldanha 2014)

[b]The specific format of the outcome data from each participant that will be used for analysis (e.g. value at a time point or change from baseline) (Saldanha 2014).

[c]Type of data: dichotomous, continuous, ordinal, counts and rates, or time-to-event (survival)

[d]How data from each group will be summarised (e.g. mean, percentage/proportion) (Saldanha 2014)

[e]The time point from which the outcome will be predicted

[f]The time point that will be used for analysis (Saldanha 2014)

[g]The studies can use different starting points to define the follow-up. For example, from recruitment, from PE diagnosis, from allocation to the study arm, from admission to the hospital, from admission to the ICU, or from the start of the treatment. As first preference, we used the start of the PE diagnosis. If this information was unavailable, we used the time provided by the study authors.

[h]Other than for those participants that died or were discharged within this period

[i]Other than for those participants that died within this period

Abbreviations
ICU: intensive care unit; PE: pulmonary embolism

All-cause mortality has the most clinical relevance and is the most critical outcome for individuals with PE. Furthermore, all-cause mortality is an objective endpoint and is not susceptible to bias by the outcome assessor. We defined different follow-up durations because we expect delayed effects of PE. However, longer follow-up periods may be complicated by competing mortality, especially in cases of secondary PE, such as in cancer patients. This issue is further explored in the discussion section below.

We defined all mortality outcomes as binary variables (i.e. dead or alive) instead of using survival methods. We made this decision because hospitalised patients often have a poor quality of life, and those who die in hospital may not benefit from extended survival (Schoenfeld 2005). Thus, the critical outcome is mortality and not survival. Secondly, survival analysis should be avoided in the intensive care unit (ICU) because it relies on the assumption of non-informative censoring (Schoenfeld 2005), that is, it assumes that the reason a patient is no longer being observed (censored) is unrelated to their risk of death (Wolkewitz 2014). This assumption is incorrect in the ICU, as discharged patients are usually in better health than patients who stay. The assumption that censoring is non-informative, therefore, generates artificially reduced survival plots (Schoenfeld 2005). Although there are statistical solutions to enable discharge to be treated as a competing event for death in the ICU (Wolkewitz 2014), we still believe that, from a clinical point of view, the relevant outcome is mortality, not survival. Thus, we excluded seemingly eligible studies if they provided data for survival only.

We did not consider all-cause mortality or PE mortality in the ICU because these would only be useful if most patients were still in the ICU at the time of analysis (Finkelstein 1994; Schoenfeld 2005). Thus, we preferred to include death in hospital, including the ICU, and after hospital discharge.

Composite mortality outcomes were ineligible for analysis in this review unless disaggregated data for our review outcomes were presented. On the other hand, we did not exclude studies that would otherwise have been eligible based on the outcome time horizon.

Settings

We included studies of PE managed in any setting. Summaries of prognosis are not meaningful unless associated with a particular strategy for treatment, so prognostic studies can aid treatment decisions. This implies that prognostic factors should ideally be evaluated in a cohort of patients treated the same way or in a randomised trial (Altman 2001). We acknowledge that combining studies with patients with PE managed in any setting assumes that all the treatments are equally effective and that the prognosis of patients is independent of the setting. This may not be true. Thus, the variation in the effects of the treatments may be a relevant source of heterogeneity in this review. We also acknowledge that differences in hospital admission rates are likely related to the hospital- and country-specific availability of hospitals, admission policies, insurance systems, and other factors. Therefore, the patients admitted may not be homogenous. However, we consider that our synthesis still provides relevant information.

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases for RCTs and controlled clinical trials without language, publication year, or publication status restrictions.

- Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web) 17 February 2023
- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 2, 2023) via the Cochrane Register of Studies Online (CRSO)
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (1946 to 17 February 2023)
- Embase Ovid (1974 to 2023 week 7)
- CINAHL Ebsco (Cumulative Index to Nursing and Allied Health Literature) (1982 to 17 February 2023)

We developed search strategies for other databases from the search strategy designed for MEDLINE. We did not combine the search strategies with methodological filters. Search strategies for major databases are provided in Appendix 3.

We also searched the following trial registers.

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/clinical-trials-registry-platform)
- ClinicalTrials.gov (https://clinicaltrials.gov/)

The most recent searches were carried out on 17 February 2023. We used Endnote 2018 for bibliographic management.

Searching other resources

We screened the reference lists of the included studies and of the systematic reviews on our topic (Jarman 2021; Stals 2022; Thachil 2022). We contacted content experts, including authors of included studies and authors of relevant systematic reviews, in order to identify any additional/unreported/ongoing studies. We handsearched documents from the Organization for the Study of Sex Differences (OSSD).

We used the Web of Science database from Clarivate (clarivate.com/products/web-of-science) to track articles that cited the primary reference for each study included in this review. We also searched the publisher websites, PubMed (www.ncbi.nlm.nih.gov/pubmed), PubPeer (https://pubpeer.com/), and the Retraction Watch database (www.retractionwatch.com) for retractions and comments related to references of included studies.

We searched for conference abstracts of major symposia from 2010. We selected this date because it marks the year the article introducing the simplified Pulmonary Embolism Severity Index (sPESI) was first published (Jimenez 2010). This paper is significant as it has subsequently influenced various clinical guidelines and practices.

1. Meetings of the OSSD: 5th edition (2010) to 16th edition (2022)
2. European Respiratory Society (ERS): 2010 to 2022
3. International Society of Thrombosis and Haemostasis (ISTH): 2010 to 2022

4. American Thoracic Society (ATS): 2010 to 2022
5. American Society of Hematology (ASH): 2010 to 2022
6. CHEST congresses: 2010 to 2022
7. Acute Cardiovascular Care (ACC): 2010 to 2023
8. European Society of Cardiology (ESC): 2010 to 2022

Data collection and analysis

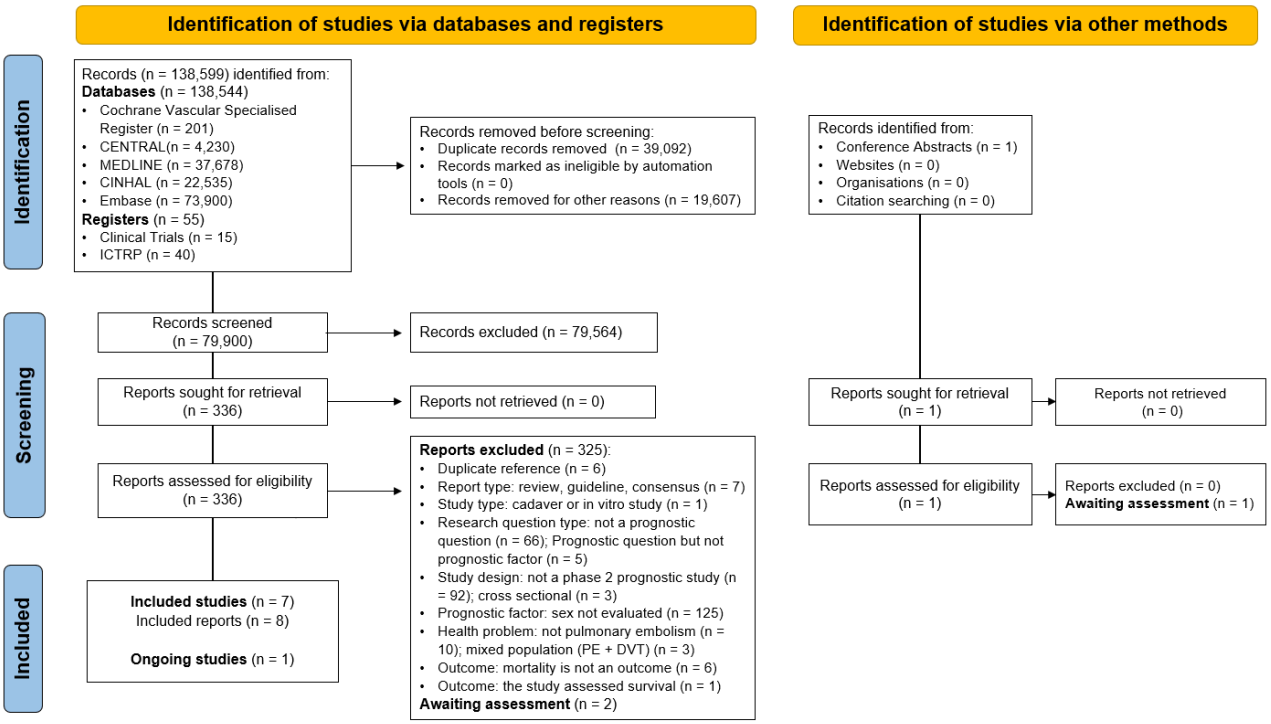
Selection of studies

Pairs of review authors (from AA, AC, AG, AS, EF, EGL, EJ, ES, JLA, LDC, MDM, MM, RM, RP, RS) independently checked titles and abstracts for inclusion. We classified the titles and abstracts into three groups: include for full-text assessment, exclude, or unclear. We obtained the full-text version of those records classified as 'include for full-text assessment' or 'unclear'. Two review authors (from AA, AC, AG, EJ, ES, JLA, LDC, MM) independently assessed the eligibility of each selected full-text article. We resolved disagreements by consensus. A third review author (from AC, EJ, ES, JLA) served as a neutral arbiter if there was disagreement. There were no restrictions on the papers' language or date of publication.

If necessary, we asked the study authors for clarification. If we could not clarify the issues and could not exclude the study for other reasons, we designated these studies as Studies awaiting classification.

We used the EPPI-Reviewer web-based software to implement the selection process (Thomas 2022). We completed a PRISMA flow chart to describe the selection process (Figure 1; Page 2021). We created tables of excluded studies detailing the main reason for excluding each study that a reader might have expected to see included in the review (Characteristics of excluded studies).

Figure 1. PRISMA flow diagram



We excluded studies that fulfilled all our review eligibility criteria other than the outcomes, i.e. studies that did not report any outcome of interest in the review; for example, a study determining whether sex is an independent prognostic factor for predicting PE patients' length of hospital stay. We acknowledge that excluding studies based on the outcomes hampers our evaluation of the risk of bias, particularly selective outcome reporting. However, including all prognostic studies independently of the outcome reported would generate an impractical workload. On the other hand, we did not exclude studies assessing mortality based on the measurement timing: we chose the most appropriate analysis time point in studies reporting several follow-ups for the same outcome, that is, the closest one to our predefined time point (see 'Type of outcomes to be predicted' above).

Data extraction and management

Two review authors (from AC, AG, EJ, ES, LDC, MM) independently extracted data from each included study. We used a consensus method to agree on the final extraction. A third review author (from AC, JLA, EJ) resolved disagreements and checked the accuracy of the numerical data in the review. We tried to contact the study authors to clarify crucial missing or unclear information. Translations of included reports were not needed. We examined retraction statements and errata for relevant information regarding each study.

Following CHARMS-PF guidance (Riley 2019), which is an adaptation of the original CHARMS checklist (Moons 2014) for systematic reviews of prognostic factor studies, we extracted data using a pre-designed spreadsheet in Microsoft Excel (Mircosoft Excel 2016). We extracted key information from each primary study and

summarised that information in the Characteristics of included studies table. See our data extraction template in Appendix 4, which we piloted with three studies to check usability.

If there were multiple reports of the same study or overlapping data sets, we collated them so that each study (not each report) was the unit of interest in the review. We extracted data from the data set with the largest sample size, the most detailed results, and the most appropriate follow-up time point. We summarised each characteristic (e.g. severity) per study. For studies reporting data by study arm, we used the Review Manager 2020 calculator to obtain the overall study estimate.

Transformations of reported data and assumptions made

We presented the associations consistently to show the role of being female as a prognostic factor. Thus, odds ratio (OR) values of less than one indicate a worse prognosis for women (higher mortality): we recalculated the associations to be in the same direction. We considered the OR and its 95% confidence interval (CI) as the measure of prognostic association in all the studies. We used the GRADEpro-GDT 2022 calculator to convert each combined OR to an absolute risk difference (ARD) to facilitate interpretation. The choice of the risk of the event in male patients (those without the prognostic factor) was obtained from external observational evidence.

When a primary study did not report the control group risk, we did not transform the ARD to OR. We did not convert hazard ratios (HRs) to ORs due to the many assumptions needed.

Assessment of risk of bias in included studies

We used the QUIPS (Quality In Prognosis Studies) tool to assess the risk of bias (RoB) in the included studies (Appendix 5; Hayden 2013; Riley 2019). The tool has six domains (with signalling items that can inform judgments of RoB in prognostic research):

- study participation (study-level domain);
- study attrition (outcome-level domain);
- prognostic factor measurement (study-level domain);
- outcome measurement (outcome-level domain);
- study confounding/adjustment for other prognostic factors (study-level domain);
- statistical analysis and reporting (study-level domain).

We assessed the six domains for each prognostic factor-outcome combination for each study. We provided a final judgment for each RoB domain and outcome by choosing one of the following options (Riley 2019): low, moderate, or high risk. Appendix 5 details the signalling items of the QUIPS tool to assess the risk of bias.

We detailed and justified judgements on RoB in a risk of bias table for each included study (see Characteristics of included studies). We also generated a table summarising the risk of bias per review outcome with data (Figure 2).

Figure 2. QUIPS tool: Quality in Prognostic Studies tool

Outcome	Study	Risk of bias with the QUIPS tool							Weight in meta-analysis
		Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting	Overall Rob	
All-cause hospital mortality	Agarwal 2015	Low	Low	Low	Low	High	Moderate: Low/Mod	High	51%
	Marshall 2017	Moderate	High	Low	Low	High	Moderate: Low/Mod	High	19%
	Pribish 2020	Low	Low	Low	Low	Low	Moderate: Low/Mod	Moderate	Non applicable
	Sedhom 2022	Low	Low	Low	Low	Low	Moderate: Low/Mod	Moderate	30%
All-cause mortality at 30 days	Barrios 2017	Low	Low	Low	Low	Low	Moderate: Mod/Low	Moderate	7%
	Borrero 2007	Low	Moderate	Low	Low	Low	Moderate: Low/Mod	Moderate	93%
PE-related mortality at 30 days	Barrios 2017	Low	Low	Low	Low	Low	Moderate: Mod/Low	Moderate	88%
	Tanabe 2018	Low	Low	Low	Moderate	High	Moderate: Mod/Mod	High	12%

Two review authors (AC and EJ) independently appraised all the domains of the QUIPS tool for each included study. JLA and AC conducted a pilot risk of bias assessment on two studies.

The final judgement for each domain was reached via consensus. A third review author (JLA) intervened by solving disagreements and checking the final decisions. If the study report did not provide information for a domain or this information was unclear, we followed a three-stage process. First, we tried to consult other publications that may have used the same data set (which is frequent in prognostic studies based on large existing cohorts) (Riley 2019). Second, we attempted to contact the authors for clarification. Third, we judged based on the available information and the consensus amongst the review authors. We were not blinded to study authors, institutions, or publication journals.

As suggested in Riley 2019, our protocol predefined the criteria to assess the signalling items and domains for our review question. We designed a Microsoft Excel form (Mircosoft Excel 2016) to extract the following key aspects: study participation, attrition, definitions of valid and reliable measurement of the index prognostic factors (see 'Types of prognostic factors'), definitions of valid and reliable measurement of the outcomes (see 'Types of outcomes'), and the core set of other prognostic factors that we judged should be adjusted for in the primary studies (Appendix 2).

Overall assessment of the risk of bias and incorporation into analyses

We considered all domains of the risk of bias tool to be very important, and we predetermined that we would take all of them into account when assessing the risk of bias. Thus, if any domain was judged to be at high risk of bias, the effect estimate was considered to have a high risk of bias. We summarised the RoB for each prognostic factor-outcome combination in two different ways: within each study (Figure 2) and across studies (Summary of findings 1; Higgins 2022).

	Interpretation	Risk of bias for each prognostic factor-outcome combination	
		Within each study across different domains	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains	Most information is from studies at low risk of bias.
Moderate risk of bias	Plausible bias that raises some doubt about the results	Moderate risk of bias for one or more key domains (and no domain rated as high risk)	Most information is from studies at low or moderate risk of bias.
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

We describe our risk of bias assessments in the Results section. We used the risk of bias assessment across studies for each prognostic effect estimation as part of our determination of the certainty of the evidence using the GRADE system (Guyatt 2011).

We meta-analysed studies regardless of their risk of bias ratings, but we planned to explore the effect of this decision by conducting sensitivity analysis.

Measures of association to be extracted

Type of measure of association

We considered the OR and its 95% CI as the measure of prognostic association in all the studies. We chose this measure because we anticipated that the OR would be the measure most commonly used in the studies: it is the only measure for dichotomous outcomes that can be estimated from case-control studies, and OR is obtained when logistic regression is used to adjust for confounders (Reeves 2011). We did not convert HRs to ORs due to the many assumptions required.

Adjusted prognostic effect estimates

We extracted the adjusted measure of association for each study and the prognostic effect estimate. We acknowledge that the studies providing the adjusted prognostic effect of a particular factor can differ in the set of adjustment covariates or in the cut-off used to dichotomise the covariates. This makes the interpretation of the meta-analysis challenging (Riley 2019). At the protocol stage, we agreed that age, history of cancer, history of chronic cardiopulmonary disease, heart rate, systolic blood pressure, and oxygen saturation would be the core set of adjustment factors for each review outcome.

If a study provided an adjusted estimate but not adjusted for our minimal set of adjustment factors, we included it in meta-analysis. However, we 'penalised' the estimate as part of the risk of bias assessment. If fewer than four of the key factors had been adjusted for in the study, we assessed the estimate as having a high risk of bias in the adjustment domain. If four or more of the key factors were adjusted for, we judged it to have a low risk of bias. If the study only adjusted for PESI/sPESI but did not detail for which individual factors they had adjusted, we marked the risk of bias domain as moderate.

Concerning the dichotomisation of our key covariates, we accepted any cut-off used by the primary authors.

Unit of analysis issues

We considered the prognostic factor (sex) and the outcome (mortality) at the participant level. Thus, we did not find unit-of-analysis errors (Deeks 2011).

Dealing with missing data

We included all the studies that investigated the role of sex as a prognostic factor in patients with PE, regardless of missing data. We contacted via email the authors of studies with missing or unclear data.

We considered the follow-up duration for all the review outcomes to start with the PE diagnosis.

Assessment of heterogeneity

We expected heterogeneity amongst the included studies to be common (Riley 2013) and assessed its presence by the methods detailed below. However, due to having an insufficient number of included studies, we could not perform subgroup analyses to explore possible causes of heterogeneity.

Assessment of clinical and methodological heterogeneity

We meta-analysed all the studies regardless of their clinical characteristics and methodological designs (as we aimed to evaluate a potential association, not causation).

Assessment of the statistical heterogeneity of the results

We assessed statistical heterogeneity by considering the following factors.

- Identification of heterogeneity (visual inspection of the prognostic effect estimates)
  - We displayed the results of clinically and methodologically comparable studies graphically (with forest plots), and we assessed the possibility of statistical heterogeneity visually.
  - We used the Chi^2 test to identify heterogeneity (deeming P value < 0.10 as significant) (Deeks 2022).
- Quantification of heterogeneity
  - We used the I^2 statistic to describe the percentage of the total variation across studies due to heterogeneity rather than sampling error (chance) (Higgins 2003). We defined an I^2 estimate greater than or equal to 50% and accompanied by a statistically significant Chi^2 P value as evidence of substantial statistical heterogeneity (Deeks 2022).
  - In meta-analyses with more than two studies, we also measured the heterogeneity using the estimate of between-study variance (Tau^2) and the 95% prediction interval (PI) (as reliance on the I^2 statistic in assessing heterogeneity may be misleading; Rucker 2008).

Assessment of reporting deficiencies

We could not examine any small-study effects due to the small number of included studies.

Data synthesis

Meta-analysis approach

We combined the results from individual studies in a meta-analysis to provide a pooled prognostic effect estimate only if the following criteria were met.

- There were enough studies (at least two).
- The studies were relatively homogeneous:
  - studies were clinically similar in terms of population and sex measurement;
  - studies were methodologically similar: we assumed that all phase-2 prognostic factor studies were methodologically comparable for determining a prognostic association, regardless of their design (e.g. cohort or case-control), but we planned to use subgroup analysis to explore whether study design contributed to heterogeneity;
  - outcomes were measured at similar follow-up points;
  - outcomes were measured with similar measurement tools;
  - studies had the same type of prognostic effect estimate measure, that is, an OR and 95% CI (or this information could be derived from the data provided in the report); and
  - the prognostic effect estimate was adjusted for at least one factor, regardless of which factor it was. If a study presented the unadjusted measure only (raw data), we did not include these data for analysis.

Statistical model for meta-analysis

We did not assume a common (fixed) prognostic effect of sex on mortality. We anticipated that the prognostic effect estimates would vary amongst studies for several reasons, such as different study populations, designs, time points and measurement of the outcomes, sets of adjustment factors, and missing data (Riley 2019). We assumed that there is no single underlying prognostic effect to estimate. Therefore, the heterogeneity amongst the study effects cannot be explained only by chance and follows a distribution across studies (Deeks 2022). Nevertheless, we considered that the underlying clinical questions were similar and pooling would be meaningful if the extra uncertainty due to that heterogeneity was adequately represented (Cornell 2014). Therefore, we applied a random-effects model (REM), which is an approach for meta-analysis that incorporates study-to-study variability beyond what would be expected by chance (Cornell 2014), allowing for unexplained heterogeneity across studies (Riley 2019).

We used the restricted maximum-likelihood estimator (REML) of Tau^2 and the Hartung-Knapp-Sidik-Jonkman (HKSJ) method for estimating standard errors, as it has consistently resulted in more adequate standard errors than the DL method, especially when the number of studies is small (IntHout 2014). We used the 'metan' command in Stata (Harbord 2008). However, even with the HKSJ method, extra caution is needed when there are fewer than six studies of unequal size (IntHout 2014). Thus, we used the DerSimonian and Laird (DL) method for sensitivity analysis. We used the inverse variance (IV) fixed-effect model (FEM) for meta-analyses of two studies. In this situation, the REM frequently has low power and does not yield informative results (Schulz 2022; Veroniki 2019). We assessed the impact of this decision in a sensitivity analysis. We used the 'metan' command in Stata (Harbord 2008) for meta-analyses including at least three studies, and RevMan (RevMan 2024) for meta-analyses of two studies.

We combined results in meta-analysis regardless of their RoB and the factors considered for adjustment.

Presentation of results

For the meta-analysis of each prognostic effect estimate, we provide the pooled estimate (OR), its 95% CI, the absolute risk difference (ARD) per 1000 patients and its 95% CI, the I^2, the estimate of Tau^2 (between-study variance) and the 95% prediction interval (PI).

An OR larger than one suggests that the female sex is associated with higher odds of mortality. However, the meaning of OR is often difficult for clinicians to understand and can be misinterpreted as RR (Boissel 1999; Deeks 2000; Deeks 2011; Sackett 1996; Sinclair 1994). This can be misleading as the OR is similar to the RR for outcomes with a low incidence (less than 10%) but exaggerates the effect with higher incidence (Zhang 1998). To

facilitate interpretation, we provide the ARD per 1000 patients for the effect of the prognostic factor. We used the GRADEPRo GDT calculator to obtain the ARD, and we considered three baseline risks in male patients based on external observational evidence. We chose an ARD of 0.5% (5 per 1000) as the threshold for identifying an important prognostic factor for a critical outcome such as mortality, that is, the minimally important difference (MID) that might influence clinical decision-making. For example, in the USA, this MID would translate into a difference of 3000 deaths per year of people with PE that could be attributed to sex (assuming 600,000 new PE cases per year).

Synthesis using other methods

If meta-analysis is not possible in future review updates, for example, due to limited evidence for a prespecified comparison (no studies or only one study) or incompletely reported outcome or effect estimates, we will perform a narrative synthesis of the available quantitative data following the *Cochrane Handbook for Systematic Reviews of Interventions* and the latest guidance on Synthesis Without Meta-analysis (SWiM) (Campbell 2020; McKenzie 2023).

Subgroup analysis and investigation of heterogeneity

Investigating heterogeneity through subgroup analysis does not generally produce useful findings unless there is a substantial number of studies (Deeks 2022). We did not perform subgroup analyses because fewer than 10 studies were included per meta-analysis.

Sensitivity analysis

We undertook the following sensitivity analyses (Table 2).

- When the primary analysis used the REM HKSJ method, we used the FEM IV and the REM DL methods.
- When the primary analysis used the FEM IV method, we used the REM HKSJ method.

Rating the certainty of the evidence and summarising findings

We assessed the certainty of the body of evidence for each prognostic effect estimation according to the recommendations of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (GRADE 2013). We used the adapted GRADE approach for questions on prognostic factors (Foroutan 2020; Huguet 2013; Iorio 2015; Westby 2018).

When evaluating the overall certainty of evidence, GRADE suggests considering the investigation phase. Evidence from phase 2 studies (explanatory research to confirm independent associations between a potential prognostic factor and the outcome) should be initially defined as high certainty. On the other hand, evidence from phase 1 explanatory studies (exploratory research that aims to identify associations between potential prognostic factors and the outcome) starts at moderate-certainty evidence (Foroutan 2020; Huguet 2013; Iorio 2015). Our certainty of the evidence assessments did not consider the investigation phase, as only phase 2 studies were eligible. Thus, all the assessments departed from high-certainty evidence. We modified this initial certainty of the evidence based on the following criteria.

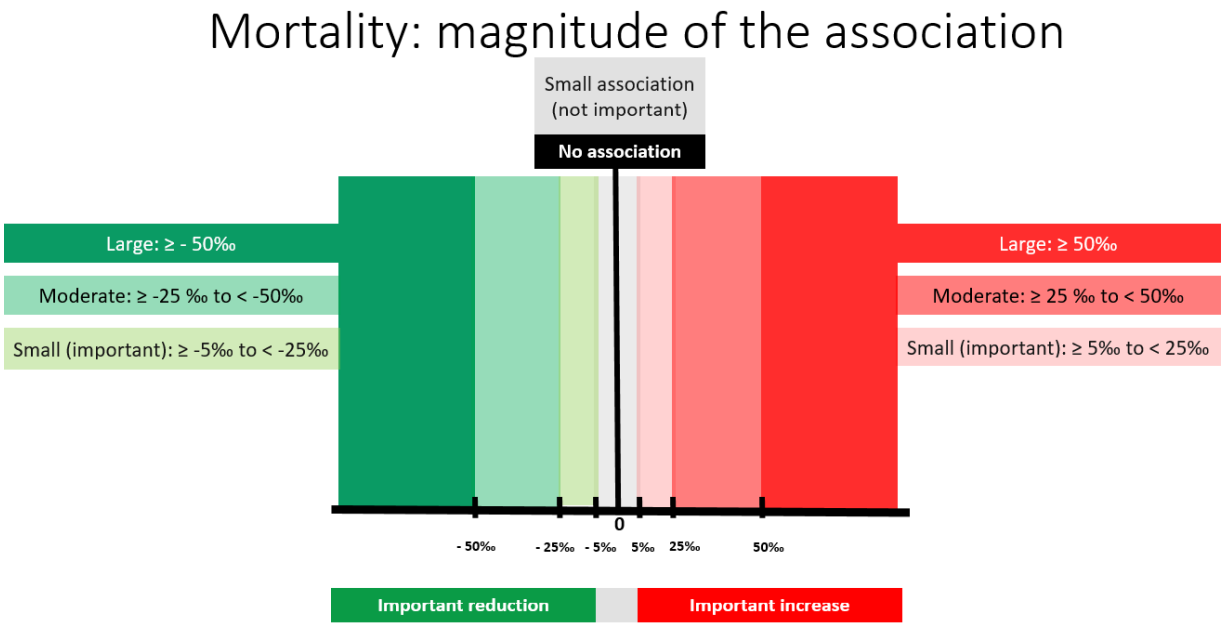
- Criteria for downgrading confidence in the prognostic effect estimate: risk of bias, inconsistency, imprecision, indirectness, and publication bias
- Criteria for upgrading confidence in the prognostic effect estimate: large effect (the dose-response criterion is not applicable in our review)

We used GRADEproGDT software (GRADEpro-GDT 2022) to create Summary of findings 1 with the review results, including the certainty of the body of evidence related to each outcome. All the review outcomes were considered critical for decision-making, so they are included in the table. The table contains all decisions to downgrade or upgrade the certainty of the evidence with footnotes and provides explanations to help the reader's understanding. Two review authors (JLA, EJ) independently assessed the certainty of the evidence for each outcome. Another review author (AC) checked the assessments. We used Foroutan 2019's table as a template.

We assessed imprecision using the confidence interval approach in a minimally contextualised setting (Zeng 2022). Considering the importance of the outcome mortality, we set an MID (i.e. the threshold of interest) at a difference of at least 0.5% deaths (i.e. 5 deaths per 1000 participants).

We followed GRADE wording to communicate the review findings for each outcome effect estimate (Santesso 2020). This approach integrates the certainty of the evidence and the magnitude of the association. We defined the magnitude by considering the central estimate of the ARD in the intermediate risk scenario. For thresholds, see Figure 3.

Figure 3. Mortality: magnitude of the association



Central estimate: Absolute Risk Difference (ARD) (‰)

RESULTS

Results of the search

Searches in electronic databases and registers up to 17 February 2023 identified 138,599 records. After removing duplicates, we screened 79,900 unique records by title and abstract. We excluded 79,564 records that did not meet the review criteria and retrieved 336 full-text reports for further examination. Through searching for studies via other methods (conferences, websites, organisations, and citation searching), we identified one additional potentially eligible record, which was classified as 'awaiting assessment' (Alsaloum 2023).

We included seven studies in the review (Agarwal 2015; Barrios 2017; Borrero 2007; Marshall 2017; Pribish 2020; Sedhom 2022; Tanabe 2018), which were described in eight reports. We found one ongoing study (SERIOUS-PE), and three studies await classification (Alsaloum 2023; Feng 2020; Rosovsky 2019). See Figure 1 for our PRISMA study selection flow diagram.

Included studies

The seven studies involved 726,293 participants (Agarwal 2015; Barrios 2017; Borrero 2007; Marshall 2017; Pribish 2020; Sedhom 2022; Tanabe 2018). Individual details of the studies are tabulated in Characteristics of included studies.

Study designs/methods

All the included studies were retrospective cohort studies. The data were collected from administrative databases (number of studies (n) = 5; 71%) (Agarwal 2015; Borrero 2007; Marshall 2017; Sedhom 2022; Tanabe 2018) or research-purpose databases (n = 2; 29%) (Barrios 2017; Pribish 2020). The observed samples at baseline totalled 726,273 participants. The study samples for the review analyses ranged from 1428 participants (Tanabe 2018) to 312,840 participants (Marshall 2017). The observed number of deaths ranged from 8953 (Agarwal 2015) to 9860 (Marshall 2017) for all-cause hospital mortality, 140 (Barrios 2017) to 1439 (Borrero 2007) for all-cause mortality at 30 days, and from 58 (Tanabe 2018) to 62 (Barrios 2017) for PE-related mortality at 30 days.

Settings

Most studies (n = 4; 57%) were published before 2018 (Agarwal 2015; Barrios 2017; Borrero 2007; Marshall 2017). The earliest recruitment took place between 2000 and 2002 (Borrero 2007), and the most recent recruitment was between 2016 and 2018 (Sedhom 2022). The studies included hospitalisations over different periods. Two studies, Agarwal 2015 and Marshall 2017, used the National Inpatient Sample (NIS) data for the analysis, from 2003 to 2011 and 2012 to 2013, respectively. Sedhom 2022 used the Nationwide Readmissions Database (NRD) from 1 January 2016 to 31 December 2018.

All the studies considered participants managed in the hospital setting. Five (71%) studies were multicentric (Agarwal 2015; Borrero 2007; Marshall 2017; Sedhom 2022; Tanabe 2018): three of them involved between 72 and 1000 centres (Agarwal 2015; Borrero 2007; Tanabe 2018), and two studies did not specify the number of centres (Marshall 2017; Sedhom 2022). Two studies were conducted in a single centre (Barrios 2017; Pribish 2020).

Five of the studies were conducted in the USA (Agarwal 2015; Borrero 2007; Marshall 2017; Pribish 2020; Sedhom 2022); one study was conducted in Spain (Barrios 2017); and one study was conducted in Japan (Tanabe 2018). No study was conducted in a low- or middle-income country.

Participant characteristics

Demographic characteristics and diagnoses

The proportion of females was higher than males in six of the seven studies; proportion of females ranged from 46.3% (Sedhom 2022) to 59.9% (Borrero 2007) of the sample. The participants' mean age was consistently over 60 years across the studies, ranging from 62.2 years (Agarwal 2015) to 68.7 years (Barrios 2017).

We assumed that all the studies confirmed the pulmonary embolism (PE) diagnosis by objective testing; this information was explicitly stated in three studies (43%) (Barrios 2017; Pribish 2020; Tanabe 2018). For PE diagnosis, the studies used ICD-9 coding (n = 4; 57%; Agarwal 2015; Borrero 2007; Marshall 2017; Pribish 2020) or ICD-10 coding (n = 2; 29%; Pribish 2020; Sedhom 2022).

In two studies, PE was the primary cause of hospitalisation (Agarwal 2015; Marshall 2017). We also presumed it to be the predominant reason for hospital admissions in Barrios 2017 and Tanabe 2018, which involved participants enroled from registries where patients had initially presented to emergency departments with symptoms of acute PE or required care for cardiac emergencies. The description of the main reason for hospitalisation was unclear in Borrero 2007 and Pribish 2020. Sedhom 2022 explicitly stated that whether PE was present upon admission or developed during the hospital stay was uncertain, noting that the study included discharge diagnoses.

Two studies (29%) included participants with primary PE (Agarwal 2015; Marshall 2017). One study (14%) also included participants with secondary or recurrent PE, representing 1.9% and 5.6% of the sample, respectively (Borrero 2007). Four studies (57%) did not state whether the PE was primary or secondary (Barrios 2017; Pribish 2020; Sedhom 2022; Tanabe 2018).

Clinical characteristics

Only three studies (43%) reported clearly if participants were symptomatic. In these studies, more than 85% of the participants presented with symptomatic PE (Barrios 2017; Pribish 2020; Tanabe 2018). All the participants with acute symptomatic PE in the studies reported this information (n = 6; 86%). Borrero 2007 did not detail the PE phase. Given the prevalent focus in the literature on symptomatic cases when discussing the prognostication of acute PE, we inferred that most participants were symptomatic unless asymptomatic or incidental PE was specifically indicated. No study reported the time between the onset of PE symptoms and the start of follow-up.

In general terms, the studies included participants with no severe PE, but the proportion of participants with severe PE ranged from 0.5% (Marshall 2017) to 70% (Barrios 2017). PE severity was described in most studies (only Agarwal 2015 omitted this information due to the inconsistent availability of data in its database). However, the approaches used for the quantification of severity were diverse: individual components of the PESI score (Borrero 2007); the sPESI score (Barrios 2017); the presence of non-massive, submassive, and massive PE (Pribish 2020; Tanabe 2018); the presence of cor pulmonale (Marshall 2017); or the presence of saddle PE, acute cor pulmonale, and/or cardiogenic shock (Sedhom 2022).

PE treatment

The hospital unit where the participants were treated was reported in two studies. Tanabe 2018 managed all participants in the cardiovascular care unit. Pribish 2020 reported that 67% of the participants were managed in the ICU during the study (but the proportion of ICU patients at baseline was not described). There was one study in which the treatment was not mentioned (Borrero 2007). In the other six studies, investigators reported that the treatments administered were reperfusion (n = 6; Agarwal 2015; Barrios 2017; Marshall 2017; Pribish 2020; Sedhom 2022; Tanabe 2018), inferior vena cava filter (n = 4; Agarwal 2015; Barrios 2017; Pribish 2020; Tanabe 2018), anticoagulation (n = 2; Pribish 2020; Tanabe 2018), and haemodynamic/respiratory support (n = 2; Pribish 2020; Sedhom 2022).

Prognostic factor

Index prognostic factor

None of the studies explicitly defined sex or the method used for sex assessment. We assumed this to be by self-report or medical record. Moreover, sex and gender terms were used inconsistently. Barrios 2017 reported the results using male patients as the reference category; however, to maintain consistency across studies, we reported results using female patients as the reference category in this study, too. The outcome was predicted from the point of admission (Borrero 2007) or treatment initiation (Barrios 2017), although this information was missing in most studies (n = 5; 71%; Agarwal 2015; Marshall 2017; Pribish 2020; Sedhom 2022; Tanabe 2018).

Comparator prognostic factors

Only one study defined all the key additional prognostic factors, which were the conditions included in the Charlson Comorbidity Index (Pribish 2020). Conversely, four studies failed to define any key factors adequately (Agarwal 2015; Marshall 2017; Sedhom 2022; Tanabe 2018). Two studies defined some factors (Barrios 2017; Borrero 2007).

Furthermore, no study detailed the methods used to measure the covariates, particularly whether uniform measurement methods were applied across all participants. Additionally, most studies (n = 5) did not report the proportion of participants with missing values for these covariates. Although the studies included only participants with complete data in their analysis, it remains unclear whether the missing values pertained specifically to the covariates.

Study outcomes and analyses

Four studies (57%) reported all-cause hospital mortality (Agarwal 2015; Marshall 2017; Pribish 2020; Sedhom 2022), two studies (29%) reported all-cause mortality at 30 days (Barrios 2017; Borrero 2007), and two studies (29%) reported PE-related mortality at 30 days (Barrios 2017; Tanabe 2018). No study reported early all-cause hospital mortality (during the first 48 hours); all-cause mortality at 30 days; all-cause mortality at 90 days; all-cause mortality at one year; PE-related hospital mortality; early PE-related hospital mortality (during the first 48 hours); or PE-related hospital mortality at 30 days.

The time points used for analysis in the studies providing data for the review outcomes were from the treatment initiation (all-cause mortality at 30 days (Barrios 2017); PE-related mortality at

30 days; Barrios 2017); and PE admission (all-cause mortality at 30 days; Borrero 2007). The remaining studies did not report this information (Agarwal 2015; Marshall 2017; Pribish 2020; Sedhom 2022; Tanabe 2018).

Five studies (71%) used a logistic regression method for adjustment: multivariable logistic regression (Barrios 2017; Marshall 2017; Tanabe 2018), random-effects logistic regression (Borrero 2007), and multivariable hierarchical logistic regression (Agarwal 2015). The remaining two studies (29%) used other techniques: Pribish 2020 used the inverse probability of treatment weighting (IPTW) to evaluate the adjusted risk, and Sedhom 2022 used a propensity score matching algorithm.

All the studies but Pribish 2020 reported the adjusted effects as an OR. Pribish 2020 reported the study effect as an ARD. We could not transform this effect measure to OR because the control group risk was not reported (only the total number of analysed participants was provided). Thus, Pribish 2020's results could not be meta-analysed and were reported separately.

Of our predefined eight key covariates of interest, the following were reported for adjustment: age (n = 7, 100%); current cancer and current chronic cardiopulmonary disease (n = 6; 86%) (Agarwal 2015; Barrios 2017; Borrero 2007; Marshall 2017; Pribish 2020; Sedhom 2022); systolic blood pressure (n = 3; 43%)(Barrios 2017; Borrero 2007; Tanabe 2018); heart rate and oxygen saturation (n = 2; 29%) (Barrios 2017; Borrero 2007); and history of chronic cardiopulmonary disease (n = 2; 29%) (Pribish 2020; Sedhom 2022). No study reported adjustments for cancer history or specified the measurement methods for the covariates or outcomes.

Excluded studies

We excluded 319 studies (325 reports) at the full-text assessment stage for the following reasons (Characteristics of excluded studies).

- **Duplicate reference** (6 reports)
- **Not a primary study:** reviews or consensus articles (7 reports)
- **Ineligible research question:** not a prognostic question (66 reports); prognosis question but not assessing a prognostic factor (5 reports)
- **Ineligible study design:** not a phase 2 prognostic study (92 reports); cross-sectional study (3 reports)
- **Ineligible population:** no PE (10 reports); mixed population (PE + deep vein thrombosis (DVT)) (3 reports); study in cadavers (1 report)
- **Ineligible prognostic factor:** sex not assessed as a prognostic factor (125 reports)
- **Ineligible outcome:** mortality not an outcome (6 reports); study assessed survival (1 report)

We had to obtain multiple full texts due to the incomplete reporting in the abstracts.

Studies awaiting classification

Three studies are awaiting classification at the time of writing this review. They are conference abstracts pending publication as peer-reviewed articles (Alsaloum 2023; Feng 2020; Rosovsky 2019).

Ongoing studies

We found one eligible ongoing study, the SERIOUS-PE study (SERIOUS-PE), which will assess sex differences in 30-day and one-year clinical outcomes in older adults with PE (aged at least 65 years). Participants have been selected from two databases: 31,273 participants (over 50% women) from a large multicentre international prospective registry of patients with objectively confirmed venous thromboembolism - the Registro Informatizado Enfermedad TromboEmbolica (RIETE) registry - from March 2001 through March 2021. The RIETE registry was started in Spain in 2001 and includes 226 enroling centres in Europe, North and South America, Africa, and Asia. To provide perspective from the USA, more than one million additional participants (hospitalised with a principal discharge diagnosis of PE between January 2001 and December 2019) have been selected from the US Medicare Fee-For-Service beneficiaries.

Risk of bias assessment of included studies

See risk of bias assessments in Characteristics of included studies and Figure 2.

We did not consider any study to have an overall low risk of bias for any of the outcomes analysed (all-cause hospital mortality, all-cause mortality at 30 days, PE-related mortality at 30 days).

Concerning all-cause hospital mortality, we judged half of the studies to be at an overall high risk of bias (n = 2; Agarwal 2015; Marshall 2017), and the remaining two studies at moderate risk (50%; Pribish 2020; Sedhom 2022). Concerning all-cause mortality at 30 days, both studies were at moderate risk of bias (100%; Barrios 2017; Borrero 2007). In relation to PE-related mortality at 30 days, we judged the overall risk of bias to be moderate in Barrios 2017 and high in Tanabe 2018.

Our judgement of overall high risk of bias was because of analyses not being adjusted for our eight key covariates (Agarwal 2015; Marshall 2017; Tanabe 2018) and study attrition (Marshall 2017). The reasons for our moderate risk judgements were plausible biases for one or more key domains that raised some doubt about the results (although no bias domain was rated as high risk of bias): study attrition in one study (Borrero 2007), and statistical analysis and reporting in all the studies (Barrios 2017; Borrero 2007; Pribish 2020; Sedhom 2022).

a. Study participation

We judged most studies (n = 6, 85.7%) to be at low risk of bias for study participation. Moreover, they reported clearly the eligible participants (inclusion and exclusion criteria) and recruitment populations, periods, and places. We judged one study (14.3%) to be at moderate risk of bias for this domain because sampling design and weights were not reported (Marshall 2017).

b. Study attrition

We judged there to be a high risk of attrition bias when missing data exceeded five per cent.

All-cause hospital mortality

Four studies informed all-cause hospital mortality (Agarwal 2015; Marshall 2017; Pribish 2020; Sedhom 2022). Three of them were at low risk of attrition bias (75%; Agarwal 2015; Pribish 2020; Sedhom

2022). We judged Marshall 2017 to be at high risk of attrition bias as 9% of the participants had at least one of the baseline characteristics or sex or clinical outcome missing. The variables and the study arm with missing data were not specified. Moreover, attrition was reported for the full sample (and not for participants with PE). Thus, a plausible bias may raise some doubts about the results.

All-cause mortality at 30 days

Two studies informed all-cause mortality at 30 days (Barrios 2017; Borrero 2007). Barrios 2017 was at low risk of attrition bias. We assessed Borrero 2007 as having a moderate risk of attrition bias. In this study, 5.7% of the study population could not be analysed due to some missing data: participant identifiers (0.5%), unknown mortality status (0.4%), and participants without key clinical findings (4.7%).

PE-related mortality at 30 days

We judged the two studies that informed this outcome to be at low risk of attrition bias (Barrios 2017; Tanabe 2018).

c. Prognostic factor measurement

No included study specified the method used for measuring the prognostic factor. Moreover, sex and gender terms were used inconsistently. However, we consider that this inadequate reporting did not cause bias and judged all the studies to be at low risk of bias concerning the prognostic factor measurement.

d. Outcome measurement

Concerning all-cause mortality outcomes (all-cause hospital mortality and all-cause mortality at 30 days), no study reported the measurement methods. Still, we consider that the risk of bias concerning the outcome measurement was probably low as there was no adjudication of the cause of death. Concerning PE-related mortality at 30 days, Barrios 2017 presented a low risk of bias for the outcome measurement as two investigators independently adjudicated the cause of death. For Tanabe 2018, another study examining 30-day PE-related mortality, we found no evidence that whether patients were male or female influenced the cause of death adjudication in PE patients; however, we assessed its risk of bias as moderate due to the study's insufficient detail on the adjudication process.

e. Adjustment for key additional prognostic factors

A study should have adjusted for at least four of our covariates of interest to be judged as a low risk of bias for this domain.

All-cause hospital mortality

Two studies (50%) were at low risk of bias (Pribish 2020; Sedhom 2022), and another two (50%) were at high risk of bias (Agarwal 2015; Marshall 2017).

All-cause mortality at 30 days

All the studies informing this outcome were at low risk of bias (Barrios 2017; Borrero 2007).

PE-related mortality at 30 days

One study informing this outcome was at low risk of bias (Barrios 2017). We judged the other study to be at high risk of bias (Tanabe 2018).

f. Statistical analysis and reporting

We assessed the statistical analysis and reporting domain as at moderate risk of bias for all the review outcomes in all included studies (n = 7; Agarwal 2015; Barrios 2017; Borrero 2007; Marshall 2017; Pribish 2020; Sedhom 2022; Tanabe 2018).

We judged the statistical analysis to be at low risk of bias in five studies (71.4%; Agarwal 2015; Borrero 2007; Marshall 2017; Pribish 2020; Sedhom 2022) and moderate risk in the other two (Barrios 2017; Tanabe 2018). The model construction strategy was unclear in Tanabe 2018. Concerning Barrios 2017, the variables included in the multivariate model seemed to be those that were significant in the univariate logistic regression. Thus, we judged its risk of bias as moderate.

Concerning the risk of selective outcome reporting, we were not able to find the protocol of any study. Thus, we could not assess the presence of selective reporting by comparing the planned outcomes with the reported ones. Consequently, we judged the risk of selective outcome reporting as moderate for all studies but one (Barrios 2017). We judged there to be a low risk of selective outcome reporting in Barrios 2017 because its corresponding author confirmed that the outcomes reported in the published article's methods were the planned outcomes.

Findings

This systematic review included seven studies. All of them reported data for at least one review outcome. Four studies reported all-cause in-hospital mortality (Agarwal 2015; Marshall 2017; Pribish 2020; Sedhom 2022), two reported all-cause mortality at 30 days (Barrios 2017; Borrero 2007), and two reported PE-related mortality at 30 days (Barrios 2017; Tanabe 2018). All but one of the studies were included in meta-analysis (Pribish 2020); we reported Pribish 2020's results narratively.

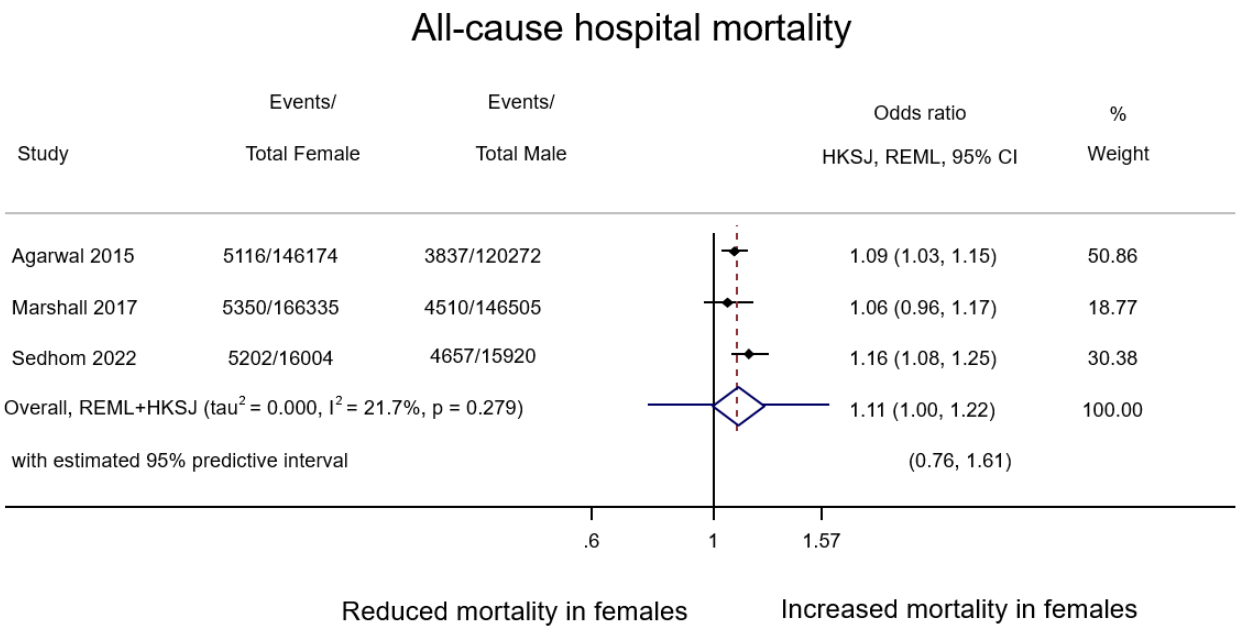
Outcome 1. All-cause hospital mortality

We investigated the independent prognostic effect of being a female patient with PE on all-cause hospital mortality. Four studies (707,218 participants) addressed this question (Agarwal 2015; Marshall 2017; Pribish 2020; Sedhom 2022). Two studies found increased all-cause hospital mortality in female patients (Agarwal 2015; Sedhom 2022), while the other two did not find evidence of differences between the sexes (Marshall 2017; Pribish 2020).

Three studies provided data that were sufficiently similar to be combined in meta-analysis (Agarwal 2015; Marshall 2017; Sedhom 2022). In female patients with PE, there may be a small (clinically important) increase in all-cause hospital mortality as compared to male patients (OR 1.11, 95% confidence interval (CI) 1.00 to 1.22; I^2 = 21.7%; 95% prediction interval (PI) 0.76 to 1.61; absolute risk difference (ARD) 13 more deaths in females per 1000 patients, 95% CI 0 to 26 more; 3 studies, 611,210 participants; observed follow-up: medians ranged 4 to 9 days; low-certainty evidence; Figure 4) (Agarwal 2015; Marshall 2017; Sedhom 2022). We downgraded the certainty of the evidence by two levels due to the serious risk of bias and serious imprecision (Summary of findings 1). The pooled

overall all-cause hospital mortality rate in each study was 32‰ (‰ = out of 1000) (Marshall 2017), 34‰ (Agarwal 2015), and 309‰ (Sedhom 2022). The adjusted odds ratios (ORs) of these studies pointed to a higher risk of all-cause hospital mortality in female patients, which suggests that the study's overall all-cause hospital mortality rate was not a confounder.

Figure 4. All-cause hospital mortality; HKSJ: Hartung-Knapp-Sidik-Jonkman adjustment; REML: Restricted Maximum Likelihood estimation.



We could not pool data from Pribish 2020 with data from the other studies due to insufficient information for estimating its OR. The study results were inconclusive for all-cause hospital mortality (ARD 2.2 fewer deaths in females per 1000 patients, 95% CI 42.1 fewer to 37.4 more). We graded the certainty of the evidence as very low due to extremely serious imprecision.

There was a lack of robustness in the primary analysis (Restricted Maximum Likelihood (REML) estimation and Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment meta-analysis) when subjected to sensitivity analysis (inverse variance fixed-effect model (IV FEM) meta-analysis). See Table 2. Consequently, we downgraded the certainty of the evidence by one level for imprecision (Summary of findings 1).

Outcome 2. Early all-cause hospital mortality (during the first 48 hours)

No study reported this outcome.

Outcome 3. All-cause hospital mortality at 30 days

No study reported this outcome.

Outcome 4. All-cause mortality at 30 days

We investigated the independent prognostic effect of being a female patient with PE on all-cause mortality at 30 days. Two studies (17,627 participants) addressed this question and were meta-analysed (Barrios 2017; Borrero 2007). The pooled overall all-cause mortality rates at 30 days were 67‰ (Barrios 2017) and 93‰ (Borrero 2007). Barrios 2017 did not find evidence of differences between sexes, while Borrero 2007 found a reduced risk of all-cause mortality at 30 days in female patients with PE.

According to the meta-analysis of the two studies (Barrios 2017; Borrero 2007), in female patients with PE, there is likely a small (clinically important) reduction in all-cause mortality at 30 days as compared to male patients (OR 0.81, 95% CI 0.72 to 0.92; I^2 = 0%; 95% PI not possible to obtain due to the insufficient number of studies; ARD 24 fewer deaths in females per 1000 patients, 95% CI 35 to 10 fewer; 2 studies, 17,627 participants; observed follow-up: not reported; moderate-certainty evidence; Analysis 1.1). We downgraded the certainty of the evidence by one level due to serious imprecision (Summary of findings 1).

Barrios 2017 reported the results using male participants as the reference category. To maintain consistency across studies, we adapted this and reported results using female participants as the reference category. There was a lack of robustness in the primary analysis (IV FE model meta-analysis) shown by sensitivity analysis. See Table 2. Consequently, we rated down one level for imprecision.

Outcome 5. All-cause mortality at 90 days

No study reported this outcome.

Outcome 6. All-cause mortality at one year

No study reported this outcome.

Outcome 7. PE-related hospital mortality

No study reported this outcome.

Outcome 8. Early PE-related hospital mortality (during the first 48 hours)

No study reported this outcome.

Outcome 9. PE-related hospital mortality at 30 days

No study reported this outcome.

Outcome 10. PE-related mortality at 30 days

We investigated the independent prognostic effect of being a female patient on PE-related mortality at 30 days. Two studies (3524 participants) addressed this question and were meta-analysed (Barrios 2017; Tanabe 2018). The pooled overall PE-related mortality rates at 30 days were 30‰ (Barrios 2017) and 40‰ (Tanabe 2018). No individual study found evidence of differences between female and male participants.

According to the meta-analysis of the two studies (Barrios 2017; Tanabe 2018), in female patients with PE, there may be little to no difference in PE-related mortality at 30 days as compared to male patients (OR 1.08, 0.55 to 2.12; I^2 = 0%; 95% PI not possible to obtain due to the insufficient number of studies; ARD 4 more deaths in females per 1000 patients, 95% CI 22 fewer to 50 more; 2 studies, 3524 participants; observed follow-up: not reported; low-certainty evidence; Analysis 1.2). We downgraded the certainty of the evidence by two levels due to very serious imprecision (Summary of findings 1).

Barrios 2017 presented results with the male sex as the reference category. Thus, we reversed the results into our reference category. The results of the primary analysis (IV FE model) were robust and not affected by sensitivity analysis. See Table 2.

DISCUSSION

This Cochrane review provides up-to-date evidence about the role of sex (being a female patient compared to a male patient) as an independent prognostic factor for predicting mortality in adults with acute symptomatic pulmonary embolism (PE). We included phase 2-confirmatory prognostic studies, that is, explanatory research aimed to confirm an independent association between a potential prognostic factor (sex) and the outcome of interest. The review attempted to address mortality in different settings and up to one year: all-cause hospital mortality; early all-cause hospital mortality (during the first 48 hours); all-cause hospital mortality at 30 days; all-cause mortality at 30 days; all-cause mortality at 90 days; all-cause mortality at one year; PE-related hospital mortality; early PE-related hospital mortality (during the first 48 hours); PE-related hospital mortality at 30 days; and PE-related mortality at 30 days.

Summary of main results

We included seven studies (eight reports) involving 726,293 participants. Six studies (724,242 participants) provided data for meta-analyses (Agarwal 2015; Barrios 2017; Borrero 2007; Marshall 2017; Sedhom 2022; Tanabe 2018). One study could not be included in meta-analysis and was described narratively (Pribish 2020).

The studies were retrospective cohorts with participants recruited and managed in hospitals between 2000 and 2018 in the US, Spain and Japan. Most studies were multicentric. No study was done in low- or middle-income countries. Patients presented with acute symptomatic PE that was generally not severe. No study stated the time between the onset of PE symptoms and the start of follow-up. The patients received different PE treatments: reperfusion, inferior vena cava filter, anticoagulation, and haemodynamic/respiratory support. No study defined sex or its ascertainment method. Sex and gender terms were used inconsistently. The prognostication time (the point from which the outcome was predicted) was frequently omitted. The heterogeneous reporting of mortality precluded meta-analyses (three studies could be meta-analysed at most). The studies provided data for three review outcomes: all-cause hospital mortality (4 studies), all-cause mortality at 30 days (2 studies), and PE-related mortality at 30 days (2 studies). No study data was found for our other predefined outcomes. All but one of the studies reported prognostic associations as ORs (the other used ARDs).

This review indicates that the independent prognostic effect of sex for predicting mortality in adults with PE is uncertain. We found moderate-certainty evidence (downgraded one level from high certainty due to imprecision) that, in female patients with PE, there is likely a small but clinically important reduction in all-cause mortality at 30 days. However, other review outcomes do not point to this lower mortality in female patients. Low-certainty evidence (downgraded by two levels due to serious risk of bias and imprecision) suggests that, in female patients with PE, there may be a small but clinically important increase in all-cause hospital mortality. There was also low-certainty evidence (downgraded two levels due to very serious imprecision) suggesting little to no difference in PE-related mortality at 30 days. No data were found on the remaining review outcomes, including sex-specific mortality data at one year. Due to an insufficient number of studies, many review processes were not implemented, particularly heterogeneity and publication bias assessments and subgroup and sensitivity analyses.

Certainty of the evidence

We used GRADE to assess the certainty of the evidence. We are moderately confident in the effect of sex on all-cause mortality at 30 days, i.e. we have moderate certainty, which means that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We graded the certainty as low for all-cause hospital mortality and PE-related mortality at 30 days, which means that our confidence in the effect estimates is limited, and the true effects may differ substantially from the effect estimate. Our reasons for downgrading the certainty of the evidence were serious imprecision and risk of bias.

The most frequent reason for downgrading the evidence was imprecision, as the 95% confidence interval (CI) of the absolute risk difference (ARD) in the moderate-risk scenario crossed the minimal important difference threshold (MID) (5 deaths per 1000 participants). We assessed imprecision following recent GRADE guidance using the CI approach in a minimally contextualised setting (Zeng 2022): aligning imprecision criterion for systematic reviews and guidelines using the approach that relies on thresholds and CI of absolute effects as a primary criterion for imprecision

rating (i.e. CI approach). We downgraded the certainty of the evidence due to imprecision by one level (all-cause hospital mortality, PE-related mortality at 30 days) or two levels (PE-related mortality at 30 days). We set our clinical threshold of interest (MID = 5‰) based on two premises. First, our review assessed mortality, an outcome for which minimal differences are relevant. Concerning mortality, a MID of five per cent was used by Zeng 2022 to judge imprecision in a systematic review of corticosteroids versus no corticosteroids for patients with sepsis. Second, sex is a non-modifiable factor affecting the whole population. Thus, an ARD of 5‰ deaths can lead to a clinically important impact. Besides, a more demanding threshold, for example, 10‰, would not modify our certainty assessments. To assess imprecision, we also evaluated the robustness of our primary analyses by comparing results across alternative statistical models. Our primary analyses for all-cause hospital mortality and all-cause mortality at 30 days lacked robustness when subjected to sensitivity analyses. Although this was a concern, we did not downgrade an additional level due to imprecision for this reason.

Concerning the risk of bias, we downgraded the certainty of the evidence by one level for all-cause hospital mortality: we judged that the proportion of information from studies at high risk of bias was sufficient to affect the interpretation of results. The lack of adjustment for at least four of our covariates was the most frequent reason for a high risk of bias. We did not downgrade all-cause mortality at 30 days or PE-related mortality at 30 days for risk of bias, as the potential limitations were unlikely to lower the confidence in the estimates.

This review employed a 5% threshold for evaluating the risk of attrition bias, which exceeds our MID of 5‰. In a worst-case scenario, this proportion of missing participant data would miss a difference 10 times higher than our MID. However, it acknowledges the pragmatic challenges associated with retrospective studies. Limited control over follow-up in such designs often leads to some degree of unavoidable attrition. Thus, our threshold balances the need for robust data analysis with the inherent limitations of retrospective research. This threshold is aligned with general clinical research standards where a five per cent loss to follow-up is typically considered acceptable for maintaining overall study integrity and feasibility. Furthermore, considering the implausibility of a worst-case scenario for mortality outcomes and the observed effect sizes exceeding the MID in two of the three outcomes with data, we are confident that relevant differences were not missed.

We planned to assess inconsistency by considering the I^2 statistic alongside the 95% prediction interval (PI) (Riley 2011; Riley 2019). We could obtain the PI for one outcome, all-cause hospital mortality, which indicated that the potential prognostic effects of sex can range from OR 0.76 to 1.61. This represents relevant heterogeneity, but we decided not to downgrade for inconsistency, as PIs tend to be imprecise in meta-analyses of a small number of studies (IntHout 2016).

Our external assumptions regarding the outcome rates for male participants, which ranged from 27‰ (Jiménez 2018) to 29‰ (Sedhom 2022), as detailed in Summary of findings 1, aligned with the overall rates (including both males and females) observed in the included studies. These ranged from 30‰ (Barrios 2017) to 309‰ (Sedhom 2022), supporting the directness of the evidence.

As we could not assess publication bias due to a lack of data (fewer than 10 studies per meta-analysis), we did not downgrade the certainty of the evidence for this reason. However, we acknowledge publication bias is endemic in prognosis research (Kyzas 2005; Riley 2019). Thus, downgrading for this reason would be reasonable as well.

Strengths and weaknesses of the review

Strengths

Our review has several methodological strengths.

First, we followed recent guidance for systematic reviews of prognostic factor studies and adhered to a published protocol. We applied GRADE to assess evidence of prognostic factors by following official guidance, including how to assess imprecision using the CI approach in a minimally contextualised setting (Huguet 2013; Iorio 2015; Foroutan 2019; Foroutan 2020; PMG 2020; Riley 2019; Santesso 2020; Zeng 2022).

Second, we formulated a clear research question following the PICOTS (population, intervention, comparator, outcome, timing, setting) format. We predefined critical items for prognostic factor questions, such as the population, index prognostic factor, comparator (key covariates for adjustment of the crude estimate), and type of outcomes to be predicted. We specified the prognostication time for each review outcome, which is essential for decision-making (Table 1). We defined the study design eligibility based on study design features more than on the design labels (Appendix 1). Finally, we prespecified a core set of adjustment factors based on a literature review, consensus, and peer reviewers' input during the protocol publication process (Appendix 2).

Third, we implemented exhaustive, non-language-restricted searches, including additional sources, such as conferences, to identify studies. The high number of records retrieved (138,599 records) minimised the risk of publication bias, an endemic problem in prognosis research (Kyzas 2005; Riley 2019).

Fourth, we selected phase-2 explanatory studies, which initially provide high certainty of the evidence for prognosis studies. This is important for estimating the independent prognostic factor of sex. The crude (unadjusted) effect may disappear after adjustment and is, therefore, not very informative: prognostication in healthcare is rarely based on a single prognostic factor but rather on information from multiple prognostic factors (Riley 2019).

Fifth, to prevent bias, at least two review authors independently performed all relevant review processes, such as study selection, risk of bias assessment, and statistical analyses. Although several review authors were authors of an included study (Barrios 2017), they did not intervene in the risk of bias assessment or analysis of this study in order to minimise bias.

Weaknesses

Our review presents some limitations that are consistent with those of a previous review performed by our team to determine the prognostic role of sex in mortality in patients with sepsis (Antequera 2021). The main limitations arise from the poor reporting of the included studies, their low number, and the inclusion of studies collecting data from administrative databases (e.g. registries).

First, a definition of sex was missing in all the included studies, and no study described the method used to ascertain it, for example, observation by healthcare staff. Moreover, sex and gender terms were used inconsistently, suggesting that researchers still misunderstand the difference between sex and gender. However, we consider that the inadequate reporting of sex did not distort the review findings as the risk of incorrect sex ascertainment is low.

Second, key study characteristics were frequently missing in study reports. For example, no study stated the time between the onset of PE symptoms and the start of follow-up. Consequently, the prognostication time, that is, the time point from which the outcome was predicted, was unclear. Another limitation was the vague description of the setting where the deaths occurred, that is, in-hospital mortality or mortality combining in-hospital and out-of-hospital deaths.

Third, we could not find a protocol for any of the studies, so we could not assess selective outcome reporting by comparing planned methods with the reported results. Consequently, we judged the risk of selective outcome reporting as unclear and the QUIPS domain 'Statistical analysis and reporting' as moderate risk. We could have implemented a less strict approach by adjudicating a low risk for studies without deviations between the methods section of the study publication and the reported results. However, we preferred our conservative approach as selective outcome reporting is frequent in prognostic factor research; for example, prognostic factors' effects were selectively and incompletely reported in 36% and 24% of oncology studies, respectively (Kempf 2018).

Fourth, due to the small number of included studies, we could not implement many review processes. For example, our review protocol planned to investigate if haemodynamic status (stable versus unstable), as a proxy of severity, could explain heterogeneity in the study results, but this was not possible. Similarly, the limited number of studies also prevented us from evaluating the risk of publication bias. We did not downgrade the certainty of the evidence for publication bias, but, as mentioned above, we acknowledge that it is an endemic issue in prognosis research (Kyzas 2005; Riley 2019) and that it may have distorted our review results.

Fifth, our review included registry-based studies. Health administrative databases present methodological challenges that may result in spurious findings when not adequately accounted for in the systematic review. For example, there might be overlapping primary data. Consequently, the same participant can be included several times in the review (Mathes 2023). Moreover, different policies to pay for hospital-acquired conditions may influence how deaths are attributed to PE. For example, the Centers for Medicare & Medicaid Services hospital payment reform in 2008, which no longer reimbursed hospitals for the treatment of hospital-acquired conditions, resulted in a 35% lower incidence of hospital-acquired PE in patients with hip or knee replacement surgery (probability value (P) = 0.015) (Gidwani 2015). The different reimbursement mechanisms may affect the adjudication of death to PE.

Sixth, this review encompasses studies that recruited patients between 2003 and 2018. During this period, several guidelines for PE were issued, introducing varying definitions, diagnostics, and treatment options, which could influence mortality trends and potentially limit the applicability of this data to current PE management practices. Conversely, including studies over this extended timeframe enhances the generalisability of our findings. It allows for a comprehensive analysis of how sex influences PE mortality across diverse clinical settings and patient populations.

Seventh, we found no 'Core Outcomes Set' (COS) for selecting the review outcomes. However, we selected the review outcomes based on relevance. That is, the outcome must be critical from a patient perspective, and the outcome must support decision-making in the management of PE patients. The COS should address the difficulties in assessing the prognosis of patients with secondary PE, that is, a PE arising as a complication from a condition like cancer. In such cases, mortality often results from non-PE complications, challenging the analysis of PE's true impact on survival. As observation periods increase, the probability of deaths from unrelated complications also rises, acting as confounding factors. This complexity makes it hard for researchers to disentangle the influence of secondary PE on mortality.

Applicability of findings to clinical practice and policy

We believe that our review identified all longitudinal studies, randomised or non-randomised, assessing the independent role of sex in predicting mortality in patients with PE. We focused on mortality up to one year from the start of the PE treatment. Thus, mortality data at longer time points were not assessed. Our findings indicate that the independent prognostic effect of sex for predicting mortality in adults with PE is uncertain, and the completeness and applicability of the evidence identified have serious limitations. Thus, the available evidence cannot support a recommendation for or against the routine consideration of sex to quantify prognosis or to guide personalised therapeutic approaches in patients with PE.

We found only seven studies, a notably small number considering the burden of PE worldwide, as well as the high number of records screened (number (n) = 79,900) and full-texts assessed for inclusion (n = 336). Moreover, the included studies provided data for only three review outcomes: all-cause hospital mortality (n = 4), all-cause mortality at 30 days (n = 2), and PE-related mortality at 30 days (n = 2). No study was found for the remaining review outcomes: early all-cause hospital mortality (during the first 48 hours); all-cause hospital mortality at 30 days; all-cause mortality at 90 days; all-cause mortality at one year; PE-related hospital mortality; early PE-related hospital mortality (during the first 48 hours); and PE-related hospital mortality at 30 days. Finally, six studies provided data for meta-analyses, and the meta-analyses included four studies at the most, so the amount of data is limited.

Several reasons explain the small amount of evidence found in our review. First, we included phase 2-confirmatory prognostic studies exclusively. Consequently, we excluded 93 phase-1 prognostic studies (Figure 1). We consider this decision sound, as exploratory studies often have widely varying results with common spurious associations, which may overstate their conclusions (Hayden 2008; Hayden 2014). Second, the low number of phase-2 studies matching our review criteria suggests that rigorous sex/gender research is not a priority. This is further supported by the lack of a clear justification for focusing on phase-1 studies instead. The situation may not change in the near future: we only found one ongoing study potentially eligible for this review (SERIOUS-PE). Third, our review considered well-defined patient-relevant outcomes, but the included studies reported outcomes inconsistently, frequently not matching our outcome definition.

This heterogeneous outcome measurement hampers evidence synthesis in prognosis research.

The applicability of the evidence is limited by the small number of included studies and their poor reporting. For example, the prognostication time, that is, the point from which the outcome was predicted, was missing in most studies (n = 5), and no study provided the time between the onset of PE symptoms and the start of follow-up. Another constraint lies in the lack of variety in terms of countries and settings. The included studies were conducted in the USA, Spain, and Japan. Thus, no study has been done in low- or middle-income countries. This represents a serious limitation, as PE also occurs in low and middle-income countries. However, five studies were multicentric, increasing the results' applicability to different settings. Although we found no compelling evidence to downgrade the certainty of the evidence for indirectness, decision-makers should consider these limitations in order to interpret the evidence in their context.

Our review demonstrates that the association of sex with mortality outcomes in patients with PE has not been investigated in detail. We still think that quantifying this relationship can help to improve PE management. Thus, we have identified a research gap, which can inform future research in this field. Moreover, our process of selecting the core set of adjustment factors may support the selection of key confounders in future risk of bias assessments. Furthermore, we agree with Uhlig 2014 that a methodological framework for developing clinical practice recommendations on prognostic biomarkers is needed.

Agreements and disagreements with other studies or reviews

We only found one systematic review assessing the role of sex as a prognostic factor for mortality in patients with PE (Thachil 2022). This review consulted PubMed and Embase till 1 April 2022 to identify published studies. Thachil 2022 concluded that PE-related mortality was higher in women, while our review found little to no difference between males and females for PE-related mortality. On the other hand, Thachil 2022 concluded that there were no sex-based differences in all-cause hospital mortality and 30-day all-cause mortality, while our review found female patients had a small (clinically important) increase in all-cause hospital mortality and a small (clinically important) reduction in all-cause mortality at 30 days. There are several reasons we can see for the differences between our conclusions and those of Thachil 2022. First, Thachil 2022 did not perform meta-analyses. Second, our review identified several studies that were missing in Thachil 2022 (Agarwal 2015; Marshall 2017; Sedhom 2022; Borrero 2007). Third, Thachil 2022 did not assess the risk of bias or the certainty of the evidence.

McHugh 2002 is a primary study of comparisons of men and women based on data from the International Cooperative Pulmonary Embolism Registry (ICOPER), a cohort of 2454 consecutive patients with PE from 52 hospitals in seven countries. We excluded this study because it reported survival (and hazard ratios). Following our protocol plan, we did not convert hazard ratios to odds ratios due to the many assumptions needed. The crude three-month mortality rates for men and women were also reported, but our review considered adjusted estimates exclusively. McHugh 2002's Kaplan-Meier survival analysis showed no significant sex differences within three months (log-rank test, P = 0.36).

AUTHORS' CONCLUSIONS

Implications for practice

Our review indicates that the independent prognostic effect of sex for predicting mortality in adults with acute pulmonary embolism (PE) is uncertain. In female patients with PE, there is likely a small but clinically important reduction in all-cause mortality at 30 days. On the other hand, in female patients with PE, there may be a small but clinically important increase in all-cause hospital mortality. There may be little to no difference between female and male patients in PE-related mortality at 30 days. There is currently no evidence from longitudinal studies on our other outcomes of interest.

Implications for research

We are unable to answer the question of whether sex is an independent prognostic factor for mortality in patients with PE. We focused on mortality outcomes up to one year from the start of the PE treatment. Mortality at longer periods was not assessed in this review.

This review highlighted the small number of studies in this area, the imprecision of the prognostic effect estimates, inadequate reporting of the studies (including omission of sex ascertainment), and a lack of standardisation in the measurement of mortality outcomes. Whether a patient is male or female may have a role in predicting mortality in people with PE, but the limited evidence means that we cannot draw a robust conclusion about the role of sex as a biomarker for PE mortality. Whether or not sex is a prognostic factor for PE remains an important question, and there is a need for further well-conducted prognosis research. Our review should prove useful to inform such future research and to provide a guide for systematic reviews of sex as a prognostic factor for mortality in patients with PE. We have detailed our main suggestions below.

Considerations for further prognosis research

We propose a prognostic factor research study with the following features.

Study protocol: prospective registration in an accessible repository

This prospective registration will allow systematic reviewers to assess the presence of selective outcome reporting.

Study design: prospective phase-2 explanatory research of adequate power/sample size

To estimate the independent prognostic factor of sex in mortality in patients with PE, explanatory research aimed to confirm an independent association between sex and the outcome of interest is needed. The study should be a prospective cohort design with adequate follow-up to measure mortality at different times. Phase-1 prognostic studies (exploratory studies) should be avoided because they often have widely varying results with common spurious associations, which may overstate their conclusions (Hayden 2008; Hayden 2014).

The study should be sufficiently powered to detect differences of small magnitude in mortality and account for adjusting factors.

Study setting: multicentre, with multiple geographic locations and resource settings

A multicentric study, including high-, middle-, and low-income settings, will help ensure the results are generalisable to a wider range of populations.

Study population

If people with different severity levels of PE are enroled and evaluated, severity should be controlled as a potential confounder. Moreover, the study results should be stratified based on severity to facilitate a better understanding of the relationship between sex and mortality according to this factor. As mentioned above, the study should be conducted, in part, in low or middle-income countries.

Selection and definition of study outcomes

To our knowledge, a 'Core Outcomes Set' for studies of the prognostic effect of sex on PE patients is not available. We propose that this should be developed, and outcomes for future primary studies should be chosen accordingly. Mortality outcomes should be defined clearly by detailing the setting (in or outwith hospital) and the period (7 days, 30 days, etc.). Mortality outcomes should be defined as binary variables (dead or alive) instead of using survival methods, since the quality of life of patients in hospitals may not benefit from prolonged survival (Schoenfeld 2005). Study authors should accurately describe how the researchers adjudicated the cause of death, as this is an important aspect of judging the risk of detection bias.

Statistical analysis plan

Researchers conducting the data analysis should avoid providing crude (unadjusted) effects, as they may disappear after adjustment. As prognostication in healthcare is rarely based on a single prognostic factor but rather on information from multiple prognostic factors (Riley 2019), the study must provide adjusted estimates and, thus, use multivariable analysis of mortality data. Moreover, survival analysis should be avoided in the ICU because it considers that the hazard of death remains unchanged when a censoring event occurs (Schoenfeld 2005; Wolkewitz 2014). This assumption is incorrect in the ICU, as discharged patients are usually in better health than patients who stay.

Study reporting

Consider the use of the Sex and Gender Equity in Research (SAGER) Guidelines for adequate ascertainment and reporting of sex and gender (Heidari 2016).

Considerations for further systematic reviews of prognostic factors

In the context of systematic reviews of sex as a prognostic factor in patients with PE, serious consideration should be given to the following aspects.

Review question formulation

A systematic review should be restricted to well-conducted studies providing adjusted effect estimates (phase-2 studies). Systematic reviewers should consider using a 'Core Outcomes Set' to select mortality outcomes in patients with PE.

Study selection process

Due to the high number of potentially relevant records, we recommend the use of search strategies with methodological filters for prognostic factor studies (Stallings 2022) and the use of artificial intelligence tools for title and abstract screening to accelerate the study identification and selection process (Van Dijk 2023). Systematic reviews including registry-based studies should avoid overlapping observations, where the same participants or data points appear in multiple studies, leading to potential duplication and bias. This issue is common in registry-based research, as large databases often contribute to multiple publications (Mathes 2023).

Statistical analysis

Data analysts should consider using the random-effects model and the Hartung-Knapp-Sidik-Jonkman (HKSJ) method for meta-analysis. This approach allows the incorporation of heterogeneity across studies, which is the most plausible scenario in prognostic research. It is also worth considering employing the 95% prediction interval to measure the heterogeneity, as relying on the I^2 statistic in the assessment of heterogeneity may be misleading (Rucker 2008).

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Editorial and peer-review contributions

Cochrane Vascular (closed in March 2023) supported the authors in the development of this review. The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Stewart Walsh, University of Galway, Ireland
- Managing Editors (provided editorial guidance to authors, edited the article): Joey Kwong and Gail Quinn, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, selected peer reviewers, collated peer-reviewer comments, supported editorial team): Sara Hales-Brittain, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Laura MacDonald, Cochrane Central Production Service
- Peer reviewers (provided comments and recommended an editorial decision): Alfonso Iorio, Department of Health Research Methods and Impact, McMaster University (methods review); Jo Platt, Central Editorial Information Specialist (search review). Two additional peer reviewers provided clinical/content peer review but chose not to be publicly acknowledged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agarwal 2015

Study characteristics

Methods	**Study design** 1. Phase 2 prognostic study 2. Retrospective cohort study **Data source** 1. Type: administrative data 2. Database: NIS database that contains discharge-level data from about 1000 hospitals across the USA **Period:** from 2003 to 2011 **Setting** • Setting: hospital • Country: USA • State: not reported • City: not reported • Number of centres: multicentric, 1000 centres

Participants	**Age (mean) in years:** 63.1 ± 18.6 females; 61.1 ± 16.2 males
	
	Sample size: 266,446 participants (146,174 female and 120,272 male). A total of 276,484 discharges with a principal diagnosis of acute PE were reported, but table 1 in the article reports 266,446 participants.
	
	Diagnosis: acute primary PE
	
	• **Classification system for PE diagnosis:** ICD-9-CM (codes 415.11, 415.12, 415.13, and 415.19)
	• **PE objective testing:** present (not explicitly reported)
	• **PE development (community, hospital):** community (PE was the main cause of hospitalisation.)
	• **Type of PE (primary, secondary, recurrent):** primary PE
	  ◦ Participants with a secondary diagnosis of PE (e.g. postsurgical) were excluded.
	• **Time between the onset of PE symptoms and the start of follow-up:** not reported
	
	PE clinical characteristics
	
	• **Acute PE:** yes
	• **Symptomatic PE:** yes (assumed by the review authors)
	• **PE severity**
	  ◦ **Method of severity quantification:** not reported
	  ◦ **Proportion of participants with severe PE:** not reported. ("Third, adverse outcomes after acute PE may be affected by numerous variables including disease severity, [...], which were not available consistently in the NIS database")
	
	Hospital unit: not reported
	
	PE treatment
	
	a. Presence of PE treatment: yes (% unknown)
	
	a. Haemodynamic and respiratory support: not reported

Agarwal 2015 *(Continued)*

- Oxygen therapy and ventilation: not reported
- Vasopressors: not reported
- Mechanical circulatory support and oxygenation/advanced life support: not reported

b. Anticoagulation: not reported

- Parenteral: not reported
- Non-vitamin K antagonist: not reported
- Vitamin K antagonist: not reported

c. Reperfusion: yes

- Thrombolysis: yes. "Figure 2. Male (13.18%) Female (12.24%). Only those patients who were eligible for thrombolysis were included in this comparison. These included patients in shock that were <75 years, without history of stroke, without bleeding on presentation, and those who were not pregnant." "Figure 5. The trend in the utilization of IVC filters (A) and thrombolysis (B). We included only those patients who were considered eligible for thrombolysis."
- Surgical embolectomy: yes. "The utilization of surgical embolectomy/endarterectomy was low in this cohort (women 0.12% and men 0.18%. Among patients presenting with shock, there was no significant difference in the utilization of surgical embolectomy/endarterectomy between men and women (adjusted OR 0.74, 95% CI 0.48 to 1.14)."
- Percutaneous catheter-directed treatment: unclear

d. Other treatment: yes: IVC filter. "Figure 2. Male (13.8%) Female (12.24%)." "With respect to the resource utilisation, there was a significantly lower utilization of IVC filters (adjusted OR 0.86, 95% CI 0.84 to 0.89) among women compared with men."

Prognostic factor	**Sex**: female **Definition:** "the primary variable of interest was patient gender, which was reported in the NIS database for every hospital admission" **Terms used:** terms for sex (female, male) and gender (women, men) were used inconsistently throughout the study. **Prognostication time**: not reported
Outcomes	**1. All-cause hospital mortality:** yes 1. **Setting:** in-hospital mortality 2. **Timing:** not reported 3. **Measurement:** routinely collected data in the NIS database 4. **Length of follow-up:** not reported **2. All-cause hospital mortality at 30 days:** no **3. Early all-cause hospital mortality (during the first 48 hours):** no **4. All-cause mortality at 30 days:** no **5. All-cause mortality at 90 days:** no **6. All-cause mortality at 1 year:** no **7. PE-related hospital mortality:** no **8. PE-related hospital mortality at 30 days:** no **9. Early PE-related hospital mortality (during the first 48 hours):** no **10. PE-related mortality at 30 days:** no

Agarwal 2015 *(Continued)*

Statistical analysis and adjustment for other covariates	**Statistical analysis:** multivariable hierarchical logistic regression analysis **Covariates for adjustment:** age, race, social-economic status, 29 comorbidities from the Elixhauser Comorbidity Index, smoking, primary payer, and hospital characteristics **Key covariates considered for risk of bias assessment (3/8)** 1. **Age:** yes 2. **History of cancer:** no 3. **Current cancer:** yes (lymphoma, metastatic cancer in Elixhauser Comorbidity Index) 4. **History of chronic cardiopulmonary disease:** no 5. **Current chronic cardiopulmonary disease:** yes (congestive heart failure, chronic pulmonary disease in Elixhauser Comorbidity Index) 6. **Heart rate:** no 7. **Systolic blood pressure:** no 8. **O2 saturation:** no
QUIPS	**Study participation** Judgement: low risk of bias Support for judgement Quote: "All hospitalizations with the principal diagnosis of acute PE were included in our study" Comment: the study participation is representative of the eligible population. **Study attrition** **All-cause hospital mortality** Judgement: low risk of bias Support for judgement Comment: 266,446 (96.4%) out of 276,484 participants were included in the analysis (figure 1 in the article). Although 'race' was not available for 22% of the participants, and the authors imputed this information, we judged this imputation did not generate plausible bias that would raise doubts about the results. **Prognostic factor measurement** Judgement: low risk of bias Support for judgement Quote: "The primary variable of interest was patient gender, which was reported in the NIS database for every hospital admission." Comment: although sex measurement is not specified, and terms were not used correctly (gender with sex categories), we consider that this inadequate reporting did not lead to bias. **Outcome measurement** **All-cause hospital mortality** Judgement: low risk of bias Support for judgement Comment: routinely collected data in NIS database. Although the authors did not report the outcome measurement methods, we considered there to be a low risk of bias. **Adjustment for key additional prognostic factors**

Agarwal 2015 *(Continued)*

All-cause hospital mortality

Judgement: high risk of bias

Support for judgement

Quote: "The analysis of all outcomes has been presented after adjusting for age, race, socioeconomic status, Elixhauser co-morbidities, smoking, primary payer, and hospital characteristics. Because the variable “race” had 22% missing data, we used multiple imputation for missing data..."

Comment: the analysis was adjusted for 3 of our 8 key covariates (age, current chronic cardiopulmonary disease, and current cancer).

Statistical analysis and reporting

All-cause hospital mortality

Judgement: moderate risk of bias

Support for judgement

a) Statistical analysis: low risk of bias

Quote: "Multivariable hierarchical logistic regression analysis was used to compare outcomes between the 2 genders."

Comment: the statistical analysis was appropriate.

b) Selective outcome reporting: moderate risk of bias

Comment: we could not access the study protocol. Therefore, we could not assess the presence of selective outcome reporting and judged the risk of bias as moderate.

Notes

Funding source: not reported

Declaration of interests: Dr Menon is a consultant for and has received a research grant from Astra Zeneca and is a consultant for Takeda pharmaceuticals. All other authors have no relevant relationships to disclose.

Contact with the correspondence author: we contacted the study contact author via email on 20 May 2022 to request information needed for our risk of bias assessment and quantitative analysis. No reply was received.

Barrios 2017

Study characteristics

Methods

Study design

1. Phase 2 prognostic study
2. Retrospective cohort study

Data source

1. Type: research purpose data
2. Database: The Ramón y Cajal Pulmonary Embolism Registry, Madrid, Spain

Period: from January 2003 to December 2016

Setting

- Setting: hospital

Barrios 2017 *(Continued)*

- Country: Spain
- State: not applicable
- City: Madrid
- Number of centres: 1

Participants	**Age (mean) in years:** 70.6 ± 16.8 females; 66.6 ± 16.2 males
	
	Sample size: 2096 participants (1092 females and 1004 males) out of 2222 participants who had an objective diagnosis of PE. Of these, 5.7% (126 of 2222 participants) were excluded because they were unavailable for follow-up (N = 83) or refused to give informed consent (N = 43).
	
	Diagnosis: acute primary PE
	
	• **Classification system for PE diagnosis:** not reported
	• **PE objective testing:** yes. "We confirmed the diagnosis of PE by objective testing that consisted of an intraluminal filling defect in segmental or larger vessels on CTPA, a high probability V/Q scintigraphy, or a lower limb venous compression ultrasonography positive for proximal DVT in a patient with chest symptoms."
	• **PE development (community, hospital):** community (review authors assumed PE was the main cause of hospitalisation.)
	• **Type of PE (primary, secondary, recurrent):** not reported
	• **Time between the onset of PE symptoms and the start of follow-up:** not reported
	
	PE clinical characteristics
	
	• **Acute PE:** yes (100%)
	• **Symptomatic PE:** yes (100%)
	• **PE severity**
	  ◦ **Method for severity quantification:** sPESI
	  ◦ **Proportion of participants with severe PE:** 70% (N = 1458)
	
	Hospital unit: not reported
	
	PE treatment
	
	a. Presence of PE treatment: yes (% unknown)
	
	a. Haemodynamic and respiratory support: not reported
	
	• Oxygen therapy and ventilation: not reported
	• Vasopressors: not reported
	• Mechanical circulatory support and oxygenation/advanced life support: not reported
	
	b. Anticoagulation: not reported
	
	• Parenteral: not reported
	• Non-vitamin K antagonist: not reported
	• Vitamin K antagonist: not reported
	
	c. Reperfusion: yes
	
	• Thrombolysis: yes. Male 54 (5.4%); female 37 (3.4%); total N = 91 (4.3%)
	• Surgical embolectomy: not reported
	• Percutaneous catheter-directed treatment: not reported
	
	d. Other treatment: yes: insertion of an IVC filter. Male 18 (1.8%); female 31 (2.8%); total N = 49 (2.3%)

Prognostic factor	**Sex**: female (converted by the review authors as results were reported in the study for male participants) **Definition:** not reported

Barrios 2017 *(Continued)*

	Terms used: terms for sex (female, male) and gender (women, men) were used inconsistently throughout the study. **Prognostication time:** after initiation of treatment
Outcomes	**1. All-cause hospital mortality:** no **2. All-cause hospital mortality at 30 days:** no **3. Early all-cause hospital mortality (during the first 48 hours):** no **4. All-cause mortality at 30 days:** yes 1. **Setting:** in-hospital and post-discharge mortality 2. **Timing:** within 30 days after initiation of treatment 3. **Measurement**: "this study used all-cause mortality through 30 days after initiation of treatment as the primary endpoint, and 30-day PE-related mortality". "Two investigators independently adjudicated the cause of deaths as fatal PE, or death from other causes" 4. **Length of follow-up:** not reported **5. All-cause mortality at 90 days:** no **6. All-cause mortality at 1 year:** no **7. PE-related hospital mortality:** no **8. PE-related hospital mortality at 30 days:** no **9. Early PE-related hospital mortality (during the first 48 hours):** no **10. PE-related mortality at 30 days:** yes 1. **Setting:** in-hospital and post-discharge mortality 2. **Timing:** within 30 days after initiation of treatment 3. **Measurement**: "this study used all-cause mortality through 30 days after initiation of treatment as the primary endpoint, and 30-day PE-related mortality". "Two investigators independently adjudicated the cause of deaths as fatal PE, or death from other causes" 4. **Length of follow-up:** 30 days ("patients were seen in the investigators' outpatient clinic at the end of the 1-month follow-up period")
Statistical analysis and adjustment for other covariates	**Statistical analysis:** multivariable logistic regression **Covariates for adjustment (12):** age, heart rate ≥ 110 bpm, arterial O2 saturation < 90%, active cancer, systolic blood pressure < 90 mmHg, dyspnoea, chest pain, syncope, congestive heart failure, recent major bleeding, deep vein thrombosis, immobilisation **Key covariates considered for risk of bias assessment (6/8)** 1. **Age:** yes 2. **History of cancer:** no 3. **Current cancer:** yes 4. **History of chronic cardiopulmonary disease:** no 5. **Current chronic cardiopulmonary disease:** yes (not reported for the outcome PE-related mortality at 30 days) 6. **Heart rate:** yes 7. **Systolic blood pressure:** yes 8. **O2 saturation:** yes
QUIPS	**Study participation** Judgement: low risk of bias

Barrios 2017 *(Continued)*

Support for judgement

Quote: "We used data from a prospective observational registry [...] all patients who have confirmed PE are enrolled. Patients with PE between January 1, 2003, and December 31, 2016, were included in this study.[...] 5.7% (126 of 2,222 patients) were excluded because they were unavailable for follow-up (n = 83), or refused to give informed consent (n = 43)"

Comment: the selection of the sample was appropriate and representative of the target population.

Study attrition

All-cause mortality at 30 days

Judgement: low risk of bias

Support for judgement

Quote: "Of these, 5.7% (126 of 2,222 patients) were excluded because they were unavailable for follow-up (n = 83) (3.7%), or refused to give informed consent (n = 43)"

Comment: 3.7% represents a low proportion of missing participant data that probably did not bias the results.

PE-related mortality at 30 days

Judgement: low risk of bias

Support for judgement

Quote: "Of these, 5.7% (126 of 2,222 patients) were excluded because they were unavailable for follow-up (n = 83), or refused to give informed consent (n = 43)"

Comment: 3.7% represents a low proportion of missing participant data that probably did not bias the results.

Prognostic factor measurement

Judgement: low risk of bias

Support for judgement

Comment: although sex measurement is not specified (and sex/gender terms were used inconsistently), we consider that this inadequate reporting did not lead to bias.

Outcome measurement

All-cause mortality at 30 days

Judgement: low risk of bias

Support for judgement

Comment: data were obtained from a prospective observational registry: "The Ramón y Cajal Pulmonary Embolism Registry". Although the authors did not report the outcome measurement methods, we considered there to be a low risk of bias.

PE-related mortality at 30 days

Judgement: low risk of bias

Support for judgement

Comment: data were obtained from a prospective observational research registry: "The Ramón y Cajal Pulmonary Embolism Registry". We considered there to be a low risk of bias for the outcome measurement as "Two investigators independently adjudicated the cause of deaths as fatal PE, or death from other causes".

Barrios 2017 *(Continued)*

Adjustment for key additional prognostic factors

All-cause mortality at 30 days

Judgement: low risk of bias

Support for judgement

Comment: 6 of 8 covariates were considered for the analysis (age, heart rate, O2, cancer, SBP, dyspnoea, chest pain, syncope, congestive heart failure, recent major bleeding, DVT, immobilisation).

PE-related mortality at 30 days

Judgement: low risk of bias

Support for judgement

Comment: 6 of 8 covariates were considered for the analysis (age, heart rate, O2, cancer, SBP, congestive heart failure).

Statistical analysis and reporting

All-cause mortality at 30 days

Judgement: moderate risk of bias

Support for judgement

a) Statistical analysis: moderate risk of bias

Quote: "For construction of the full models, we considered variables with imbalance between the groups at baseline for inclusion. During model construction, we did not remove variables that showed evidence of confounding (i.e., the coefficient of the variable changed by more than 10% when removed from the full model) for the effect of gender on the outcome undergoing analysis"

Comment: the variables included in the multivariate model seemed to be those that were significant in the univariate logistic regression. Thus, we judged the risk of bias as moderate.

b) Selective outcome reporting: low risk of bias

Comment: we could not access the study protocol. We judged the risk of bias as low: the contact author confirmed that the outcomes reported in the published article's methods section were the planned ones.

PE-related mortality at 30 days

Judgement: moderate risk of bias

Support for judgement

a) Statistical analysis: moderate risk of bias

Quote: "For construction of the full models, we considered variables with imbalance between the groups at baseline for inclusion. During model construction, we did not remove variables that showed evidence of confounding (i.e., the coefficient of the variable changed by more than 10% when removed from the full model) for the effect of gender on the outcome undergoing analysis"

Comment: the variables included in the multivariate model seemed to be those that were significant in the univariate logistic regression. Thus, we judged the risk of bias as moderate.

b) Selective outcome reporting: low risk of bias

Comment: we could not access the study protocol. We judged the risk of bias as low: the contact author confirmed that the outcomes reported in the published article's methods section were the planned ones.

Barrios 2017 *(Continued)*

Notes	**Funding source:** project supported by Grant PIE1600050 SEXCOMPLEX from Instituto de Salud Carlos III to DJ, Spanish Ministry of Economy and Competitiveness. CIBERDEM is also an initiative of Instituto de Salud Carlos III. This work was also supported in part by Fondo Europeo de Desarrollo Regional FEDER to DJ. **Declaration of interests:** the authors declared no potential conflicts of interest with respect to the research, authorship, and publication of the article. **Contact with the correspondence author:** we contacted the contact author via email on 1 July 2023 requesting information needed for our risk of bias assessment. The information was provided.

Borrero 2007

Study characteristics

Methods	**Study design** 1. Phase 2 prognostic study 2. Retrospective cohort study **Data source** 1. Type: administrative data 2. Database: PHC4 Database (for non-governmental acute care hospitals in Pennsylvania, USA) **Period:** from January 2000 to November 2002 **Setting** • Setting: hospital • Country: USA • State: Pennsylvania • City: not reported • Number of centres: multicentric, 186 centres

Participants	**Age (mean) in years:** 64.9 females; 62.5 males
	
	Sample size: 15,531 participants (9304 females and 6227 males). Of the 16,467 patient discharges that met all eligibility criteria in the PHC4 database, 90 (0.5%) patients with missing patient identifiers, 70 (0.4%) with unknown mortality status, and 776 (4.7%) who did not have key clinical findings were excluded.
	
	Diagnosis: acute primary PE (not reported)
	
	• **Classification system for PE diagnosis:** ICD-9-CM (415.1, 415.11, 415.19, and 673.20–.24)
	• **PE objective testing:** present (not explicitly reported)
	• **PE development (community, hospital):** unclear
	• **Type of PE (primary, secondary, recurrent):** primary, secondary, and recurrent PE
	• **Time between the onset of PE symptoms and the start of follow-up:** not reported
	
	PE clinical characteristics
	
	• **Acute PE:** not reported
	• **Symptomatic PE:** yes (assumed by the review authors)
	• **PE severity**
	  ◦ **Method for severity quantification:** PESI
	  ◦ **Proportion of participants with severe PE:** not reported ("Because sex is a component of this risk score, we used the individual components of the PESI rather than the composite score")

Borrero 2007 *(Continued)*

Hospital unit: not reported

PE treatment: participants were treated for PE, but the type of treatment received was not specified.

a. Presence of PE treatment: not reported

a. Haemodynamic and respiratory support: not reported

- Oxygen therapy and ventilation: not reported
- Vasopressors: not reported
- Mechanical circulatory support and oxygenation/advanced life support: not reported

b. Anticoagulation: not reported

- Parenteral: not reported
- Non-vitamin K antagonist: not reported
- Vitamin K antagonist: not reported

c. Reperfusion: not reported

- Thrombolysis: not reported
- Surgical embolectomy: not reported
- Percutaneous catheter-directed treatment: not reported

d. Other treatment: not reported

Prognostic factor	**Sex**: female **Definition:** not reported **Terms used:** terms for sex (female, male) and gender (women, men) were used inconsistently throughout the study. **Prognostication time:** admission for PE
Outcomes	**1. All-cause hospital mortality:** no **2. All-cause hospital mortality at 30 days:** no **3. Early all-cause hospital mortality (during the first 48 hours):** no **4. All-cause mortality at 30 days:** yes 1. **Setting:** in-hospital and postdischarge mortality 2. **Timing:** within 30 days of admission for PE 3. **Measurement**: data came from the National Death Index, a central computerised index of death record information that is available in the United States to investigators in health research. 4. **Length of follow-up:** not reported **5. All-cause mortality at 90 days:** no **6. All-cause mortality at 1 year:** no **7. PE-related hospital mortality:** no **8. PE-related hospital mortality at 30 days:** no **9. Early PE-related hospital mortality (during the first 48 hours):** no **10. PE-related mortality at 30 days:** no

Borrero 2007 *(Continued)*

Statistical analysis and adjustment for other covariates	**Statistical analysis:** random-effects logistic regression (hospital site as the random effect) **Covariates for adjustment:** age, sex, the presence of 3 comorbid conditions (cancer, chronic lung disease, and heart failure), and 6 clinical factors (pulse ≥ 110 beats per minute, systolic blood pressure < 100 mmHg, respiratory rate ≥ 30 per minute, body temperature < 36°C, altered mental status, and O2 saturation < 90%) **Key covariates considered for risk of bias assessment (6/8)** 1. **Age:** yes 2. **History of cancer:** no 3. **Current cancer:** yes 4. **History of chronic cardiopulmonary disease:** no 5. **Current chronic cardiopulmonary disease:** yes 6. **Heart rate:** yes 7. **Systolic blood pressure:** yes 8. **O2 saturation:** yes
QUIPS	**Study participation** Judgement: low risk of bias Support for judgement Quote: "The cohort comprised all patients aged 18 years who were discharged with a primary diagnosis of PE from January 2000 to November 2002 based on ICD-9-CM codes 415.1, 415.11, 415.19, and 673.20–.24. We also included patients who had a secondary diagnosis of PE". Comment: the selection of the sample was appropriate and representative of the target population. **Study attrition** **All-cause mortality at 30 days** Judgement: moderate risk of bias Support for judgement Quote: "We excluded 90 (0.5%) patients with missing patient identifiers, 70 (0.4%) patients with unknown mortality status, and 776 (4.7%) patients who did not have key clinical findings." Comment: 5.7% of the population could not be analysed due to some kind of missing data: patient identifiers (0.5%), unknown mortality status (0.4%), and patients without key clinical findings (4.7%). Although the total proportion of missing participant data was over our predefined threshold of 5%, we did not judge the risk of bias as high because the distribution of missing participant data across study arms was not reported. Thus, it was difficult to judge the impact of missing participant data. **Prognostic factor measurement** Judgement: low risk of bias Support for judgement Comment: although sex measurement is not specified (sex/gender terms were used inconsistently), we consider this inadequate reporting did not lead to bias. **Outcome measurement** **All-cause mortality at 30 days** Judgement: low risk of bias Support for judgement

Borrero 2007 *(Continued)*

Quote: "Our study outcome was death from all causes within 30 days of admission for PE, which included both in-hospital and post-discharge death".
Quote: "We obtained mortality data by linking study patients to the National Death Index, a central computerized index of death record information that is available in the USA to investigators in health research."

Comment: all-cause mortality status was obtained from the National Death Index. Although the authors did not report the outcome measurement methods, we consider there was a low risk of bias.

Adjustment for key additional prognostic factors

All-cause mortality at 30 days

Judgement: low risk of bias

Support for judgement

Comment: 6 of 8 key covariates were considered for the analysis: age, current cancer, current chronic cardiopulmonary disease, heart rate, systolic blood pressure, and O2 saturation.

Statistical analysis and reporting

All-cause mortality at 30 days

Judgement: moderate risk of bias

Support for judgement

a) Statistical analysis: low risk of bias

Quote: "We used a random effects logistic regression model to assess the effect of sex on 30-day mortality."

Comment: the statistical analysis was appropriate.

b) Selective outcome reporting: moderate risk of bias

Comment: we could not access the study protocol. Therefore, we could not assess the presence of selective outcome reporting and judged the risk of bias as moderate.

Notes	**Funding source:** study partially funded by a grant from the National Heart, Lung, and Blood Institute (1 R21 HL075521-01A1) **Declaration of interests:** DA was partially supported by the Clinical Epidemiology Center, University of Lausanne. SA received a career development award from the VA Health Services Research and Development Office and the Robert Wood Johnson Foundation's Harold Amos Faculty Development Award. MJF was supported in part by a K24 Mid-Career Development Award from the National Institute of Allergy and Infectious Diseases. **Contact with the correspondence author:** we did not make contact as the email address for the contact person was inactive.

Marshall 2017

Study characteristics	
Methods	**Study design** 1. Phase 2 prognostic study 2. Retrospective cohort study **Data source**

Marshall 2017 *(Continued)*

1. Type: administrative data
2. Database: NIS database. The NIS database is the largest publicly available all-player inpatient database in the USA.

Period: from January 2012 to December 2013

Setting

- Setting: hospital
- Country: USA
- State: not reported
- City: not reported
- Number of centres: multicentric, number of centres not reported

Participants	**Age (mean) in years:** 64.66 ± 0.1 females; 61.69 ± 0.1 males
	
	Sample size (weighted sample): 312,840 participants (166,335 females and 146,505 males)
	
	Diagnosis: acute primary PE
	
	• **Classification system for PE diagnosis:** ICD-9-CM codes of 415.11, 415.12, 415.13, 415.19
	  ◦ Exclude: 453.71–453.79, 416.2, V12.51,453.81, 453.83, 453.87, 453.89, 453.6
	• **PE objective testing:** present (not explicitly reported)
	• **PE development (community, hospital):** community (PE was the main cause of hospitalisation.)
	• **Type of PE (primary, secondary, recurrent):** primary PE
	• **Time between the onset of PE symptoms and the start of follow-up:** not reported
	
	PE clinical characteristics
	
	• **Acute PE:** yes
	• **Symptomatic PE:** yes (assumed by the review authors)
	• **PE severity**
	  ◦ **Method for severity quantification:** presence or absence of cor pulmonale (hypertrophy and dilation of the right ventricle of the heart due to pulmonary hypertension, often linked to pulmonary parenchymal or vascular diseases such as pulmonary embolism).
	  ◦ **Proportion of participants with severe PE:** 0.5% (N = 1510)
	
	Hospital unit: not reported
	
	PE treatment
	
	a. Presence of PE treatment: yes (% unknown)
	
	"The NIS database does not allow for analysis of medication administration either during hospitalization or upon discharge"
	
	a. Haemodynamic and respiratory support: not reported
	
	• Oxygen therapy and ventilation: not reported
	• Vasopressors: not reported
	• Mechanical circulatory support and oxygenation/advanced life support: not reported
	
	b. Anticoagulation: not reported
	
	• Parenteral: not reported
	• Non-vitamin K antagonist: not reported
	• Vitamin K antagonist: not reported
	
	c. Reperfusion: yes
	
	• Thrombolysis: not reported

Marshall 2017 *(Continued)*

	• Surgical embolectomy: yes, "the percentage of patients undergoing surgical thrombectomy as part of VTE management is presented in Table 2B. Thrombectomy male 4390 (3.0%) female 4395 (2.6%)" • Percutaneous catheter-directed treatment: unclear d. Other treatment: not reported
Prognostic factor	**Sex**: female **Definition:** not provided **Terms used:** terms for sex (female, male) and gender (women, men) were used inconsistently throughout the study. **Prognostication time:** not reported
Outcomes	**1. All-cause hospital mortality:** yes 1. **Setting:** in-hospital mortality 2. **Timing:** not reported 3. **Measurement**: NIS Description of Core Data Elements coding for 'DIED' (inpatient mortality) 4. **Length of follow-up:** 4 days (median) **2. All-cause hospital mortality at 30 days:** no **3. Early all-cause hospital mortality (during the first 48 hours):** no **4. All-cause mortality at 30 days:** no **5. All-cause mortality at 90 days:** no **6. All-cause mortality at 1 year:** no **7. PE-related hospital mortality:** no **8. PE-related hospital mortality at 30 days:** no **9. Early PE-related hospital mortality (during the first 48 hours):** no **10. PE-related mortality at 30 days:** no
Statistical analysis and adjustment for other covariates	**Statistical analysis:** multivariable logistic regression. **Covariates for adjustment:** age, race, insurance status, hospital division, and medical comorbidities (NIS Severity File Data Elements, which captures 29 discrete conditions labelled 'comorbidities' that are extracted from the AHRQ comorbidity severity files.) **Key covariates considered for risk of bias assessment (3/8)** 1. **Age:** yes 2. **History of cancer:** unclear 3. **Current cancer:** yes (solid tumour and metastatic cancer) 4. **History of chronic cardiopulmonary disease:** unclear 5. **Current chronic cardiopulmonary disease:** yes (congestive heart failure, chronic pulmonary disease, peripheral vascular disorder) 6. **Heart rate:** no 7. **Systolic blood pressure:** no 8. **O2 saturation:** no
QUIPS	**Study participation** Judgement: moderate risk of bias

Marshall 2017 *(Continued)*

Support for judgement

Quote: "All analyses accounted for the sampling design and survey weights".
Quote: "A total of 107,896 patients met the inclusion criteria for the 2-year period between 1 January 2012 and 31 December 2013 (weighted total = 539,430)"

Comment: the reporting was unclear. The study applied a weighted sample, but no methods of sampling design or survey weights were reported.

Study attrition

All-cause hospital mortality

Judgement: high risk of bias

Support for judgement

Quote: "Nine percent of patients were missing at least one of the baseline characteristics, sex, or clinical outcome. No single variable was missing more than 5%. Hot deck imputation was used to create a complete data set by substituting missing values from subjects who were similar to those missing data. A similarity score between subjects was measured using all available data. Missing values were substituted from the subject who was most similar to each recipient. Of the 10 patients missing sex, five were imputed as male, and five were imputed as female. Clinical outcome results were calculated using the completed data set."

Comment: the authors report that for 9% of participants, at least one of the baseline characteristics, sex, or clinical outcome was missing; for which variables and in which study arm was not specified. Moreover, no information about attrition for participants with PE was given. Thus, there may be plausible bias that raises some doubt about the results.

Prognostic factor measurement

Judgement: low risk of bias

Support for judgement

Comment: sex information was collected from the NIS Core Data Elements. Whether a participant was male or female was missing for 10 out of 107,896 participants, and of these, five were imputed as male and five as female. Although sex measurement is not specified (sex/gender terms were used inconsistently), we consider this inadequate reporting did not lead to bias.

Outcome measurement

All-cause hospital mortality

Judgement: low risk of bias

Support for judgement

Quote: "Outcomes were defined using specific NIS Description of Data Elements coding for 'DIED' (inpatient mortality)".

Comment: the data were collected from administrative databases. Although the authors did not report the outcome measurement methods, we consider the risk of bias was low.

Adjustment for key additional prognostic factors

All-cause hospital mortality

Judgement: high risk of bias

Support for judgement

Comment: the analysis was adjusted for 3 of our 8 key covariates (age, current chronic cardiopulmonary disease, and current cancer).

Marshall 2017 *(Continued)*

	Statistical analysis and reporting **All-cause hospital mortality** Judgement: moderate risk of bias Support for judgement a) Statistical analysis: low risk of bias Quote: "In-hospital mortality was compared between men and women by OR, which was estimated using logistic regression. Logistic regression was also used to estimate the odds ratio for mortality between men and women, controlling for confounders." Comment: the statistical analysis was appropriate. b) Selective outcome reporting: moderate risk of bias Comment: we could not access the study protocol. Therefore, we could not assess the presence of selective outcome reporting and judged the risk of bias as moderate.
Notes	**Funding source:** this work was supported by small-grant funding from the Mayo Clinic Hematology-Oncology Outcomes Research (HONOR) Group. **Declaration of interests:** the authors declared no potential conflicts of interest with respect to the research, authorship, and publication of the article. **Contact with the correspondence author:** we contacted the study contact author via email on 25 May 2022. We requested information on comorbidities, risk of bias, and quantitative analysis. No reply was received.

Pribish 2020

Study characteristics	
Methods	**Study design** 1. Phase 2 prognostic study 2. Retrospective cohort study **Data source** 1. Type: research purpose data 2. Database: MASCOT registry from the BIDMC **Period:** from August 2012 to July 2018 **Setting** • Setting: hospital • Country: USA • State: Massachusetts • City: Boston • Number of centres: 1
Participants	**Sample size:** 2031 participants (1081 females and 950 males). Only 1932 (95.1%) out of 2031 participants with complete data were analysed. **Age (mean) in years:** 63.8 ± 17.4 females; 62.3 ± 15.0 males **Diagnosis:** acute primary PE

Pribish 2020 *(Continued)*

- **Classification system for PE diagnosis:** ICD-9 (415.13, 415.19) and ICD-10 (I26.02, I26.09, I26.92, I26.99) codes
- **PE objective testing:** yes (diagnostic imaging performed: CT scan, VQ scan, angiogram)
- **PE development (community, hospital)**: unclear
- **Type of PE (primary, secondary, recurrent):** not reported
- **Time between the onset of PE symptoms and the start of follow-up:** not reported

PE clinical characteristics

- **Acute PE:** yes
- **Symptomatic PE:** yes (85.6%)
- **PE severity**
  - **Method for severity quantification:** massive ("associated with hypotension, vasopressor or inotrope requirement, cardiac arrest, or lactate elevated above 5 mmol/L")
  - **Proportion of participants with severe PE:** 4.3% (N = 86)

Hospital unit: reported but unclear. 67% of the participants were attended to in the ICU during the study. However, the proportion of ICU participants at baseline was not described.

PE treatment

a. Presence of PE treatment: yes

a. Haemodynamic and respiratory support: yes

- Oxygen therapy and ventilation: not reported
- Vasopressors: yes (women 8.2%; men 7.9%)
- Mechanical circulatory support and oxygenation/advanced life support: yes: ECMO (women 0.4%; men 0.5%)

b. Anticoagulation: yes (women 95%; men 93.7%)

- Parenteral: yes; heparin IV (women 74.4%; men 74.4%)
- Non-vitamin K antagonist: not reported
- Vitamin K antagonist: not reported
- LMWH (women 17.5%; men 16.3%); DOAC (women 1.7%; men 1.9%); other (women 1.5%; men 1.2%)

c. Reperfusion: yes

- Thrombolysis: yes: full-dose IV fibrinolysis (women 1.9%; men 1.0%); 1/2 dose IV fibrinolysis (women 1.6%; men 1.2%)
- Surgical embolectomy: yes (women 0.1%; men 0.2%)
- Percutaneous catheter-directed treatment: yes (US-facilitated catheter fibrinolysis (women 2.2%; men 1.8%); non-US catheter fibrinolysis (women 0.3%; men 0.1%); non-lytic catheter-based therapy (women 0.4%; men 0.1%)

d. Other treatment: yes: IVC: women 8.5%; men 8.6%

Prognostic factor	**Sex**: female **Definition:** not provided **Terms used:** terms for sex (female, male) and gender (women, men) were used inconsistently throughout the study. **Prognostication time:** not reported
Outcomes	**1. All-cause hospital mortality:** yes 1. **Setting:** in-hospital mortality 2. **Timing:** not reported

Pribish 2020 *(Continued)*

3. **Measurement**: a retrospective chart review was performed to confirm outcomes, too.
4. **Length of follow-up:** not reported

2. All-cause hospital mortality at 30 days: no

3. Early all-cause hospital mortality (during the first 48 hours): no

4. All-cause mortality at 30 days: no

5. All-cause mortality at 90 days: no

6. All-cause mortality at 1 year: no

7. PE-related hospital mortality: no

8. PE-related hospital mortality at 30 days: no

9. Early PE-related hospital mortality (during the first 48 hours): no

10. PE-related mortality at 30 days: no

Statistical analysis and adjustment for other covariates	**Statistical analysis:** propensity score with inverse probability of treatment weighting **Covariates for adjustment:** age, CCI, PE risk factors, markers of illness severity, and year of presentation (to account for the influence of the development and implementation of a PERT program in August 2015) **Key covariates considered for risk of bias assessment (4/8)** 1. **Age:** yes 2. **History of cancer:** unclear 3. **Current cancer:** yes **(**haematologic and solid malignancy assessed in CCI) 4. **History of chronic cardiopulmonary disease:** yes (prior myocardial infarction, cerebrovascular accident, and transient ischaemic attack assessed in CCI) 5. **Current chronic cardiopulmonary disease:** yes (hypertension, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, pulmonary hypertension assessed, peripheral artery disease in CCI) 6. **Heart rate:** no 7. **Systolic blood pressure:** no 8. **O2 saturation:** no
QUIPS	**Study participation** Judgement: low risk of bias Support for judgement Quote: "We included all patients with acute PE who were admitted to BIDMC between August 2012 and July 2018." Comment: the study participation was representative of the eligible population. **Study attrition** **All-cause hospital mortality** Judgement: low risk of bias Support for judgement Comment: 1932 (95.1%) out of 2031 participants with complete data were analysed. There were missing participant data for 4.9% of the participants. **Prognostic factor measurement**

Pribish 2020 *(Continued)*

Judgement: low risk of bias

Support for judgement

Quote: "Retrospective chart review was performed to confirm the diagnosis of acute PE and to evaluate patient demographics…"

Comment: sex information was collected from the MASCOT registry from the BIDMC. Although sex measurement is not specified (sex/gender terms were used inconsistently), we consider that this inadequate reporting did not lead to bias.

Outcome measurement

All-cause hospital mortality

Judgement: low risk of bias

Support for judgement

Quote: "Retrospective chart review was performed to confirm the diagnosis of acute PE and to evaluate patient demographics, comorbidities, clinical presentation, PE risk factors, PE severity, diagnostic studies, treatment modalities, and outcomes for each patient presenting with acute PE."

Comment: in-hospital mortality was collected from the MASCOT research registry from the BIDMC. Although the authors did not report the outcome measurement methods, we consider there was a low risk of bias.

Adjustment for key additional prognostic factors

All-cause hospital mortality

Judgement: low risk of bias

Support for judgement

Quote: "Covariates incorporated in the model included age, comorbidities (using the list of chronic comorbid health conditions included in the CCI, PE risk factors, markers of illness severity, and year of presentation (to account for the influence of the development and implementation of a PERT program at our institution in August 2015)."

Comment: the analysis was adjusted for 4 of our 8 key covariates (age, history and current chronic cardiopulmonary disease, and current cancer). Although the authors did not report the measurement methods, we consider that all were valid and reliable because key covariates were extracted from the MASCOT registry from their hospital.

Statistical analysis and reporting

1. All-cause hospital mortality

Judgement: moderate risk of bias

Support for judgement

a) Statistical analysis: low risk of bias

Quote: "To account for differences in characteristics, we used inverse probability of treatment weighting (IPTW) to evaluate the adjusted risk of the following outcomes between men and women: major bleeding, survival to discharge."

Comment: the statistical analysis was appropriate.

b) Selective outcome reporting: moderate risk of bias

Comment: we could not access the study protocol. Therefore, we could not assess the presence of selective outcome reporting and judged the risk of bias as moderate.

Pribish 2020 *(Continued)*

Notes	**Funding source:** the authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Eric Secemsky is funded in part by a NIH/NHLBI K23H-L150290. **Declaration of interests:** Eric A Secemsky: research grants to BIDMC: AstraZeneca, BD, Boston Scientific, Cook, CSI, Medtronic, Philips, and UCSF; consulting/speaking: Abbott, Bayer, BD, Cook, CSI, Janssen, Medtronic, and Philips. The authors declare that there are no other conflicts of interest. **Contact with the correspondence author:** we contacted the contact author via email on 23 May 2022. We requested information we needed about the risk of bias and quantitative analysis. No reply was received.

Sedhom 2022

Study characteristics

Methods	**Study design** 1. Phase 2 prognostic study 2. Retrospective cohort study **Data source** 1. Type: administrative data 2. Database: NRD, HCUP from the AHQR for this analysis **Period:** from January 2016 to December 2018 **Setting** • Setting: hospital • Country: USA • State: not reported • City: not reported • Number of centres: multicentric, number of centres not reported
Participants	**Sample size:** a total of 125,901 hospitalisations with high-risk PE were identified during the study period (58,253 (46.3%) women and 67,648 (53.7%) men. The high-risk PE cohort was defined as PE with one of the following: mechanical ventilation, requirement for vasopressor, cardiogenic shock, use of CDT including US-facilitated CDT, CDE, systemic thrombolysis, or surgical embolectomy (i.e. the cohort included patients with massive PE as well as some patients with submassive PE who received CDI or required mechanical ventilation.) After propensity score matching, 31,924 hospitalisations were included (16,004 women and 15,920 men). **Age (median (IQR)) in years:** 65 (52 to 74) females; 62 (52 to 72) males **Diagnosis:** acute primary PE (discharge diagnoses) • **Classification system for PE diagnosis:** ICD-10-CM • **PE objective testing:** present (not explicitly reported) • **PE development (community, hospital)**: reported but unclear • **Type of PE (primary, secondary, recurrent):** not reported • **Time between the onset of PE symptoms and the start of follow-up:** not reported **PE clinical characteristics**

Sedhom 2022 *(Continued)*

- **Acute PE:** yes
- **Symptomatic PE:** yes (assumed by the review authors)
- **PE severity**
  - **Method for severity quantification:** saddle PE, acute cor pulmonale, cardiogenic shock
  - **Proportion of participants with severe PE:** (% after matching) saddle PE 14.9% (N = 4741), acute cor pulmonale 15.4% (N = 4934), and cardiogenic shock 16.6% (N = 4664)

Hospital unit: not reported

PE treatment: presence of PE treatment: yes

a. Haemodynamic and respiratory support: yes

- Oxygen therapy and ventilation: yes. Women (35,289; 60.6%); men (42,344, 62.6%)
- Vasopressors: yes. Women (4273; 7.3%); men (4594; 6.8%)
- Mechanical circulatory support and oxygenation/advanced life support: yes
  - Mechanical circulatory support: women (562; 0.96%); men (877;1.3%)
  - ECMO: women (82; 0.1%); men (56; 0.1%)

b. Anticoagulation: not reported

- Parenteral: not reported
- Non-vitamin K antagonist: not reported
- Vitamin K antagonist: not reported

c. Reperfusion: yes

- Thrombolysis: yes (systemic). Women (10,665; 18.3%); men (11,536, 17.1%)
- Surgical embolectomy: yes. Women (768; 1.3%); men (877; 1.3%)
- Percutaneous catheter-directed treatment: yes. CTD: women (10,665; 18.3%); men (11,536; 17.1%). US CTD: women (2411; 4.1%); men (2612; 3.9%). CDE: women (2396; 4.1%); men (2620; 3.9%)

d. Other treatment: no

Prognostic factor

Sex: female

Definition: not provided

Terms used: terms for sex (female, male) and gender (women, men) were used inconsistently throughout the study.

Prognostication time: not reported

- Quote: "Additionally, the NRD uses discharge not admission diagnoses, so we could not ascertain if PE was present on admission or later during the course of hospitalization."
- Comment: we could not determine if PE was present on admission or later during the course of hospitalisation.

Outcomes

1. All-cause hospital mortality: yes

1. **Setting:** in-hospital mortality
2. **Timing:** not reported
3. **Measurement**: not reported
4. **Length of follow-up:** 9 days (median)

2. All-cause hospital mortality at 30 days: no

3. Early all-cause hospital mortality (during the first 48 hours): no

4. All-cause mortality at 30 days: no

5. All-cause mortality at 90 days: no

Sedhom 2022 *(Continued)*

	6. All-cause mortality at 1 year: no **7. PE-related hospital mortality:** no **8. PE-related hospital mortality at 30 days:** no **9. Early PE-related hospital mortality (during the first 48 hours):** no **10. PE-related mortality at 30 days:** no
Statistical analysis and adjustment for other covariates	**Statistical analysis:** propensity score matching algorithm with multivariable logistic regression **Covariates for adjustment:** using a propensity score matching algorithm with multivariable logistic regression conditioned on 26 variables: age, obesity, morbid obesity, anaemia, hypertension, atrial fibrillation, diabetes mellitus, heart failure, carotid disease, chronic lung disease, pulmonary circulation disease, coagulopathy, peripheral vascular disease, renal failure, liver disease, history of coronary artery bypass graft, history of stroke, history of myocardial infarction, solid tumours without metastases, metastatic cancer, nonseptic shock, saddle PE, cor pulmonale, use of vasopressors, hospital teaching status, and hospital size **Key covariates considered for risk of bias assessment (4/8)** 1. **Age:** yes 2. **History of cancer:** no 3. **Current cancer:** yes (solid tumour and metastatic cancer) 4. **History of chronic cardiopulmonary disease:** yes (history of coronary artery bypass graft, history of stroke, history of myocardial infarction) 5. **Current chronic cardiopulmonary disease:** yes (heart failure, chronic lung disease, cor pulmonale, hypertension) 6. **Heart rate:** no 7. **Systolic blood pressure:** no 8. **O2 saturation:** no
QUIPS	**Study participation** Judgement: low risk of bias Support for judgement Quote: "We used the Nationwide Readmissions Database (NRD), Healthcare Cost and Utilization Project (HCUP) from the Agency for Healthcare Research and Quality for this analysis. The NRD contains discharge data from 28 geographically dispersed US states, accounting for ~60% of the total USA resident population and 58.2% of all USA hospitalizations." Comment: the study participants were probably representative of the eligible population. **Study attrition** **All-cause hospital mortality** Judgement: low risk of bias Support for judgement Comment: there was a difference of 93,977 hospitalisations before and after propensity score matching. After consulting with Cochrane Prognosis, we judged that this difference probably did not lead to bias. **Prognostic factor measurement** Judgement: low risk of bias Support for judgement

Sedhom 2022 *(Continued)*

Comment: although sex measurement is not specified (sex/gender terms were used inconsistently), we consider this inadequate reporting did not lead to bias.

Outcome measurement

All-cause hospital mortality

Judgement: low risk of bias

Support for judgement

Comment: although the authors did not report the outcome measurement methods, we consider the risk of bias to be low.

Adjustment for key additional prognostic factors

All-cause hospital mortality

Judgement: low risk of bias

Support for judgement

Quote: "We used propensity score matching to account for the differences in the baseline patient and hospital-related characteristics and advanced therapies. We created two propensity score-matched groups (women vs men) using a propensity score matching algorithm with multivariable logistic regression conditioned on 26 variables."

Comment: the analysis was adjusted for 4 of our 8 key covariates (age, current cancer, history of current chronic cardiopulmonary disease, current chronic cardiopulmonary disease). Although the authors did not report the measurement methods, we consider that all were valid and reliable because key covariates were extracted from the NRD, HCUP from the AHRQ.

Statistical analysis and reporting

All-cause hospital mortality

Judgement: moderate risk of bias

Support for judgement

a) Statistical analysis: low risk of bias

Quote: "We used propensity score matching to account for the differences in the baseline patient and hospital-related characteristics and advanced therapies. We created two propensity score-matched groups (women vs men) using a propensity score matching algorithm with multivariable logistic regression conditioned on 26 variables."

Comment: the statistical analysis was appropriate

b) Selective outcome reporting: moderate risk of bias

Comment: we could not access the study protocol. Therefore, we could not assess the presence of selective outcome reporting and judged the risk of bias as moderate.

Notes

Funding source: not reported

Declaration of interests: Dr Weinberg has received consultant fees from Magneto Thrombectomy Solutions and is the PI for Penumbra, Inc. Dr Elgendy has received research grants from Caladrius Biosciences Inc. The remaining authors report no potential competing interests.

Contact with the correspondence author: we requested the study protocol via email. The author replied that there was no study protocol.

Tanabe 2018

Study characteristics	
Methods	**Study design** 1. Phase 2 prognostic study 2. Retrospective cohort study **Data source** 1. Type: administrative data 2. Database: The Tokyo CCU Network (72 affiliated hospitals) **Period:** between 2010 and 2014 **Setting** • Setting: hospital • Country: Japan • State: not applicable • City: Tokyo • Number of centres: multicentric, 72 centres

Participants	**Age (mean):** 68.0 ± 16.1 females; 60.9 ± 15.6 males
	
	Sample size: 1428 participants (795 females and 633 males)
	
	A total of 1492 consecutive APE patients enroled in the CCU network registry survey forms, which included symptoms, vital signs, blood examinations, imaging data, treatment, and prognosis. Of 1492 enroled, the exclusion criteria applied were: patients with insufficient data (n = 59), APE of non-thrombus origin (n = 5; fat or tumour emboli).
	
	Diagnosis: acute primary PE
	
	• **Classification system for PE diagnosis:** not reported
	• **PE objective testing:** yes (enhanced computed tomography (CT) (N = 1323), pulmonary scintigraphy (N = 28), pulmonary angiography (N = 21), autopsy (N = 1)
	• **PE development (community, hospital):** community (review authors assumed PE was the main cause of hospitalisation)
	• **Type of PE (primary, secondary, recurrent):** not reported
	• **Time between the onset of PE symptoms and the start of follow-up:** not reported
	
	PE clinical characteristics
	
	• **Acute PE:** yes
	• **Symptomatic PE:** yes (98.4%)
	• **PE Severity:**
	  ◦ **Method for severity quantification:** massive ("right heart dysfunction was present with vital signs indicative of shock, or systolic blood pressure decreased by>40mmHg")
	  ◦ **Proportion of participants with severe PE:** 12.1% (N = 173)
	
	Hospital unit: cardiovascular care unit. "First, we evaluated the APE patients treated at the CCUs whereas the less severe cases treated in general wards were not included in this study"
	
	a. Presence of PE treatment: yes (% unknown)
	
	a. Haemodynamic and respiratory support: not reported
	
	• Oxygen therapy and ventilation: not reported
	• Vasopressors: not reported

Tanabe 2018 *(Continued)*

- Mechanical circulatory support and oxygenation/advanced life support: not reported

b. Anticoagulation: yes (male 52.4% of 633; female 55.7% of 795)

- Parenteral: not reported
- Non-vitamin K antagonist: not reported
- Vitamin K antagonist: not reported

c. Reperfusion: yes

- Thrombolysis: yes: male 208 (33.0% of 633); female 219 (27.5% of 795)
- Surgical embolectomy: yes (male 1.3% of 633; female 1.1% out of 795)
- Percutaneous catheter-directed treatment: yes (male 5.1% of 633; female 4.8% of 795)

d. Other treatment: yes: usage rate of IVC filter (male 37.3% of 633; female 31.9% of 795)

Prognostic factor	**Sex**: female sex **Definition:** not provided **Terms used:** terms for sex (female, male) and gender (women, men) were used inconsistently throughout the study **Prognostication time:** not reported
Outcomes	**1. All-cause hospital mortality:** no **2. All-cause hospital mortality at 30 days:** no **3. Early all-cause hospital mortality (during the first 48 hours):** no **4. All-cause mortality at 30 days:** no **5. All-cause mortality at 90 days:** no **6. All-cause mortality at one year:** no **7. PE-related hospital mortality:** no **8. PE-related hospital mortality at 30 days:** no **9. Early PE-related hospital mortality (during the first 48 hours):** no **10. PE-related mortality at 30 days:** yes 1. **Setting:** not reported 2. **Timing:** not reported 3. **Measurement**: unclear. The process to adjudicate the cause of death was not reported ("the data obtained are analyzed by the Tokyo CCU Network Scientific Committee"). 4. **Length of follow:** not reported
Statistical analysis and adjustment for other covariates	**Statistical analysis:** several potential predictors for PE-related 30-day mortality were also identified on single predictor analysis. Of these, the risk factors with P value < 0.10 on univariate analysis were evaluated on multivariate regression analysis. **Covariates for adjustment:** clinical predictors for PE-related 30-day mortality were assessed by multivariate regression analysis: age, systolic blood pressure, systolic pulmonary arterial pressure, brain natriuretic peptide, and inferior vena cave filter use. **Key covariates considered for risk of bias assessment (2/8)** 1. **Age:** yes 2. **History of cancer:** no

Tanabe 2018 *(Continued)*

3. **Current cancer:** no
4. **History of chronic cardiopulmonary disease:** no
5. **Current chronic cardiopulmonary disease:** no
6. **Heart rate:** no
7. **Systolic blood pressure:** yes
8. **O2 saturation:** no

QUIPS	**Study participation** Judgement: low risk of bias Support for judgement Quote: "All patients treated within the CCU network affiliated hospitals are enrolled". "Patients with PE between 2010 and 2014". "The Tokyo cardiovascular care unit (CCU) Network was established in 1978 and operates through 72 affiliated hospitals" "In the total 1,492 APE patients enrolled, the exclusion criteria was: patients with insufficient data (n = 59), APE of nonthrombus origin (n = 5; fat or tumor emboli). The remaining 1,428 subjects consisting of 633 men and 795 women were enrolled in this study." Comment: the sample selection was correct and representative of the target population. **Study attrition** **PE-related mortality at 30 days** Judgement: low risk of bias Support for judgement Quote: "In the total 1,492 APE patients enrolled, the exclusion criteria was: patients with insufficient data (n = 59), APE of non-thrombus origin (n = 5; fat or tumor emboli). The remaining 1,428 subjects consisting of 633 men and 795 women were enrolled in this study". Comment: only 4% of participants were excluded due to insufficient data. **Prognostic factor measurement** Judgement: low risk of bias Support for judgement Comment: although sex measurement is not specified (sex/gender terms were used inconsistently), we consider this inadequate reporting did not lead to bias. **Outcome measurement** **PE-related mortality at 30 days** Judgement: moderate risk of bias Support for judgement Quote: "All patients treated within the CCU network affiliated hospitals are enrolled within the registry and the data obtained are analyzed by the Tokyo CCU Network Scientific Committee". Comment: the process to adjudicate the cause of death was not reported. While we did not find compelling evidence that patient sex influenced the adjudication of cause of death in people diagnosed with PE, we assessed the risk of bias as moderate. This assessment underscores the study's lack of detail regarding the process for adjudicating the cause of death. **Adjustment for key additional prognostic factors** **PE-related mortality at 30 days** Judgement: high risk of bias

Tanabe 2018 *(Continued)*

	Support for judgement Comment: 2 of our 8 critical covariates were considered for the analysis (age, systolic blood pressure). **Statistical analysis and reporting** **PE-related mortality at 30 days** Judgement: moderate risk of bias Support for judgement a) Statistical analysis: moderate risk of bias Quote: "Several potential predictors for PE-related 30-day mortality were also identified on single predictor analysis. Of these, the risk factors with p value <0.10 on univariate analysis were evaluated on multivariate regression analysis" Comment: model construction strategy was unclear. In the multivariate analysis, not all variables with a value of P < 0.10 were included. The methods section did not indicate the criteria for maintaining a variable in the multivariable model. b) Selective outcome reporting: moderate risk of bias Comment: we could not access the study protocol. Therefore, we could not assess the presence of selective outcome reporting and judged the risk of bias as moderate.
Notes	**Funding source:** not reported **Declaration of interests:** the study authors have no conflicts of interest to disclose. **Contact with the correspondence author:** we attempted to contact the author via email but received no response.

AHQR: Agency for Healthcare Research and Quality; APE: acute pulmonary embolism; BIDMC: Beth Israel Deaconess Medical Center; CCI: Charlson Comorbidity Index; CCU: cardiovascular care unit; CDE: catheter-directed embolectomy; CDI: catheter-directed intervention; CDT: catheter-directed thrombolysis; CM: Clinical Modification; CT: computerised tomography; CTPA: computerised tomography pulmonary angiography; DJ: David Jiménez. DOAC: direct oral anticoagulants; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; HCUP: Healthcare Cost and Utilization Project; ICD: International Classification of Diseases; ICU: intensive care unit; IPTW: inverse probability of treatment weighting; IQR: interquartile range; IVC: inferior vena cava filter; LMWH: low-molecular-weight heparin; N: number of participants; NIS: National Inpatient Sample; NRD: Nationwide Readmissions Database; MASCOT: Massive And Submassive Clot On-call Team; NIS: Nationwide Inpatient Sample; O2: oxygen; OR: odds ratio; P: probability; PE: pulmonary embolism; PERT: pulmonary embolism response team; PESI: Pulmonary Embolism Scale Index; PHC4: Pennsylvania Health Care Cost Containment Council; SBP: systolic blood pressure; sPESI: simplified PESI (Pulmonary Embolism Scale Index); US: ultrasound scan; USA: United States of America; VTE: venous thromboembolism; VQ: ventilation-perfusion

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agolli 2020	Exclude on study design: not a phase 2 prognostic study.
Akgullu 2013	Exclude on prognostic factor: sex is not the prognostic factor studied.
Alarcon 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Alikhan 2014	Exclude on study design: not a phase 2 prognostic study.
Aller 2011	Exclude on study design: not a phase 2 prognostic study.

Study	Reason for exclusion
Aller-Fernandez 2011	Exclude on study design: not a phase 2 prognostic study.
Almeida 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Alonso-Martinez 2011	Exclude on study design: not a phase 2 prognostic study.
Alonso-Martinez 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Al Otair 2009	Exclude on study design: not a phase 2 prognostic study.
Amar 2013	Exclude on type of research question: not a prognostic question.
Andersson 2012	Exclude on study design: not a phase 2 prognostic study.
Andersson 2017	Exclude on study design: not a phase 2 prognostic study.
Antero 2022	Exclude on prognostic factor: sex is not the prognostic factor studied
Anwer 2010	Exclude on study design: not a phase 2 prognostic study.
Arellanes 2019a	Exclude on study design: not a phase 2 prognostic study.
Arellanes 2019b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Arellanes 2019c	Exclude on prognostic factor: sex is not the prognostic factor studied.
Arellanes 2019d	Exclude on prognostic factor: sex is not the prognostic factor studied.
Aujesky 2008	Exclude on study design: not a phase 2 prognostic study.
Aujesky 2009	Exclude on prognostic factor: sex is not the prognostic factor studied.
Bajaj 2014	Exclude on type of report: review, guideline, consensus.
Barco 2016	Exclude on prognostic factor: sex is not the prognostic factor studied.
Barco 2020a	Exclude on type of research question: not a prognostic question.
Barco 2020b	Exclude on type of research question: not a prognostic question
Barco 2020c	Exclude on type of research question: not a prognostic question
Barco 2021a	Exclude on type of research question: not a prognostic question.
Barco 2021b	Exclude on type of research question: not a prognostic question
Becattini 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.
Beneze 2014	Exclude on type of research question: not a prognostic question.
Beyer-Westendorf 2013	Exclude on study design: not a phase 2 prognostic study.
Bhatia 2022	Exclude on study design: not a phase 2 prognostic study
Bilbao 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.

Study	Reason for exclusion
Buchanan 2020	Exclude on study design: not a phase 2 prognostic study
Budaj-Fidecka 2011	Exclude on study design: not a phase 2 prognostic study.
Bumroongkit 2022	Exclude on study design: cross sectional
Buppajarntham 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.
Caldeira 2021	Exclude on prognostic factor: sex is not the prognostic factor studied
Casazza 2012	Exclude on study design: not a phase 2 prognostic study.
Castillo 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Cetinoglu 2015	Exclude on study design: not a phase 2 prognostic study.
Chan 2009	Exclude on prognostic factor: sex is not the prognostic factor studied.
Chan 2022	Exclude on pathology: mixed population (PE + DVT).
Charoenpong 2013a	Exclude on prognostic factor: sex is not the prognostic factor studied.
Charoenpong 2013b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Chen 2013	Exclude on prognostic factor: sex is not the prognostic factor studied.
Chen 2022	Exclude on study design: not a phase 2 prognostic study.
Chopard 2018	Exclude on prognostic factor: sex is not the prognostic factor studied.
Chow 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Ciarambino 2019	Exclude on study design: not a phase 2 prognostic study.
Cigalini 2019	Exclude on type of research question: not a prognostic question.
Cimini 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Cohen 2013	Exclude on study design: not a phase 2 prognostic study.
Courtney 2009	Exclude on prognostic factor: sex is not the prognostic factor studied.
Coyne 2022	Exclude on study design: not a phase 2 prognostic study.
Dahhan 2015	Exclude on study design: not a phase 2 prognostic study.
Dahhan 2016	Exclude on prognostic factor: sex is not the prognostic factor studied.
Darze 2016	Exclude on type of research question: not a prognostic question.
De Miguel-Diez 2020	Exclude on study design: not a phase 2 prognostic study.
De-Miguel-Diez 2021a	Exclude on prognostic factor: sex is not the prognostic factor studied.
De-Miguel-Diez 2021b	Exclude on prognostic factor: sex is not the prognostic factor studied.

Study	Reason for exclusion
De Moreuil 2021	Exclude on pathology: not pulmonary embolism.
Deng 2015	Exclude on study design: not a phase 2 prognostic study.
Dentali 2014	Exclude on type of research question: not a prognostic question.
Dentali 2016	Exclude on study design: not a phase 2 prognostic study.
Donze 2011	Exclude on prognostic factor: sex is not the prognostic factor studied.
Duplyakov 2013	Exclude on prognostic factor: sex is not the prognostic factor studied.
Duplyakov 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Dursunoglu 2007	Exclude on study design: not a phase 2 prognostic study.
Dzudovic 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Ebner 2017	Exclude on type of research question: not a prognostic question.
Ebner 2020	Exclude on type of research question: not a prognostic question.
Echegaray 2003	Exclude on study design: not a phase 2 prognostic study.
El Ghoul 2020	Exclude on study design: not a phase 2 prognostic study.
El Mourid 2019	Exclude on study design: not a phase 2 prognostic study.
Erlikh 2020	Exclude on type of research question: not a prognostic question.
Fabbian 2013	Exclude on prognostic factor: sex is not the prognostic factor studied.
Fabbian 2016	Exclude on study design: not a phase 2 prognostic study.
Fadhil 2018	Exclude on type of research question: not a prognostic question.
Faghihi 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Faghihi 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Fang 2013	Exclude on prognostic factor: sex is not the prognostic factor studied.
Feng 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Fernandes 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Fesenko 2011	Exclude on study design: not a phase 2 prognostic study.
Filipecki 1994	Exclude on study design: not a phase 2 prognostic study.
Fletcher-Sanfeliu 2020	Exclude on study design: not a phase 2 prognostic study.
Font 2012	Exclude on type of research question: not a prognostic question.
Font 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.

Study	Reason for exclusion
Freitas 2017	Exclude on study design: not a phase 2 prognostic study.
Friz 2016	Exclude on prognostic factor: sex is not the prognostic factor studied.
Furlan 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gallerani 1994	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gallerani 1996	Exclude on type of research question: not a prognostic question.
Gallerani 2018	Exclude on prognostic factor: sex is not the prognostic factor studied.
Garcia 2017	Exclude on prognostic factor: sex is not the prognostic factor studied.
Garcia-Sanz 2014	Exclude on study design: not a phase 2 prognostic study.
Geibel 2007	Exclude on study design: not a phase 2 prognostic study.
George 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.
George 2018	Exclude on type of research question: not a prognostic question.
Gergely 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.
Ghaye 2006	Exclude on prognostic factor: sex is not the prognostic factor studied.
Giustozzi 2021	Exclude on pathology: mixed population (PE + DVT).
Gok 2020	Exclude on study design: not a phase 2 prognostic study.
Gök 2020	Exclude on study design: not a phase 2 prognostic study.
Gokcek 2022	Exclude on type of research question: prognostic question, but not prognostic factor question.
Golamari 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Goldberg 2016	Exclude on prognostic factor: sex is not the prognostic factor studied.
Goldhaber 1999	Exclude on prognostic factor: sex is not the prognostic factor studied
Goldhaber 2001	Exclude on type of report: review, guideline, consensus.
Golpe 2011	Exclude on type of research question: prognostic question, but not prognostic factor question.
Goncalves 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.
Goncalves 2015	Exclude on study design: not a phase 2 prognostic study.
Goncalves 2017	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gonzalez 2016	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gonzalez 2018	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gouveia 2016	Exclude on study design: not a phase 2 prognostic study.

Study	Reason for exclusion
Grilz 2018	Exclude on prognostic factor: sex is not the prognostic factor studied.
Guerreiro 2018	Exclude on prognostic factor: sex is not the prognostic factor studied.
Guerreiro 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Guijarro 2008a	Exclude on type of research question: not a prognostic question.
Guijarro 2008b	Exclude on study design: not a phase 2 prognostic study.
Gul 2012a	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gul 2012b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gul 2012c	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gulen 2017	Exclude on prognostic factor: sex is not the prognostic factor studied.
Gupta 2020	Exclude on study design: not a phase 2 prognostic study.
Hobohm 2021	Exclude on type of research question: not a prognostic question.
Hoskin 2021	Exclude on study design: not a phase 2 prognostic study.
Hyun 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Janke 2000	Exclude on study design: not a phase 2 prognostic study.
Janus 2022	Exclude on prognostic factor: sex is not the prognostic factor studied.
Jenab 2016	Exclude on prognostic factor: sex is not the prognostic factor studied.
Jenab 2017	Exclude on prognostic factor: sex is not the prognostic factor studied.
Jimenez 2009	Exclude on prognostic factor: sex is not the prognostic factor studied.
Jiménez 2022	Exclude on prognostic factor: sex is not the prognostic factor studied.
Jug 2016	Exclude on study design: not a phase 2 prognostic study.
Jung 2011	Exclude on prognostic factor: sex is not the prognostic factor studied.
Jupiter 2019	Exclude on type of research question: not a prognostic question.
Justo 2017	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kaballo 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kabrhel 2014	Exclude on study design: not a phase 2 prognostic study.
Kaczynska 2005	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kadlec 2015	Exclude on type of research question: not a prognostic question.
Kanwar 2018	Exclude on study design: not a phase 2 prognostic study.

Study	Reason for exclusion
Karaarslan 2018	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kasapoglu 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kasper 1997	Exclude on prognostic factor: sex is not the prognostic factor studied.
Keller 2014a	Exclude on prognostic factor: sex is not the prognostic factor studied.
Keller 2014b	Exclude on outcome: mortality is not an outcome.
Keller 2017	Exclude on study design: not a phase 2 prognostic study.
Keller 2018	Exclude on prognostic factor: sex is not the prognostic factor studied.
Keller 2019a	Exclude on study design: not a phase 2 prognostic study.
Keller 2019b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Keller 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kempny 2017	Exclude on study design: not a phase 2 prognostic study.
Kempny 2019	Exclude on study design: not a phase 2 prognostic study.
Khaing 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Khan 2010	Exclude on study design: not a phase 2 prognostic study.
Kirhan 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kitamukai 2003	Exclude on type of research question: not a prognostic question.
Kjaergaard 2009	Exclude on prognostic factor: sex is not the prognostic factor studied.
KlilDrori 2016	Exclude on type of research question: not a prognostic question.
Klingenberg 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kochmareva 2016a	Exclude on study design: not a phase 2 prognostic study.
Kochmareva 2016b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kostrubiec 2010a	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kostrubiec 2010b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kostrubiec 2010c	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kostrubiec 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kresoja 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kroger 2010	Exclude on type of research question: not a prognostic question.
Kroger 2012	Exclude on type of research question: not a prognostic question.

Study	Reason for exclusion
Krol 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kucher 2005	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kukla 2009	Exclude on type of research question: not a prognostic question.
Kukla 2010	Exclude on type of research question: not a prognostic question.
Kukla 2011a	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kukla 2011b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kukla 2013a	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kukla 2013b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kukla 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kukla 2015a	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kukla 2015b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kukla 2015c	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kurakina 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kurnicka 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kuroiwa 2006	Exclude on study design: not a phase 2 prognostic study.
Kurzyna 2009	Exclude on prognostic factor: sex is not the prognostic factor studied.
Kyrle 2004	Exclude on study design: not a phase 2 prognostic study.
Kyrle 2005	Exclude on type of report: review, guideline, consensus.
Lankeit 2010	Exclude on type of research question: not a prognostic question.
Laporte 2008	Exclude on study design: not a phase 2 prognostic study.
Laribi 2014	Exclude on type of research question: not a prognostic question.
Lasica 2010	Exclude on prognostic factor: sex is not the prognostic factor studied.
Lazaro 2016	Exclude on prognostic factor: sex is not the prognostic factor studied.
Lilienfeld 1990	Exclude on study design: cross sectional.
Liu 2017	Exclude on study design: not a phase 2 prognostic study.
Lopez-Alcalde 2021	Exclude on type of report: review, guidelines, consensus.
Mansour 2017	Exclude on pathology: not pulmonary embolism.
Martin-Martos 2015	Exclude on study design: not a phase 2 prognostic study.

Study	Reason for exclusion
Martin-Martos 2017	Exclude on pathology: not pulmonary embolism.
Matijasevic 2021	Exclude on study design: not a phase 2 prognostic study.
McHugh 2002	Exclude on outcome: the study reported survival (and HR). Following our protocol plan, we did not convert HRs to ORs due to the many assumptions needed. The crude (not adjusted) 3-month mortality rates for men and women were also reported.
Meier 2016	Exclude on study design: not a phase 2 prognostic study.
Meisinger 2019	Exclude on type of report: review, guideline, consensus.
Melgaard 2019	Exclude on type of research question: not a prognostic question.
Memtsoudis 2009	Exclude on study design: not a phase 2 prognostic study.
Minges 2013	Exclude on type of research question: not a prognostic question.
Minges 2015	Exclude on study design: not a phase 2 prognostic study.
Miranda 2018	Exclude on type of research question: not a prognostic question.
Mizuno 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Monreal 2021	Exclude on type of research question: not a prognostic question.
Moretti 2010	Exclude on type of research question: not a prognostic question.
Mullova 2019	Exclude on study design: not a phase 2 prognostic study.
Muralidharan 2021	Exclude on study design: not a phase 2 prognostic study.
Murata 2018	Exclude on study design: not a phase 2 prognostic study.
Mustehsan 2019	Exclude on prognostic factor: sex is not the prognostic factor studied.
Nauffal 2010	Exclude on prognostic factor: sex is not the prognostic factor studied.
Nayyar 2016	Exclude on study design: not a phase 2 prognostic study.
Neiva 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Ng 2013	Exclude on prognostic factor: sex is not the prognostic factor studied.
Nilius 2021	Exclude on pathology: mixed population (PE + DVT).
Nori 2013	Exclude on study design: not a phase 2 prognostic study.
Obayashi 2010	Exclude on study design: not a phase 2 prognostic study.
Obradovic 2016	Exclude on study design: not a phase 2 prognostic study.
Ogeng'o 2011	Exclude on type of research question: not a prognostic question.
Olie 2015	Exclude on type of research question: not a prognostic question.

Study	Reason for exclusion
Olie 2017	Exclude on prognostic factor: sex is not the prognostic factor studied.
Oliveira 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Osken 2021	Exclude on prognostic factor: sex is not the prognostic factor studied.
Ozsu 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Ozsu 2017	Exclude on study design: not a phase 2 prognostic study.
Paiva 2011	Exclude on study design: not a phase 2 prognostic study.
Pala 2016	Exclude on study design: not a phase 2 prognostic study.
Palminteri 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.
Panigada 2016	Exclude on study design: not a phase 2 prognostic study.
Park 2009	Exclude on type of research question: not a prognostic question.
Patil 2013	Exclude on type of research question: not a prognostic question.
Pedro 2017	Exclude on study design: not a phase 2 prognostic study.
Phillips 2021	Exclude on prognostic factor: sex is not the prognostic factor studied.
Polo 2015	Exclude on study design: not a phase 2 prognostic study.
Polo 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Prandoni 2019	Exclude on type of research question: not a prognostic question.
Proctor 2004	Exclude on type of research question: not a prognostic question.
Punukollu 2005	Exclude on prognostic factor: sex is not the prognostic factor studied.
Quah 2016	Exclude on type of research question: not a prognostic question.
Quinn 1992	Exclude on type of research question: not a prognostic question.
Ramos 2015	Exclude on type of research question: not a prognostic question.
Rao 2018	Exclude on type of research question: not a prognostic question.
Regaieg 2017	Exclude on type of research question: not a prognostic question.
Righini 2010	Exclude on type of research question: not a prognostic question.
Rimbas 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Robert-Ebadi 2010	Exclude on type of research question: not a prognostic question.
Roca 2011	Exclude on prognostic factor: sex is not the prognostic factor studied.
Rocha 2020	Exclude on type of research question: not a prognostic question.

Study	Reason for exclusion
Rodger 2015	Exclude on type of research question: not a prognostic question.
Rodrigues 2013	Exclude on prognostic factor: sex is not the prognostic factor studied.
Rodriguez 2012	Exclude on study design: not a phase 2 prognostic study.
Roldan 2014	Exclude on study design: not a phase 2 prognostic study.
Rosencher 2011	Exclude on pathology: not pulmonary embolism.
Sakuma 2002	Exclude on study design: not a phase 2 prognostic study.
Sakuma 2007	Exclude on study type: cadaver or in vitro study.
Samkoff 1981	Exclude on type of research question: not a prognostic question.
Sandal 2016	Exclude on study design: not a phase 2 prognostic study.
Sandal 2021	Exclude on study design: not a phase 2 prognostic study.
Savioli 2020	Exclude on prognostic factor: sex is not the prognostic factor studied.
Savioli 2021a	Exclude on prognostic factor: sex is not the prognostic factor studied.
Savioli 2021b	Exclude on prognostic factor: sex is not the prognostic factor studied.
Savioli 2022	Exclude on type of research question: not a prognostic question.
Scheres 2017	Exclude on type of research question: not a prognostic question.
Secemsky 2018	Exclude on type of research question: not a prognostic question.
Sequeira 1992	Exclude on type of research question: prognostic question, but not prognostic factor question.
Seravalle 2015	Exclude on type of research question: not a prognostic question.
Shah 2018	Exclude on study design: not a phase 2 prognostic study.
Shalhoub 2018	Exclude on pathology: not pulmonary embolism.
Shiraev 2013	Exclude on type of research question: not a prognostic question.
Shirakawa 2015	Exclude on prognostic factor: sex is not the prognostic factor studied.
Shirakawa 2016	Exclude on prognostic factor: sex is not the prognostic factor studied.
Siddique 1998a	Exclude on type of research question: not a prognostic question.
Siddique 1998b	Exclude on type of research question: not a prognostic question.
Silverstein 1998	Exclude on type of research question: not a prognostic question.
Simoes 2018	Exclude on type of research question: not a prognostic question.
Spencer 2010	Exclude on study design: not a phase 2 prognostic study.

Study	Reason for exclusion
Sridhara 2019	Exclude on outcome: mortality is not an outcome.
Stein 1999	Exclude on type of research question: not a prognostic question.
Tafur 2018	Exclude on pathology: not pulmonary embolism.
Tan 2006	Exclude on study design: not a phase 2 prognostic study.
Tanabe 2016	Exclude on type of research question: not a prognostic question.
Tierney 2021	Exclude on study design: not a phase 2 prognostic study.
Tormene 2011	Exclude on type of report: review, guideline, consensus.
Tsai 2012	Exclude on study design: not a phase 2 prognostic study.
Tsymbalyuk 2012	Exclude on type of research question: not a prognostic question.
Tzoran 2017	Exclude on type of research question: not a prognostic question.
Valerio 2020	Exclude on study design: not a phase 2 prognostic study.
Verso 2010	Exclude on pathology: not pulmonary embolism.
Verso 2012	Exclude on study design: not a phase 2 prognostic study.
Weberova 2012	Exclude on study design: not a phase 2 prognostic study.
Weberova 2014	Exclude on prognostic factor: sex is not the prognostic factor studied.
Werth 2013	Exclude on study design: not a phase 2 prognostic study.
White 2004	Exclude on pathology: not pulmonary embolism.
White 2006	Exclude on outcome: mortality is not an outcome.
Working 2017	Exclude on study design: not a phase 2 prognostic study.
Wort 2017	Exclude on study design: not a phase 2 prognostic study.
Yang 2019	Exclude on outcome: mortality is not an outcome (free recurrence survival)
Yang 2020	Exclude on outcome: mortality is not an outcome (free recurrence survival))
Yildirimturk 2012	Exclude on study design: not a phase 2 prognostic study.
Yoo 2012	Exclude on prognostic factor: sex is not the prognostic factor studied.
Yoshikawa 2018	Exclude on pathology: not pulmonary embolism.
Yoshikawa 2019	Exclude on pathology: not pulmonary embolism.
Yuan 2019	Exclude on outcome: mortality is not an outcome (free recurrence survival))
Zanova 2013	Exclude on type of research question: not a prognostic question.

Study	Reason for exclusion
Zhang 2018	Exclude on type of research question: prognostic question, but not prognostic factor question.
Zhang 2019	Exclude on type of research question: prognostic question, but not prognostic factor question.
Zhu 2013	Exclude on study design: not a phase 2 prognostic study.
Zoller 2011	Exclude on type of research question: not a prognostic question.
Zoller 2013a	Exclude on type of report: review, guideline, consensus.
Zoller 2013b	Exclude on type of research question: not a prognostic question.
Zondag 2010	Exclude on prognostic factor: sex is not the prognostic factor studied.

DVT: deep vein thrombosis; HR: hazard ratio; PE: pulmonary embolism; OR: odds ratio

Characteristics of studies awaiting classification *[ordered by study ID]*

Alsaloum 2023

Notes	The study is only presented as a conference abstract.

Feng 2020

Notes	The study is only presented as a conference abstract. Author was contacted (11 November 2022), but we received no response.

Rosovsky 2019

Notes	The study is only presented as a conference abstract. At the time of the review submission, the full article had been submitted but not yet published.

Characteristics of ongoing studies *[ordered by study ID]*

SERIOUS-PE

Study name	SERIOUS-PE study
Starting date	March 2001
Contact information	Behnood Bikdeli: bbikdeli@bwh.harvard.edu, behnood.bikdeli@yale.edu
Notes	Protocol/design paper

Databases are being cleaned and prepared. According to this design paper, analyses will be forthcoming in subsequent manuscripts.

DATA AND ANALYSES

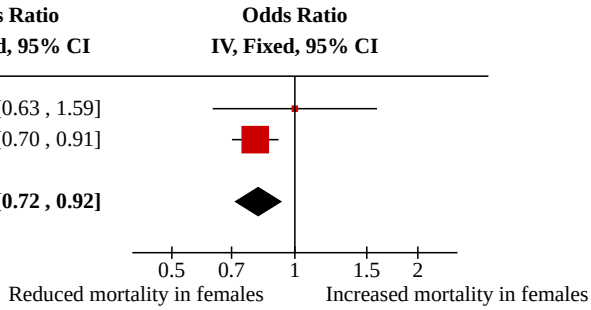
Comparison 1. Being female as a prognostic factor for mortality in adults with acute symptomatic pulmonary embolism

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at 30 days	2		Odds Ratio (IV, Fixed, 95% CI)	0.81 [0.72, 0.92]
1.2 PE-related mortality at 30 days	2		Odds Ratio (IV, Fixed, 95% CI)	1.08 [0.55, 2.12]

Analysis 1.1. Comparison 1: Being female as a prognostic factor for mortality in adults with acute symptomatic pulmonary embolism, Outcome 1: All-cause mortality at 30 days

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Barrios 2017	0	0.23617	7.4%	1.00 [0.63 , 1.59]
Borrero 2007	-0.223144	0.066931	92.6%	0.80 [0.70 , 0.91]
Total			**100.0%**	**0.81 [0.72 , 0.92]**

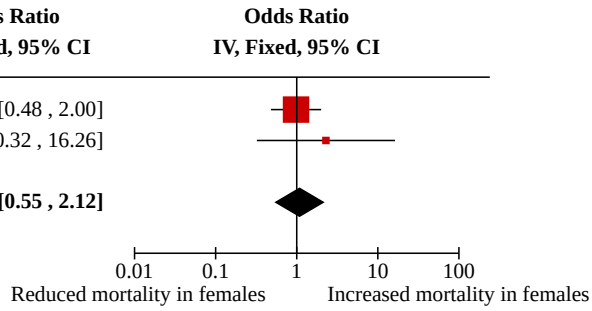
Test for overall effect: Z = 3.21 (P = 0.001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%



Analysis 1.2. Comparison 1: Being female as a prognostic factor for mortality in adults with acute symptomatic pulmonary embolism, Outcome 2: PE-related mortality at 30 days

Study or Subgroup	log[OR]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Barrios 2017	-0.020203	0.364067	88.3%	0.98 [0.48 , 2.00]
Tanabe 2018	0.828552	1.000048	11.7%	2.29 [0.32 , 16.26]
Total			**100.0%**	**1.08 [0.55 , 2.12]**

Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.43); I² = 0%



ADDITIONAL TABLES

Table 1. Review question in PICOTS format

Population	Adults, hospitalised or not, treated for acute symptomatic pulmonary embolism confirmed by objective testing

Table 1. Review question in PICOTS format *(Continued)*

Index prognostic factor	Sex: being a female patient	
Comparator	Covariates: age, history of cancer, current cancer, history of chronic cardiopulmonary disease, current chronic cardiopulmonary disease, heart rate, systolic blood pressure, and O2 saturation	
Outcomes of interest	**Timing - prognostication time**	**Timing - over what period the outcome is predicted**
All-cause hospital mortality	At PE diagnosis	During the hospital stay: the longest follow-up provided by the study authors
		Early hospital mortality (during the first 48 hours)
		At 30 days
All-cause mortality		At 30 days
		At 90 days
		At 1 year
PE-related hospital mortality		During the hospital stay: the longest follow-up provided by the study authors
		Early PE-related hospital mortality (during the first 48 hours)
		At 30 days
PE-related mortality		At 30 days
Setting	Patients with PE managed in any setting. Death can occur at the hospital or not.	

O2: oxygen; PE: pulmonary embolism; PICOTS: population, intervention, comparator, outcome, timing, setting

Table 2. Sensitivity analysis

	Primary analysis	**Sensitivity analysis**	**Primary analysis robust?**
Outcome: all-cause hospital mortality	3 studies: REM + HKSJ: OR 1.11 (95% CI 1.00 to 1.22)	IV FEM: OR 1.11 (95% CI 1.06 to 1.15)	No
		REM + DL: OR 1.11 (95% CI 1.05 to 1.16)	No
Outcome: all-cause mortality at 30 days	2 studies: IV FEM: OR 0.81 (95% CI 0.72 to 0.92)	REM + HKSJ: OR 0.81 (95% CI 0.39 to 1.69)	No
Outcome: PE-related mortality at 30 days	2 studies: IV FEM: OR 1.08 (95% CI 0.55 to 2.12)	REM + HKSJ: OR 1.08 (95% CI 0.03 to 34.95)	Yes

DL: DerSimonian and Laird; FEM: fixed-effect model; HKSJ: Hartung, Knapp, Sidik, and Jonkman; IV: inverse variance; OR: odds ratio; PE: pulmonary embolism; REM: random-effects model

APPENDICES

Appendix 1. Study design features

There is no standardised nomenclature for non-randomised studies (NRS). This can cause problems when defining the types of studies to include in a systematic review and when deciding on the eligibility of the primary studies (Lopez-Alcalde 2018; Polus 2017; Reeves 2011; Tugwell 2017). Our review considered explicit study design features (not only design labels) to define the design eligibility and when assessing studies for selection. The Cochrane Non-randomised Studies Methods Group (NRSMG) (Reeves 2011) proposed to conisider items 1 to 5. We considered additional criteria relevant to prognostic studies (items 6 to 9).

1. **Unit of allocation (individual or group level)**: not applicable as there is no allocation of intervention in our review question
2. **Comparison**: between two groups of participants (males and females)
3. **Method of allocation of study participants to groups (randomised or not randomised)**: not applicable as there is no allocation of the prognostic factor in our review question
4. **The prospective or retrospective character of each study part:** any. We also included studies that did not describe whether they were prospective or retrospective (as these aspects are rarely reported).
   a. **Identification of participants:** prospective, retrospective, or unclear
   b. **Assessment of baseline:** prospective, retrospective, or unclear
   c. **Evaluation of outcomes:** prospective, retrospective, or unclear
   d. **Generation of hypothesis:** prospective, retrospective, or unclear
5. **Variables to assess the comparability between study groups**
   a. **Potential additional prognostic factors**
      i. For a study to be eligible, we required the study authors to have tried to determine the adjusted prognostic value of sex - that is, its prognostic value independent of other existing prognostic factors, such as age or history of cancer. Thus, for a study to be eligible, study authors should have taken into consideration additional prognostic factors (apart from sex) by using a particular design approach to control for confounding or by using a specific method to measure and adjust for confounding in the analysis. We did not require the consideration of specific covariates, the use of a particular design approach to control for confounding, or the use of a particular method to measure and adjust for confounding in the analysis. Our data extraction and risk of bias assessments considered the covariates that were measured, controlled (by the study design), and adjusted (by the analysis). See below 'Comparator' and Appendix 2 for additional prognostic factors.
   b. **Baseline assessment of outcome:** not applicable as we did not require this criterion for inclusion
6. **Temporal sequence:** we only included longitudinal studies, that is, studies that collect data over a period of time. Thus, we excluded cross-sectional studies (studies that collect data only once or in a short time) because they do not allow the assessment of the proper temporal sequence for the study covariates.
7. **The phase of prognostic factor investigation:** phase 2-confirmatory, that is, explanatory research aimed to confirm an independent association between a potential prognostic factor (sex) and the outcome of interest. A phase-2 study seeks to measure the independent effect of a prognostic factor while controlling for other factors (Hayden 2008; Hayden 2014) and is recognisable by its objective statement that outlines a specific prognostic factor of interest (Hayden 2008).
8. **Follow-up period to measure the outcome:** as defined for each outcome (see below)
9. **Data sources used in the study:** studies were eligible irrespective of their data origin (data collected exclusively for research purposes or based on administrative databases). For example, a phase-2 prognostic study based on a database obtained for a randomised controlled trial was eligible. On the other hand, although we acknowledge the ongoing controversy about the accuracy of administrative databases for the identification of pulmonary embolism cases (Burles 2017), these sources were eligible as well. However, we planned to assess the impact of this decision by conducting sensitivity analysis.

Appendix 2. Key covariates for the adjustment of mortality estimates in patients with pulmonary embolism

We identified the key covariates for adjustment through a non-systematic review of the literature and discussion with the review team according to the following process.

Step	Method	Potential additional prognostic factors	Source

(Continued)

1. Preliminary searches to identify potential prognostic factors on mortality in patients with pulmonary embolism	1. PubMed search: "pulmonary embolism" [Title]) AND "prognostic factor" [Title] 2. Embase search: "prognostic factor":ti AND 'pulmonary embolism':ti 3. Initial discussion with review team members	Red cell distribution width	Sen 2014
		Right ventricular dysfunction	Cho 2014
		Glomerular filtration rate	Gibietis 2019
		Hyponatremia	Scherz 2010
		Leukocytes	Jo 2013
		Systemic Inflammatory Response Syndrome	Jo 2013
2. Identify prognostic models for mortality in patients with pulmonary embolism	We considered the factors considered in the simplified Pulmonary Embolism Severity Index (PESI) prognostic model (Jimenez 2010).	Age History of cancer History of chronic cardiopulmonary disease Heart rate Systolic blood pressure Oxygen saturation	Jimenez 2010
3. Prioritisation of additional prognostic factors in GRADEPro-GDT (GRADEpro-GDT 2022)	a. We circulated the preliminary list of prognostic factors to our systematic review team. b. The review authors commented on the factors already listed and/or added new ones to the list. c. The review team received a newly revised list and was asked to prioritise the factors, ranking them from 1 to 9, with 1 being of the least importance and 9 of the highest importance. d. We sent a new list of potential prognostic factors to group them according to their relative importance (1 to 3 points: not relevant; 4 to 6 points: important; 7 to 9 points: critical). e. We asked the review team to confirm the final list of key additional prognostic factors.		
4. Final decision	We agreed on the final list of covariates.		

Appendix 3. Search strategies

Source	Search strategy	Hits retrieved
1. Cochrane Vascular Specialised Register via the CRS-Web Date of most recent search: 17 February 2023	#1 Pulmonary Embolism AND INREGISTER	Jan 2021: 170
	#2 Thromboembolism AND INREGISTER	June 2022: 17
	#3 Thrombosis AND INREGISTER	Feb 2023: 14
	#4 Venous Thromboembolism AND INREGISTER	
	#5 Venous Thrombosis AND INREGISTER	
	#6 #1 OR #2 OR #3 OR #4 OR #5	
	#7 Sex Factors AND INREGISTER	

(Continued)

	#8 Sex Characteristics AND INREGISTER #9 Sex Distribution AND INREGISTER #10 Sex AND INREGISTER #11 Men AND INREGISTER #12 WOMen AND INREGISTER #13 gender AND INREGISTER #14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 #15 prognos* AND INREGISTER #16 Mortality AND INREGISTER #17 Follow-Up Studies AND INREGISTER #18 Incidence AND INREGISTER #19 #15 OR #16 OR #17 OR #18 #20 #19 AND #14 AND #6	
2. CENTRAL via the CRSO Date of most recent search: 17 February 2023	#1 MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL AND CENTRAL:TARGET #2 MESH DESCRIPTOR Thromboembolism EXPLODE ALL AND CENTRAL:TARGET #3 MESH DESCRIPTOR Thrombosis EXPLODE ALL AND CENTRAL:TARGET #4 MESH DESCRIPTOR Venous Thromboembolism EXPLODE ALL AND CENTRAL:TARGET #5 MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL AND CENTRAL:TARGET #6 (((vein* or ven*) adj thromb*)):AB,TI AND CENTRAL:TARGET #7 (blood adj3 clot*):AB,TI AND CENTRAL:TARGET #8 "deep vein thrombosis":AB,TI AND CENTRAL:TARGET #9 (lung adj3 clot*):AB,TI AND CENTRAL:TARGET #10 (DVT or VTE):AB,TI AND CENTRAL:TARGET #11 "peripheral vascular thrombosis":AB,TI AND CENTRAL:TARGET #12 "post-thrombotic syndrome":AB,TI AND CENTRAL:TARGET #13 "pulmonary embolism":AB,TI AND CENTRAL:TARGET #14 (pulmonary adj3 clot*):AB,TI AND CENTRAL:TARGET #15 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*):AB,TI AND CENTRAL:TARGET #16 "venous thromboembolism":AB,TI AND CENTRAL:TARGET #17 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	Jan 2021: 3539 June 2022: 509 Feb 2023: 182

(Continued)

#18 MESH DESCRIPTOR Sex Factors EXPLODE ALL AND CENTRAL:TARGET

#19 MESH DESCRIPTOR Sex Characteristics EXPLODE ALL AND CENTRAL:TARGET

#20 MESH DESCRIPTOR Sex Distribution EXPLODE ALL AND CENTRAL:TARGET

#21 MESH DESCRIPTOR Sex EXPLODE ALL AND CENTRAL:TARGET

#22 MESH DESCRIPTOR Sex Ratio EXPLODE ALL AND CENTRAL:TARGET

#23 MESH DESCRIPTOR Women's Health EXPLODE ALL AND CENTRAL:TARGET

#24 MESH DESCRIPTOR Men's Health EXPLODE ALL AND CENTRAL:TARGET

#25 (boy*):AB,TI AND CENTRAL:TARGET

#26 (female*):AB,TI AND CENTRAL:TARGET

#27 (gender):AB,TI AND CENTRAL:TARGET

#28 (girl*):AB,TI AND CENTRAL:TARGET

#29 (male*):AB,TI AND CENTRAL:TARGET

#30 (maternal):AB,TI AND CENTRAL:TARGET

#31 (men):AB,TI AND CENTRAL:TARGET

#32 (postnatal):AB,TI AND CENTRAL:TARGET

#33 (pregnan*):AB,TI AND CENTRAL:TARGET

#34 (sex):AB,TI AND CENTRAL:TARGET

#35 (women):AB,TI AND CENTRAL:TARGET

#36 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35

#37 #17 AND #36

#38 MESH DESCRIPTOR Mortality EXPLODE ALL AND CENTRAL:TARGET

#39 MESH DESCRIPTOR Follow-Up Studies EXPLODE ALL AND CENTRAL:TARGET

#40 MESH DESCRIPTOR Incidence EXPLODE ALL AND CENTRAL:TARGET

#41 MESH DESCRIPTOR Survival Analysis EXPLODE ALL AND CENTRAL:TARGET

#42 (prognos*):AB,TI AND CENTRAL:TARGET

#43 (predict*):AB,TI AND CENTRAL:TARGET

#44 (course*):AB,TI AND CENTRAL:TARGET

#45 ("disease history"):AB,TI AND CENTRAL:TARGET

#46 (mortality):AB,TI AND CENTRAL:TARGET

#47 (outcome*):AB,TI AND CENTRAL:TARGET

#48 #47 OR #46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38

#49 #48 AND #37

(Continued)

3. Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present Date of most recent search: 17 February 2023	1 Pulmonary Embolism/ 2 Thromboembolism/ 3 Thrombosis/ 4 exp Venous Thromboembolism/ 5 exp Venous Thrombosis/ 6 ((vein* or ven*) adj thromb*).ti,ab. 7 (blood adj3 clot*).ti,ab. 8 deep vein thrombosis.ti,ab. 9 (lung adj3 clot*).ti,ab. 10 (DVT or VTE).ti,ab. 11 peripheral vascular thrombosis.ti,ab. 12 post-thrombotic syndrome.ti,ab. 13 pulmonary embolism.ti,ab. 14 (pulmonary adj3 clot*).ti,ab. 15 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboembolic* or thrombos* or embol* or microembol*).ti,ab. 16 venous thromboembolism.ti,ab. 17 or/1-16 18 exp Sex Factors/ 19 exp Sex Characteristics/ 20 exp Sex Distribution/ 21 exp Sex/ 22 exp Sex Ratio/ 23 exp Women's Health/ 24 exp Men's Health/ 25 boy*.ti,ab. 26 female*.ti,ab. 27 gender.ti,ab. 28 girl*.ti,ab. 29 male*.ti,ab. 30 maternal.ti,ab. 31 men.ti,ab. 32 postnatal.ti,ab. 33 pregnan*.ti,ab.	Jan 2021: 31,238 June 2022: 3910 Feb 2023: 2530

(Continued)

	34 sex.ti,ab.	
	35 women.ti,ab.	
	36 or/18-35	
	37 17 and 36	
	38 exp Mortality/	
	39 exp Follow-Up Studies/	
	40 exp Incidence/	
	41 exp Survival Analysis/	
	42 prognos*.ti,ab.	
	43 predict*.ti,ab.	
	44 course*.ti,ab.	
	45 "disease history".ti,ab.	
	46 mortality.ti,ab.	
	47 outcome*.ti,ab.	
	48 or/38-47	
	49 37 and 48	
	50 exp animals/ not humans.sh.	
	51 49 not 50	
4. EMBASE via OVID (Date of most recent search: 17 February 2023)	1 lung embolism/	Jan 2021: 57,177 June 2022: 11,398 Feb 2023: 5325
	2 thromboembolism/	
	3 exp venous thromboembolism/	
	4 exp vein thrombosis/	
	5 ((vein* or ven*) adj thromb*).ti,ab.	
	6 (blood adj3 clot*).ti,ab.	
	7 "deep vein thrombosis".ti,ab	
	8 (lung adj3 clot*).ti,ab.	
	9 "peripheral vascular thrombosis".ti,ab.	
	10 "post-thrombotic syndrome".ti,ab.	
	11 "pulmonary embolism".ti,ab.	
	12 (pulmonary adj3 clot*).ti,ab.	
	13 (thrombopro* or thrombotic* or thrombolic* or thromboemboli* or embol* or microembol*).ti,ab.	
	14 "venous thromboembolism".ti,ab.	
	15 or/1-14	

(Continued)

	16 exp sex factor/	
	17 exp sexual characteristics/	
	18 exp sex ratio/	
	19 exp women's health/	
	20 exp men's health/	
	21 boy*.ti,ab.	
	22 female*.ti,ab.	
	23 gender.ti,ab.	
	24 girl*.ti,ab.	
	25 male*.ti,ab.	
	26 maternal.ti,ab.	
	27 men.ti,ab.	
	28 postnatal.ti,ab.	
	29 pregnan*.ti,ab.	
	30 sex.ti,ab.	
	31 women.ti,ab.	
	32 or/16-31	
	33 15 and 32	
	34 exp mortality/	
	35 exp incidence/	
	36 exp survival analysis/	
	37 prognos*.ti,ab.	
	38 predict*.ti,ab.	
	39 course*.ti,ab.	
	40 "disease history".ti,ab.	
	41 mortality.ti,ab.	
	42 outcome*.ti,ab.	
	43 or/34-42	
	44 33 and 43	
5. CINAHL via Ebsco (Date of most recent search: 17 February 2023)	S41 S31 AND S40 S40 S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 S39 TX outcome* S38 TX mortality S37 TX "disease history"	Jan 2021: 19,694 June 2022: 1770 Feb 2023: 1071

(Continued)

S36 TX course*

S35 TX predict*

S34 TX prognos*

S33 (MH "Survival Analysis+")

S32 (MH "Incidence")

S31 S15 AND S30

S30 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29

S29 TX women

S28 TX sex

S27 TX pregnan*

S26 TX postnatal

S25 TX men

S24 TX maternal

S23 TX male*

S22 TX girl*

S21 TX gender

S20 TX female*

S19 TX boy*

S18 (MH "Men's Health")

S17 (MH "Women's Health")

S16 (MH "Sex Factors")

S15 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14

S14 TX "venous thromboembolism"

S13 TX thrombopro* or thrombotic* or thrombolic* or thromboemboli* or embol* or microembol*

S12 TX pulmonary N3 clot*

S11 TX "pulmonary embolism"

S10 TX "post-thrombotic syndrome"

S9 TX "peripheral vascular thrombosis"

S8 TX lung N3 clot*

S7 TX "deep vein thrombosis"

S6 TX blood N3 clot*

S5 TX ((vein* or ven*) N thromb*)

S4 (MH "Venous Thrombosis+")

(Continued)

	S3 (MH "Venous Thromboembolism") S2 (MH "Thromboembolism") S1 (MH "Pulmonary Embolism")	
6. Clinicaltrials.gov (Date of most recent search: 17 February 2023)	Sex Factors OR Sex Characteristics OR Sex Distribution OR Sex OR MEN OR WOMEN OR GENDER | Pulmonary Embolism OR Thromboembolism OR Thrombosis OR Venous Thrombosis | prognos* OR Mortality OR Follow-Up Studies OR Incidence	Jan 2021: 14 June 2022: 1 Feb 2023: 0
7. ICTRP Search Portal (Date of most recent search: 17 February 2023)	Sex Factors OR Sex Characteristics OR Sex Distribution OR Sex OR Men OR women or gender |AND Pulmonary Embolism OR Thromboembolism OR Thrombosis OR Venous Thrombosis	June 2022: 40 Feb 2023: 0
TOTAL before de-duplication		Jan 2021: 111,832 June 2022: 17,645 Feb 2023: 9122

Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CRS: Cochrane Register of Studies; ICTRP: World Health Organization International Clinical Trials Registry Platform

Appendix 4. Data extraction template

- Dates, country, and setting in which the study was conducted
- Study design
- Eligibility criteria
- Participants' details
- Pulmonary embolism diagnostic criteria
- Treatment details
- Details of the prognostic factor:
  - sex definition;
  - sex measurement (e.g. self-reported or by genotyping of a blood sample).
- Definition of start points (baseline)
- Outcomes reported
- For each review outcome, we extracted the information as described in the 'Types of outcome measures' section (Saldanha 2014).
- Duration of study follow-up
- Type of analysis:
  - explanatory/confirmatory;
  - presence of a valid study registration;
  - presence of a valid protocol;
  - logistic regression/Cox regression;
  - adjustments done for other prognostic factors (if any) to estimate the prognostic association;
  - covariates used in the adjusted analysis
  - age limit used to dichotomise age or other variables (if adopted).
- Association measures for the prognostic factor and each review outcome:
  - type of association measure, e.g. odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs);
  - confidence interval (CI), variance, and standard error (SE);
  - details on any adjustment factors used;

- unadjusted and the adjusted measure of association (if available).
- Methods used to handle missing data
- Attrition:
  - loss to follow-up;
  - reasons.
- Information to assess the risk of bias
- Data needed to perform the meta-analyses, such as the estimates and their corresponding standard errors or confidence intervals

Appendix 5. QUIPS tool (quality in prognostic factor studies)

Signalling questions and risk of bias ratings (Riley 2019)

Domain 1: participant selection

Signalling items

- Adequate participation in the study by eligible persons.
- Description of the target population or population of interest.
- Description of the baseline study sample.
- Adequate description of the sampling frame and recruitment.
- Adequate description of the period and place of recruitment.
- Adequate description of inclusion and exclusion criteria.

Risk of bias ratings

- High: the relationship between the prognostic factor and outcome is very likely to be different for participants and eligible non-participants.
- Moderate: the relationship between the prognostic factor and outcome may be different for participants and eligible non-participants.
- Low: the relationship between the prognostic factor and outcome is unlikely to be different for participants and eligible non-participants.

Domain 2: study attrition

Signalling items

- Adequate response rate for study participants.
- Description of attempts to collect information on participants who dropped out.
- Reasons for loss to follow-up are provided.
- Adequate description of participants lost to follow-up.
- There are no important differences between participants who completed the study and those who did not.

Risk of bias ratings

- High: the relationship between the prognostic factor and outcome is very likely to be different for completing and non-completing participants.
- Moderate: the relationship between the prognostic factor and outcome may be different for completing and non-completing participants.
- Low: the relationship between the prognostic factor and outcome is unlikely to be different for completing and non-completing participants.

Domain 3: prognostic factor measurement

Signalling items

- A clear definition or description of the prognostic factor is provided.
- Method of PF measurement is valid and reliable.
- Continuous variables are reported or appropriate cutpoints are used.
- The method and setting of measurement of prognostic factor is the same for all study participants.
- Adequate proportion of the study sample has complete data for the prognostic factor.
- Appropriate methods of imputation are used for missing prognostic factor data.

Risk of bias ratings

- High: the measurement of the prognostic factor is very likely to be different for different levels of the outcome of interest.
- Moderate: the measurement of the prognostic factor may be different for different levels of the outcome of interest.
- Low: the measurement of the prognostic factor is unlikely to be different for different levels of the outcome of interest.

Domain 4: outcome measurement

Signalling items

- A clear definition of the outcome is provided.
- Method of outcome measurement used is valid and reliable.
- The method and setting of outcome measurement is the same for all study participants.

Risk of bias ratings

- High: the measurement of the outcome is very likely to be different related to the baseline level of the prognostic factor.
- Moderate: the measurement of the outcome may be different related to the baseline level of the prognostic factor.
- Low: the measurement of the outcome is unlikely to be different related to the baseline level of the prognostic factor.

Domain 5: adjustment for other prognostic factors

Signalling items

- All other important prognostic factors are measured.
- Clear definitions of the important prognostic factors measured are provided.
- Measurement of all important prognostic factors is valid and reliable.
- The method and setting of prognostic factor measurement are the same for all study participants.
- Appropriate methods are used to deal with missing values of prognostic factors, such as multiple imputation.
- Important prognostic factors are accounted for in the study design.
- Important prognostic factors are accounted for in the analysis.

Risk of bias ratings

- High: the observed effect of the prognostic factor on the outcome is very likely to be distorted by another factor related to the PF and outcome.
- Moderate: the observed effect of the prognostic factor on outcome may be distorted by another factor related to the PF and outcome.
- Low: the observed effect of the prognostic factor on outcome is unlikely to be distorted by another factor related to the PF and outcome.

Domain 6: statistical analysis and reporting

Signalling items

- Sufficient presentation of data to assess the adequacy of the analytic strategy.
- Strategy for model building is appropriate and is based on a conceptual framework or model.
- The selected statistical model is adequate for the design of the study.
- There is no selective reporting of results.

Risk of bias ratings

- High: the reported results are very likely to be spurious or biased related to analysis or reporting.
- Moderate: the reported results may be spurious or biased related to analysis or reporting.
- Low: the reported results are unlikely to be spurious or biased related to analysis or reporting.

HISTORY

Protocol first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

Jesús López Alcalde (JLA): guarantor of the review; conceiving the review; designing the review; co-ordinating the review; data collection for the review; screening search results; organising retrieval of papers; screening retrieved papers against inclusion criteria; appraising risk

of bias; extracting data from papers; assessing the certainty of the evidence; data management for the review; entering data into RevMan; analysis of data; interpretation of data; providing a methodological perspective; writing the review; performing previous work that was the foundation of the current study.

Elena Jiménez (EJ) and Andrea Correa-Pérez (AC): data collection for the review; screening search results; organising retrieval of papers; screening retrieved papers against inclusion criteria; appraising risk of bias; extracting data from papers; assessing the certainty of the evidence; writing to authors of papers for additional information; providing additional data about papers; obtaining and screening data on unpublished studies; data management for the review; entering data into RevMan; analysis of data; interpretation of data; providing a methodological perspective; writing the review; providing general advice on the review.

Elena Stallings (ES): data collection for the review; screening search results; organising retrieval of papers; screening retrieved papers against inclusion criteria; appraising risk of bias; extracting data from papers; writing to authors of papers for additional information; providing additional data about papers; obtaining and screening data on unpublished studies; data management for the review; entering data into RevMan; analysis of data; interpretation of data; providing a methodological perspective; providing general advice on the review.

Javier Zamora (JZ) and David Jimenez (DJ): conceiving the review; designing the review; analysis of data; interpretation of data; providing a methodological perspective; writing the review; providing general advice on the review; securing funding for the review; performing previous work that was the foundation of the current study.

Noelia Alvarez-Diaz (NAD): organising retrieval of papers; screening; providing a methodological perspective; providing general advice on the review.

Alfonso Muriel (AM), Borja Manuel Fernandez-Felix (BF), Andrea Gaetano Gil (AG): data collection for the review; appraising risk of bias; extracting data from papers; analysis of data; interpretation of data; providing a methodological perspective; providing general advice on the review.

Alba M Antequera Martín (AA), Elia Fernández-Martínez (EF), Aurora Solier (AS), Raymond Stallings (RS), Eduardo García Laredo (EGL), Marcos de Miguel (MDM), Raquel Morillo Guerrero (RM), Raquel Pérez (RP): screening search results; screening retrieved papers against inclusion criteria; obtaining and screening data on unpublished studies; data management for the review; interpretation of data; providing a methodological perspective; providing general advice on the review.

Miriam Mateos-Haro (MM), Laura del Campo Albendea (LDC): screening search results; screening retrieved papers against inclusion criteria; obtaining and screening data on unpublished studies; data management for the review; entering data into RevMan; analysis of data; Interpretation of data; providing a methodological perspective; providing general advice on the review.

DECLARATIONS OF INTEREST

AA: none known
ACP: none known
AGG: none known
AM: Astellas Pharma (speaker; payment made to institution)
AS: no relevant interests; works as a pulmonologist at Ramon y Cajal Hospital
BMFF: none known
DJ: Bristol-Meiers-Squibb, LEO Pharma Inc., Pfizer, ROVI, Sanofi (speaker); works as a health professional at Hospital Universitario Ramon y Cajal, Madrid, Spain; involved in Barrios 2017 (this work was supported by Grant PIE1600050 SEXCOMPLEX from Instituto de Salud Carlos III to DJ, Spanish Ministry of Economy and Competitiveness. Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM) is also an initiative of Instituto de Salud Carlos III; also supported in part by Fondo Europeo de Desarrollo Regional FEDER to DJ).
EGL: none known
ES: none known
EFM: no relevant interests; Universidad de Huelva (employment)
EJT: none known
JZ: none known
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  Support in the form of a salary

External sources

- SEXCOMPLEX, Spain

  This study is part of the SEXCOMPLEX project ('Influence of sex and sex hormones on human chronic disorders of complex etiology'), a two-year project (2017 to 2019) co-ordinated by Hospital Ramón y Cajal (Madrid, Spain). The SEXCOMPLEX project was supported by Instituto de Salud Carlos III (Plan Estatal de I + D + i 2013–2016) and co-financed by the European Development Regional Fund 'A way to achieve Europe' (ERDF) grant number PIE16/00050. These funding sources had no role in the design, execution, analysis, or interpretation of this review, nor in decisions regarding its publication, including whether to publish, the timing of submission, or the choice of journal for dissemination.
- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK

  The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

a. Changes from the protocol

Protocol	Review
Include studies regardless if the patients were treated for PE or not	We meant that we would include studies with adults treated for PE regardless of whether the treatment was reported.
Exclude studies where the participants did not have confirmed PE	We assumed objective testing if the PE was classified according to an internationally recognised system, such as the ICD coding. Thus, if the only information about the diagnosis was the ICD coding, we included the study.
Select a 'Core Outcomes Set' for this review by searching the COMET initiative database (https://www.comet-initiative.org)	We found one core outcome set, but it focused on trials in children. Therefore, it was ineligible for our review. Consequently, we selected the review outcomes based on the following criteria: 1) the outcome must be critical from a patient perspective; and 2) the outcome must support decision-making in the management of PE patients.
"For an experimental study to be eligible, it must have used either the control group alone or the entire study cohort adjusted for the intervention"	We would have used data from either the intervention group alone or the entire study cohort adjusted for the intervention (to reflect the presence of PE treatment).
Outcomes	We added two outcomes ("all-cause mortality at 30 days" and "PE-related mortality at 30 days") to reflect deaths occurring during this period during the hospital stay or after discharge.
EPPI-Reviewer software (Thomas 2022) for data extraction	We used Microsoft Excel (Mircosoft Excel 2016).
'Metareg' command in Stata for meta-analysis with the HKSJ method. Random effects model (REM) for all meta-analyses	The 'metan' command was used in Stata, as it also implements the graphics. We used the inverse variance (IV) fixed-effect model (FEM) for meta-analyses with two studies, as the random effects model (REM) frequently has low power and does not yield informative results in this situation. We used RevMan for meta-analyses of two studies.
Defined the clinical importance of the observed prognostic associations for relative effects (small: odds ratio < 1.2; moderate: between 1.2 and 2; large: > 2)	Following recent GRADE guidance (Zeng 2022), we used a minimally contextualised approach based on a predefined threshold in the risk difference.

Defined an absolute risk of 5% (50 per 1000) as the threshold for identifying a relevant association	Considering the importance of the outcome (mortality), we set a 0.5% threshold, as proposed in Zeng 2022.

Changes in the byline: Sanders van Doorn S and Carlos Quezada Loaiza were authors of the review protocol but were not part of the final review. The following review authors were not part of the protocol team: Elena Jimenez Tejero, Andrea Correa-Pérez, Andrea Gaetano Gil, Laura del Campo Albendea, Miriam Mateos-Haro, Raymond Stallings, Eduardo García Laredo, Aurora Solier, Elia Fernández-Martínez, Raquel Morillo Guerrero, Marcos de Miguel, Alba Antequera.

b. Methods not implemented

We could not implement the following methods but plan to use them in future review updates if enough studies are found.

Transformations of reported data and assumptions made

We will transform reported data to use data from as many studies as possible. Thus, we will restore the missing information and standardise the data to our desired format. We will consider the following sources to convert data: Westby 2018 ('Measures of association' section), Riley 2019 ('Methods to restore the missing information upon data extraction' section), and the *Cochrane Handbook for Systematic Reviews of Interventions* (sections 5.6 and 15.4.4.4 (Li 2022; Schünemann 2022). Moreover, we will perform additional conversions with the calculator available in Review Manager 2020. Before concluding that the necessary information to calculate a prognostic association is unavailable, we will consult the Cochrane Prognosis Methods Group. We will not transform absolute risk differences (ARDs) to odds ratios (ORs) when the control risk is not reported. We will not convert hazard ratios to ORs due to the many assumptions needed. If results from multivariable analyses in the primary studies are reported in another form, we will convert these to ORs at a particular time.

To compute the absolute risk difference from an OR, if we are not able to estimate the risk of the event in those without the prognostic factor from external evidence, we will use the Absolute Risk Calculator (https://hiru.mcmaster.ca/AbsoluteRiskCalculator/).

Adjusted prognostic effect estimates

If the same study presents different estimates for the same outcome, each of them adjusted for different factors, we will extract the estimate adjusted for the maximum number of our key covariates for meta-analysis. If there are several estimations, all having adjusted for our key covariates, we will consider the estimate adjusted for more of our key covariates. Concerning the dichotomisation of our key covariates, we will accept any cut-off used by the primary authors. We acknowledge that different cut-offs for the same covariate may occur amongst studies and that this situation may affect the prognostic estimate obtained in our review. Thus, we will perform a sensitivity analysis to assess the impact of our decision by excluding studies that have adjusted for Pulmonary Embolism Severity Index (PESI) (or PESI simplified) measured as a categorical variable.

Unit of analysis issues

For unit-of-analysis errors that cannot be re-analysed, we will meta-analyse the estimations but will assess their risk of bias in the domain 'Statistical analysis and reporting'.

Dealing with missing data

We will consider the follow-up for all the review outcomes to start with the PE diagnosis. However, if the follow-up is reported from other time points, such as the start of the treatment, we will use this data for the analyses. We acknowledge that different strategies in the included studies to handle missing participant data may introduce heterogeneity in the results. We will repeat the meta-analysis to assess the effect of excluding studies that did not adopt multiple imputation techniques to address missing values.

Assessment of statistical heterogeneity

We will attempt to explain heterogeneity by conducting predefined subgroup analyses (if the number of studies found is sufficient). See 'Subgroup analysis and investigation of heterogeneity'.

Assessment of reporting biases

We will assess publication bias for each meta-analysis (if the meta-analysis includes at least 10 studies) by doing the following.

- Visual inspection of the funnel plot: we will consider apparent asymmetry in the funnel plot, that is, a higher proportion of smaller studies in one direction, as strong evidence of potential small-study effects (Riley 2019).
- Use of test for asymmetry: we will test for asymmetry at the 10% significance level using the Peters' test (Peters 2006; Riley 2019; Sterne 2011).
- Interpretation of small-study effects: we will interpret the presence of small-study effects with caution as it may be due to chance, heterogeneity, publication bias or selective reporting. All of these situations are frequent in prognosis research (Kyzas 2007a; Kyzas

2007b; Riley 2019), and it is difficult to disentangle them (Riley 2019). We will judge small-study effects to be caused by heterogeneity rather than publication bias if the smaller studies used fewer adjustment factors for the analysis. This may explain why these small studies present larger prognostic effects.

Statistical model for meta-analysis

We will combine results in a meta-analysis independently of their risk of bias ratings and the factors considered for adjustment. We will assess the impact of this decision by sensitivity analysis. If there are enough studies, we will follow Riley 2019's guidance, which states that if restricting the analysis to the subset of studies at low risk of bias resolves previous issues of small-study effects, then it gives even more credence to presenting conclusions on the meta-analysis results based only on the studies with low risk of bias.

Subgroup analysis and investigation of heterogeneity

We plan to investigate heterogeneity by subgroup analysis of the following prespecified factors.

- Assessment of clinical heterogeneity
  - **Participants' mean age:** less than 45 years versus older than 45
  - **Setting:** study participants initially managed at the hospital versus participants managed in the outpatient setting
  - **Geographic region:** Europe and North America versus other regions
  - **Measurement of the prognostic factor (sex):** measured at the start of PE diagnosis versus measured at the start of PE treatment
  - **Reperfusion treatment for PE:** participants who received reperfusion treatment for PE (thrombolysis or surgical embolectomy) versus participants who did not
  - **Haemodynamic status:** stable versus unstable (as defined by the study authors)
- Assessment of methodological heterogeneity
  - **Study design:** experimental studies versus cohort studies versus case-control studies
  - **Study design:** experimental studies versus observational studies
  - **Risk of bias:** studies with high risk of bias (RoB) versus studies with low or moderate RoB

As having received PE treatment is a review inclusion criterion, we will not perform subgroup analysis based on being treated for PE versus not treated for PE.

Sensitivity analysis

We will perform the remaining planned sensitivity analyses by including or excluding studies in meta-analysis as below.

- Exclude studies with high RoB
- Include only studies with prospective outcomes assessments
- Include only observational studies
- Exclude the studies that measured the index prognostic factor (sex) at the start of PE treatment (instead of diagnosis)
- Exclude studies that used routinely collected hospital administrative databases
- Exclude studies that adjusted for PESI (or PESI simplified) measured as a categorical variable
- Exclude studies that provided an adjusted estimate but did not adjust for all our core covariates
- Exclude studies that did not adopt multiple imputation techniques for missing participant data

Conclusions and summary of findings

We will downgrade the certainty of the evidence in secondary analyses of RCTs by one level due to indirectness, as these studies present participants' restrictions relevant to our review questions (Foroutan 2020).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Bias; Prognosis; *Pulmonary Embolism [mortality] [therapy]; Sex Factors

MeSH check words

Adult; Aged; Female; Humans; Male; Middle Aged