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Systematic Review

Sex-Based Differences in the Presentation and Outcomes of Acute Pulmonary Embolism: A Systematic Review and Meta-Analysis

Yu Zhang, MD; Yu Qiu, MD; Jinming Luo, MD; Jian Zhang, MD; Qingqing Yan, MD

Taizhou First People's Hospital Intensive Care Unit, Taizhou City, Zhejiang Province, China

Abstract

Background: The study aimed to review differences in the presentation and outcomes of acute pulmonary embolism (PE) between men and women.

Methods: PubMed, CENTRAL, Web of Science, and Embase were searched for studies comparing clinical features or outcomes of PE between men and women. Baseline comorbidities, risk factors, clinical features, and mortality rates were also compared between men and women.

Results: Fourteen studies were included. It was noted that men presented with PE at a statistically significantly younger age than women ($P < .001$). Smoking history ($P < .001$), lung disease ($P = .004$), malignancy ($P = .02$), and unprovoked PE ($P = .004$) were significantly more frequent among men than among women. There was no difference between the sexes for hypertension, diabetes, and a history of recent immobilization. A significantly higher proportion of men presented with chest pain ($P = .02$) and hemoptysis ($P < .001$), whereas syncope ($P = .005$) was more frequent in women. Compared with men, women had a higher proportion of high-risk PE ($P = .003$). There was no difference in the use of thrombolytic therapy or inferior vena cava filter. Neither crude nor adjusted mortality rates were significantly different between men and women.

Conclusion: This review found that the age at presentation, comorbidities, and symptoms of PE differed between men and women. Limited data also suggest that women more frequently had high-risk PE compared with men, but the use of thrombolytic therapy did not differ between the 2 sexes. Importantly, both crude and adjusted data show that the mortality rate did not differ between men and women.

Keywords: Venous thromboembolism; sex; mortality; lung; pulmonary disease; male; female

Introduction

Acute pulmonary embolism (PE) is a common thromboembolic disorder and the third-most common cause of cardiovascular mortality in the United States. Data indicate that the incidence of PE has increased from 3 per 100 people to more than 6.5 per 100 people in the past 2 decades.[1] Clinically, a PE that is large enough to cause significant hemodynamic compromise can result in remarkable morbidity and mortality.[2] Because much of the research on cardiovascular diseases (CVDs) has been conducted in male-dominated cohorts, however, there is a scarcity of knowledge on how sex influences the morbidity and mortality rates of these diseases.[3]

It is now well known that sex differences exist in the risk and outcomes of CVDs. Men are more prone to such illnesses, especially coronary artery disease and stroke, along with an increased risk of mortality with CVDs.[4,5] Men and women have similar risk factors for CVDs, but the relative risk of each factor varies by sex.[3] Sex-based differences in presentation and treatment have been shown in patients with acute coronary syndrome.[6] Similar differences exist for stroke, with sex-based differences in risk, treatment, and outcomes after the event.[7] In this context,

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Corresponding author: Qingqing Yan, MD, Taizhou First People's Hospital Intensive Care Unit, No. 218, Hengjie Rd, Dongcheng St, Huangyan District, Taizhou City, Zhejiang Province, China (shengmingdezhizhuo@yeah.net)
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the American Heart Association and the World Heart Federation have recommended that more research be conducted to obtain evidence on sex-specific differences in various CVDs.[8]

Over the past 2 decades, numerous studies have compared the clinical presentation and outcomes of PE between men and women,[9-12] but results have been variable and limited by the small sample sizes of most studies. A thorough systematic review and meta-analysis are needed to comprehensively evaluate the sex-based difference in PE. Because no such analysis has been conducted to date, the current study pooled data from studies published in the year 2000 or later to compare the comorbidities, risk factors, clinical presentation, and mortality rates of PE between men and women.

Key Points

- Women present with PE at a much younger age and frequently with high-risk disease.
- Comorbidities and symptoms at presentation differ between the 2 sexes.
- Mortality rates of PE do not differ between men and women.

Abbreviations and Acronyms

CVD	cardiovascular disease
OR	odds ratio
PE	pulmonary embolism
PESI	Pulmonary Embolism Severity Index
sPESI	simplified Pulmonary Embolism Severity Index

Methods

The PROSPERO registration (No. CRD42022366268) of the review was initiated before beginning the study. The standard guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement were taken into account during the conduct of the review.[13]

Literature Search

The search strategy involved 2 independent reviewers examining the databases of PubMed, CENTRAL, Web of Science, and Embase electronically. The search was conducted without any language restrictions. To obtain only current and relevant evidence, the databases were searched for studies published between January 1, 2000, and October 13, 2022. To identify relevant publications, combinations of the following keywords were used: *gender, sex, men, women, male, female,* and *pulmonary embolism.* A detailed description of the search is shown in Supplementary Table I. The search results from every database were combined for screening by the 2 reviewers. When deduplication was complete, the articles were sorted by their titles and abstracts. Full texts of relevant articles were obtained, and they were read by both reviewers against the eligibility criteria. All discrepancies between the reviewers were solved by discussion with a third reviewer.

Eligibility Criteria

The population, exposure, comparison, outcomes, and study type inclusion criteria of the review were as follows:

- Population: patients with PE
- Exposure: male
- Comparison: female
- Outcomes: clinical features or outcomes, including mortality and recurrence
- Study type: all types

Single-arm studies, studies not reporting separate data for PE, studies with overlapping or duplicate data, unpublished data, and review articles were excluded. For studies with duplicate data, the study reporting the maximum outcomes and with the maximum sample size was included. Studies with a sample size of at least 50 patients per group were included to avoid small sample size bias.

Data Extraction and Quality Assessment

Two reviewers were independently involved in data collection. Details of authors; study location; study type; sample size; age; smoking status; obesity; hypertension; diabetes; lung disease; recent immobilization; coronary artery disease; malignancy; unprovoked PE; symptoms such as dyspnea, chest pain, hemoptysis, and syncope; treatment modalities such as thrombolytic therapy and inferior vena cava filter; high-risk PE; and outcomes such as death and PE recurrence were collected.

Quality assessment was conducted using the Newcastle-Ottawa Scale.[14] Every study was examined for study population selection, comparability, and outcomes. These components were given a maximum of 4, 2, and 3 points, respectively. Two reviewers were involved in the quality assessment, and any disagreements were solved by discussion with a third reviewer.

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Statistical Analysis

The meta-analysis was performed using Review Manager (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration]). Meta-analysis was conducted for all demographic, clinical, and outcome variables if data were available from at least 5 studies. Dichotomous data were combined using the DerSimonian and Laird random-effects model to calculate pooled odds ratios (ORs) with 95% CIs. Continuous variables were pooled to obtain the mean difference. Adjusted data on mortality were also extracted where available and pooled to ORs. The I^2 statistic was used to assess interstudy heterogeneity. Funnel plots were generated, and the Egger test was used to test for publication bias. A sensitivity analysis was conducted to judge the effect of each study on the meta-analysis results. We excluded 1 study at a time in the meta-analysis software to check whether there was any change in the significance of the results. $P<.05$ was considered statistically significant.

Results

The total number of results after the literature search was 9,495, of which 5,811 were duplicates and hence removed. The remaining 3,684 articles were screened, and 26 were selected for full-text review. Finally, a total of 14 studies were included in the analysis[9-12,15-24] (Fig. 1). The inter-reviewer agreement for study selection was high ($\kappa=0.9$).

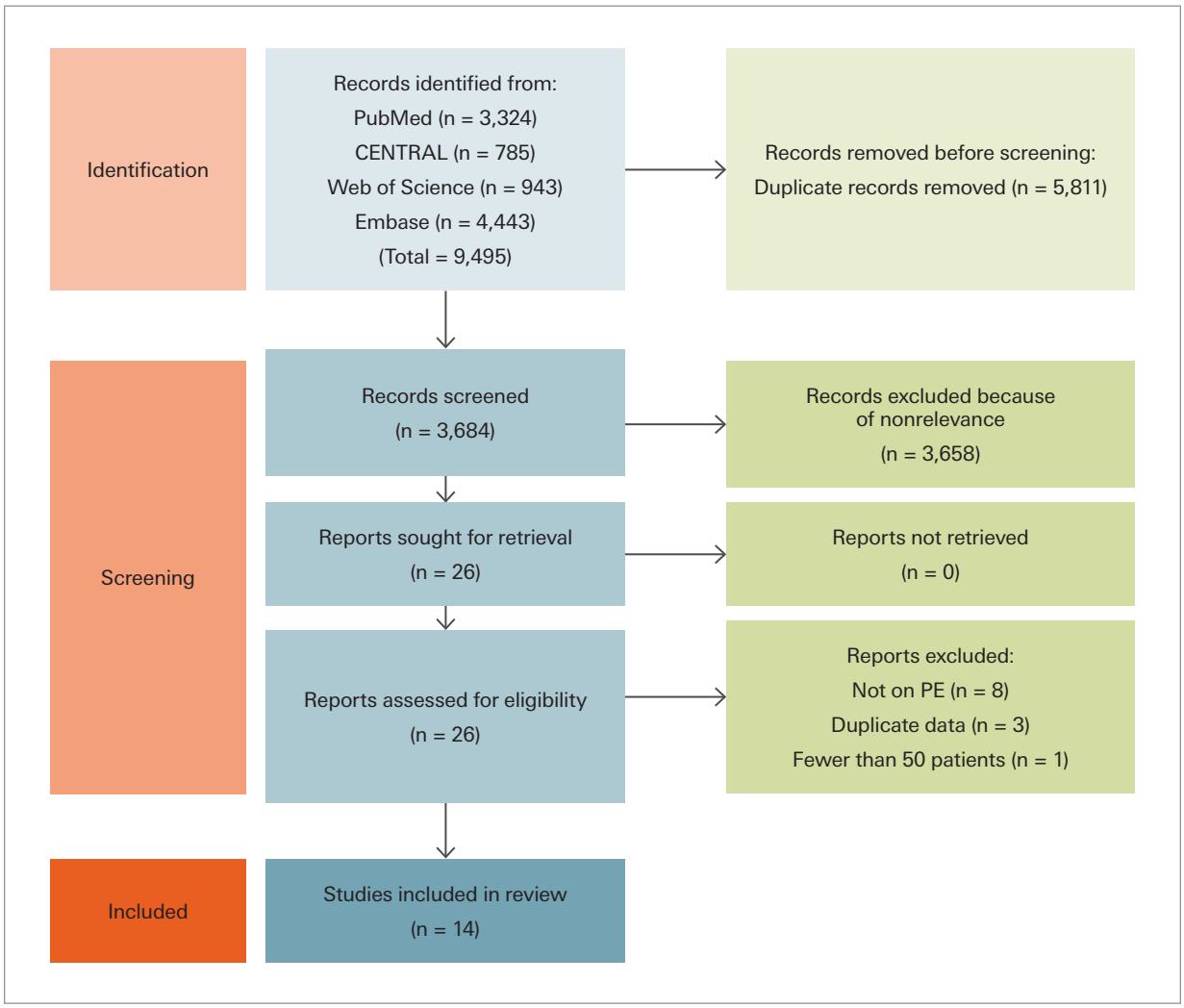

Fig. 1 Study flowchart

CENTRAL, Cochrane Central Register of Controlled Trials; PE, pulmonary embolism.

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Data extracted from the studies are presented in Table I[9-12,15-24] and Table II.[9-12,15-24] All studies were observational and conducted in different countries. The sample size of the studies ranged from 72 to 146,174 patients per group. On meta-analysis of age in years, it was noted that men presented with PE at a statistically significantly younger age than women (mean difference, −4.01 years; 95% CI, −5.07 to −2.94; I^2 = 74%; P < .00001) (Fig. 2). The number of smokers among men was significantly higher than among women (OR, 2.34; 95% CI, 1.55-3.55; I^2 = 91%; P < .0001) (Fig. 3). The frequency of hypertension was not significantly different between men and women (OR, 0.83; 95% CI, 0.69-1.00 I^2 = 80%; P = .05) (Fig. 4). On the exclusion of Pribish et al[10] from the analysis, the results indicated a significantly lower frequency of hypertension among men (OR, 0.76; 95% CI, 0.61-0.94; I^2 = 78%; P = .01). There was no difference in the number of patients with diabetes between groups (OR, 1.04; 95% CI, 0.92-1.17; I^2 = 35%; P = .57) (Fig. 5). Lung disease was significantly more frequent among men than among women (OR, 1.68; 95% CI, 1.18-2.40; I^2 = 98%; P = .004) (Supplementary Fig. 1). There was no statistically significant difference in the history of recent immobilization between men and women (OR, 0.79; 95% CI, 0.61-1.03; I^2 = 88%; P = .08) (Supplementary Fig. 2). On the exclusion of McHugh et al[19] from the analysis, a significantly lower number of men had a history of recent immobilization (OR, 0.72; 95% CI, 0.63-0.82; I^2 = 36%; P < .00001). The incidence of coexisting malignancy was significantly higher among men than among women (OR, 1.14; 95% CI, 1.02-1.27; I^2 = 72%; P = .02) (Supplementary Fig. 3); however, these results were not stable on sensitivity analysis and turned nonsignificant on exclusion of Borrero et al[20] (OR, 1.11; 95% CI, 0.96-1.28; I^2 = 69%; P = .17), Agarwal et al[24] (OR, 1.12; 95% CI, 0.95-1.32; I^2 = 73%; P = .18), and Barrios et al[17] (OR, 1.12; 95% CI, 0.99-1.25; I^2 = 74%; P = .07). It was also noted that men had a significantly higher incidence of unprovoked PE than women (OR, 1.29; 95% CI, 1.08-1.53; I^2 = 50%; P = .004) (Supplementary Fig. 4).

On analysis of symptoms, there was no significant difference between men and women for dyspnea (OR, 0.84; 95% CI, 0.70-1.01; I^2 = 67%; P = .06) (Supplementary Fig. 5). On exclusion of Deng et al[23] (OR, 0.80; 95% CI, 0.69-0.93; I^2 = 51%; P = .003) and Barrios et al[17] (OR, 0.79; 95% CI, 0.66-0.94; I^2 = 49%; P = .007), the results indicated significantly lower presentation of dyspnea among men. Also, a significantly higher proportion of men presented with chest pain (OR, 1.27; 95% CI, 1.05-1.54; I^2 = 69%; P = .02) (Supplementary Fig. 6) and hemoptysis (OR, 2.12; 95% CI, 1.67-2.69; I^2 = 0%; P < .00001) (Supplementary Fig. 7) compared with women. The presentation of syncope, however, was significantly lower among men than among women (OR, 0.83; 95% CI, 0.72-0.94; I^2 = 0%; P = .005) (Supplementary Fig. 8). These results turned nonsignificant on exclusion of Barrios et al[17] (OR, 0.86; 95% CI, 0.74-1.01; I^2 = 0%; P = .06). Comparing the 2 groups, women had a higher proportion of high-risk PE (OR, 0.83; 95% CI, 0.74-0.94; I^2 = 0%; P = .003) (Supplementary Fig. 9).

With respect to treatment, there was no difference in the use of thrombolytic therapy between men and women (OR, 1.08; 95% CI, 0.80-1.24; I^2 = 82%; P = .98) (Supplementary Fig. 10). Similarly, there was no difference in inferior vena cava filter use between men and women (OR, 1.09; 95% CI, 1.00-1.20; I^2 = 32%; P = .06) (Supplementary Fig. 11).

For outcomes, the majority of studies reported data on mortality. A combined analysis of 12 studies showed no statistically significant difference in the risk of mortality between men and women (OR, 0.93; 95% CI, 0.82-1.06; I^2 = 62%; P = .30) (Supplementary Fig. 12). The results did not change on the exclusion of any study during sensitivity analysis. Also, there was no evidence of publication bias (P = .85 for Egger test) (Supplementary Fig. 13). On pooled analysis of adjusted data from 6 studies, we noted similar results, with no difference in mortality between men and women (OR, 0.94; 95% CI, 0.75-1.17; I^2 = 85%; P = .57) (Supplementary Fig. 14). These results also did not change in significance during sensitivity analysis. The Newcastle-Ottawa Scale score of the studies ranged from 5 to 8 (Table II). The inter-reviewer agreement for quality assessment was high (κ = 0.9).

Discussion

Several anatomic and physiologic differences exist between men and women that can modulate the pathophysiology, morbidity, and mortality rates of several diseases. Such differences have already been well elucidated for cardiovascular, lung, autoimmune, and neurologic disorders.[8,25-28] Another major difference between the 2 sexes is neurohormonal modulation, especially by estrogen-related compounds; importantly, exogenous estrogens are an accepted risk factor for PE.[29] Therefore, biological sex could play an important role in the patho-

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TABLE I. Details of Included Studies

Study	Country	Diagnosis of PE	Sex	Sample size, No.	Age, mean (SD), y	Smoking, No.	Obesity, No.	HT, No.	DM, No.	Lung disease, No.	Recent immobilization, No.	CAD, No.	Malignancy, No.	Unprovoked PE, No.
McHugh, et al[19] (2002)	US	CTPA or V/Q scan or autopsy	Men Women	1,095 1,359	60.7 (15.5) 63.5 (17.4)	NR NR	NR NR	NR NR	NR NR	175 136	296 294	NR NR	252 299	NR NR
Borrero, et al[20] (2007)	US	NR	Men Women	6,227 9,304	NR NR	NR NR	NR NR	NR NR	NR NR	1,261 1,607	NR NR	NR NR	1,366 1,680	NR NR
Geibel, et al[21] (2007)	Germany	NR	Men Women	291 428	NR NR	NR NR	NR NR	NR NR	NR NR	38 32	97 150	NR NR	32 53	NR NR
Blanco-Molina, et al[22] (2014)	MC	Multinational	Men Women	10,979 12,838	66 (16) 69 (17)	NR NR	NR NR	NR NR	NR NR	2,052 1,318	2,173 3,167	NR NR	NR NR	5,286 5,517
Agarwal, et al[24] (2015)	US	*ICD* codes	Men Women	120,272 146,174	61.1 (16.2)[a] 63.1 (18.6)[a]	31,906 24,731	14,213 23,855	59,877 76,445	22,952 27,990	28,680 36,636	NR NR	NR NR	16,976 18,460	NR NR
Deng, et al[23] (2015)	China	CTPA or clinical	Men Women	73 76	72.6 (14.7) 75 (15.1)	NR NR	NR NR	NR NR	NR NR	23 11	24 38	NR NR	NR NR	NR NR
Obradović, et al[15] (2016)	Serbia	CTPA	Men Women	72 72	56 (17) 64 (15)	20 6	10 23	NR NR	NR NR	NR NR	NR NR	10 3	5 11	39 33
Panigada[16] (2016)	Italy	CTPA or V/Q scan or clinical	Men Women	180 272	73.5 (12.4) 77.6 (12)	NR NR	NR NR	NR NR	NR NR	36 27	64 126	NR NR	71 65	43 70
Barrios, et al[17] (2017)	Spain	CTPA or V/Q scan	Men Women	1,004 1,092	66.6 (16.2) 70.6 (16.8)	NR NR	NR NR	NR NR	NR NR	136 33	160 252	NR NR	232 200	NR NR
Tanabe, et al[18] (2018)	Japan	CTPA or V/Q scan or autopsy	Men Women	633 795	60.9 (15.6) 68 (16.1)	186 70	NR NR	231 317	90 90	NR NR	NR NR	29 31	30 46	NR NR
Keller, et al[9] (2019)	Germany	NR	Men	251 318	NR NR	NR NR	NR NR	NR NR	39 58	38 43	NR NR	63 43	52 43	153 151
Dzudovic, et al[11] (2020)	Serbia	European guidelines	Men Women	294 294	60 (14) 65.5 (16)	58 26	54 91	141 175	44 55	34 29	NR NR	NR	29 43	165 129
Oliveira, et al[12] (2020)	Portugal	CTPA or V/Q scan	Men Women	213 364	62 (19) 67 (18)	NR NR	NR NR	97 221	43 71	NR NR	NR NR	NR NR	NR NR	139 237
Pribish, et al[10] (2020)	US	*ICD* codes	Men Women	950 1,081	62.3 (15) 63.8 (17.4)	131 122	17 34	510 545	195 191	84 107	NR NR	92 71	284 333	NR NR

[a]Mean (SE).

CAD, coronary artery disease; CTPA, computed tomography pulmonary angiography; DM, diabetes mellitus; HT, hypertension; *ICD, International Classification of Diseases;* MC, multicentric; NR, not reported; PE, pulmonary embolism; V/Q, ventilation-perfusion.

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TABLE II. Symptoms and Outcomes Reported, by Included Studies

Study	Groups	Sample size, No.	Dyspnea, No.	Chest pain, No.	Hemoptysis, No.	Syncope, No.	Thrombolytic therapy, No.	IVC filter, No.	High-risk PE, No.	Death, No.	Recurrent PE, No.	NOS score
McHugh, et al[19] (2002)	Men	1,095	865	559	99	142	NR	NR	NR	186	81	5
	Women	1,359	1,142	639	68	190	NR	NR	NR	255	109	
Borrero, et al[20] (2007)	Men	6,227	NR	NR	NR	NR	NR	NR	NR	609	NR	8
	Women	9,304	NR	NR	NR	NR	NR	NR	NR	830	NR	
Geibel, et al[21] (2007)	Men	291	NR	NR	NR	60	73	NR	0	26	53	6
	Women	428	NR	NR	NR	120	96	NR	0	43	64	
Blanco-Molina, et al[22] (2014)	Men	10,979	NR	NR	NR	NR	117	341	NR	NR	NR	8
	Women	12,838	NR	NR	NR	NR	111	360	NR	NR	NR	
Agarwal, et al[24] (2015)	Men	120,272	NR	NR	NR	NR	26,400	15,852	NR	3,837	NR	8
	Women	146,174	NR	NR	NR	NR	39,087	17,892	NR	5,116	NR	
Deng, et al[23] (2015)	Men	73	57	16	NR	6	NR	NR	NR	6	NR	6
	Women	76	45	7	NR	12	NR	NR	NR	5	NR	
Obradović, et al[15] (2016)	Men	72	62	32	13	11	42	NR	10	11	NR	7
	Women	72	65	14	4	13	44	NR	18	19	NR	
Panigada[16] (2016)	Men	180	NR	NR	NR	NR	7	0	31	22	NR	6
	Women	272	NR	NR	NR	NR	15	5	50	21	NR	
Barrios, et al[17] (2017)	Men	1,004	454	717	NR	125	54	18	686	NR	NR	8
	Women	1,092	482	797	NR	175	37	31	772	NR	NR	
Tanabe, et al[18] (2018)	Men	633	354	111	NR	NR	209	235	205	27	NR	8
	Women	795	487	107	NR	NR	219	254	296	49	NR	
Keller, et al[9] (2019)	Men	251	207	133	13	55	NR	0	30	18	6	6
	Women	318	280	161	6	65	NR	0	38	253	3	
Dzudovic, et al[11] (2020)	Men	294	247	111	37	NR	97	NR	33	34	NR	6
	Women	294	254	91	16	NR	102	NR	47	48	NR	
Oliveira, et al[12] (2020)	Men	213	NR	NR	NR	NR	22	NR	NR	100	NR	8
	Women	364	NR	NR	NR	NR	45	NR	NR	140	NR	
Pribish, et al[10] (2020)	Men	950	494	299	38	41	20	82	34	50	9	8
	Women	1081	646	326	21	53	37	92	52	82	20	

IVC, inferior vena cava; NOS, Newcastle-Ottawa Scale; NR, not reported.

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Study or Subgroup	Men Mean	Men SD	Men Total	Women Mean	Women SD	Women Total	Weight	Mean Difference IV, Random, 95% CI	Year
McHugh, et al19 (2002)	60.7	15.5	1095	63.5	17.4	1359	13.4%	−2.80 [−4.10, −1.50]	2002
Blanco-Molina, et al22 (2014)	66	16	10979	69	17	12838	16.3%	−3.00 [−3.42, −2.58]	2014
Agarwal, et al24 (2015)	61.1	5,618.2011	120272	63.1	7,111.2838	146174	0.0%	−2.00 [−50.34, 46.34]	2015
Deng, et al23 (2015)	72.6	14.7	73	75	15.1	76	3.8%	−2.40 [−7.18, 2.38]	2015
Obradović, et al15 (2016)	56	17	72	64	15	72	3.3%	−8.00 [−13.24, −2.76]	2015
Panigada, et al16 (2016)	73.5	12.4	180	77.6	12	272	9.4%	−4.10 [−6.41, −1.79]	2016
Barrios, et al17 (2017)	66.6	16.2	1004	70.6	16.8	1092	12.9%	−4.00 [−5.41, −2.59]	2017
Tanabe, et al18 (2018)	60.9	15.6	633	68	16.1	795	12.0%	−7.10 [−8.75, −5.45]	2018
Dzudovic, et al11 (2020)	60	14	294	65.5	16	294	9.0%	−5.50 [−7.93, −3.07]	2020
Oliveira, et al12 (2020)	62	19	213	67	18	364	6.8%	−5.00 [−8.15, −1.85]	2020
Pribish, et al10 (2020)	62.3	15	950	63.8	17.4	1081	13.0%	−1.50 [−2.91, −0.09]	2020
Total (95% CI)			**135765**			**164417**	**100.0%**	**−4.01 [−5.07, −2.94]**	

Heterogeneity: $Tau^2 = 1.77$; $Chi^2 = 37.97$, df = 10 ($P < 0.0001$); $I^2 = 74\%$
Test for overall effect: $Z = 7.35$ ($P < 0.00001$)

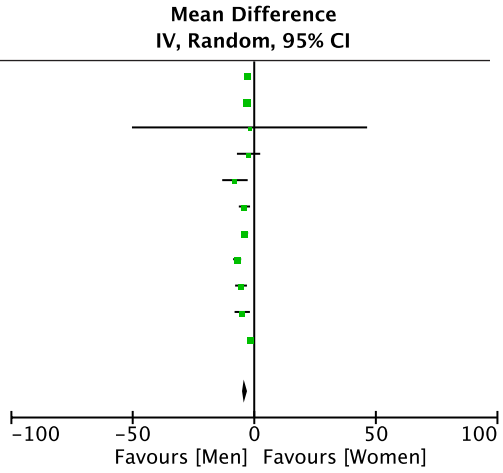

Fig. 2 Meta-analysis of age between men and women with pulmonary embolism

IV, inverse variance.

Study or Subgroup	Men Events	Men Total	Women Events	Women Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Agarwal, et al24 (2015)	31906	120272	24731	146174	25.4%	1.77 [1.74, 1.81]	2015
Obradović, et al15 (2016)	20	72	6	72	10.5%	4.23 [1.58, 11.30]	2015
Tanabe, et al18 (2018)	186	633	70	795	22.4%	4.31 [3.20, 5.81]	2018
Pribish, et al10 (2020)	131	950	122	1081	23.0%	1.26 [0.97, 1.64]	2020
Dzudovic, et al11 (2020)	58	294	26	294	18.7%	2.53 [1.54, 4.15]	2020
Total (95% CI)		**122221**		**148416**	**100.0%**	**2.34 [1.55, 3.55]**	
Total events	32301		24955				

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 45.36$, df = 4 ($P < 0.00001$); $I^2 = 91\%$
Test for overall effect: $Z = 4.02$ ($P < 0.0001$)

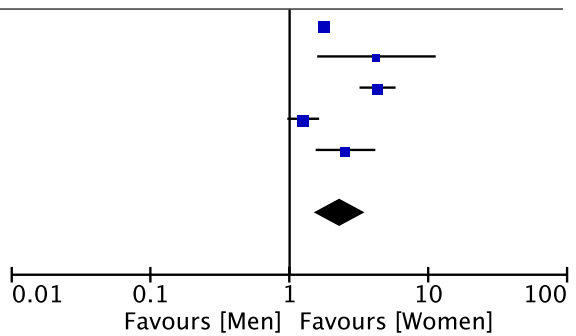

Fig. 3 Meta-analysis of smoking between men and women with pulmonary embolism

M-H, Mantel-Haenszel; IV, inverse variance.

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Study or Subgroup	Men Events	Men Total	Women Events	Women Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Agarwal, et al24 (2015)	59877	120272	76445	146174	28.4%	0.90 [0.89, 0.92]	2015
Tanabe, et al18 (2018)	231	633	317	795	20.3%	0.87 [0.70, 1.07]	2018
Dzudovic, et al11 (2020)	141	294	175	294	14.8%	0.63 [0.45, 0.87]	2020
Oliveira, et al12 (2020)	97	213	221	364	14.1%	0.54 [0.38, 0.76]	2020
Pribish, et al10 (2020)	510	950	545	1081	22.5%	1.14 [0.96, 1.36]	2020
Total (95% CI)		**122362**		**148708**	**100.0%**	**0.83 [0.69, 1.00]**	
Total events	60856		77703				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 20.42$, df = 4 (P = 0.0004); $I^2 = 80\%$
Test for overall effect: Z = 1.99 (P = 0.05)

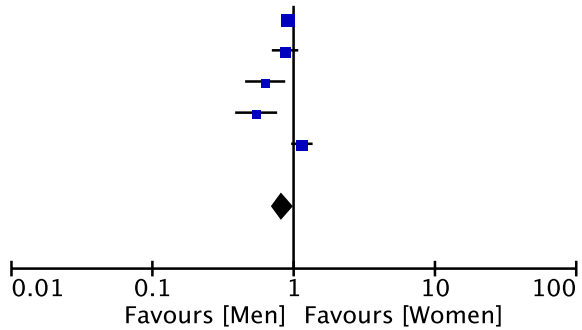

Fig. 4 Meta-analysis of hypertension between men and women with pulmonary embolism
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IV, inverse variance.

Study or Subgroup	Men Events	Men Total	Women Events	Women Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Agarwal, et al24 (2015)	22952	120272	27990	146174	49.5%	1.00 [0.98, 1.02]	2015
Tanabe, et al18 (2018)	90	633	90	795	11.5%	1.30 [0.95, 1.78]	2018
Keller, et al9 (2019)	39	251	58	318	6.5%	0.82 [0.53, 1.29]	2019
Dzudovic, et al11 (2020)	44	294	55	294	6.7%	0.76 [0.50, 1.18]	2020
Oliveira, et al12 (2020)	43	213	71	364	7.0%	1.04 [0.68, 1.59]	2020
Pribish, et al10 (2020)	195	950	191	1081	18.7%	1.20 [0.96, 1.50]	2020
Total (95% CI)		**122613**		**149026**	**100.0%**	**1.04 [0.92, 1.17]**	
Total events	23363		28455				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.69$, df = 5 (P = 0.17); $I^2 = 35\%$
Test for overall effect: Z = 0.57 (P = 0.57)

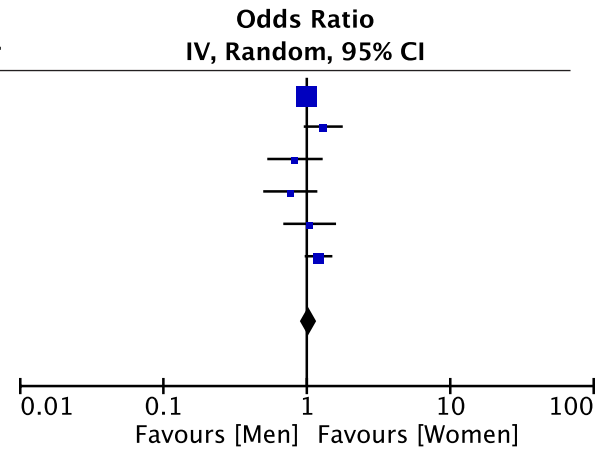

Fig. 5 Meta-analysis of diabetes between men and women with pulmonary embolism

IV, inverse variance.

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physiology and outcome of PE.[30] To this point, there has been no pooled evidence in the literature to elucidate the influence of sex on PE. This meta-analysis compared the age at presentation, baseline comorbidities, risk factors, symptoms, treatment, and outcomes of PE between men and women. It should be stated at the outset that the data pooled in the meta-analysis were primarily limited by the reporting of the included studies. Many of the baseline comorbidities, risk factors, clinical features, and outcomes could not be compared because they were not reported by all included studies. Also, to avoid small sample size bias, a meta-analysis was conducted only if there were at least 5 studies reporting similar data.

Pulmonary embolism is primarily seen in older individuals, and its incidence increases 2-fold every decade after 40 years of age.[31] In the present analysis, it was noted that the mean age at presentation with PE for both men and women was 60 years. There was a statistically significant difference between the 2 groups, with the mean age for men being 4 years lower, although such a minuscule difference would likely have negligible clinical significance. The age of the study population also depends on geographical variations and study methods, factors reflected in the high heterogeneity of the meta-analysis. The review found that men were more often smokers and more often had lung disease, malignancy, and unprovoked PE, whereas there were no differences in the history of diabetes or hypertension. These differences reflect the general behavioral pattern of men who smoke more frequently and consequently have lung diseases.[32] The malignancy rate may also reflect global cancer incidence rates. The recent GLOBOCAN estimates have shown that the worldwide cancer incidence rate is 19% higher in men than in women.[33]

Several risk factors have been identified for PE, including prior thromboembolism, major trauma, recent surgery, immobilization, and exogenous estrogen administration. Many of these factors could not be analyzed in the meta-analysis owing to a lack of data. It was noted that the history of recent immobilization did not differ between women and men, but it has been reported previously that women are more prone to immobilization after surgery, which could lead to a higher incidence of thromboembolism in female patients.[34] Another factor is external hormonal therapy, which is a well-established risk factor for women. Estrogen-based oral contraceptive pills and estrogen hormone replacement therapy have been shown to increase the risk of venous thromboembolism among women.[35] The relative risk is different based on the type of estrogen, however, and endogenous sex hormones are not associated with an increased risk.[30] Furthermore, many other demographic variables, such as diet and physical activity, can influence PE risk, all of which could not be assessed in the current review.

A few differences were noted in the presentation of PE between men and women. Although the incidence of dyspnea was not significantly different between the 2 groups, a significantly higher proportion of men presented with chest pain and hemoptysis. Also, syncope was more frequently seen in women than in men. Such differences in presentation have been noted in other diseases, as well, although without any clear explanation.[6] Further in the analysis, it was noted that women presented more frequently with high-risk PE. Risk assessment for PE is conducted using the Pulmonary Embolism Severity Index (PESI) or the simplified PESI (sPESI), which classify individuals into low-, intermediate-, and high-risk categories. Although sex was a factor in the PESI score, the sPESI in 2010 did not find sex to be a predictor of mortality.[36] Research suggests that sPESI may predict fatal outcomes more precisely in women, although it has good performance in both sexes.[37] Future research on sex-based prognostic indicators should provide better evidence of such differences.

With respect to treatment, there was no difference in the use of thrombolytic therapy or inferior vena cava filter between men and women. Also, no difference was noted in mortality rates after PE between sexes. With respect to mortality, maximum studies were included in the meta-analysis with data from 291,088 patients, thereby increasing the statistical power of the results. The lack of publication bias and no change in the effect size on sensitivity analysis also strengthen the results of the review. Importantly, because this analysis was of crude mortality rates, it can be confounded by several variables. In addition, mortality after PE can be affected by factors such as patient age, comorbidities, risk factors, location of PE, severity, and the treatment protocol.[2] In an attempt to generate more robust results, we also extracted multivariable adjusted ratios and pooled them in a meta-analysis. Although only 6 studies were available for this analysis, the results confirmed that there was no difference in the risk of mortality after PE between the 2 sexes. Outcomes of PE also include the risk of recurrence, quality of life, and exercise tolerance in the long term. One prospective study from Canada has shown that compared with men, women had diminished exercise tolerance and worse quality of life after PE after adjustment for confounding factors.[38] At this point,

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however, this review could not quantitatively analyze these outcomes.

Limitations

Several limitations exist with this review. Many of the outcomes had moderate to high heterogeneity; therefore, the results should be interpreted with caution. The heterogeneity can be explained by different inclusion criteria, heterogenous study populations, variable data-collection methods, and several sources of bias. Because of limited data and several differences among the studies, however, a subgroup analysis for such variables was not possible. Second, outcome data were limited to mortality, which varied from in-hospital mortality to early mortality (within 6 months). No long-term results were available, and most studies did not adjust for confounders. Third, the review was unable to quantitatively analyze PE characteristics such as its location, cardiac function, and laboratory values. This information would have provided further insight into differences by sex.

The strengths of the review lie in the large number of studies in the analysis. A sensitivity analysis was conducted to check the stability of the results. Only contemporary data from after 2000 were included to present this meta-analysis on sex differences for PE.

Conclusion

This review showed that the age at presentation, comorbidities, and symptoms of PE differ between men and women. Limited data also suggest that women more frequently have high-risk PE than men, but the use of thrombolytic therapy does not differ between the sexes. Importantly, both crude and adjusted data showed that the mortality rate does not differ between men and women. Results should be interpreted with caution owing to high interstudy heterogeneity in several analyses. Further research should be conducted to provide insight into differences in other characteristics and outcomes of PE between the 2 sexes.

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