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Cognitive Differences between Men and Women who Fracture their Hip and Impact on Six-Month Survival

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Abstract

Background/Objectives—There is limited research in cognition and its relationship to mortality after hip fracture among men compared to women. Therefore, the goals of this study were to: (1) compare men and women who fractured their hip on cognition after hospital discharge, and (2) examine the impact of cognition on the differential risk of 6-month mortality between men and women post fracture.

Design—Prospective cohort study

Setting—Eight hospitals in Baltimore, Maryland.

Participants—Frequency matched 168 male and 171 female hip fracture patients, ages 65 or older, living in the community before fracture

Measurements—Cognition assed by Modified Mini-Mental State Examination (3MS, and derived MMSE score), Hooper Visual Organization test (HVOT), and Trail-making test (Trails A & B) within 22 days of hospital admission, and 6-month mortality.

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Ann Gruber-Baldini was involved in: study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.

Mina Hosseni was involved in: analysis and interpretation of data, and preparation of manuscript.

Denise Orwig was involved in: study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.

Lynn Grattan was involved in: analysis and interpretation of data, and preparation of manuscript.

Nancy Chiles Shaffer was involved in: analysis and interpretation of data, and preparation of manuscript.

Marc Hochberg was involved in: study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.

Jay Magaziner was involved in: study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.

CONFLICT OF INTEREST

Denise Orwig has had consulting agreements in the past year with Kinexum, Sanofi and Viking. Jay Magaziner has had consulting agreements in the past year with Ammonett, LLC, Novartis, Scholar Rock, and Viking. The other authors of this study have no conflicts of interest to report.

Results—Men had more impaired cognitive scores on 3MS, MMSE, HVOT, and Trails A (p<.05) at baseline. These statistically significant differences between men and women remained on MMSE and HVOT after controlling for pre-fracture dementia, in-hospital delirium, age, education, race, and comorbidity. Men had higher 6-month mortality rates (HR=4.4, p<.001). Cognitive measures were also significantly associated with mortality, including 3MS, HVOT, and Trails B. Among the cognitive measures, higher 3MS was most protective for mortality (HR=0.98, p<.001), both unadjusted and adjusted for other cognitive scales, comorbidity, delirium, and pre-existing dementia. The highest mortality was among men with 3MS<78, with 26.3% dying within 6 months. The effects of cognition on mortality did not differ by sex.

Conclusion—Men display greater levels of cognitive impairment within the first 22 days of hip fracture than women, and cognitive limitations increase the risk of mortality in both men and women.

Keywords

hip fracture; sex differences; mortality; cognitive impairment; dementia

Background

Hip fracture is a condition that greatly increases disability and mortality risk.[1] While typically occuring in older women, the number of men who will experience a hip fracture will increase in the coming decades.[2] An estimated 25–30% of the approximately 290,000 hip fractures in the U.S. currently occur in men.[3] It is estimated that by 2025, the number of hip fractures in men will be the same as that currently seen in women, making this an emerging public health concern for older men, their families, and the healthcare system.[4] Compared to women, men who fracture a hip have an increased risk of mortality,[5] and more comorbid diseases, [6,8–10] despite their younger age at the time of fracture.[6,7]

Dementia is also a known risk factor for hip fracture.[11] It is estimated that 35–61% of hip fracture patients exhibit some sort of cognitive impairment during hospitalization,[12] with estimates of pre-existing dementia around 20%.[12] Previous studies have shown that dementia, delirium, and general cognitive impairment are predictive of poorer functional recovery[13] and higher mortality.[12,14] There is limited research in cognition after hip fracture among men and the impact of cognition on the observed sex differences in mortality.[15]

Therefore, the goals of this study were to: (1) Compare cognitive functioning between men and women who fractured their hip, including measures of global cognition; visual search, sequencing, and motor tracking speed; executive control; and visual spatial analysis; and (2) Examine the impact of cognition on the differential risk of mortality between men and women over 6 months post fracture.

Methods

Subjects

The prospective cohort was made up of community-dwelling patients aged 65 years or older admitted during the study period to any of the 8 study hospitals in the Baltimore Hip Studies

network for surgical repair of hip fracture who provided consent (or whose proxy provided consent) to participate within 15 days of admission. Recruitment for men was ongoing while recruitment of women was frequency-matched with men within each hospital. This strategy ensured equal numbers of women and men enrolled throughout the study to avoid confounding by secular and institutional differences in patterns of care. The protocol was approved by the Institutional Review Board (IRB) at the University of Maryland Baltimore, as well as each study hospital's IRB.

Individuals were excluded if: had a pathologic fracture; not ambulating 6 months prior to the fracture; not English speaking; lived more than 70 miles from the hospital; weighed over 300 pounds; or hardware in contralateral hip. During the recruitment period May 2006 – June 2011, 1709 hip fracture patients were screened; 917 (54%) were eligible (405 males, 512 females). A total of 180 men and 182 women consented to participate in the study. Twenty-three participants were withdrawn (five participants failed to provide data at baseline and another 18 participants were removed from analytic sample as a result of an IRB-requested post procedure audit), leaving a final sample of 339 (168 men, 171 women).

In-person assessments were conducted within 22 days of hospital admission (Mean=15.8, S.D.=5.0), typically after hospital discharge by research interviewers trained by a licensed neuropsychologist (LG). Fifty-five percent were conducted in rehabilitation or skilled nursing facilities, 35% at participant's residence, and 10% while still hospitalized. For these analyses, 166 men and 168 women had one or more cognitive measures completed at the baseline assessment.

Measures

Cognition—Cognitive status was assessed using three standardized tests administered to all participants. Measures were selected to include those that have been well validated on patients with known neurologic disease (e.g., cerebrovascular disease, Alzheimer's Disease) as well as normal aging populations; demonstrated good reliability and validity; and minimized participant burden. During all cognitive assessments, the potential interference from sensory deficits was minimized using standard neuropsychological examination strategies such as large print forms and making sure participants used glasses and hearing aids (supplemental magnifying glasses and/or sound amplifiers were provided as necessary).

The Modified Mini-Mental State Examination (3MS)[16] is based on the Mini-Mental State Exam (MMSE).[17] The 3MS modified the 0–30 scale through 4 additional items, some additional stimuli within items, and a more graded scoring to create a 0–100 scale. The original MMSE score can be derived from the 3MS. As is widely accepted, if a subject was unable to perform items for physical reasons, the mean was recomputed excluding those items not performed (rescaled back to 100). While varying cut points exist for the 3MS, a score below 78 is often considered cognitively impaired.[18]

The Trail-Making Test (Trails A & B)—Trails A is considered a task of visual search, sequencing, and psychomotor tracking speed while Trails B adds an element of executive control (set-switching) abilities.[19] Both instruments were administered and scored as seconds to task completion (range 1–301) according to standard procedures.[20] Higher scores

indicate slower or worse responses. Scores of 301 (one second slower than maximum time) were assigned if not finished in five minutes.

The Hooper Visual Organization Test (HVOT)[21] measures visual spatial analytic skills. For successful performance, the participant must identify common objects from fragmented visual information. Scores range from 0–30, with higher scores indicative of better cognition.

Demographics and health status—Demographic and other descriptive information about diagnosis of dementia or delirium were obtained from hospital medical chart abstraction or interview with participants or surrogates. Vital status and date of death were ascertained through monthly telephone calls to the participant or proxy.

Statistical Methods

Baseline differences were analyzed by sex using Students' t-tests (for continuous variables) and chi-square tests (for dichotomous variables). Linear regression models were used to determine whether sex differences remained after controlling for dementia diagnosis, delirium (noted in chart), age, race, educational attainment, and Charlson comorbidity score. Proportional hazards models were used to estimate hazard ratios (HRs) for death in the initial 6 months (183 days) by each cognitive variable as separate models and as a combined model with sex and all cognitive measures controlling for pre-existing dementia, delirium, and Charlson comorbidity. All analyses were performed using SAS 9.3 (SAS Institute, Inc, Cary, NC).

Results

Among the 166 men and 168 women in this sample, baseline differences were observed for most cognitive measures but few demographics (Table 1). Both groups were predominately white, with an average age over 80, and educational level above high school graduation. Men had significantly higher Charlson comorbidity scores ($p<.001$). Men had a higher frequency of diagnosed dementia (17%) than women (11%), although this difference was not statistically significant. Overall, fewer than 10% of the sample had delirium identified in the hospital chart.

Men were more impaired on most cognitive measures, including the 3MS, MMSE, HVOT, and Trails A ($p<.05$) (Table 1). Twenty-nine percent of men scored in the cognitively impaired range on the 3MS (<78), compared to 16% of women. For HVOT, 33% of men and 21% of women scored in the most impaired category (HVOT<15). Men were slower on Trails A, with 48% scoring over 78 seconds compared to 35% of women. These statistically significant differences between men and women remained for MMSE ($p=.03$) and HVOT ($p=.02$) after controlling for pre-existing dementia, in-hospital delirium, Charlson comorbidity score, age, education, and race (3MS $p=.17$, Trails A $p=.15$). Men and women did not differ statistically on the Trails B, nor on any of the derived scores from Trails A to B (the delta or the ratio scores). Even among the subsample with no history of dementia (*bottom of* Table 1), significant differences remained between men and women after hip fracture for 3MS, MMSE, Trails A, and HVOT.

The overall proportion of hip fracture patients who died within 6 months of fracture, and breakdowns by sex and 3MS scores, are presented in Table 2. Among men with impaired 3MS scores (3MS<78), 32% died within 6 months, compared to 15% among cognitively impaired women and 11% among non-impaired men. In contrast, women without cognitive impairment (3MS>=78) had a 6-month mortality of 2%.

In proportional hazards models, 3MS, HVOT, and Trails B were significantly associated with mortality (p<.05) (see Table 3). Among the cognitive measures, 3MS was the most predictive of mortality, even when controlling for other cognitive scales and when dementia diagnosis, delirium, and comorbidity were controlled for (3MS HR=0.95). Despite the impact of cognition, the mortality rates were still statistically significantly higher among men (HR=3.3) when controlling for cognition, although the effect was no longer significant (HR=2.5, p=.12) when adjusting for pre-existing dementia, in-hospital delirium, and comorbidity in addition to all cognitive variables. There were no significant sex by cognition interaction effects (all p>.10).

Discussion

In this sample of men and women after hip fracture, men had more cognitive impairment at baseline (within 22 days of hospital admission) and higher 6-month mortality. The higher mortality for men remained after controlling for all the cognitive measures and was large (although not statistically significant) after controlling for history of Alzheimer's disease or dementia, delirium from hospital chart, and comorbidities. We believe the loss of significance in this final model for sex may be an issue of collinearity or power, as the effect of sex was still significant when controlling for just 3MS and dementia, delirium, and comorbidity (without the other cognitive measures) or when controlling for all the cognitive measures without the diagnoses variables.

It is well known that dementia, delirium, and overall cognitive status impact recovery from hip fracture.[13,22] The impact of sex differences and cognition on mortality in hip fracture patients is less well known. Tseng and colleagues[23] examined recovery patterns among 162 hip fracture patients in Taiwan and found that men and those with low MMSE scores had worse recovery. Samuelsson et al.[15] examined 2,134 hip fracture patients in Sweden, and while they found no sex differences in cognition (using the Short Portable Mental Status Questionnaire), they identified a stronger sex effect on 4-month mortality among those with cognitive dysfunction, such that only 6% of men and 6% women without cognitive dysfunction died, while 31% of men with cognitive dysfunction died compared to 19% in women with cognitive dysfunction. In contrast, our study failed to detect interaction effects of sex with cognition, but did find main effects of both sex and cognition on mortality, such that the highest mortality was among men with cognitive impairment on the 3MS (where 32% of men died within 6 months compared to 15% among women). In contrast, our female hip fracture participants without 3MS cognitive impairment (3MS>=78) had a 6-month mortality of 2%.

High levels of cognitive impairment were observed for both men and women in this sample. To our knowledge, no previous hip fracture studies used this cognitive battery. Although

previous work using the MMSE found 42% or more obtained scores below 24 while hospitalized;[13,24] average MMSE scores in this study were higher: 25 (men) and 26 (women). In contrast, one study of 30 men versus 130 women using the Short Portable Mental Status Questionnaire (SPMSQ)[25] found more impairment among women (27%) compared to men (20%)(p=.08) after hip fracture. This finding may be due to the fact that the SPMSQ assesses fewer cognitive domains than the MMSE.

On average, our sample of hip fracture patients had higher cognitive impairment scores than those seen in other samples of persons over age 80 without hip fracture. For example, average 3MS scores for community-dwelling adults over 80 with a high school education have been shown to range from 85 (Cache county men ages 90+)[26] to 92 (MrOS study of men).[27] Scores in patients in this study, with an average education of 13 years, were an average 86 for women and 82 for men. When those with dementia were excluded, the means were 89 for women and 85 for men, which was more in line with community-dwelling estimates.

The average HVOT scores in our sample were16.7 for men and 18.6 for women. Walsh, Lichtenberg, and Rowe (1997)[28] reported HVOT means for 144 geriatric rehabilitation patients ages 60–95 of 18.6 for cognitively intact, 14.9 for mildly cognitively impaired, and 12.5 for moderately to severely impaired. Our scores for female hip fracture participants were within the normal range for geriatric rehabilitation patients, but the scores for men (17.0 when excluding dementia) were consistent with a mild level of cognitive impairment.[28]

For Trail-Making tests, we found that men were significantly slower than women on Trails A, (97 seconds versus 81 seconds, respectively), which measures visual search, sequencing, and motor tracking speed. In contrast, there was no significant difference between sexes for Trails B (219 for men versus 201 for women), which incorporates an element of executive control (set shifting) to the procedure. Previous research on community-dwelling elderly ages 80+ has found a mean of 56 seconds for Trails A (170 seconds for Trail B).[29] Other studies have found slower speeds, with scores of 67 to 73 seconds for Trails A,[30,31] and scores of 123[27] to 255 seconds[30] for Trails B. Taking this into consideration, the means in both of our sex groups remained much higher (slower) for Trails A, even after excluding those with dementia.

There are some limitations to be noted in our study. We had no pre-fracture assessments of cognitive function and thus our estimates of pre-fracture dysfunction were limited to chart diagnoses of dementia. We also relied upon chart recording for documentation of in-hospital delirium. Since hospital charts are known to under report dementia and delirium,[32,33] the possibility exists that our hip fracture sample included people with unrecognized dementia and delirium.

Our research is the first to document cognitive deficits beyond general cognition in hip fracture patients by including specific measures of visual search, sequencing, and tracking speed as well as visual spatial and analytic skills. The average age of hip fracture patients was 82–83, and normative data are limited among the over 80 age group, especially for those

who were recently hospitalized. Overall, our sample demonstrated a higher level of impairment than the currently published literature in this age group. The deficits in visual spatial and analytic skills, as well as visual tracking and perceptual motor speed, raise the possibility that capacities beyond memory and general cognitive impairment require management and/or intervention in geriatric rehabilitation after hip fracture.[28] It is known that delirium persists longer in older patients,[13] and this research suggests that monitoring cognition after hospital discharge may be helpful in identifying patients at risk for short-term mortality. Additional information on the cognitive domains assessed in this study might also provide guidance for rehabilitation and safety goals, including navigating stairs, curbs, or other obstacles or when to resume driving.

Our study also adds to the growing body of evidence that finds men have more cognitive difficulties and higher mortality than women after a hip fracture. Given the importance of cognitive function for understanding and participating in therapeutic interventions, our study serves to emphasize the need to consider how men and women differ after hip fracture and how understanding these sex differences as well as the specific nature of cognitive deficits may inform design of future interventions for both men and women after hip fracture.

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Table 1

Differences between Men and Women Hip Fracture Patients

		Men (n=166)			Women (n=168)		
Variable	**n**	**Mean /n**	**S.D./%**	**n**	**Mean /n**	**S.D./%**	**p-value**
Age (mean, SD)	166	80.4	(7.8)	168	81.5	(7.9)	0.21
Non-white	162	16	9.9%	163	11	6.8%	0.31
Education (mean, SD)	159	13.2	(3.8)	164	13.1	(3.0)	0.75
% <HS (<12)		41	25.8%		29	17.7%	0.08
Charlson comorbidity index	165	2.4	(1.8)	168	1.6	(1.6)	<.001
Dementia/Alzheimer's Hx	165	28	17.0%	168	18	10.7%	0.10
Delirium in Hospital	165	16	9.7%	168	15	8.9%	0.82
3MS (mean, SD)	164	82.3	(16.4)	167	86.2	(16.4)	0.031
3MS cutpoints:							
Not impaired (78–100)	164	117	71.3%	167	141	84.4%	0.009
Impaired (66–77)	164	28	17.1%	167	12	7.2%	
Severely impaired (<66)	164	19	11.6%	167	14	8.4%	
Derived MMSE (mean, SD)	164	24.6	(5.0)	168	26.2	(4.8)	0.003
Trails A time (mean, SD)	135	97.1	(68.5)	144	81.0	(57.1)	0.033
Trails A>78		65	48.2%		50	34.7%	0.023
Trails B time (mean, SD)	122	218.5	(83.4)	134	201.2	(84.4)	0.10
Trails B>273		52	42.6%		44	32.8%	0.11
Trails delta B-A (mean, SD)	122	129.6	(68.1)	134	127.9	(68.0)	0.84
Delta 133+		59	48.4%		59	44.0%	0.49
Delta 187+		33	27.1%		34	25.4%	0.76
Trails ratio B/A (mean, SD)	122	2.9	(1.2)	134	3.1	(1.6)	0.18
Ratio 3+		43	35.3%		57	42.5%	0.23
HVOT (mean, SD)	144	16.7	(5.7)	150	18.6	(6.2)	0.009
<15		47	32.6%		32	21.3%	0.007
15–18		38	26.4%		34	22.7%	
19–23		43	29.9%		46	30.7%	
24–30		16	11.1%		38	25.3%	
Among those without a diagnoses of Alzheimer's disease or dementia:							

	Men (n=166)			Women (n=168)			
Variable	**n**	**Mean /n**	**S.D./%**	**n**	**Mean /n**	**S.D./%**	**p-value**
3MS	135	85.2	(14.0)	149	88.9	(11.7)	0.014
MMSE	135	25.5	(4.3)	150	26.9	(3.5)	0.002
Trails A time	114	92.3	(65.8)	132	75.8	(49.5)	0.026
Trails B time	106	211.8	(83.2)	124	197.8	(85.0)	0.21
Trails delta	106	124.7	(67.9)	124	127.1	(68.9)	0.78
Trails ratio	106	2.9	(1.2)	124	3.1	(1.6)	0.11
HVOT	121	17.0	(5.8)	137	18.9	(6.0)	0.008

Table 2

Six-month Mortality by Sex and 3MS

	Men		Women		Total	
	n	#(%) died	n	#(%) died	n	#(%) died
Overall	166	29 (17.5%)	168	7 (4.2%)	334	36 (10.8%)
Cognitively Impaired (3MS<78)	47	15 (31.9%)	26	4 (15.4%)	73	19 (26.0%)
Cognitively Intact (3MS>= 78)	117	13 (11.1%)	141	3 (2.1%)	258	16 (6.2%)
Missing 3MS	2	1 (50.0%)	1	0 (0.0%)	3	1 (33.0%)

Table 3

Cognitive Measures and Sex as Predictors of 6-month Mortality (Proportional Hazards models)

Measure	HR	95% CI	P
Men (vs. Women)	4.443	(1.946, 10.142)	<0.001
Separate models by cognitive variables			
3MS	0.977	(0.965,	<0.001
Men (vs. Women)	3.995	(1.743, 9.155)	0.001
HVOT	0.939	(0.883, 0.998)	0.042
Men (vs. Women)	4.396	(1.660, 11.634)	0.003
Trails A	1.004	(0.999, 1.009)	0.082
Men (vs. Women)	3.682	(1.357, 9.990)	0.011
Trails B	1.007	(1.001, 1.014)	0.026
Men (vs. Women)	4.164	(1.389, 12.484)	0.011
Trails Difference (B-A)	1.004	(0.997, 1.011)	0.23
Men (vs. Women)	4.589	(1.534, 13.726)	0.006
Trails Ratio (B/A)	0.963	(0.695, 1.391)	0.92
Men (vs. Women)	4.585	(1.530, 13.746)	0.007
Multivariate Models (all cognitive measures combined)			
3MS	0.936	(0.899, 0.975)	0.002
HVOT	1.045	(0.942, 1.160)	0.40
Trails A	1.002	(0.994, 1.011)	0.57
Trails B	1.002	(0.993, 1.010)	0.67
Men (vs. Women)	3.261	(1.053, 10.100)	0.040
Multivariate Models (all cognitive measures combined) with adjustment for delirium, dementia and comorbidity			
3MS	0.945	(0.901, 0.991)	0.020
HVOT	1.044	(0.931, 1.172)	0.46
Trails A	1.003	(0.994, 1.011)	0.55
Trails B	1.001	(0.992, 1.010)	0.80
Men (vs. Women)	2.522	(0.758, 8.103)	0.12

Note: All models were tested for sex by cognition interactions, which were all n.s. (p>.10)