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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.