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Sex Differences in Hip Fracture Surgery: Preoperative Risk Factors for Delirium and Postoperative Outcomes

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Abstract

Objectives—To describe the differences observed in risk factors for delirium and outcomes between men and women undergoing hip fracture repair surgery.

Design—Prospective cohort study.

Setting—Academic medical center.

Participants—Individuals with acute hip fracture admitted to an academic medical center (N=431).

Measurements—Information on preoperative demographic characteristics, medical history, laboratory results, and postoperative outcomes was obtained according to history and chart review. Delirium was assessed using the Confusion Assessment Method.

Results—The overall incidence of postoperative delirium was 34%, with men more likely to experience postoperative delirium (44.8%) than women (30.2%) ($P = .004$). Male sex was associated with postoperative delirium in individuals with hip fracture, even after adjusting for other preoperative risk factors. Other significant preoperative risk factors included age, dementia, Parkinson's disease, and American Society of Anesthesiologists classification. Men were also

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more likely to experience other postoperative complications and have longer hospital length of stay.

Conclusion—Men are at higher risk of postoperative delirium after hip fracture repair than women and have more postoperative surgical complications. Their higher risk of postoperative delirium may be due to their underlying preoperative disease severity.

Keywords

hip fracture; delirium; postoperative; risk factors; sex

The number of hip fractures in adults aged 65 and older continues to rise in the United States, with most recent estimates approaching 300,000 hip fractures per year by 2030.¹ Hip fracture is costly, with estimated annual Medicare expenditures of \$2.9 billion.² It is also associated with a multitude of complications, including long rehabilitation, loss of independence, and high mortality.³

Hip fracture in the United States is more common in women, although their rate of hip fracture is decreasing, possibly because of increases in bone mineral density.⁴ That said, an increase in the number of hip fractures in men has offset the decrease in hip fracture rate in women. One study that used National Hospital Discharge Data estimated that the number of hip fractures in women is projected to decrease by 3.5% between 2010 and 2030 and to increase by almost 52% in men.¹ The reasons for the increase in the number of hip fractures in men may include an aging population with greater number of men at risk of osteoporosis and under recognition and under treatment of osteoporosis in men.⁵ This trend of increasing number of hip fractures in men is troubling because mortality from hip fracture is much higher in men than women, with one study showing 1-year mortality of 37.5% in men and 28.2% in women.⁶

A well-known complication of hip fracture surgery is postoperative delirium, with an incidence ranging from 13% to 56%.⁷ Similar to hip fracture, delirium is associated with high healthcare costs, poor functional recovery,⁸ and institutionalization.⁹ The effect of preoperative cognitive status on magnitude and types of risk factors for delirium after hip fracture surgery was recently examined.¹⁰ Among the risk factors for postoperative delirium was male sex, particularly in individuals without dementia.¹⁰ Associations between sex and delirium have been reported in various clinical settings, including surgery,^{11,12} but some studies have failed to find an association with sex.^{11,13-15}

In addition to delirium, the incidences of other postoperative complications are also reported to be higher in men.¹⁶ Although many studies have reported sex differences in outcomes after hip fracture, these have tended to focus on longer-term outcomes,^{17, 18} and few have reported on the immediate postoperative period, which can be a time of high morbidity and mortality for individuals with hip fracture.

The goal of the present study was to describe differences in preoperative risk factors associated with postoperative delirium between men and women undergoing hip fracture repair surgery as the first step in understanding the association between male sex and

delirium. Whether men have more postoperative complications than women in this population was also explored.

METHODS

Study Design

Individuals aged 65 and older consecutively undergoing hip fracture repair ($n = 726$) were approached for consent to collect their perioperative clinical data for research purposes from 1999 and 2008 at the Johns Hopkins Bayview Medical Center. The Johns Hopkins institutional review board approved the study, and all participants gave informed consent. Individuals who a trained research nurse determined had preoperative delirium based on the Confusion Assessment Method (CAM) ¹⁹ were ineligible for the study. Of the remaining eligible individuals, 431 consented to participate in the study. Postoperative delirium was measured using the CAM on the second postoperative day (POD2), to allow for optimal detection of postoperative delirium without potential residual effects of anesthesia. Geriatricians had assessed most participants preoperatively, and a geriatric consultation service followed them postoperatively throughout their hospitalization.

Predisposing factors were chosen based on previous data analyses and literature review. ^{7, 10, 20} Some of these risk factors were identified and validated in medical patients ²⁰ and later separately validated in individuals undergoing hip surgery.²¹ Preoperative risk factors were obtained from chart review and interview and categorized into demographic, neurological, psychiatric, and medical comorbidities and laboratory results. A diagnosis of probable dementia was assigned if a participant had a Mini-Mental Status Examination score of less than 24 or a diagnosis of dementia from a geriatrician from the preoperative evaluation. Laboratory abnormalities were defined a hematocrit less than 41% for men and less than 36% for women (anemia), blood urea nitrogen:creatinine ratio greater than 20 (azotemia), and a white blood cell count greater than 11,000/ μ L (leukocytosis). Those who had a Foley catheter in place at the time of discharge were assumed to have urinary retention.

Analyses

A series of selected preoperative and postoperative risk factors were compared between men and women. The Student *t*-test was used for continuous variables and the Fisher exact test for categorical or binary variables. Odds ratios for the associations between each preoperative risk factor and delirium were estimated using bivariate analysis separately according to sex. A baseline risk factor was included in the multivariate model if the risk factor was significant at the level of $P \leq .05$ in all participants or in subgroups based on sex. To determine whether the effect of a risk factor varied according to sex, interaction terms were created with each baseline risk factor and the sex variable. Only statistically significant interaction terms were kept in the final multivariate logistic regression model. Fitted probabilities were then calculated based on logistic regression parameter estimates. All analyses were conducted using Stata (StataCorp LP, College Station, TX).

RESULTS

The incidence of postoperative delirium was 34% and was greater in men (44.8%) than women (30.2%) ($P=.004$). At baseline, men were younger than women by an average of 2 years and were more likely to be black and to have a history of active alcohol use. None of the baseline neurological and psychiatric conditions differed significantly between men and women, although men had significantly more comorbidities, including history of coronary artery disease, chronic obstructive pulmonary disease, cancer, chronic renal insufficiency, and syncope. The only exception was the presence of hypothyroidism, which was significantly higher in women than men. There were significantly more women with lower American Society of Anesthesiologists (ASA) classification, which is a preoperative assessment of disease severity. A significantly greater percentage of women than men had azotemia and leukocytosis but not anemia (Table 1). Next, associations between preoperative risk factors and postoperative delirium were assessed in all participants and separately according to sex. Of the demographic characteristics, only age remained significantly associated with postoperative delirium in bivariate analysis. As expected, dementia diagnosis was strongly associated with delirium in the combined group as well as separated according to sex. Parkinson's disease was associated with postoperative delirium in the combined group, but this was based on a small number of subjects. Some of the preoperative risk factors such as history of congestive heart failure (CHF), atrial fibrillation, number of comorbidities, and ASA classification were significantly associated with postoperative delirium in the combined group, but when separated according to sex, CHF and number of comorbidities remained statistically significant in women, but only ASA classification remained statistically significant in men and women. None of the laboratory abnormalities were significantly associated with postoperative delirium in bivariate analysis (Table 2).

In the multivariate analysis, sex was independently associated with postoperative delirium after adjusting for other risk factors. Other risk factors that were strongly associated with postoperative delirium also included age, dementia, Parkinson's disease, and ASA classification (Table 2). Fitted probabilities of postoperative delirium as a function of sex and age showed that risk of postoperative delirium increased by 2% for every 5-year increase in age in women and decreased by 1% for every 5-year increase in age in men.

The incidence of postoperative complications was higher in men than women for all of the 11 outcomes examined. Three of the complications (delirium, acute renal failure, urinary retention) were significantly more likely to occur in men than women, and there was a trend toward significance in two others (pneumonia and new arrhythmia) (Table 3). The association between urinary retention and acute renal failure was not significant (data not shown). Men also had a longer hospital stay (8.0 ± 5.8 days) than women (6.3 ± 3.9 days) ($P = .006$). There was no difference in discharge destination between men and women, with most participants discharged to rehabilitation centers.

DISCUSSION

There were differences in preoperative risk factors associated with postoperative delirium between men and women undergoing hip fracture repair. The association between male sex

and postoperative delirium remained strong even after adjusting for other risk factors. It was also found that the incidence of other immediate postoperative complications, including acute renal failure and urinary retention, were significantly higher in men.

One factor that may contribute to the strong association between male sex and postoperative delirium is underlying disease severity. Even though the men in this study were slightly younger than the women on average, they had poorer overall health at baseline as demonstrated by more comorbidities and a greater likelihood of an ASA classification of 3 or 4. The strength of association with ASA classification and postoperative delirium in bivariate analysis was stronger in men as well. These findings are consistent with the literature, which has shown that men have higher ASA classifications at the time of admission for hip fracture than women.¹⁶ ASA classification was originally developed for the standardization of physical status and is based on an anesthesiologist's global impression of an individual's disease severity and overall health. Higher preoperative ASA classification has been found to be associated with higher risk of postoperative delirium in various surgical procedures,^{22, 23} including hip fracture repair.²⁴ In the current study, ASA rating may have captured global disease severity, which may not be detected when individual comorbidities are examined separately, although the limitation of ASA classification is that it is a subjective scoring system and may be subject to interrater variability, which may limit the generalizability of the findings.²⁵ In addition, because the association between sex and postoperative delirium remained strong even after adjusting for other factors including comorbidities and ASA classification, it is likely that there are other risk factors that are associated with male sex that were not factored into the model. In terms of sex-specific associations between individual medical conditions and postoperative delirium, there was a significant association between history of CHF and delirium in women but not in men. In addition, even though baseline laboratory abnormalities were more common in women than men, there was no significant association between any of these laboratory abnormalities and postoperative delirium. Because laboratory abnormalities have been found to be important preoperative risk factors in other studies,²⁶ these differences may also be due to different cutoffs used to define the normal range of laboratory values.

In addition to postoperative delirium, men also had a higher incidence of complications in the immediate postoperative period, which may be reflected in their longer length of hospital stay. This is similar to another study in which the incidence of complications was higher in men than women for seven of the 11 complications studied.¹⁶ In the current study, the most common complication in men and women was postoperative delirium, urinary tract infection (UTI) was second, and pneumonia and CHF were the third most-common complications in men. This is similar to another study of postoperative outcomes based on male veterans, which showed that the most common postoperative complications were UTI and pneumonia.²⁷ Delirium was not examined as one of the complications in this study, which draws attention to the fact that the most common postoperative complications may be missed when delirium is not actively screened. Because the incidence of postoperative acute renal failure and urinary retention was significantly higher in men than women, whether there was an association between these two outcomes possibly due to obstructive uropathy was examined, but no significant association was found.

Although a sex-specific association with postoperative delirium was shown to be more significant in participants without dementia in a previous study,¹⁰ it was not possible to stratify the risk factors according to sex and dementia status in the current study because of the limited number of subjects. It was also not possible to examine the associations with other important preoperative risk factors for delirium such as frailty and functional status. In addition, even though it is thought that the increase in the number of hip fractures in men may be partly due to a greater proportion of men at risk of osteoporosis, it was not possible to obtain preoperative mineral bone density data because of the acute nature of hip fracture.

Although the current study was focused on preoperative risk factors, a few intraoperative factors, including surgical procedures and perioperative transfusion, were recently examined, and a potentially higher risk of postoperative delirium was found with arthroplasty with cement and screw or plate procedure than with an intramedullary nail procedure. Having more red blood cell transfusions was also found to be associated with a higher incidence of postoperative delirium. Male sex was independently associated with greater risk of postoperative delirium even after adjusting for the surgical procedures and the number of red blood cell transfusions.²⁸ There were no significant differences in anesthesia methods used (general vs regional) between men and women. The association between postoperative risk factors and incident delirium was not examined because the temporal association between the postoperative complication (e.g., UTI) and the onset of delirium could not be established. These factors may explain the residual association between sex and postoperative delirium that preoperative risk factors alone did not entirely account for, although high pain score after surgery, which was one of the postoperative risk factors examined in a previous study, was not associated with delirium in this study population.²⁹

What is still unclear is the possible biological explanation for the differences between the sexes. Differences in postsurgical outcomes between men and women have been studied in various surgical specialties,³⁰ and these differences may be partly due to sex differences in baseline immune system activity and immune responses to stressors.^{31, 32} One study has shown that men have a greater C-reactive protein response to endotoxin challenge than women,³² but the data on sex differences in inflammatory response are not always consistent and are sometimes contradictory.^{30, 31} Because inflammation is thought to play an important role in the pathogenesis of delirium,³³ this is an important area that will need to be further explored. Examining whether a higher burden of comorbidities at baseline predisposed the men to have a higher level of baseline inflammation or heightened their immune response to stress and how these factors correlate with sex hormones in the setting of hip fracture surgery would be the next steps in this study.

The strengths of this study included limiting the study population to hip fracture repair and excluding individuals with preoperative delirium, which allowed preoperative risk factors for incident delirium after surgery to be assessed. The data were collected prospectively, and delirium was assessed using the state-of-the-art CAM, a standardized delirium assessment tool. In addition, building on previous work, this study is one of the first to conduct an in-depth analysis to describe sex differences in preoperative risk factors of delirium in individuals with hip fracture.

This study suggests that men who sustain a hip fracture are at higher risk of postoperative delirium partly because of poorer health at the time of admission. They are also at higher risk of developing other postoperative complications and have longer hospital stays. Future studies are needed to examine sex differences in other important preoperative risk factors such as frailty, functional impairment, and disease severity and their associations with postoperative delirium and other outcomes. Because the number of men with hip fracture is expected to rise, more attention needs to be paid to their care to reduce adverse outcomes in the immediate perioperative period and in the long term.

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Table 1

Baseline Data of 431 Men and Women with Hip Fracture Repair: Demographic and Preoperative Characteristics

Risk Factors	Total, N = 431	Male, n = 116	Female, n = 315	P-Value
Demographic				
Age, mean±SD	80.7 ± 6.9	79.0 ± 6.9	81.0± 6.8	.005
Black, n (%)	17 (3.9)	12 (10.3)	5 (1.6)	<.001
Current smoking, n (%)	67 (15.5)	24 (20.7)	43 (13.7)	.08
Current alcohol use, n (%)	51 (11.8)	29 (25.0)	22 (7.0)	<.001
Body mass index, kg/m ² , n (%) ^a				
<18.5 (underweight)	48 (13.4)	8 (8.2)	40 (15.4)	.17
18.5–24.9 (normal)	168 (46.9)	53 (54.1)	115 (44.2)	
25.0–29.9 (overweight)	103 (28.8)	25 (25.5)	78 (30)	
30.0 (obese)	39 (10.9)	12 (12.2)	27 (10.4)	
Neurological and psychiatric, n (%)				
Dementia	142 (33.0)	37 (31.9)	105 (33.3)	.78
Clinical history of previous stroke, transient ischemic attack, or carotid endarterectomy	84 (19.5)	26 (22.4)	58 (18.4)	.36
Depression	71 (16.5)	16 (13.8)	55 (17.5)	.35
Psychiatric disorder other than depression	41 (9.56)	9 (7.76)	32 (10.2)	.44
Parkinson's disease	13 (3.0)	5 (4.3)	8 (2.6)	.34
Medical				
Hypertension, n (%)	314 (72.9)	88 (75.8)	226 (71.7)	.42
Coronary artery disease, n (%) ^b	125 (29.0)	46 (39.7)	79 (25.1)	.003
Diabetes mellitus, n (%)	102 (23.7)	35 (30.2)	67 (21.3)	.06
Chronic obstructive pulmonary disease, n (%)	92 (21.3)	37 (31.9)	55 (17.5)	.001
CHF, n (%) ^c	86 (20.0)	22 (19.0)	64 (20.3)	.74
Atrial fibrillation, n (%)	83 (19.3)	28 (24.1)	55 (17.5)	.12
Cancer, n (%)	66 (15.3)	25 (21.6)	41 (13.0)	.03
Hypothyroidism, n (%)	64 (14.9)	7 (6.0)	57 (18.1)	.002
PVD, n (%) ^d	53 (12.3)	20 (17.2)	33 (10.5)	.06
Chronic renal insufficiency, n (%) ^e	48 (11.1)	20 (17.2)	28 (9.0)	.02
Syncope, n (%)	22 (5.1)	10 (8.6)	12 (3.8)	.05
Number of comorbidities, mean±SD)	4.8±2.5	5.0±2.6	4.8±2.4	.34
American Society of Anesthesiologists classification, n (%) ^f				
2	72 (17.2)	10 (9.0)	62 (19.7)	.03

Risk Factors	Total, N = 431	Male, n = 116	Female, n = 315	P-Value
3	290 (69.4)	84 (75.7)	206 (65.4)	
4	56 (13.4)	17 (15.3)	39 (12.4)	
Laboratory, n (%)				
Anemia ^g	235 (54.5)	90 (77.6)	145 (46.0)	<.001
Azotemia ^h	222 (51.5)	44 (37.9)	178 (56.5)	<.001
Leukocytosis ⁱ	139 (32.3)	28 (24.1)	111 (35.2)	.03

^aAnalysis based on available data (N = 358).

^bClinical history of previous myocardial infarction, angina pectoris, or coronary revascularization (angioplasty, coronary artery bypass graft).

^cDocumentation of prior hospital admission with congestive heart failure (CHF) or ejection fraction < 40%.

^dHistory or surgical procedure performed for peripheral vascular disease (PVD), claudication, interarm asymmetry in blood pressure.

^eSerum creatinine > 1.5 mg/dL in men, > 1.3 mg/dL in women.

^f1= healthy, 2= mild systemic disease, 3= severe systemic disease, 4= severe systemic disease that is a constant threat to life.³⁴

^gMale hematocrit <41%, female hematocrit <36%.

^hBlood urea nitrogen:creatinine ratio >20.

ⁱ>11,000 /μL white blood cells in initial complete blood cell count.

Table 2
Bivariate and Multivariate Analyses of Preoperative Risk Factors for Postoperative Delirium

Risk Factor	Bivariate Analyses According to Sex			Multivariate Analyses	
	Total, N=431	Male, n=116	Female, n=315		
	Odds Ratio (95% Confidence Interval) P-Value				
Demographic					
Sex					2.07 (1.24–3.45) .005
Age	1.05 (1.02–1.08) .002	0.99 (0.94–1.05) .75	1.09 (1.05–1.14) <.001		1.08 (1.03–1.13) .001
Race	1.15 (0.51–2.63) .74	0.85 (0.25–2.86) .79	1.10 (0.34–3.52) .87		
Current smoking	0.84 (0.48–1.47) .53	1.25 (0.51–3.08) .63	0.56 (0.26–1.21) .14		
Current alcohol use	0.93 (0.50–1.74) .83	0.81 (0.35–1.91) .64	0.64 (0.23–1.79) .40		
Age by sex					0.90 (0.83–0.96) .003
Body mass index	0.83 (0.64–1.09) .18	0.76 (0.46–1.27) .30	0.84 (0.61–1.15) .28		
Neurological and psychiatric					
Dementia	3.34 (2.19–5.11) <.001	3.30 (1.45–7.47) .004	3.54 (2.13–5.88) <.001		2.83 (1.75–4.56) <.001
Clinical history of previous stroke, transient ischemic attack, or carotid endarterectomy	1.61 (0.99–2.63) .06	2.15 (0.87–5.30) .10	1.39 (0.76–2.53) .28		
Depression diagnosis	1.20 (0.73–2.05) .51	2.76 (0.88–8.68) .08	0.97 (0.51–1.85) .93		
Psychiatric disorder	1.56 (0.81–2.99) .182	1.57 (0.40–6.17) .52	1.65 (0.78–3.50) .19		
Parkinson's disease	3.18 (1.02–9.89) .05	5.17 (0.56–47.7) .15	2.35 (0.58–9.61) .23		5.17 (1.18–23.60) .03
Medical					
Hypertension	0.94 (0.60–1.47) .79	0.94 (0.40–2.20) .88	0.91 (0.53–1.55) .72		—
Coronary artery disease	0.97 (0.62–1.51) .90	0.71 (0.33–1.51) .37	1.00 (0.58–1.74) >.99		—
Diabetes mellitus	0.72 (0.44–1.17) .19	0.44 (0.19–1.01) .05 ^a	0.84 (0.46–1.54) .57		0.64 (0.36–1.13) .12
Chronic obstructive pulmonary disease	0.91 (0.55–1.48) .69	1.23 (0.56–2.69) .61	0.59 (0.29–1.17) .13		—
Congestive heart failure	1.63 (1.01–2.65) .05	0.70 (0.27–1.84) .47	2.30 (1.30–4.05) .004		1.29 (0.68–2.47) .43
Atrial fibrillation	1.66 (1.01–2.71) .04	1.72 (0.72–4.1) .22	1.54 (0.84–2.82) .17		0.99 (0.55–1.78) .97
Cancer	0.97 (0.56–1.70) .93	0.83 (0.34–2.07) .70	0.94 (0.46–1.94) .87		

Risk Factor	Bivariate Analyses According to Sex				Multivariate Analyses	
	Total, N=431		Male, n=116	Female, n=315		
	Odds Ratio (95% Confidence Interval) P-Value					
Hypothyroidism	0.87 (0.49–1.54)	.64	1.67 (0.36–7.81)	.52	0.90 (0.48–1.70)	.75
Peripheral vascular disease	1.47 (0.82–2.66)	.20	1.43 (0.53–3.83)	.48	1.36 (0.64–2.88)	.43
Chronic renal insufficiency	1.05 (0.56–1.96)	.88	0.99 (0.38–2.61)	.98	0.91 (0.38–2.14)	.82
Syncope	1.98 (0.84–4.69)	.12	1.23 (0.34–4.52)	.75	2.38 (0.75–7.59)	.14
Number of comorbidities	1.17 (1.08–1.28)	<.001	1.15 (0.99–1.33)	.08	1.19 (1.07–1.32)	.001
American Society of Anesthesiologists classification	2.47 (1.66–3.69)	<.001	3.18 (1.32–7.69)	.01	2.21 (1.40–3.50)	.001
Laboratory						
Anemia	0.97 (0.65–1.44)	.86	0.78 (0.33–1.87)	.58	0.80 (0.49–1.31)	.38
Azotemia	1.08 (0.72–1.61)	.72	1.23 (0.58–2.63)	.59	1.22 (0.74–2.01)	.44
Leukocytosis	0.87 (0.56–1.35)	.54	1.89 (0.79–4.55)	.16	0.72 (0.43–1.22)	.22

^aP=.05—removing diabetes mellitus did not significantly change the effect size or statistical significance of the other variables in the multivariate model.

Table 3

Differences in Postoperative Complications of Hip Fracture Repair According to Sex.

Complication	Total, N = 431	Male, n = 116	Female, n = 315	P- Value
	n (%)			
Delirium	147 (34.1)	52 (44.8)	95 (30.2)	.004
Urinary tract infection	77 (17.9)	22 (19.0)	55 (17.5)	.69
Congestive heart failure	48 (11.1)	16 (13.8)	32 (10.2)	.28
Pneumonia	41 (9.5)	16 (13.8)	25 (7.9)	.06
Acute renal failure	39 (9.0)	17 (14.7)	22 (7.0)	.01
New arrhythmia	38 (8.8)	15 (12.9)	23 (7.3)	.06
Urinary retention ^a	25 (5.8)	13 (11.2)	12 (0.6)	.003
Myocardial infarction	25 (5.8)	9 (7.8)	16 (5.1)	.28
Return to operating room	12 (2.8)	4 (21.6)	8 (13.0)	.63
Falls	8 (1.9)	4 (3.4)	4 (1.3)	.13
Deep venous thrombosis, pulmonary embolism	7 (1.6)	2 (1.7)	5 (1.6)	.92

^aParticipants discharged from hospital with Foley catheter in place.