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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

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Conclusion

BACKGROUND

Description of the condition

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) occurs when venous thrombi dislodge from their sites of formation and embolize to the pulmonary artery circulation system (Konstantinides 2014). About 50% of the patients with pelvic vein thrombosis or proximal leg DVT develop PE, which is often asymptomatic (Kearon 2012). About 90% of pulmonary emboli originate from the lower extremities, with most involving the proximal veins (Lee 2016). Acute PE is the most severe clinical presentation of VTE (Konstantinides 2014).

Diagnosis

Clinical recognition of PE is often inaccurate due to the signs and symptoms of PE being non-specific. Unfortunately, there is no test available that is sensitive and specific enough to confirm or exclude an acute symptomatic PE diagnosis. Therefore, in order to diagnose the disease it is necessary to combine clinical probability, D-dimer results, and imaging testing. In patients assessed for suspected PE, it has been shown that adherence to proven diagnostic algorithms improves patient prognosis (Kearon 2012; Konstantinides 2014; Roy 2006). The clinical probability of the patient having PE is the first thing to be assessed and with this information physicians can identify patients who require anticoagulant treatment whilst waiting on the results of the diagnostic tests. Clinical decision rules (CDR) have been proposed that combine items from the patient's clinical history, initial examination and sometimes from the chest x-rays or laboratory tests. The Wells and Geneva scores are the most extensively validated CDRs (Wells 2000).

Predisposing factors

PE is now recognised as a complex (multifactorial) disease. It involves both environmental exposures (e.g. clinical risk factors) as well as genetic and environmental interactions. When PE is associated with precipitating risk factors (such as surgery, cancer, trauma, immobilisation, pregnancy, or oral contraceptive use), it is classified as provoked or secondary (Kearon 2016a; Konstantinides 2014). When there are no precipitating factors, it is known as unprovoked (Kearon 2016a), spontaneous, or idiopathic. On the other hand, there are several conditions, only present in females, that are well-established risk factors for VTE. Relevant examples include pregnancy and the postpartum period (James 2006; Kujovich 2004; Marik 2008; Morris 2010), the use of oral contraceptives, which are the most common cause of thrombosis in young women (Peragallo Urrutia 2013; Stegeman 2013), and hormone replacement therapy (Cushman 2004).

Risk stratification

According to the 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 (SBP ≥ 90 mm Hg), 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.

In patients with acute symptomatic PE, initial treatment decisions should be driven by their risk of short-term mortality and other adverse outcomes. When patients have a high-risk for PE associated complications (i.e. haemodynamically unstable patients) they need to be admitted to an intensive care unit (ICU) and be given early recanalisation (i.e. thrombolysis, percutaneous or surgical embolectomy) in addition to standard anticoagulation (Konstantinides 2014). In normotensive patients, there is a need for further risk stratification in order to differentiate patients who have a low-risk of early PE complications from those with an intermediate-high risk of PE complications. Low-risk PE patients may not need to be admitted to hospital, and thus could take advantage of either full outpatient anticoagulant therapy or a shortened hospital stay. Conversely, intermediate- or high-risk PE patients have a higher risk of PE complications due to preserved systemic arterial pressure; therefore, these patients could benefit from an intensification of therapy (Barrios 2018). Several issues should be taken into consideration during risk stratification, including the risk of bleeding from anticoagulants or thrombotic therapy, the risk of early venous thromboembolism recurrence and the consequences of these risks.

Treatment

In patients with high-risk PE, the primary cause of death is acute right ventricle failure. Therefore, the first stage of treatment is providing haemodynamic and respiratory support. The next step of treatment is usually anticoagulation for at least three months, as this can prevent premature death (Kearon 2016b; Konstantinides 2014).

Epidemiology

PE is relatively common worldwide, and its incidence is increasing (Alotaibi 2016; Belohlavek 2013). PE represents the most common cause of vascular death after myocardial infarction and stroke, and is the leading preventable cause of death in hospitalised patients (Tapson 2008). No exact worldwide epidemiological data are available, and most PE cases are undiagnosed and thus untreated (Cohen 2007). In addition, many countries, especially those classed as developing countries, lack population-based estimates for thrombotic conditions (Wendelboe 2016). However, the incidence of PE is estimated to be approximately 60 to 70 per 100,000 of the general population in Europe (Belohlavek 2013). In the US, the frequency of PE increased from 1998 to 2006, with the rate of PE detection nearly doubling without any change in mortality (Murphy 2017). With better technology, clinicians are better equipped to detect previously missed pulmonary emboli, but these are not necessarily clinically relevant (Doherty 2017; Wiener 2013). The US Centers for Disease Control and Prevention (CDC) estimate between 60,000 to 100,000 deaths per annum from PE in the US (CDC 2015), which represents 0.4% of all deaths in the country per annum (Murphy 2017). The mortality data from Australia and the UK show a similar frequency to the US, representing 0.2% (Australian Bureau of Statistics 2015), and 0.4% (British Lung Foundation 2015; Office for National Statistics 2013) of all deaths, respectively.

Description of the prognostic factor

A prognostic factor is a characteristic in people with a given health condition (a start point) that is associated with a subsequent clinical outcome (an endpoint) (Hemingway 2013; Riley 2013). Therefore, prognostic factors distinguish groups of people with

a different average prognosis (Riley 2013). The importance of prognosis research is increasingly recognised, as chronic health conditions and diseases are increasingly common and costly.

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

In this review, we will assess the potential role of sex (i.e. being a male or a female) as a prognostic factor in patients with PE. This review will not evaluate the association between gender or sexual orientation and the outcomes of patients with PE.

Health outcomes

We will assess the association between sex (being a male or a female) and mortality in patients with PE by evaluating the outcomes of all-cause mortality and PE-related mortality. All-cause mortality is death from any cause following the diagnosis of PE. PE-related mortality is defined as death confirmed by autopsy, or those deaths following a clinically severe PE, in the absence of any alternative diagnosis (Muriel 2014).

Why it is important to do this review

PE is the most common cause of vascular death after myocardial infarction and stroke, and the leading preventable cause of death in hospitalised patients (Tapson 2008). Therefore, the effective management of PE is among the top priorities for improving survival rates in patients with thromboembolic disorders.

Prognostic factor research aims to identify factors associated with clinical outcomes in people with a particular disease or health condition (Hemingway 2013; Riley 2013). There can be different uses of the evidence on individual prognostic factors:

1. to define modifiable targets for interventions to improve outcomes;
2. to build blocks for prognostic models; and
3. to determine predictors of differential treatment response (Riley 2013).

Prognostic factors are relevant to patient management as they help to stratify patients by different risk groups, thus helping to reduce morbidity and mortality (Riley 2013). The identification of prognostic factors is a crucial step within the current drive towards personalised medicine (Riley 2013; Trusheim 2007).

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, there are still very few studies that have explored sex differences within VTE (Blanco-Molina 2014). There are inconsistent data in studies of patients with proven acute PE, in regard to the relationship between sex and adverse outcome rates. For example, in a study of 276,484 patients with acute PE, in-hospital mortality was significantly higher in females compared to males (Agarwal 2015). However, in another study, male patients were seen to have a higher risk of 30-day death compared to female patients (Aujesky 2005). Conversely, three other studies found no significant association between sex and prognosis (Jimenez 2010; Keller 2019; Panigada 2016).

Therefore, it is critical to determine if there are sex differences in the clinical course of patients treated for PE, as this may inform different approaches for its detection, monitoring and management between males and females. The determination of the prognostic value of sex can be particularly important to support decisions when the benefit-risk balance of an intervention is not clear. Some examples identified in recent clinical guidelines (Kearon 2016b; Konstantinides 2019) are as follows:

- the choice of the optimal anticoagulant drug(s) and regimen (Kearon 2016b), particularly in patients with renal insufficiency and creatinine clearance greater than 30 mL/min (Konstantinides 2019);
- the decision to administer reduced-dose thrombolysis and catheter-based reperfusion modalities in patients with intermediate- or high-risk PE (Konstantinides 2019);
- the criteria for selecting patients for early discharge (Konstantinides 2019).

In addition, the predictors of early PE-related death remain to be determined, and these predictors would be useful to identify possible candidates for reperfusion treatment among patients with intermediate-risk PE (Konstantinides 2019). To know the role of sex as a prognostic factor in patients with PE is also essential for professionals involved in drug discovery and development and for authorities responsible for the regulation and implementation of drug development programmes.

OBJECTIVES

To determine whether sex (i.e. being a male or a female) is an independent (i.e. autonomous) prognostic factor for predicting mortality in adults with acute symptomatic PE. See Table 1 for a formulation of the review question in population, index prognostic factor, comparator, outcome(s), timing, and setting (PICOTS) format.

METHODS

This protocol follows the methods proposed in other Cochrane prognosis reviews (Hayden 2014; Skoetz 2017; Westby 2018). Moreover, we followed the guidance provided in Riley 2019 and the general protocol template of the Cochrane Prognosis Methods Group (Cochrane Prognosis Methods Group 2019). Our protocol report adheres to the guideline for Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) Statement (Shamseer 2015). The review report will conform to the guidance of the PRISMA Statement (Liberati 2009), supplemented with the CHARMS-Prognostic factor checklist (Moons 2014). We will also follow the guidance for systematic reviews and meta-analyses of prognostic factor studies (Riley 2019).

Criteria for considering studies for this review

We have formulated the review question according to the PICOTS system. This format is based on the CHARMS checklist and informs

the objective and the eligibility criteria for the review (Debray 2017; Moons 2014; Riley 2019). See Table 1.

Types of studies

We will include any longitudinal study, randomised or non-randomised, investigating the prognostic significance of sex in adults with PE for predicting mortality. In practical terms, the following study designs will be eligible (Foroutan 2020): a) observational studies (e.g. cohort studies, case-control studies, or database linkage studies); and b) 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 control group alone or the entire study cohort adjusted for the intervention.

We will exclude the following study designs, but we will report them in the 'Characteristics of excluded studies' table if the remaining eligibility criteria were met:

- **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, but they will not be 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 high number of 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 will exclude these studies because our review aims to determine the prognostic role of just one factor.
- **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 patient 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:** for example, a randomised controlled trial (RCT) or other study reporting only treatment effect modification data

We will not exclude any study based on sample size, duration of follow-up, publication status, publication year or language. We will exclude studies that fulfil all our review eligibility criteria, but do not assess or report our outcomes of interest (see 'Selection of studies,' below).

Appendix 1 details the study design features (i.e. more than the reported study design labels) that we have considered to define study design eligibility.

Types of participants

We will include all adults, hospitalised or not, treated for acute symptomatic PE confirmed by objective testing, such as pulmonary angiography, ventilation/perfusion lung scan, or another validated measurement.

- **Adult:** person aged 16 years or older (in many settings, age 16 is when patients leave paediatric care and enter adult care)
- **PE:** defined as the dislodgement of venous thrombi from their site of formation and their embolization to the pulmonary artery circulation system (Konstantinides 2014)
- **Acute**: the follow-up should start no later than fifteen days after diagnosis
- **Symptomatic:** at least chest symptoms must be present, such as dyspnoea or chest pain
- **Objective testing confirmation:** we will consider the following as 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 will include studies regardless if the patients were treated for PE or not, providing the diagnosis for PE was confirmed.

We will exclude studies with at least one of the following characteristics.

- Studies conducted in animals, cadavers or *in vitro*
- Studies conducted in females or males only, as they do not allow determination of the role of sex
- Studies conducted with healthy volunteers
- Studies where all the participants were children or adolescents (younger than age 16). We will exclude these studies because PE presents clinical and prognostic peculiarities in these age groups, as compared with in adults (Navanandan 2019; Zaidi 2017)
- Studies where the participants did not have confirmed PE
- Studies including only a subset of the participants relevant to our review question will not be eligible but will be listed in the 'Characteristics of excluded studies' table if they meet the remaining review criteria, but we are unable to extract the data of interest.

Types of prognostic factors

Index prognostic factor

We will include studies that assess the role of sex as a prognostic factor. Sex, categorised as female or male, relates to a set of 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 will preferably include studies ascertaining sex by genotyping of a blood sample (Clayton 2016). However, we will accept any assessment of sex as provided by the study authors.

The concepts of sex and gender are distinct but interrelated (Doull 2010). However, this review will not assess the role of gender as a prognostic factor. 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 described and reported in published articles (Doull 2010; Lopez-Alcalde 2019; Runnels 2014; Welch 2017). If the reporting is unclear or incorrect, we will try to contact the authors for clarification. If no additional information is provided, we will generally assume that the study is considering sex, unless the authors explicitly state that they have evaluated the social aspect.

Other covariates

The focus of this review will be on the adjusted prognostic value of sex, that is, its prognostic effect after adjusting for other covariates. Adjustment for the following key covariates, most taken from the scale of the Simplified PESI (sPESI) (Jimenez 2010) for mortality in patients with PE, will be of interest: age, history of cancer, current cancer, history of chronic cardiopulmonary disease, current chronic cardiopulmonary disease, heart rate, systolic blood pressure, and O_2 saturation. We will consider this list to assess the adjustment domain in the 'Risk of bias' tool (see 'Assessment of risk of bias in included studies').

Please note that we anticipate that we may modify the draft list, if and when we find new evidence that justifies any changes. Appendix 2 describes the process that we followed in selecting the covariates for adjustment.

Type of outcomes to be predicted, and timing

We will consider all-cause mortality and PE-related mortality measured at different time points, all of them defined as primary outcomes. We provide the complete definition for each outcome according to the criteria adapted from Saldanha 2014.

Outcome	Definition	Specific measurement[a]	Specific metric[b]	Type of data[c]	Method of aggregation[d]	Timing		
						Time of prognostication[e]	Over what period the outcomes are predicted by these factors[f]	Minimum follow-up of the study participants to consider the outcome in the review
1. All-cause hospital mortality	Death from any cause occurring at the 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: to be measured preferably at the start of PE diagnosis[g]	The longest follow-up provided by the study authors	None
2. All-cause hospital mortality at 30 days	Death from any cause occurring at the 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 the participants must be followed for at least 30 days after PE diagnosis[i]
3. All-cause mortality at 90 days	Death from any cause occurring at the 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 the participants must be followed for at least 90 days after PE diagnosis[i]
4. Early hospital mortality (during the first 48 hours)	Death from any cause occurring at the 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 the participants must be followed for at least 48 hours after PE diagnosis[i]
5. All-cause mortality at one year	Death from any cause occurring at the hospital or after discharge during the first year following the start of PE diagnosis	Any, as reported by the study authors	Value at a time-point	•Dichotomous	Proportion		One year from PE diagnosis	All the participants must be followed for at least one year after PE diagnosis[i]

				•Event of interest: death			
6. PE-related hospital mortality	Death due to PE occurring at the hospital	Preferably, death confirmed by autopsy or death following a clinically severe PE, either initially or shortly after an objectively confirmed recurrent event, in the absence of any alternative diagnosis (Muriel 2014)[h]	Value at a time-point	•Dichotomous •Event of interest: death	Proportion	The longest follow-up provided by the study authors	None
7. PE related hospital mortality at 30 days	Death due to PE occurring at the 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 the participants must be followed for at least 30 days after PE diagnosis[i]
8. Early PE-related hospital mortality (during the first 48 hours)	Death due to PE occurring at the 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 the participants must be followed for at least 48 hours after PE diagnosis[i]

Footnotes:

[a]The specific measurement or technique/instrument used to make the measurement

[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)

[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)

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

[f]The time-point that will be used for analysis

[g]We anticipate that the studies may use different starting points to define the follow-up. For example, from the recruitment, from the diagnosis of PE, from the allocation to the study arm, from the admission to the hospital, from the admission to the ICU or from the start of the treatment. We will preferably use the start of the PE diagnosis, but if this information is not available, we will consider the time as provided by the study authors. We will assess the impact of this decision by sensitivity analysis.

[h]However, we will admit any definition as provided by the authors

[i]Except for those participants that died or were discharged within this period

jExcept for those participants that died within this period

PE: pulmonary embolism

We attempted to select a 'Core Outcomes Set' for this review by searching the COMET initiative database (www.comet-initiative.org). We found one defined and published set, but this focused on trials in children and therefore was not addressing our review question. As a consequence, we have selected the outcomes listed above based on the following criteria:

1. the outcome must be critical from a patient perspective;
2. the outcome must support decision-making in the management of patients with PE.

We chose 'all-cause mortality' as a primary outcome because it has the greatest clinical relevance and is the most important outcome for individuals with PE. Furthermore, all-cause mortality is an objective endpoint and is not susceptible to be biased by the outcome assessor. We have also defined different follow-up durations because we expect delayed effects of PE.

We defined all mortality outcomes as binary variables (dead or alive), instead of using survival methods. We took this decision as the quality of life of patients in the hospital can be very poor, so patients who die in the hospital do not benefit if the duration of their survival is prolonged (Schoenfeld 2005); thus, the critical outcome is mortality and not patient survival. Secondly, some PE patients may be treated in the ICU: survival analysis should be avoided in the ICU context (Schoenfeld 2005) because Kaplan-Meier survival analysis assumes that censoring is non-informative; that is, it considers that the hazard of death remains unchanged when a censoring event occurs (Wolkewitz 2014). However, this assumption is incorrect in the ICU, as discharged patients are usually in a better health condition than patients who stay. The assumption that censoring is non-informative therefore generates artificially reduced survival plots (Schoenfeld 2005). There are statistical solutions to treat discharge as a competing event for death in the ICU (Wolkewitz 2014), but we believe that from a clinical point of view, the relevant outcome is mortality and not survival.

We will not consider all-cause mortality in the ICU or PE mortality in the ICU because they would only be useful if the majority of patients were still in the ICU at the time of analysis (Finkelstein 1994; Schoenfeld 2005). Thus, we will consider all-cause mortality to include all deaths at the hospital, inclusive of ICU deaths.

Setting

We will include studies involving patients with PE managed in any setting. Summaries of prognosis are not meaningful unless associated with a particular strategy for treatment so that prognostic studies can aid decisions about treatment. This implies that ideally, prognostic factors should be evaluated either 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 to be 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 will still provide relevant information. Moreover, we will try to explore the role of the region where the studies were carried out by subgroup analysis.

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist aims to identify all relevant studies regardless of language or publication status (published, unpublished, in press, or in progress).

The Information Specialist will search the following databases for relevant studies:

- the Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web);
- the Cochrane Central Register of Controlled Trials (CENTRAL) 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 onwards);
- Embase Ovid (from 1974 onwards);
- CINAHL Ebsco (from 1982 onwards).

The Information Specialist has devised a draft search strategy for MEDLINE which is displayed in Appendix 3.This will be used as the basis for search strategies for the other databases listed.

The Information Specialist will search the following trials registries:

- The World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch);
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We will screen the reference lists of retrieved included trials and of systematic reviews on our topic.

We will contact experts on the topic (including authors of included studies, authors of systematic reviews) to identify any additional, unreported or ongoing studies.

We will handsearch documents of the Organization for the Study of Sex Differences (OSSD).

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

We will search for conference abstracts of major symposia from 2010.

1. Meetings of the OSSD: 5th edition (2010) to 14th edition (2019)
2. European Respiratory Society (ERS): 2010 to 2019
3. International Society of Thrombosis and Haemostasis (ISTH): 2010 to 2019
4. American Thoracic Society (ATS): 2010 to 2019
5. American Society of Hematology (ASH): 2010 to 2019
6. CHEST congress (CHEST): 2010 to 2019

7. Acute Cardiovascular Care (ACC): 2010 to 2019
8. European Society of Cardiology (ESC): 2010 to 2019

Data collection and analysis

Selection of studies

Two of six review authors (BF, CAQL, DJ, ES, JLA, RP), will independently check all titles and abstracts for inclusion. We will classify the titles and abstracts into four groups: 'obviously irrelevant', 'potentially eligible', 'potentially excluded' or 'unclear'. We will obtain the full-text version of those records classified as 'potentially eligible', 'potentially excluded' or 'unclear'. Two of six review authors (BF, CAQL, DJ, ES, JLA, RP) will independently assess the eligibility of each selected full-text article. We will resolve disagreements by consensus. In the case of disagreement, a third review author (one of AM, DJ, JLA or JZ) will serve as a neutral arbiter. There will be no restriction on language or date of publication of the papers.

If necessary, we will ask the study authors for clarification. If we cannot clarify the issues and we cannot exclude the study for any reason we will put these studies into 'awaiting classification'.

We will use the EPPI-Reviewer web-based software (Park 2018) to implement the selection process. We will complete a PRISMA flow chart to describe the selection process (Liberati 2009). We will also create tables describing the characteristics of excluded studies. These tables will detail the main reason for exclusion for studies that a reader might otherwise expect to see included in the review.

If there are multiple reports of the same study or data sets that overlap, we will collate them so that each study (not each report), is the unit of interest in the review. We will extract data from the data set with the largest sample size, most detailed results and the most appropriate follow-up.

We will exclude studies that fulfil all our review eligibility criteria, except the outcomes, i.e. studies in which no outcome of interest for the review was assessed or reported. For example, we will exclude a phase-2 prognostic study that aimed to determine whether sex is an independent prognostic factor for predicting the length of stay of patients with PE. We acknowledge that the exclusion of studies based on the reporting of the outcomes will hamper our evaluation of the risk of bias derived from selective outcome reporting. However, we anticipate that including all prognostic studies independently of the outcome reported will generate a workload that unaffordable to the team resources. On the other hand, we will not exclude studies based on their timing. For studies reporting several follow-ups for the same outcome, we will choose the most appropriate one for analysis.

Data extraction and management

Two of five review authors (BF, CAQ, DJ, ES and JLA) will independently extract data of each included study. We will use a consensus method to agree on the final extraction. A third review author (JZ or JLA) will intervene if there are disagreements. A third review author (AM) will check the accuracy of the numeric data in the review. We will try to obtain crucial missing information or clarification from study authors or organisations. If necessary, we will translate the included reports. We will examine any relevant retraction statements and errata for relevant information regarding each included study.

We will use the CHARMS-PF guidance to extract data (Riley 2019). This form adapts the original CHARMS checklist (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies) for prognostic factor studies (Moons 2014), based on the experience of conducting systematic reviews of prognostic factor studies (Riley 2019). We will extract key information from each primary study.

- 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 (for example, self-reported or by genotyping of blood sample)
- Definition of start points
- Outcomes reported
- For each review outcome, we will extract 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
  - Adjustment done for other prognostic factors (if any) to estimate the prognostic association
  - The 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
  - We plan to extract the unadjusted and the adjusted measure of association (if available)
- Methods used to handle missing data
- Attrition:
  - Loss to follow-up
  - Reasons
- Information to assess applicability
- Information to assess risk of bias
- Data needed to perform the meta-analyses, such as the estimates, and their corresponding standard errors or confidence intervals.

We will use the online EPPI-Reviewer software (Park 2018), to build the data extraction templates and extract the data. We will pilot the data extraction form with five studies for usability. We will summarise the information retrieved in a table detailing the characteristics of each included study.

Transformations of reported data and assumptions made

The two key elements that must be extracted from each primary study to estimate the effect of a prognostic factor with a meta-analysis are the prognostic factor effect estimate and its precision (that is, the SE or the 95% CI) (Riley 2019). If needed, we plan to undertake transformations of reported data to use data from as many studies as possible. Thus, we will attempt to restore the missing information and to standardise the data to our desired format.

To convert the data, we plan to follow the guidance described in Westby 2018 ('Measures of association' section), Riley 2019 ('Methods to restore the missing information upon data extraction' section), and the *Cochrane Handbook* Section 7.7 (Higgins 2011) and Section 12.5.4 (Schünemann 2011). If needed, we will perform the conversions with the calculator available in Review Manager 5.3 (Review Manager 2014). Before concluding that the necessary information to calculate a prognostic association is not available, we will consult Cochrane Prognosis Methods.

We will present the associations consistently, that is, associations above one will indicate a worse prognosis for women (higher mortality). If necessary, we will recalculate the associations to be in the same direction.

As stated below in 'Type of measure of association', we will attempt to consider the OR and its 95% CI as the common measure of prognostic association in all the studies. We will also try to convert the combined OR to an absolute risk reduction (ARR) to facilitate its interpretation. To compute the ARR from an OR, we will use the Absolute Risk Calculator provided by the Health Information Research Unit at McMaster University (hiru.mcmaster.ca/AbsoluteRiskCalculator). We will also obtain the lower and upper limits of the CI 95% of the ARR by applying the same formula to the lower and upper confidence limits of the adjusted OR.

Assessment of risk of bias in included studies

Tool to assess the risk of bias

We will use the QUIPS (Quality In Prognosis Studies) tool to assess the risk of bias (RoB) (Hayden 2013; Riley 2019). The tool has six domains (with signalling questions related to each domain that can inform judgments of RoB in prognostic research):

1. Study participation
2. Study attrition
3. Prognostic factor measurement
4. Outcome measurement
5. Adjustment for other prognostic factors
6. Statistical analysis and reporting

For each study, we will label the six domains for each prognostic factor-outcome combination. Therefore, we will assess the RoB per outcome. We will make a judgement for each domain choosing one of the following options (Riley 2019):

- Low risk: the criterion is adequately fulfilled in the study
- High risk: the criterion is not adequately fulfilled in the study
- Moderate risk: there is not sufficient information provided to be able to make a clear judgement on the RoB.

We will detail and justify judgements on RoB in a 'Risk of bias table' for each included study. We will also generate RoB graphs and figures.

Overall assessment of the risk of bias and incorporation into analyses

All the tool domains will be 'key domains' for RoB. Thus, we will summarise the RoB for each prognostic factor-outcome combination in two different manners, 'within each study' and 'across studies' (Higgins 2011).

	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 is 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 will describe the RoB among the included studies in the results section. Also, we will consider the RoB across studies for each prognostic effect estimation, as part of the determination of the quality of the evidence with the GRADE system (Guyatt 2011).

We will meta-analyse studies independently of their RoB, but we will explore the effect of this decision by carrying out a sensitivity analysis.

Procedure to assess the risk of bias

Two of five review authors (AM, BF, DJ, ES, JLA) will independently appraise all the domains of the QUIPS tool for each included study. We will agree on the final judgements for each domain via consensus. A second review author (JLA or JZ) will intervene if there are disagreements. A third review author (AM) will check the final decisions. If the study report does not provide information for a domain, or this information is not clear, we will follow a three-stage process. First, we will 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, if we cannot solve the doubt, we will attempt to contact the authors for clarification. Third, if we do not clarify the issue, we will make judgments based on the available information and the consensus between the review authors. We will not be blinded to study authors, institution or journal of publication.

As suggested in Riley 2019, we will define in advance criteria to assess the signalling items and domains for our specific review question, as this will probably facilitate reproducibility in our judgements. In particular, we will use our data extraction template in EPPI-reviewer (Park 2018) to define the following key aspects, many of them already pre-defined in this protocol:

1. Study participation
2. Attrition
3. Definitions of sufficiently valid and reliable measurement of the index prognostic factors (see 'Types of prognostic factors')
4. Definitions of sufficiently valid and reliable measurement of the outcomes (see 'Types of outcomes')
5. The core set of other (adjustment) prognostic factors that are deemed necessary for the primary studies to adjust for (see 'Comparator prognostic factors' and Appendix 3).

Measures of association to be extracted

Type of measure of association

We will attempt to consider the OR and its 95% CI as the measure of prognostic association in all the studies. We have chosen this measure because we anticipate that the OR will be the most common measure used in the primary 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). If results from multivariable analyses in the primary studies are reported in another form, we will attempt to convert these to ORs at a particular time point (See 'Data extraction and management' above). If we find a study reporting a hazard ratio (HR), we will not attempt to convert the HR to OR and we will perform meta-analysis based on HRs.

Adjusted prognostic effect estimates

We will extract the adjusted measure of association for each study and 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). We agree that age, history of cancer, history of chronic cardiopulmonary disease, heart rate, systolic blood pressure, and O_2 saturation will be the core set of adjustment factors for each review outcome.

If a study provides adjusted estimates but not adjusted for our minimal set of adjustment factors, we will meta-analyse the study, but we will 'penalise' the estimate as part of the RoB assessment (we will assess the impact of this decision by sensitivity analysis). If less than four of the key factors are adjusted for in the study, it will be assessed as high risk of bias in the adjustment domain of the risk of bias tool. However, if four or more of the key factors are adjusted for, the study will be defined as low risk of bias for this domain. If the study only adjusted for PESI/sPESI but did not detail for which individual factors they had adjusted, we will mark the RoB domain as moderate.

If the same study presents different estimates for the same outcome, each of them adjusted for different factors, we will extract for meta-analysis the estimate that has adjusted for the maximum number of our key covariates. If there are several estimations, all of them having adjusted for our key covariates, we will consider the estimate adjusted for more of our key covariates in total. We assume that this will minimise the risk of confounding bias in the estimation.

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 will occur among studies and that this situation may affect the prognostic estimate obtained in our review. Thus, we will perform sensitivity analysis to assess the impact of our decision by excluding studies that have adjusted for PESI (or PESI simplified) measured as a categorical variable.

Direction of the associations

We will present the associations consistently, that is, associations above one will indicate a worse prognosis for women (higher mortality). See 'Data extraction and management' for how we will recalculate associations to be in the same direction.

Unit of analysis issues

The prognostic factor (sex) and outcome (mortality) will both be considered at the patient level. Thus, we do not anticipate that there will be unit of analysis errors (Deeks 2011). However, in the case that we find any unit of analysis error which cannot be handled, we will meta-analyse the estimation, but take into account the associated RoB as part of the domain 'Statistical analysis and reporting' of the RoB assessment.

Dealing with missing data

We plan to include all the studies that investigated the role of sex as a prognostic factor in patients with PE regardless of the presence of missing data. We plan to contact study authors to request missing data. For all the review outcomes we will consider the follow-up to start after PE diagnosis. However, if the study reports only the follow-up from other time points, such as the start of the treatment or the start of the symptoms, we will use this data for the analyses.

We acknowledge that the presence of different strategies in the included studies to handle missing participant data may introduce heterogeneity in the results. We plan to repeat the meta-analysis to assess the effect of excluding studies that did not adopt multiple imputation techniques to deal with missing values.

Assessment of heterogeneity

We expect that heterogeneity between the included studies will be common (Riley 2013). We plan to synthesise all the associations found about the prognostic effect of sex with mortality outcomes in patients with PE. We do not expect to meta-analyse the prognostic within relevant subgroups. However, we will assess the presence of heterogeneity following a two-step process.

- Assessment of clinical and methodological heterogeneity

We plan to meta-analyse all the studies regardless of their clinical characteristics and their study design (as we plan to evaluate a potential association and not causation). However, we will attempt to use subgroup analyses to explore possible causes of heterogeneity that are clinical or methodological (see 'Subgroup analysis and investigation of heterogeneity').

- Assessment of statistical heterogeneity of the results

We will assess the statistical heterogeneity across the meta-analysed results considering the following factors:

- Identification of heterogeneity
  * Visual inspection of the prognostic effect estimates: we will display graphically the results of clinically and methodologically comparable studies with forest plots, and we will assess the possibility of statistical heterogeneity visually.
  * The Chi^2 P value: we will use the chi-squared test for identifying heterogeneity (Chi^2 P value < 0.10 will be significant) (Deeks 2011).
- Quantification of heterogeneity
  * Use of the I^2 statistic: the I^2 statistic describes the percentage of the total variation across studies that is due to heterogeneity rather than sampling error (chance) (Higgins 2003). We will define 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 (Chapter 9. *Cochrane Handbook*) (Section 9.5.2; Deeks 2011).
  * Use of the Tau^2 and the 95% prediction interval: we will also measure the heterogeneity using the estimate of between-study variance (Tau^2) in a random-effects model, as reliance on the I^2 statistic in assessing heterogeneity may be misleading (Rucker 2008). We will also report an approximate 95% prediction interval indicating the potential true prognostic effect of a factor in a new population (Riley 2011; Riley 2019).

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

Assessment of reporting biases

We plan to examine the presence of 'small-study effects', that is, the presence of a systematic difference in prognostic effect estimates for small studies and large studies (Riley 2019; Sterne 2011). We will assess publication bias for each meta-analysis (if the meta-analysis includes at least ten studies) by:

- Visual inspection of the funnel plot: we will interpret as a strong potential for small-study effects the apparent asymmetry of the funnel plot with a higher proportion of smaller studies in one particular direction (Riley 2019).
- Use of test for asymmetry; we will also test for asymmetry at the 10% level using the Peters' test for ORs (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 chance, heterogeneity, publication bias and selective reporting. All these situations are frequent in prognosis research (Kyzas 2007a; Kyzas 2007b; Riley 2019) and it is difficult to disentangle them (Riley 2019). We will consider that small-study effects are caused by heterogeneity rather than by publication bias if the smaller studies used fewer adjustment factors for the analysis. This may explain why these small studies presented larger prognostic effects.

Data synthesis

Data synthesis and meta-analysis approaches

We plan to combine the results from individual studies in a meta-analysis to provide a pooled prognostic effect estimate only if the following criteria are met:

- there are enough studies (at least two studies);
- the studies are sufficiently homogeneous:
  * the studies are clinically similar in terms of population and sex measurement;
  * the studies are methodologically similar: we will consider that all phase-2 prognostic factor studies are methodologically comparable studies to determine a prognostic association (independently of their design). However, we plan to explore if the study design explains heterogeneity (see subgroup analysis);
  * the outcomes are measured at similar follow-up points;
  * the outcomes are measured with similar measurement tools;
  * the studies have the same type of prognostic effect estimate measure, that is, an OR and 95% CI (or, at least, this information can be obtained);
  * the prognostic effect estimate has been adjusted for at least one factor (independently of the factors considered for adjustment). If a study presents the unadjusted measure only (raw data), we will not include this data for analysis.

Statistical model for meta-analysis

We will not assume a common (fixed) prognostic effect of sex on mortality. We anticipate that the prognostic effect estimates will vary among studies due to several reasons, in particular, due to the presence of different study populations, designs, prognostic effect measures (OR and RR), unavailability of SE, different time points and measurement of the outcomes, various sets of adjustment factors and due to missing data (Riley 2019). Thus, we will assume that there is not a single underlying prognostic effect to estimate and therefore the heterogeneity among the study effects cannot be explained by chance alone and follow a distribution across studies (Deeks 2011). However, we still consider that the underlying clinical questions will be similar enough and pooling will be meaningful if the extra uncertainty due to that heterogeneity is adequately represented (Cornell 2014). Therefore, we will apply

a random-effects model, which is an approach for meta-analysis that incorporates study-to-study variability beyond what would be expected by chance (Cornell 2014), and that allows for unexplained heterogeneity across studies (Riley 2019).

The DerSimonian and Laird (DL) method is the most commonly used random-effects model, and is available in Review Manager 5 statistical software (Review Manager 2014). However, this method has long been challenged (Veroniki 2019) because it produces a 95% CI that is too narrow (and P values that are typically too small) under two circumstances that this review will probably meet: a small number of studies and the presence of substantive differences among study estimates (Cornell 2014; Riley 2019). Therefore, we plan to use the Hartung-Knapp-Sidik-Jonkman (HKSJ) method for random effects meta-analysis, as it has shown to consistently result in more adequate error rates than the DL method, especially when the number of studies is small (IntHout 2014). However, we will take into consideration that even with the HKSJ method, extra caution is needed when there are less than six studies of very unequal sizes (IntHout 2014). We plan to use the Cochrane Review Manager 5 software (Review Manager 2014) for organising the text of the review. We will use the 'metareg' command in Stata to perform the meta-analysis with the HKSJ method (Harbord 2008).

We plan to combine results in a meta-analysis independently of their RoB and the factors considered for adjustment. However, we will assess the impact of this decision by sensitivity analysis. We also plan to evaluate the influence of the statistical model used to pool data on the prognostic effect estimate (see 'Sensitivity analysis').

If we find relevant unexplained statistical heterogeneity, we will still meta-analyse the data, but we will downgrade the certainty of the prognostic effect estimate as part of the GRADE assessment (see below). If we detect that the meta-analysis is inappropriate for other reasons, we will not combine results. However, we will undertake a narrative analysis of studies, providing a descriptive presentation of results with supporting tables.

If there are enough studies, we will follow the guidance in Riley 2019, which states that if restricting the analysis to the subset of studies at low RoB resolves previous issues of small-study effects, then it gives even more credence to focus conclusions on the meta-analysis results based only on the studies with low risk of bias.

Presentation of results

For the meta-analysis of each prognostic effect estimate we plan to provide the pooled estimate based on the random-effects approach (the average prognostic effect of sex), its Hartung-Knapp 95% CI, the I^2, the estimate of Tau^2 (between-study variance) and the 95% prediction interval for the prognostic effect in a single population, as done in Westby 2018 and suggested in Riley 2011 and Riley 2019.

An OR larger than one will suggest that female sex is associated with higher odds of mortality. For relative effects, we will define the clinical importance of the observed prognostic associations as follows: small: OR < 1.2; moderate: OR between 1.2 and 2; large: OR > 2. For absolute risk differences, we will consider an absolute risk of 5% (50 per 1000) as the threshold for identifying an important prognostic factor.

The meaning of OR is difficult to understand (Boissel 1999; Deeks 2011; Sackett 1996; Sinclair 1994). Moreover, ORs tend to be interpreted as RRs by clinicians (Deeks 2000). This can be misleading, as the OR is similar to the RR for outcomes with a low incidence (< 10%), but the OR exaggerates the effect when the incidence of the outcome increases (Zhang 1998). This may be the case in our review, because all-cause mortality in patients who are treated for PE is 30% in high-income countries (Klok 2010; Ng 2011), while the PE-related mortality in patients treated for PE is estimated between 2% and 10% (Belohlavek 2013; den Exter 2013; Konstantinides 2016). To facilitate interpretation of the results, we will undertake each meta-analysis based on ORs, and express the meta-analysis as an OR. However, the 'Summary of findings' table(s) will also present illustrative comparative risks and the absolute risk reductions (ARR) for the effect of the prognostic factor. To calculate the ARRs we will consider a range of different prevalences of the prognostic factor (being a female) and different risks of the outcome in the entire cohort. See 'Transformations of reported data and assumptions made' for details on the formula we will use to convert the data.

Subgroup analysis and investigation of heterogeneity

We plan to investigate if the following prespecified factors can explain heterogeneity If there are at least two studies per subgroup:

- Assessment of clinical heterogeneity
  - **Mean participants' age:** less than 45 years versus older than 45
  - **Setting:** patients managed at the hospital versus patients managed at the outpatient setting
  - **Measurement of the prognostic factor (sex):** measured at the start of PE diagnosis versus measured at the start of PE treatment
  - **Treated for PE:** participants treated for PE versus participants not treated for PE. It is estimated that in Europe around 30% of PE-related deaths occur before receiving any treatment for PE (Belohlavek 2013). Moreover, these numbers can be even higher in low resource settings (Wendelboe 2016)
  - **Reperfusion treatment for PE:** patients who received reperfusion treatment for PE (thrombolysis or surgical embolectomy) versus patients who did not
  - **Haemodynamic status:** stable versus unstable (as defined by the study authors)
  - **Geographic region:** Europe and North America versus other regions
- 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 RoB versus studies with low or moderate RoB

Sensitivity analysis

We plan to undertake the following sensitivity analysis if there are sufficient studies.

- We will repeat the meta-analysis to assess the effect of including only studies with prospective assessment of outcomes.

- We will repeat the meta-analysis to assess the effect of including only observational studies.
- We will repeat the meta-analysis to assess the effect of excluding the studies that the Index prognostic factor (sex) was measured at the start of PE treatment (instead of diagnosis).
- We will repeat the meta-analysis to assess the effect of excluding studies that have used routinely collected hospital administrative databases.
- We will repeat the meta-analysis to assess the effect of excluding studies that have adjusted for PESI (or PESI simplified) measured as a categorical variable.
- We will repeat the meta-analysis to assess the effect of excluding studies with high RoB.
- We will repeat the meta-analysis to assess the effect of excluding studies that have provided an adjusted estimate but that did not adjust for all our core set of covariates.
- We will repeat the meta-analysis to assess the effect of excluding studies that did not adopt multiple imputation techniques to deal with missing participant data.
- We will repeat the meta-analysis to assess the effect of using a fixed-effect model.
- We will repeat the meta-analysis based on the DL method.

Conclusions and summary of findings

We will assess 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 will use the adapted GRADE approach for questions on prognostic factors (Foroutan 2020; Huguet 2013; Iorio 2015; Westby 2018). GRADE initially considers evidence from phase 2 studies as high certainty. However, this initial certainty of evidence can be modified, based on the following criteria:

- Criteria for downgrading confidence in the prognostic effect estimate: RoB, inconsistency, imprecision, indirectness and publication bias
- Criteria for upgrading confidence in the prognostic effect estimate: large effect

We will consider that the best evidence regarding a prognostic factor normally comes from observational studies (cohort studies, registries, or database linkage studies). Thus, we will provide an initial high-certainty rating to the body of the evidence based on these studies (Foroutan 2020; Iorio 2015). On the other hand, the certainty of the evidence for secondary analyses of RCTs will be probably lower due to the presence of restrictions of patients relevant for our review questions (Foroutan 2020). We will assess these restrictions as part of the assessment of indirectness with GRADE.

We will not consider the phase of investigation of studies in our assessment of the strength of the evidence available, as only phase 2 studies will be eligible.

We will use GRADEproGDT software (GRADEpro-GDT 2015) to create 'Summary of findings' tables with the main results of the review, including the certainty of the body of evidence related to each outcome. All the review outcomes are critical for decision making, so they will be included in the table. The 'Summary of findings' table will contain all decisions to down- or upgrade the certainty of the evidence with footnotes, and provide explanations to help the reader's understanding of the review where necessary. Two review authors (JLA, ES) will assess the certainty of the evidence found for each outcomes. Another review author (AM) will check the assessments. We have included a template 'Summary of findings' table in Table 2. We will create one table for each of the main comparisons of the review (if there are more than one).

RESULTS

DISCUSSION

AUTHORS' CONCLUSIONS

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ADDITIONAL TABLES

Table 1. Review question in PICOTS format

Population	Adults, hospitalised or not, treated for acute symptomatic PE confirmed by objective testing
Index prognostic factor	Sex (being a female)
Comparator	Age, history of cancer, current cancer, history of chronic cardiopulmonary disease, current chronic cardiopulmonary disease, heart rate, systolic blood pressure, and O_2 saturation

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

Outcome 1	All-cause mortality
Timing	During the hospital stay
	At 30 days
	At 90 days
	Early hospital mortality (during the first 48 h)
	At one year
Outcome 2	PE-related mortality
Timing	During the hospital stay
	At 30 days
	Early PE related hospital mortality (during the first 48 hours)
Setting	Patients with PE managed in any setting.

PE: pulmonary embolism

Table 2. Draft 'Summary of findings' table

Does being a female compared with being a male help predict mortality in adults with acute symptomatic PE?

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

Settings: any

Index prognostic factor: being a female

Comparator: age, history of cancer, current cancer, history of chronic cardiopulmonary disease, current chronic cardiopulmonary disease, heart rate, systolic blood pressure, and O_2 saturation

Prognostic factor	Outcome	Study results and measurements	Absolute effect estimates* (95% CI)		Certainty in the effect estimates (Quality of the evidence)	Plain text summary
			Assumed risk in men	Corresponding risk in women		
Sex (female versus male)	**All-cause hospital mortality** (follow up: the longest follow-up provided by the study authors)	**OR [value]** (95% CI [value] to [value]) Based on data from XXXX patients in XX studies	**X per 1000**	**X per 1000** Difference: XX more/less per 1000 (CI 95% X more/less - X more/less)	**Very / Low / Moderate / High** Due to	
Sex (female versus male)	**All-cause hospital mortality** (at 30 days)	**OR [value]** (95% CI [value] to [value]) Based on data from XXXX patients in XX studies	**X per 1000**	**X per 1000** Difference: XX more/less per 1000 (CI 95% X more/less - X more/less)	**Very / Low / Moderate / High** Due to	

Table 2. Draft 'Summary of findings' table *(Continued)*

Sex (female versus male)	**All-cause mortality** (at 90 days)	**OR [value]** (95% CI [value] to [value]) Based on data from XXXX patients in XX studies	**X per 1000** — Difference: XX more/less per 1000 (CI 95% X more/less - X more/less)	**X per 1000**	**Very / Low / Moderate / High** Due to ....
Sex (female versus male)	**Early hospital mortality** (during the first 48 hours)	**OR [value]** (95% CI [value] to [value]) Based on data from XXXX patients in XX studies	**X per 1000** — Difference: XX more/less per 1000 (CI 95% X more/less - X more/less)	**X per 1000**	**Very / Low / Moderate / High** Due to ....
Sex (female versus male)	**All-cause mortality** (at one year)	**OR [value]** (95% CI [value] to [value]) Based on data from XXXX patients in XX studies	**X per 1000** — Difference: XX more/less per 1000 (CI 95% X more/less - X more/less)	**X per 1000**	**Very / Low / Moderate / High** Due to ....
Sex (female versus male)	**PE-related hospital mortality** (follow up: the longest follow-up provided by the study authors)	**OR [value]** (95% CI [value] to [value]) Based on data from XXXX patients in XX studies	**X per 1000** — Difference: XX more/less per 1000 (CI 95% X more/less - X more/less)	**X per 1000**	**Very / Low / Moderate / High** Due to ....
Sex (female versus male)	**PE-related hospital mortality** (at 30 days)	**OR [value]** (95% CI [value] to [value]) Based on data from XXXX patients in XX studies	**X per 1000** — Difference: XX more/less per 1000 (CI 95% X more/less - X more/less)	**X per 1000**	**Very / Low / Moderate / High** Due to ....
Sex (female versus male)	**Early PE-related hospital mortality** (during the first 48 hours)	**OR [value]** (95% CI [value] to [value]) Based on data from XXXX patients in XX studies	**X per 1000** — Difference: XX more/less per 1000 (CI 95% X more/less - X more/less)	**X per 1000**	**Very / Low / Moderate / High** Due to ....

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations:
CI: confidence interval; **OR:** odds ratio; **PE**: pulmonary embolism
GRADE Working Group grades of evidence:
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

APPENDICES

Appendix 1. Study design features

There is no standardised nomenclature for non-randomised studies (NRS), and 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). We consider here explicit study design features (not only the study design labels) to define the design eligibility. Moreover, we will take these features into account when assessing studies for selection. The Cochrane Non-randomised Studies Methods Group (NRSMG) (Reeves 2011), proposes to define items 1 to 5. We will also consider additional criteria relevant for prognostic studies (items 6 to 9).

1. **Unit of allocation (individual or group level)**: not applicable as there is no allocation of an 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 an intervention in our review question
4. **Prospective or retrospective character of each study part:** any. We will also include studies that did not describe if 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 will require that the study has tried to determine the adjusted prognostic value of sex - that is, its prognostic value independently of other existing prognostic factors such as age, or history of cancer. Thus, for a study to be eligible it 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 will 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 will consider 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 will not require this criterion for inclusion
6. **Temporal sequence:** we will only include longitudinal studies, that is, studies that collect data over a period of time. Thus, we will exclude cross-sectional studies (studies that collect data only once and in one short period of time). We considered admitting cross-sectional studies for two reasons. First, our review question does not aim to test a causal association between sex and the outcomes. Second, we know the temporal sequence as the potential prognostic factor (sex) always comes before any outcome. However, we excluded cross-sectional studies because they do not allow the assessment of the proper temporal sequence for the study covariates.
7. **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 will be eligible independently 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 would be eligible. On the other hand, we acknowledge that there is an ongoing controversy about the accuracy of administrative databases for the identification of PE cases (Burles 2017); these studies will be eligible as well, but we will assess the impact of this decision by sensitivity analysis.

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

We identified the key covariates for adjustment both from non systematic review of the literature, and in discussion with clinicians of the review team according to the following process.

Step	Method	Potential additional prognostic factors	Source
1. Preliminary searches to identify potential prognostic factors on	1. PubMed search:“pulmonary embolism”[Title]) AND “prognostic factor”[Title]	Red cell distribution width	Sen 2014

(Continued)

mortality in patients with pulmonary embolism	2. Embase search: 'prognostic factor':ti AND 'pulmonary embolism':ti 3. Initial discussion with review team members	Right ventricular dysfunction (RVD)	Cho 2014
		Glomerular filtration rate	Gibietis 2019
		Hyponatremia	Scherz 2010
		Leukocytes	Jo 2013
		SIRS	Jo 2013
2. Identify prognostic models for mortality in patients with pulmonary embolism	We considered the factors considered in the simplified PESI prognostic model (Jimenez 2010)	• Age • History of cancer • History of chronic cardiopulmonary disease • Heart rate • Systolic blood pressure • O_2 saturation	Jimenez 2010
3. Prioritisation of additional prognostic factors in GRADEPro GDT (GRADEpro-GDT 2015)	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 new revised list and were asked to prioritise the factors, ranking them from 1 to 9, with 1 being of least importance and 9 of the highest importance. d. We sent a new list of potential prognostic factors to group the factors 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 the final list of covariates		

Appendix 3. MEDLINE search strategy

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 thromboemboli* 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.

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

HISTORY

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CONTRIBUTIONS OF AUTHORS

JLA: guarantor of the review, conceiving the review, designing the review, coordinating the review, designing search strategies, methodological input, providing a policy perspective, writing the protocol, editing the protocol, study selection, data extraction, risk of bias assessment, statistical analysis, writing of the review
ES: conceiving the review, designing the review, designing search strategies, methodological input, providing a policy perspective, writing the protocol, editing the protocol, study selection, data extraction, risk of bias assessment, statistical analysis, writing of the review
JZ: conceiving the review, designing the review, methodological input, providing a policy perspective, writing the protocol, risk of bias assessment, statistical analysis
AM: methodological input, providing a policy perspective, writing the protocol, risk of bias assessment, statistical analysis
SvD: designing the review, providing a policy perspective, writing the protocol
NAD: designing search strategies, providing a policy perspective, writing the protocol
BF: providing a policy perspective, writing the protocol, study selection, data extraction, risk of bias assessment, statistical analysis
CAQ: clinical input, providing a policy perspective, writing the protocol, study selection, data extraction
RP: clinical input, providing a policy perspective, writing the protocol, study selection
DJ: conceiving the review, designing the review, methodological input, clinical input, providing a policy perspective, writing the protocol, study selection, data extraction, statistical analysis, writing of the review

DECLARATIONS OF INTEREST

JLA: none known
ES: none known. This review will form part of the thesis of Elena Stallings, who is enrolled in doctoral studies with the Department of Health Sciences at the Universidad de Alcala, Madrid
JZ: none known
AM: none known
SvD: none known
NAD: none known
BF: none known
CAQL: none known
RP: none known
DJ: has declared that he received payment for consultancy (Bayer, Bristol-Meiers-Squibb, Daiichi-Sankyo, Pfizer, ROVI, Sanofi), lecture and education presentations (Bayer, Bristol-Meiers-Squibb, Daiichi-Sankyo, Merck-Sharp-Dome, Pfizer, ROVI, Sanofi) and from grants (Daiichi-Sankyo)

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