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Sex disparities in hospitalization and mortality rates for venous thromboembolism

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Abstract Venous thromboembolism (VTE) is a major health problem for both men and women. Whether sex disparities exist for outcomes after acute VTE is unknown. We sought to measure sex-specific rates of hospitalization for and mortality from acute VTE. We used a population-based administrative dataset from Alberta, Canada, covering the years 2002 to 2012. We used Poisson regression to measure the incidence rate ratio for hospitalization and Cox regression to test for sex disparities in short-term all-cause mortality after adjusting for potential confounders. Of those diagnosed with VTE, 55.9% were women. The proportion of hospitalized women for VTE was 24.4 versus 27.8% in men ($p<0.001$). The risk adjusted incidence rate ratio for VTE hospitalization increased with age for both sex. While women younger than 80 years old were less likely to be hospitalized than men, sex disparities for the risk of hospitalization were not significant after age 80 ($p=0.93$). The adjusted 90-day all-cause mortality rate for women was 4.0% compared to 4.9% in men (adjusted HR = 1.0, $p=0.49$). Women with acute VTE were less likely than men to be hospitalized in most age groups, but sex disparities in short-term all-cause mortality were not found.

Keywords AB-VTE · Pulmonary embolism · Deep vein thrombosis · Sex · Mortality · Hospitalization

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Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common vascular condition that carries significant risks for morbidity and mortality [1]. While clearly VTE is a major health problem for both men and women, there may be sex disparities in the epidemiology and outcomes of VTE. Women are uniquely exposed to known VTE risk factors such as hormone replacement therapy, estrogen containing oral contraceptives, pregnancy [2] and the postpartum period [3]. Reports in the literature on sex disparities in VTE epidemiology report conflicting results. Some studies evaluating sex disparities in the incidence and recurrence of VTE have found no significant difference in VTE incidence between men and women [4, 5] regardless of the age group. A higher incidence of VTE among women was described in a nationwide study in the United States [6] and a community study in France [7]. Some studies have suggested a higher VTE incidence in women of childbearing age than in men of the same age, while the incidence of VTE in men older than 45 years of age [1, 8] was either higher than in women or not statistically different [9].

In a previous study of a population-based cohort in Alberta, Canada, we found that young women aged 18–39 years old had a significantly higher incidence of acute VTE than men of the same age group. The adjusted incidence rate ratio (IRR) of VTE in men versus women for this age group was 0.45 (95% CI 0.42–0.47). There was no statistically significant difference between sex in older age groups [10].

There are even less data analyzing whether sex disparities exist in VTE outcomes. Agarwal et al. [11] assessed differences in outcomes, treatment and complications between women and men in patients admitted for PE, and

found higher complication rates and adverse events among women than among men. A systematic review assessing the efficacy and safety of new oral anticoagulants compared to vitamin K antagonists in treating acute VTE generally found no difference in these outcomes per sex [12]. Current data on sex disparities in hospitalization rates of VTE and mortality are limited. Two studies observed a higher hospitalization rate among women [13, 14], whereas one study did not find a difference between sex [15].

To address the paucity of data regarding the impact of sex on acute VTE outcomes, we sought to measure the sex-specific rates of admission to hospital as well as short-term all-cause mortality rates in a population-based sample using administrative health databases in the province of Alberta, Canada.

Methods

Study design

We performed a population-based retrospectively-ascertained cohort study from the Alberta-Venous Thromboembolism (AB-VTE) database by linking five provincial health administrative databases from April 1, 2002 to March 31, 2012 in Alberta, Canada.

Data source

Data for the current analysis were obtained from the AB-VTE database that contains ambulatory care data from the emergency department and the outpatient clinic visits, hospital inpatient discharge data, physician claims data, population registry data and vital statistics. The ambulatory care database provides up to 10 diagnostic and 10 procedure codes, whereas the hospital inpatient database provides up to 25 diagnostic and 20 procedure codes for each hospitalization record for this 10 year period. Alberta Vital Statistics provide mortality data in Alberta. A description of the AB-VTE database design can be found in a previous publication [10].

Study population

We only included residents of Alberta aged 18 years or older having an inpatient or outpatient diagnostic code of DVT and/or PE and who were covered by an Albertan health care insurance plan between April 1, 2004 and March 31, 2012. The diagnosis of acute VTE was definite if the patient had a diagnostic event code within 7 days of a VTE-related imaging code. A validated case-defining criteria was previously created for this purpose [16]. The following codes were used to define DVT: ICD-9 CM: 451.1. 451.2, 451.8, 451.9, 453.2, 453.8, or 453.9; ICD-10: I80.2, I80.3, I80.1, I82.8, I80.9, I82.9, I80.8, O22.3, O22.9, or O87.1. Whereas, ICD-9 CM: 415.0 and 415.1 and ICD-10: I26.9, I26.0 codes were used to define PE. Patients coded with both DVT and PE were analyzed with the PE cohort. Using a 2-year washout period for each patient, only the incident cases of VTE were considered from the time of entry to the study until their death or the end of the study (March 31, 2012). The validation of the accuracy of our case finding algorithm in detecting acute symptomatic VTE has been previously done against chart audit in Alberta [16] with a specificity of 83.07%, a specificity of 97.11% and a positive predictive value of 83.1%.

Study outcomes and covariates

The primary outcomes of our study were the hospitalization rates and 90-day all-cause mortality rates among men and women diagnosed with VTE. Outcomes were stratified by sex. Comorbidities were defined as those found in the Charlson Comorbidity Index [17] and recorded from the ambulatory care and inpatient databases if they were present within 1 year prior to the visit for VTE. Risk factors were reported if they were present before the identification of VTE and included diagnosis of cancer 1 year before the event, major surgery, major trauma, hip fracture within the previous 3 months, ongoing or recent pregnancy (within 3 months from delivery) and hospitalization for other causes for more than 3 days in the last 3 months.

Statistical analysis

We presented continuous variables as means and standard deviations and categorical variables as frequencies and percentages in the description of baseline characteristics. We calculated the rate of hospitalization for each sex by dividing the number of patients per sex admitted to the hospital by the total number of patients with VTE per sex stratified by event type (PE or DVT). A multivariate Poisson regression model was constructed to calculate the IRR for hospitalization of DVT and PE. Because of the significant interaction between sex and age groups, outcomes were reported by age groups for each sex. We also used multivariate Cox regression analysis models to assess any sex disparities in short-term (<90 days) all-cause mortality. All outcomes were adjusted for age, comorbidities, year of diagnosis and provoking factors. A 2-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata (Stata Statistical Software: Release 13; StataCorp LP, College Station, TX).

Results

Over the 10 year period of our study, 31,656 incident cases of acute symptomatic venous thromboembolism were identified in Alberta. 17,681 out of these 31,656 patients (55.9%) diagnosed with acute VTE were female. Of these women, 4979 cases were diagnosed with PE (28.2%) compared to 12,702 cases diagnosed with DVT (71.8%). As for men, 3662 of 13,975 had PE (26.2%) and 10,313 had DVT (73.8%). The overall mean age of women diagnosed with VTE was 56.5 (±19.7) years, compared to 58.7 (±16.6) years for men ($p < 0.001$). The prevalence of comorbidities was generally lower in women with VTE than men. In women versus men with acute VTE, the prevalence of hypertension was the highest among all the comorbidities (18.5 vs. 20.6%, $p < 0.001$) followed by malignancy (15.0 vs. 17.9%, $p < 0.001$), and diabetes mellitus (10.4 vs. 13.3%, $p < 0.001$). Recent hospitalization for more than 3 days in the last 3 months was the most common risk factor among women and men but higher in men (28.7 vs. 31.9%, $p < 0.001$) while pregnancy and postpartum were associated with 6.9 and 3.9% of acute VTE in women respectively. In women, 54.8% of venous thromboembolic events were unprovoked compared to 55.3% in men ($p = 0.32$) and 15.0% were cancer associated compared to 17.9% in men ($p < 0.001$). Table 1 summarizes baseline characteristics, comorbidities and risk factors.

Hospitalization rate

During the study period, 4311 of 17,681 women were admitted for VTE (24.4%) compared to 3887 of 13,975 men (27.8%) ($p < 0.001$). 13.5% of these women were admitted for PE and 10.9% for DVT (Table 2; Fig. 1). The hospitalization rates of DVT and PE among men and women is given in Table 3. After adjusting for comorbidities, year of diagnosis and provoking factors, we found that the risk adjusted incidence rate ratio for hospitalization of DVT and PE increased significantly with age for both sex. Men aged 40–59 years old were 1.7 times more likely to be admitted to the hospital for DVT compared to the younger age group (18–39 years old) (95% CI 1.6–1.9). This rate increased to 2.3 fold in those 80 years and older (95% CI 2.1–2.6). Similarly, women were 1.5 times (95% CI 1.4–1.7) more likely to be hospitalized for DVT at 40–59 years old and more than 2.3 times as likely at 80 years of age or older (95% CI 2.1–2.6) compared to the younger age group (18–39 years old). Patients with PE were at higher risk of being admitted than those with DVT for the same age group. The risk for PE hospitalization increased with age to reach about 11 fold in the elderly for both sex. Women were less likely to be hospitalized than men for both conditions (DVT and PE)

Table 1 Patient demographics, comorbidities and risk factors stratified by sex

	Women (N, %)	Men (N, %)
Total number of VTE cases	31,656	
VTE	17,681 (55.9)	13,975 (44.1)
PE	4979 (28.2)	3662 (26.2)
DVT	12,702 (71.8)	10,313 (73.8)
Mean of age, years	56.5	58.7
Age groups		
18–39	4209 (23.8)	1898 (13.6)
40–59	5380 (30.4)	5303 (37.9)
60–79	5470 (30.9)	5162 (36.9)
≥80	2622 (14.8)	1612 (11.5)
Comorbidities (<1 year)		
Acute myocardial infarction	500 (2.8)	777 (5.6)
Congestive heart failure	899 (5.1)	884 (6.3)
Peripheral vascular disease	394 (2.2)	525 (3.8)
Cerebrovascular accident	553 (3.1)	565 (4.0)
Chronic obstructive pulmonary disease	1938 (11.0)	1561 (11.2)
Peptic ulcer disease	210 (1.2)	214 (1.5)
Liver disease	227 (1.3)	274 (2.0)
Diabetes mellitus	1841 (10.4)	1851 (13.2)
Renal disease	528 (3.0)	668 (4.8)
Malignancy (except skin)	2654 (15.0)	2504 (17.9)
Anemia	1507 (8.5)	1133 (8.1)
Thrombocytopenia	159 (0.9)	167 (1.2)
Hypertension	3263 (18.5)	2874 (20.6)
Neurological disease	548 (3.1)	507 (3.6)
Dementia	375 (2.1)	220 (1.6)
Connective tissue disease	402 (2.3)	158 (1.1)
Hemiplegia	120 (0.7)	163 (1.2)
AIDS	5 (0.0)	25 (0.2)
Valvular disease	300 (1.7)	277 (2.0)
Falls	1785 (10.1)	1152 (8.2)
Alcoholism	206 (1.2)	492 (3.5)
Hypothyroidism	721 (4.1)	254 (1.8)
Risk factors (<90 days)		
Recent hospitalization (≥3 days)	5067 (28.7)	4453 (31.9)
Ongoing pregnancy	1219 (6.9)	0
Recent delivery	697 (3.9)	0
Fractured hip	150 (0.8)	76 (0.5)
Hip joint replacement	215 (1.2)	193 (1.4)
Knee joint replacement	398 (2.3)	241 (1.7)
Major trauma	357 (2.0)	349 (2.5)
Major surgery	389 (2.2)	429 (3.1)
Cancer associated events	2654 (15.0)	2504 (17.9)
Provoked events	6728 (38.1)	5140 (36.8)
Unprovoked events	9682 (54.8)	7731 (55.3)

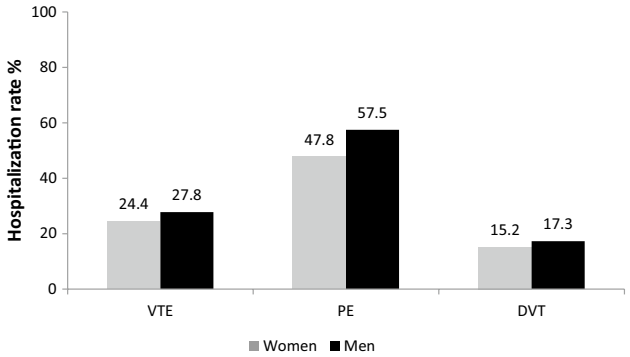

Fig. 1 Hospitalization rates for venous thromboembolism, pulmonary embolism and deep vein thrombosis by sex

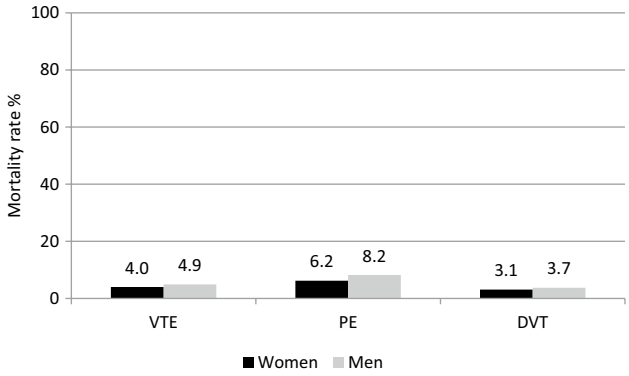

Fig. 2 90-day all-cause mortality rates for venous thromboembolism, pulmonary embolism and deep vein thrombosis by sex

Table 2 Hospitalization rates and 90 day all-cause mortality rates for venous thromboembolism, pulmonary embolism and deep vein thrombosis by sex

	Women	Men	p value
Hospitalization rate, N (%)			
VTE	4311 (24.4)	3887 (27.8)	<0.0001
PE	2382 (47.8)	2107 (57.5)	
DVT	1929 (15.2%)	1780 (17.3)	
Mortality rate, N (%)			
VTE	703 (4.0)	688 (4.9)	0.49
PE	307 (6.2)	302 (8.2)	
DVT	396 (3.1)	386 (3.7)	

Table 3 Risk-adjusted incidence rate ratio (IRR) for hospitalization with pulmonary embolism and deep vein thrombosis among men and women stratified by age groups

	IRR (95% CI) Women	IRR (95% CI) Men	p value
DVT			
Age groups			
18–39	1	1	
40–59	1.5 (1.4–1.7)	1.7 (1.6–1.9)	<0.001
60–79	1.8 (1.6–1.9)	1.9 (1.8–2.1)	0.02
≥80	2.3 (2.1–2.6)	2.3 (2.1–2.6)	0.93
PE			
Age groups			
18–39	4.9 (4.5–5.4)	7.8 (6.7–9.1)	<0.001
40–59	7.3 (6.4–8.4)	8.5 (7.4–9.7)	<0.001
60–79	8.7 (7.6–9.9)	9.4 (8.3–10.8)	0.02
≥80	11.4	11.3	0.93

if they were less than 80 years old (Table 3), but after age 80, there were no significant sex disparities for the risk of hospitalization (p = 0.93).

Short-term all-cause mortality rate

Women with VTE had a 90-day all-cause mortality rate of 4.0% (6.2% in the group of patients having PE and 3.1% in those having DVT) compared to 4.9% in men (8.2% in patients diagnosed with PE and 3.7% in those diagnosed with DVT) (Table 2; Fig. 2). After adjusting for comorbidities, year of diagnosis, age and risk factors, we did not find sex disparities in the rate of short-term all-cause mortality (HR 1.0, 95% CI 0.9–1.2; p = 0.49).

Discussion

In a population-based cohort of acute VTE in Alberta, Canada, we found statistically significant sex disparities for hospitalization among certain age groups, but no differences in 90-day all-cause mortality. In our study, men younger than 80 years old had a higher likelihood to be hospitalized than women of the same age group. These findings were in contrast with the few published reports available on sex disparities, as they found the opposite. In a study estimating the changes of hospitalization rates of PE in Australia over a 10-year period among sex and age groups, women had a significantly higher rate of hospitalization than men over the study period. They also reported that young women had a higher mortality [13]. Minges et al. reported a similar rate of PE hospitalization between sex after adjusting for age and race between 1999 and 2010 [15]. Another study of women in their reproductive age showed that the rate of admission due to VTE increased over the study period whereas that of men did not [14]. Overall, our results support that sex disparities in rates of hospitalization for acute VTE are present and real.

Possible explanations for the apparent higher admission rates in men include the slightly higher age in men at presentation, as well as incomplete adjustment for confounders.

In our cohort, men had a statistically higher rate of certain comorbidities (hypertension, cancer and diabetes) but the higher rate of admission was still seen after adjustment for comorbidities. Patient and physician choices play an important role in the admission decision. Women may tend to refuse hospitalization because they have other responsibilities as caregivers [18]. Women may also be more apt to seek medical advice than men [19, 20]. This role may permit earlier diagnosis and treatment of the condition before the development of complications that could warrant hospitalization. Moreover, the lower admission rate for women could be explained by the fact that some women might misinterpret the signs and symptoms of PE as being those of anxiety because of the similarity of presentation especially in the young age group [21], therefore, they might refuse to seek medical advice or to be admitted to hospital. Others suggest that women have a better knowledge about their health and report their health issues more accurately than men [22]. This may alter the decision of admission and undergoing further investigations. Further research is required to identify what factors determine a decision for or against hospitalization for acute VTE, and how sex influences this decision.

We did not find a difference in short term all-cause mortality between men and women after adjustment for confounders. Although we could not specify the deaths related to VTE, our findings are consistent with two prior reports that studied PE and DVT specific mortality. The first, a study conducted in England, reported primary PE mortality was not statistically different between sex [23]. The second, a review on the efficacy and safety of new oral anticoagulants, found a similar VTE mortality for both sex [12]. Other reports of sex disparities in short-term mortality for VTE are conflicting. Horlander et al. observed a higher mortality rates in men compared to women between 1979 and 1998 [24]. Similarly, Minges et al. reported a higher 30-day and 6-month mortality rates for PE in men than in women [15]. In contrast, Shiraev et al. observed a higher mortality rate of PE among women in Australia, particularly in the young age group [13]. The conflicting reports in the literature regarding the difference in mortality between sex depend probably on the study population and the number of autopsies studied.

Our study was retrospective observational in nature, and therefore limited by potential bias. Administrative data are imperfect and less accurate than gold standard methods of ascertaining the diagnosis of DVT or PE such as imaging tests. The use of a 2-year washout period for incident case assessment might mask the true admission and mortality rates of both sex. Furthermore, we were unable to ascertain how some risk factors for thrombosis may impact thrombosis severity but which may be unequally distributed between men and women, including smoking, pregnancy [3], oral contraceptives (OCP) [14] or hormone replacement therapy (HRT) use [25]. In addition, our administrative data does not provide information about medications, vital signs and the severity of the condition which could help interpreting the differences. Finally, we relied on the vital statistics to identify death, but we could not accurately identify the exact cause of death. Therefore, we reported all-cause mortality because VTE-related mortality cannot be identified using this database.

Our study has several strengths. Our cohort was large and population-based, and therefore included all cases of acute VTE in the province of Alberta over the time period studied, limiting bias. Our results are therefore likely generalizable to other jurisdictions of similar size and with a universal healthcare system. In addition, we used a validated case-defining criteria using the ICD-9 and ICD-10 codes for both DVT and PE as well as diagnostic procedures codes that has been established in previous studies [16].

Conclusion

In a population-based cohort of acute VTE, we found lower rates of hospitalization for acute VTE in women compared with men in most age groups, even after adjustment for confounders, including comorbidities. However, we did not identify any sex disparities in short-term all-cause mortality associated with acute VTE. More research is required to identify the causes and consequences of these sex disparities associated with VTE.

Compliance with ethical standards

Conflict of interest M.S. McMurtry is supported by the Heart and Stroke Foundation, Canada. C. Wu received honoraria and consultancy fees from Pfizer and LEO Pharma. G Alotaibi is supported by a scholarship from King Saud University.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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