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Sex Differences in Management and Outcomes Among Patients With High-Risk Pulmonary Embolism: A Nationwide Analysis

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Sex Differences in Management and Outcomes Among Patients With High-Risk Pulmonary Embolism: A Nationwide Analysis

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Abstract

Objective: To examine the sex differences in management and outcomes among patients with high-risk acute pulmonary embolism (PE).

Patients and Methods: The Nationwide Readmissions Database was used to identify hospitalizations with high-risk PE from January 1, 2016, to December 31, 2018. Differences in use of advanced therapies, in-hospital mortality, and bleeding events were compared between men and women.

Results: A total of 125,901 weighted hospitalizations with high-risk PE were identified during the study period; 46.3% were women (n=58,253). Women were older and had a higher prevalence of several comorbidities and risk factors of PE such as morbid obesity, diabetes mellitus, chronic pulmonary disease, heart failure, and metastatic cancer. Systemic thrombolysis and catheter-directed interventions were more commonly used among women; however, mechanical circulatory support was less frequently used. In-hospital mortality was higher among women in the unadjusted analysis (30.7% vs 27.8%, $P<.001$) and after propensity score matching (odds ratio [OR], 1.16; 95% confidence interval [CI], 1.08 to 1.25; $P<.001$), whereas the rates of intracranial hemorrhage and non−intracranial hemorrhage were not different. On multivariate regression analysis, female sex (OR, 1.18; 95% CI, 1.15 to 1.21; $P<.001$) was independently associated with increased odds of in-hospital mortality.

Conclusion: In this contemporary observational cohort of patients admitted with high-risk PE, women had higher rates of in-hospital mortality despite receiving advanced therapies more frequently, whereas the rate of major bleeding events was not different from men. Efforts are needed to minimize the excess mortality observed among women.

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Pulmonary embolism (PE) is a leading cause of morbidity and is the third common etiology of cardiovascular mortality worldwide. The annual mortality rate from acute PE in the United States in 2017 was estimated to be 4.1 to 4.5 deaths per 100,000 population.[1,2] Patients presenting with massive PE (defined as those with sustained hypotension, shock, or requiring inotropic support) and submassive PE (defined as those without hypotension but with evidence of right ventricular dysfunction or myocardial injury)[3] have considerably higher mortality rates (ie, up to 14% in submassive PE and more than 50% in massive PE).[4-6] Traditionally, treatment of massive PE involved the prompt restoration of pulmonary perfusion via systemic thrombolysis, and surgical embolectomy in those whom systemic thrombolysis has failed or is contraindicated.[7] In recent years, there have been several advancements in the management of high-risk patients with the introduction of catheter-directed interventions (CDIs) including catheter-directed thrombolysis (CDT) and catheter-directed embolectomy (CDE).[8]

Prior studies evaluating the sex differences in management and outcomes of acute PE have primarily included all-comers

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irrespective of the severity. Those studies have shown inconsistent findings depending on the period and population examined. For example, some earlier studies suggested higher mortality in men compared with women[9-12]; however, other recent studies showed that mortality was not different[13-18] or was even higher in women, especially in the younger age group (25 to 64 years of age).[2,19,20] Importantly, none of these studies focused on the high-risk patients with acute PE. To better address these knowledge gaps, we aimed to examine the sex differences in presentation, management, and outcomes among patients with high-risk PE from a contemporary nationally representative dataset.

PATIENTS AND METHODS

Data Source

We used the Nationwide Readmissions Database (NRD), Healthcare Cost and Utilization Project (HCUP) from the Agency for Healthcare Research and Quality for this analysis. The NRD contains discharge data from 28 geographically dispersed US states, accounting for ∼60% of the total US resident population and 58.2% of all US hospitalizations. We identified the cohort, procedures, and outcomes using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) and procedure classification system codes. The codes used are summarized in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org).

Study Population

We identified hospitalizations with any diagnosis of acute PE using ICD-10-CM for the years 2016−2018. The high-risk PE cohort was defined as PE with one of the following: mechanical ventilation, requirement for vasopressor, cardiogenic shock, use of CDT including ultrasound-facilitated CDT, CDE, systemic thrombolysis, or surgical embolectomy (ie, the cohort included patients with massive PE as well as some patients with submassive PE who received CDI or required mechanical ventilation).[21,22] Admissions with ST-segment elevation myocardial infarction, acute ischemic stroke, acute limb ischemia, and PE during pregnancy, labor or puerperium were excluded.

Patient and hospital-level variables provided by HCUP NRD were used to identify demographics and baseline characteristics. The Elixhauser method was used to assess comorbidities.[23] The other comorbidities were identified using appropriate ICD-10-CM codes (Supplemental Table 1). The NRD is a publicly available database with de-identified hospitalization records; therefore, this study was exempt from institutional review board approval.

Outcomes

The main outcome of interest was the difference in all-cause in-hospital mortality between women and men. The secondary outcomes were the differences in length of stay (LOS), intracranial hemorrhage (ICH) and non-ICH bleeding events which included respiratory tract hemorrhage (ie, epistaxis, hemoptysis, and hemorrhage from the respiratory passages), hemothorax, gastrointestinal hemorrhage, retroperitoneal bleeding, hematuria, hemarthrosis, hemopericardium, intraocular hemorrhage, and unspecified postprocedural bleeding.

We also examined the differences in the use of advanced therapies (ie, CDT, CDE, surgical embolectomy, systemic thrombolysis, and mechanical circulatory support [MCS]). Mechanical circulatory support included any of the following: extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump, and Impella.

In addition, we examined the trends in mortality across the 3 years by quarters. The 30-day urgent readmissions rates were also examined in the unadjusted cohort. For the readmission rates, we excluded those admitted in December of each calendar year (30-day readmissions for hospitalizations in December could not be obtained because the NRD does not cross the calendar year) and those who died during the index admission. We identified the proportion of urgent 30-readmissions due to PE and major bleeding using the ICD-10 procedural classification system codes of the first three recorded readmission diagnoses.

Statistical Analysis

All analyses were conducted using the appropriate weighting, stratifying, and clustering samples following HCUP regulations.[24,25] Continuous variables were summarized as medians and interquartile ranges (IQR); (25th and 75th percentiles) and compared with the Mann-Whitney U test. Categorical variables were displayed as numbers and percentages and compared with Pearson's χ^2 or Fisher exact tests. All *P* values are two-sided with a significance threshold less than .05. Trend analysis was performed using the Poisson regression method.

We used propensity score matching to account for the differences in the baseline patient and hospital-related characteristics and advanced therapies. We created two propensity score-matched groups (women vs men) using a propensity score matching algorithm with multivariable logistic regression conditioned on 26 variables: age, obesity, morbid obesity, anemia, hypertension, atrial fibrillation, diabetes mellitus, heart failure, carotid disease, chronic lung disease, pulmonary circulation disease, coagulopathy, peripheral vascular disease, renal failure, liver disease, history of coronary artery bypass graft, history of stroke, history of myocardial infarction, solid tumors without metastases, metastatic cancer, nonseptic shock, saddle PE, cor pulmonale, use of vasopressors, hospital teaching status, and hospital size. We used a nearest-neighbor 1:1 matching algorithm without replacement with a caliper width of 0.2 the standard deviation (SD) of the logit of the propensity score. The success of matching was examined by comparing standardized mean differences in the distribution of the covariates between the two treatment strategies. Additionally, we performed a secondary multivariable regression analysis for the unadjusted cohort to determine the independent variables associated with increased risk in-hospital mortality. The model included the following 24 variables: age, female sex, morbid obesity, anemia, hypertension, atrial fibrillation, diabetes mellitus, heart failure, chronic lung disease, pulmonary circulation disease, coagulopathy, renal failure, liver disease, solid tumors without metastases, metastatic cancer, cardiogenic shock, saddle PE, cor pulmonale, hospital size, and type of advanced therapies (ie, CDT, CDE, systemic thrombolysis, surgical embolectomy, and MCS). All variables were forced into the multivariable model using the enter method. Finally, we compared in-hospital mortality between men and women across different subgroups in the propensity-matched cohort. Statistical analyses were performed using STATA software for Windows (version 16.0. College Station, TX: StataCorp LLC) and IBM SPSS Statistics for Windows (version 27.0. Armonk, NY: IBM Corp).

RESULTS

A total of 125,901 weighted hospitalizations with high-risk PE were identified during the study period; 58,253 (46.3%) were women. Women were older (65 [IQR, 52-74] years vs 62 [IQR, 52-72] years; *P*<.001) with higher prevalence of morbid obesity (18.3% vs 12.3%; *P*<.001), diabetes mellitus (29% vs 28.3%; *P*=.006), anemia (30% vs 23%; *P*<.001), chronic pulmonary disease (28.5% vs 26.4%; *P*<.001), heart failure (25.6% vs 24.6%; *P*<.001), and metastatic cancer (8.5% vs 6.7%; *P*<.001), but lower prevalence of coagulopathy (20.4% vs 21.5%; *P*<.001), pulmonary circulation disease (51.5% vs 54.9%; *P*<.001), atrial fibrillation (17.4% vs 20.9%; *P*<.001), renal failure (15.6% vs 17.3%; *P*<.001), liver disease (4.9% vs 6.4%; *P*<.001), and peripheral vascular disease (7.2% vs 8.5%; *P*<.001). The use of systemic thrombolysis (18.3% vs 17.1%; *P*<.001), CDT (17.3% vs 16.6%; *P*=.002), and CDE (4.1% vs 3.9%; *P*=.03) was more common among women. Women were less likely to receive MCS (1% vs 1.3%; *P*<.001) whereas the use of surgical embolectomy was not different between both groups. The differences in demographics, comorbidities, and hospital characteristics between both groups

TABLE 1. Baseline Patients and Hospital Characteristics Among Women vs Men With High-risk PE[a,b]

	Before matching			After matching		
	Women (n=58,253), n (%)	Men (n=67,648), n (%)	*P*	Women (n=16,004), n (%)	Men (n=15,920), n (%)	*P*
Median age (IQR), y	65 (52-74)	62 (52-72)	<.001	63 (51-74)	63 (53-72)	.03
Comorbidities						
Morbid obesity	10,645 (18.3)	8335 (12.3)	<.001	2110 (13.2)	2130 (13.4)	.73
Hypertension	33,690 (57.8)	39,064 (57.7)	.75	9472 (59.2)	9537 (59.9)	.39
Diabetes mellitus	16,901 (29)	19,148 (28.3)	.006	4871 (30.4)	4908 (30.8)	.60
Anemia	17,486 (30)	15,586 (23)	<.001	4110 (25.7)	4155 (26.1)	.59
Coagulopathy	11,888 (20.4)	14,547 (21.5)	<.001	3836 (24)	3779 (23.7)	.75
Pulmonary circulation disease	30,018 (51.5)	37,162 (54.9)	<.001	9045 (56.5)	8909 (56)	.51
Chronic pulmonary disease	16,598 (28.5)	17,868 (26.4)	<.001	4622 (28.9)	4515 (28.4)	.49
Atrial fibrillation/flutter	10,151 (17.4)	14,120 (20.9)	<.001	3547 (22.2)	3604 (22.6)	.51
Heart failure	14,927 (25.6)	16,629 (24.6)	<.001	4510 (28.2)	4311 (27.1)	.15
Prior MI	1893 (3.2)	3581 (5.3)	<.001	795 (5)	878 (5.5)	.16
Prior PCI	207 (0.4)	294 (0.4)	.03	51 (0.3)	71 (0.4)	.18
Prior CABG	1036 (1.8)	2629 (3.9)	<.001	539 (3.4)	615 (3.9)	.10
Prior stroke	2763 (4.7)	2928 (4.3)	<.001	812 (5.1)	748 (4.7)	.34
Renal failure	9073 (15.6)	11,671 (17.3)	<.001	3170 (19.8)	3027 (19)	.20
Liver disease	2874 (4.9)	4342 (6.4)	<.001	1103 (6.9)	1130 (7.1)	.61
Metastatic cancer	4977 (8.5)	4535 (6.7)	<.001	1283 (8)	1193 (7.5)	.24
Solid tumor without metastases	2764 (4.7)	3378 (5)	.04	906 (5.7)	850 (5.3)	.38
Peripheral vascular disease	4185 (7.2)	5721 (8.5)	<.001	1531 (9.6)	1341 (8.4)	.02
Presentation and severity						
Saddle PE	8133 (14)	9550 (14.1)	.430	2415 (15.1)	2326 (14.6)	.43
Acute cor pulmonale	9472 (16.3)	9550 (14.1)	<.001	2504 (15.6)	2430 (15.3)	.54
Cardiogenic shock	7926 (13.6)	8827 (13)	.004	2353 (14.7)	2311 (14.5)	.76
Hospital characteristics						
Large hospital	37,099 (63.7)	43,682 (64.6)	.001	10,038 (62.7)	9939 (62.4)	.72
Teaching hospital	44,538 (76.5)	52,744 (78)	<.001	12,314 (76.9)	12,117 (76.1)	.22
Treatment modalities						
Systemic thrombolysis	10,665 (18.3)	11,536 (17.1)	<.001	2688 (16.8)	2570 (16.1)	.30
Surgical embolectomy	768 (1.3)	877 (1.3)	.747	239 (1.5)	209 (1.3)	.30
CDT	10,054 (17.3)	11,225 (16.6)	.002	2446 (15.3)	2555 (16)	.23
CDE	2396 (4.1)	2620 (3.9)	.030	627 (3.9)	592 (3.7)	.55
US-facilitated CDT	2411 (4.1)	2612 (3.9)	.012	618 (3.9)	628 (3.9)	.80
Circulatory and ventilatory support						
Vasopressors	4273 (7.3)	4594 (6.8)	<.001	1286 (8)	1289 (8.1)	.90
Mechanical ventillation	35,289 (60.6)	42,344 (62.6)	<.001	10,147 (63.4)	10,135 (63.7)	.77
Mechanical circulatory support	562 (0.96)	877 (1.3)	<.001	182 (1.1)	252 (1.6)	.02
Impella	180 (0.3)	258 (0.4)	.031	44 (0.3)	73 (0.5)	.06
ECMO	82 (0.1)	56 (0.1)	.002	25 (0.2)	22 (0.1)	.70
IABP	324 (0.6)	622 (0.9)	<.001	119 (0.7)	180 (1.1)	.01

[a]CABG = coronary artery bypass surgery; CDE = catheter-directed embolectomy; CDT = catheter-directed thrombolysis; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; MI = myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism; US = ultrasound.
[b]Large hospitals were defined based on Healthcare Cost and Utilization Project definition which is based on hospital beds and are specific to the hospital's location and teaching status (https://www.hcup-us.ahrq.gov/db/vars/hosp_bedsize/nisnote.jsp) as follows; Northeastern region: rural ≥100; urban nonteaching ≥200, and urban teaching ≥425 beds. Midwest region: rural ≥50, urban nonteaching ≥175, and urban teaching ≥375 beds. Southern region: rural ≥75, urban nonteaching ≥200, and urban teaching ≥450 beds. Western region: rural ≥45, urban nonteaching ≥175, and urban teaching ≥325 beds.

are shown in Table 1. After propensity score matching, 31,924 weighted hospitalizations were included (women, n=16,004; men, n=15,920). The differences in baseline and hospital characteristics between those who were and were not included in the propensity score analysis are shown in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org).

Outcomes

In the unadjusted analysis, the rate of all-cause in-hospital mortality was higher among women (30.7% vs 27.8%; *P*<.001). In-hospital mortality has decreased among women (34.3% in 2016 Q1 vs 28.9% in 2018 Q4; *P* trend<.001) and men (30.1% in 2016 Q1 vs 26.4% in 2018 Q4; *P* trend<.001) during the study period (Figure 1).

The rate of ICH was lower among women compared with men (3.1% vs 3.7%; *P*<.001) but the rate of non-ICH bleeding events did not differ between both sexes (28% vs 27.9%; *P*=.68). The LOS was shorter among women (8 [IQR, 4-16] days vs 9 [IQR, 4-20] days; *P*<.001) (Table 2).

After propensity score matching, the rate of all-cause in-hospital mortality remained significantly higher among women (32.5% vs 29.3%; odds ratio [OR], 1.16; 95% CI, 1.08 to 1.25; *P*<.001). There was no difference in the rates of ICH and non-ICH bleeding events as shown in Table 2 and the Supplemental Figure (available online at http://www.mayoclinicproceedings.org).

On subgroup analysis, adjusted all-cause in-hospital mortality rates were not different between women and men in those aged greater than 65 years (adjusted OR, 1.05; 95% CI, 0.95 to 1.17; *P*=.30), presenting with cardiogenic shock (adjusted OR, 1.08; 95% CI, 0.91 to 1.29; *P*=.35), receiving systemic thrombolysis (adjusted OR, 1.10; 95% CI, 0.90 to 1.34; *P*=.37), and receiving surgical embolectomy (adjusted OR, 0.74; 95% CI, 0.38 to 1.45; *P*=.38). However, adjusted all-cause in-hospital mortality was higher among women receiving CDT (adjusted OR, 1.51; 95% CI, 1.04 to 2.20; *P*=.03) and CDE (adjusted OR, 2.57; 95% CI, 1.51 to 4.36; *P*<.001) (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org).

Variables Independently Associated With In-hospital Mortality

On multivariate regression analysis, female sex was independently associated with increased odds of in-hospital mortality among admissions with high-risk PE (OR, 1.18; 95% CI, 1.15 to 1.21; *P*<.001). Other variables associated with increased in-hospital mortality included age, diabetes mellitus, heart failure, pulmonary circulation disease, liver and kidney diseases, metastatic cancer, coagulopathy, and cardiogenic shock. Use

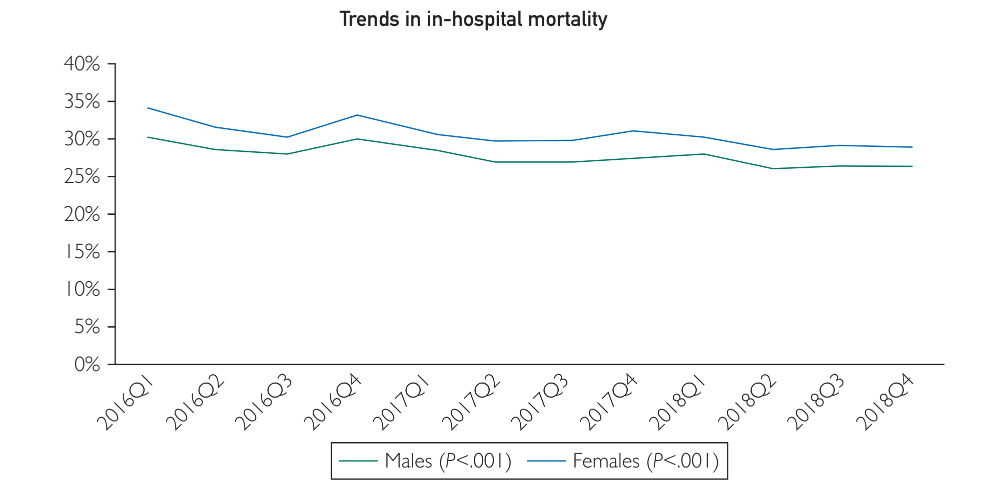

FIGURE 1. National trends of in-hospital mortality among women versus men with high-risk pulmonary embolism.

TABLE 2. In-hospital Outcomes Among Women vs Men With High-risk Pulmonary Embolism[a]

	Unadjusted incidences, n (%)			Propensity-matched incidences, n (%)				
Outcomes	Women (58,253)	Men (67,648)	*P*	Women (16,004)	Men (15,920)	Odds ratio	95% CI	*P*
In-hospital mortality	17,871 (30.7)	18,839 (27.8)	<.001	5,202 (32.5)	4,657 (29.3)	1.16	1.08, 1.25	<.001
Cardiac arrest	10,339 (17.7)	10,981 (16.2)	<.001	3,042 (19)	2,726 (17.1)	1.13	1.04,1.23	.003
Discharge to a facility	14,935 (25.6)	17,041 (25.2)	.07	4,064 (25.4)	4,025 (25.3)	1.01	0.94, 1.08	.87
ICH[b]	1,784 (3.1)	2,484 (3.7)	<.001	517 (3.2)	555 (3.5)	0.92	0.76, 1.12	.43
Non-ICH								
Respiratory tract hemorrhage[c]	2,447 (4.2)	3,447 (5.1)	<.001	659 (4.1)	811 (5.1)	0.80	0.68, 0.94	.006
Hematuria	1,305 (2.2)	2,515 (3.7)	<.001	339 (2.1)	617 (3.9)	0.54	0.43, 0.66	<.001
Gastrointestinal bleeding	4,135 (7.1)	5,196 (7.7)	<.001	1,235 (7.7)	1,305 (8.2)	0.94	0.82, 1.07	.34
Hemarthrosis	547 (0.9)	477 (0.7)	<.001	169 (1.1)	117 (0.7)	1.44	0.99, 2.13	.06
Retroperitoneal bleeding	954 (1.6)	970 (1.4)	.003	322 (2)	230 (1.4)	1.40	1.05, 1.87	.02
Hemothorax	379 (0.7)	628 (0.9)	<.001	140 (0.9)	168 (1.1)	0.83	0.57, 1.20	.32
Hemopericardium	88 (0.2)	79 (0.1)	.10	33 (0.2)	18 (0.1)	1.82	0.74, 4.65	.18
Intraocular hemorrhage	20 (0)	14 (0)	.17	NR	NR	0.83	0.13, 4.92	.81
Unspecified postprocedural bleeding	449 (0.8)	502 (0.7)	.56	128 (0.8)	118 (0.7)	1.08	0.73, 1.59	.69
Blood transfuison	9,916 (17)	9,799 (14.5)	<.001	2,865 (17.9)	2,433 (15.3)	1.21	1.12, 1.32	<.001
Non-ICH or blood transfusion	16,320 (28)	18,880 (27.9)	.68	4,681 (29.2)	4,611 (29)	1.01	0.94, 1.09	.72
Median LOS, (IQR); days, mean (SD), days	8 (4-16); 13.3 (±17.5)	9 (4-20); 15.3 (±20.1)	<.001	8 (4-17); 14.3 (±19.4)	9 (4-19); 15.3 (±20.3)			<.001

[a]ICH = intracranial hemorrhage; LOS = length of stay; NR= not reportable.

[b]Non-ICH bleeding included respiratory tract hemorrhage, hemothorax, gastrointestinal hemorrhage, retroperitoneal bleeding, hematuria, hemarthrosis, hemopericardium, intraocular hemorrhage and unspecified postprocedural bleeding.

[c]Respiratory tract hemorrhage: epistaxis, hemoptysis, and hemorrhage from the respiratory passages.

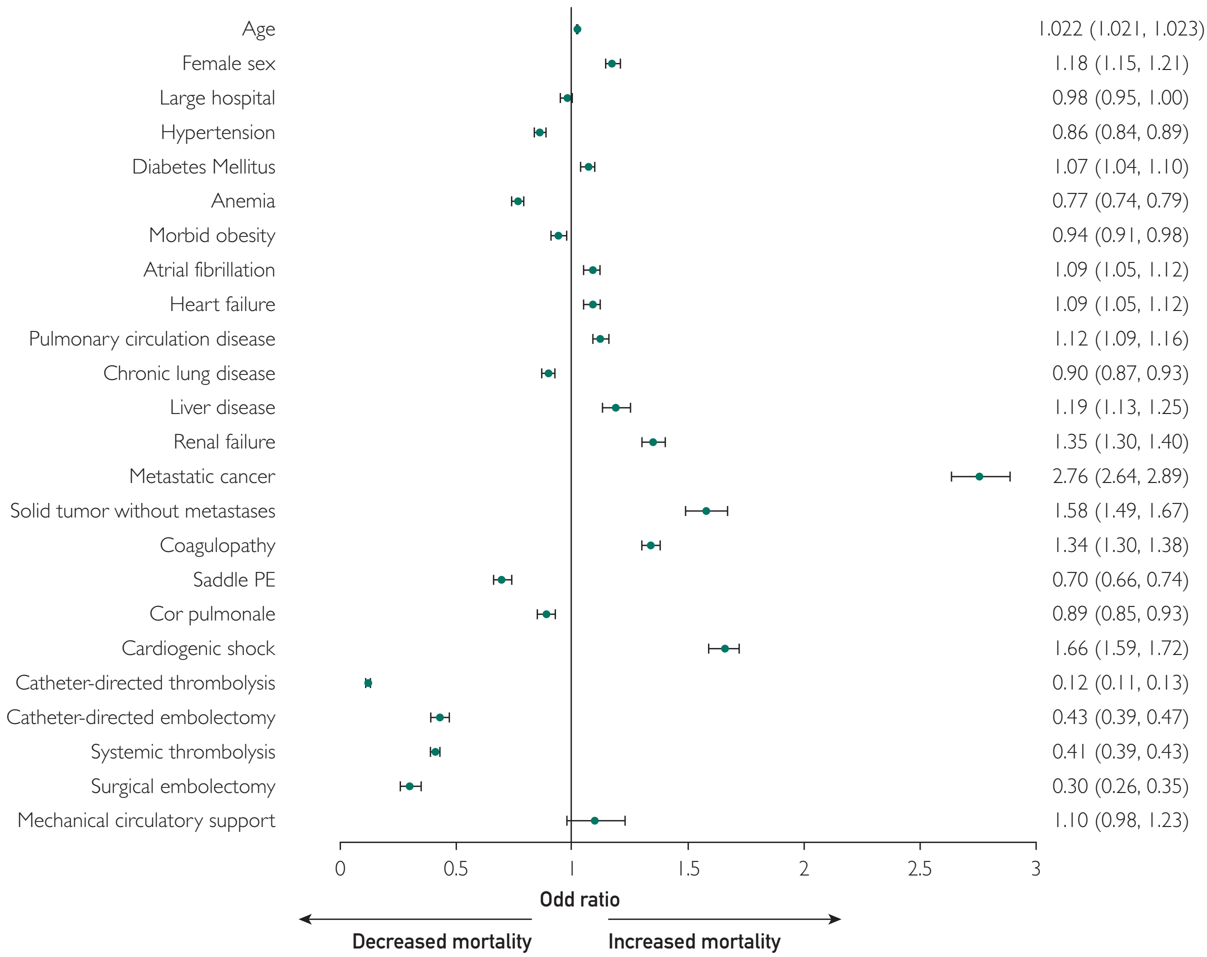

FIGURE 2. Multivariate regression analysis representing the independent variables associated with in-hospital mortality in patients with high-risk pulmonary embolism. PE, pulmonary embolism.

of CDT (OR, 0.12; 95% CI, 0.11 to 0.13; $P<.001$), CDE (OR, 0.43; 95% CI, 0.39 to 0.47; $P<.001$), systemic thrombolysis (OR, 0.41; 95% CI, 0.33 to 0.43; $P<.001$), and surgical embolectomy (OR, 0.30; 95% CI, 0.26 to 0.35; $P<.001$) were associated with lower odds of in-hospital mortality (Figure 2).

Urgent 30-Day Readmission Rates

The overall rate of urgent 30-day readmissions was 14.4% with a median time to readmission of 10 days (IQR, 4-18 days). Among urgent readmissions, 8.8% were due to recurrent PE, 5.5% due to non-ICH bleeding, and 1.3% due to ICH. There was no difference in the overall rate of urgent 30-day readmissions (14.7% vs 14.2%; $P=.09$), readmissions due to recurrent PE (8.6% vs 9.1%; $P=.36$), readmissions due to non-ICH bleeding (5.4% vs 5.6%; $P=.74$), and readmissions due to ICH (1.2% vs 1.4%; $P=.22$) between women and men.

DISCUSSION

In this large nationwide observational analysis of ∼126,000 hospitalizations with high-risk PE, we investigated the sex differences in management and outcomes. The main findings of this study were as follows: 1) women were older and had a higher prevalence of some comorbidities and risk factors

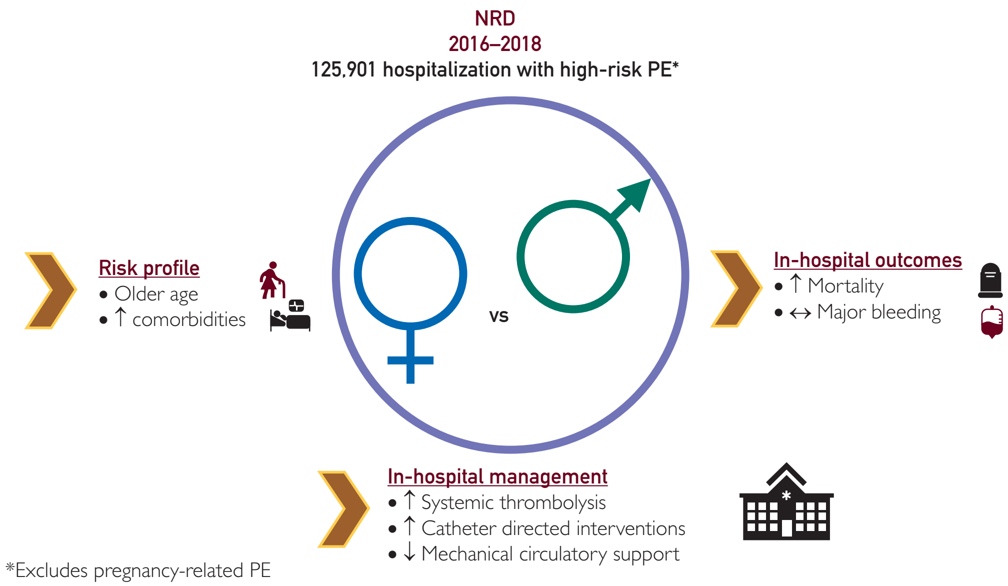

FIGURE 3. Summary of the findings of the study. NRD, nationwide readmission database; PE, pulmonary embolism.

for PE such as morbid obesity, diabetes mellitus, anemia, chronic pulmonary disease, heart failure, and metastatic cancer; 2) women were more likely to receive systemic thrombolysis, CDT, and CDE, but less MCS compared with men; 3) the rates of in-hospital mortality were higher among women in both the unadjusted analysis and after propensity score matching; 4) on multivariate regression analysis adjusting for patient and hospital characteristics, female sex was independently associated with higher odds of in-hospital mortality, whereas the use of advanced therapies was associated with lower odds of in-hospital mortality; and 5) the rates of ICH and non-ICH bleeding and urgent 30-day readmissions were not different between both sexes (Figure 3).

Among all-comers with PE irrespective of the severity, some earlier studies have shown that men had higher mortality compared with women across different racial groups in the United States[9–11] and Japan.[12] However, the results of recent studies have been conflicting with some studies showing similar mortality in both sexes,[13-18] and others have reported higher mortality among women.[19,20] Studies have also shown that mortality from acute PE declined over time in both men and women, but the decline was less pronounced among women.[11] The current study shows that women admitted with high-risk PE had higher rates of in-hospital mortality compared with men, even after adjusting for age and baseline characteristics. Additionally, in-hospital mortality in both sexes was high, highlighting that better risk stratification tools and therapies are needed to improve the prognosis in this high-risk cohort.

Some reasons might explain the higher rates of mortality among women and those reasons could be related to the biological (ie, sex) differences where women may have different disease expression and/or responses to therapy. There are also sociocultural (ie, gender) factors where women might be treated differently merely based on their gender.[26] Similar to prior studies,[14,15,20] our analysis showed that women were older and had a higher prevalence of some comorbidities and risk factors for PE. Women may have delayed presentation leading to a worse prognosis. Higher pain tolerance or misinterpretation of the symptoms of PE by women might lead to delay in seeking medical advice. Furthermore, the response to therapies might differ between men and women. One study of patients with submassive PE has shown that early systemic thrombolysis (<24 hours) compared with heparin was associated with lower 30-day mortality in men but not in women.[27] Additionally, the rates of major bleeding were higher in women receiving thrombolysis, although the rates of bleeding were not different in our analysis. Mortality was higher in women among those receiving CDT or CDE in our study. Whether this is related to women having smaller size pulmonary arteries[28,29] is unclear.

In the current study, we did not observe a significant disparity in the use of advanced therapies based on sex, aside from the lower rates of using MCS in women. In another US tertiary center analysis of all-comers with PE, there was no difference in the use of CDT, CDE, surgical embolectomy, and ECMO between both sexes.[15] Other studies have also shown similar rates of thrombolysis between men and women.[18-20] The role of CDI in the treatment of PE is rapidly evolving.[30] However, most of the trials examining CDI in acute PE focused on right ventricular/left ventricular ratio as a surrogate marker for improved short-term outcomes with no data on mortality benefit.[31] Societal guidelines recommend systemic thrombolysis as the first reperfusion therapy in patients with high-risk PE, whereas CDI is considered an alternative to surgical embolectomy in patients who fail or have a contraindication to systemic thrombolysis.[7,31−33] Our findings show that advanced therapies were associated with lower in-hospital mortality suggesting that these therapies were associated with improved outcomes in carefully selected patients with high-risk PE. We also found that the use of MCS was lower in women despite having similar rates of cardiogenic shock to men. Our data are consistent with prior analyses showing that women with cardiogenic shock receive MCS less frequently than men especially in the setting of acute myocardial infarction.[34−38] Clinicians may be hesitant to use large-bore MCS in women given the increased risk of vascular complications due to the smaller caliber of the femoral artery.[35,39]

Although the rates of in-hospital bleeding events were not different between both sexes in our study, the sites of bleeding differed. Men had higher rates of respiratory tract hemorrhage and hematuria, whereas women had higher rates of retroperitoneal hemorrhage and blood transfusion. Intracranial hemorrhage was similar between both sexes. Similar to our results, recent observational studies from the United States and Japan found similar rates of major bleeding, fatal bleeding, ICH, and blood transfusion between both sexes.[15,17] An analysis of the Registro Informatizado de Enfermedad TromboEmbolica (RIETE) registry found that female sex was not an independent predictor of major bleeding following venous thromboembolism.[18] On the other hand, a retrospective study from Spain found that the 30-day risk of major bleeding in women was ∼2 times higher than men,[20] and a recent meta-analysis showed that women receiving anticoagulation for venous thromboembolism might be at a marginally higher risk of major bleeding compared with men.[40] However, this was not the case in our analysis in which the 30-day readmission rate due to bleeding was not different between both sexes.

Study Limitations

To the best of our knowledge, this study is the first to examine the sex differences in management and outcomes of patients with high-risk PE. The strengths of this investigation are driven by the large sample size with national representation. However, the findings of this study should be interpreted in the context of some limitations. First, this study is a retrospective observational study with its inherent limitation of selection bias. We tried to mitigate that by performing propensity score matching and multivariable regression analyses. Second, given the administrative nature of the NRD, the study is subject to coding errors and data quality at the site of collection, without the ability to adjudicate accuracy. Additionally, the NRD uses discharge not admission diagnoses, so we could not ascertain if PE was present on admission or later during the course of hospitalization. The NRD does not cross the calendar year, so it is impossible to track if the same patient was readmitted in a different year. Third, we excluded any PE occurring during pregnancy because this is a sex-specific risk factor for PE. Although this might be considered a limitation, it removes the confounding of pregnancy from this analysis. Fourth, the temporal relationship of certain outcomes cannot be reliably established. Fifth, data on discharge medications — including anticoagulation — and compliance are not available in the NRD. In addition, the database lacks data on the use of oral contraceptives or hormonal replacement therapy. Sixth, long-term outcomes, including long-term mortality and bleeding, could not be assessed. Seventh, the clinical reasoning for choosing one modality of advanced therapy vs the other could not be determined, and the exact reason behind the lower MCS use in women remains unclear. Finally, the NRD lacks data on imaging and cardiac biomarkers which could help better risk-stratify patients (especially those with submassive PE) and might influence the decision regarding the use of advanced therapies.

CONCLUSION

In this contemporary observational cohort of patients admitted with high-risk PE, women had higher rates of in-hospital mortality despite receiving advanced therapies more frequently, whereas the rate of major bleeding events was not different from men. The rates of in-hospital mortality did not change in both sexes. These findings have important implications, as we strive for equitable care, irrespective of biological sex. Efforts are needed to minimize the excess mortality observed among women.

POTENTIAL COMPETING INTERESTS

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

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CDE,** catheter-directed embolectomy; **CDI,** catheter-directed intervention; **CDT,** catheter-directed thrombolysis; **ICH,** intracranial hemorrhage; **MCS,** mechanical circulatory support; **NRD,** Nationwide Readmissions Database; **OR,** odds ratio; **PE,** pulmonary embolism; **US-CDT,** ultrasound-facilitated catheter-directed thrombolysis

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