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Impact of delirium after hip fracture surgery on one-year mortality in patients with or without dementia: A case of effect modification

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Abstract

Objectives: We evaluated whether delirium after hip fracture repair modifies the relationship between baseline dementia and one-year mortality after surgery.

Methods: Patients age ≥ 65 undergoing hip fracture repair surgery at John Hopkins Bayview Medical Center between 1999 and 2009 were eligible for this prospective cohort study. Baseline probable dementia was defined as either preoperatively-diagnosed dementia per geriatrician or < 24 on Mini Mental State Examination. Delirium was assessed using the Confusion Assessment Method. Four cognitive groups were defined: 1) neither probable dementia nor delirium (NDD), 2) probable dementia only, 3) delirium only, or 4) delirium superimposed on dementia (DSD). Primary outcome of mortality was obtained through hospital records, obituaries, the National Death Index, and Social Security Death Index.

Results: The current sample comprises 466 subjects (average age 80.8 ± 7.0 years; 73.6% female). Of these, 77 (17%) were categorized as DSD, 68 (15%) probable dementia only, 73 (16%) delirium only, and 248 (53%) NDD. Cox regression revealed that DSD subjects had a significantly higher hazard of one-year mortality than NDD subjects (HR 1.71, 95% CI 1.06, 2.77) after adjusting for age, sex, medical comorbidity, and surgery duration. Trends toward greater mortality for probable-dementia and delirium only subjects were not significant—HR 1.42 (0.80, 2.52) and 1.12 (0.64, 1.95).

Conclusions: Delirium after hip fracture repair surgery in patients with preoperative dementia modifies the risk of mortality over the first postoperative year. Patients with DSD have a nearly two-fold greater odds of one-year mortality than those without dementia or delirium.

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Conflict of Interest Disclosures:

The authors report no conflicts of interest.

Keywords

delirium; dementia; neurocognitive impairment; mortality; survival; hip fracture repair surgery

Objective:

Delirium is a common neuropsychiatric complication after surgery among the elderly (1), and post-surgical delirium is associated with greater morbidity and mortality, longer length of hospital stay, and higher rates of institutionalization (2–5). Among putative predisposing factors, pre-surgical diagnosis of dementia is the most consistently reported risk factor for incident delirium among surgical patients (6–9). Therefore, pre-surgical evaluation for dementia is critical for risk stratification for post-surgical delirium among the elderly (10). However, despite high prevalence (40–89%) of delirium among dementia patients in the general hospital (11), little is known about the natural history and outcomes of delirium superimposed on dementia (DSD), especially after surgery. In fact, the few available studies on outcomes of DSD have focused on non-surgical populations or mixed populations (12, 13), and their findings are not readily generalizable to surgical populations.

Hip fracture repair is one of the most common surgical procedures among the elderly, and these patients are at considerably increased risk of morbidity and mortality. Post-surgical delirium may occur in more than half of elderly patients after hip fracture repair (11). Several studies have examined either delirium or dementia as a risk factor for decreased survival in hip fracture repair (14–16). Few studies, though, have examined delirium and dementia together in a large enough sample to elucidate the potential relationship between delirium and dementia as well as their combined effect on post-surgical mortality. In fact, even the few available studies on survival outcomes of non-surgical patients with DSD have been conflicting (17–19). To address the paucity of data in this area, we aimed to evaluate the differential impact of post-surgical delirium on one-year mortality among hip fracture repair patients either with or without dementia.

Methods:**1. Study Sample and Design:**

The protocol for this prospective cohort study was approved by the Committee on Human Research, the Institutional Review Board for Johns Hopkins Bayview Medical Center. Between 1999 and 2009, 726 consecutive hip fracture repair patients above age 65 were approached for consent for collection of their perioperative clinical data for research purposes. During the consent process, those with pre-operative delirium ($n = 131$; 18%) ascertained by a trained research nurse based on the Confusion Assessment Method (CAM) (20) were ineligible for this study. Of the remaining 595 eligible patients, 480 (81%) consented to participate in this study. Excluding 14 participants with incomplete delirium assessment data, the remaining 466 subjects (age: 80.8 ± 7.0 years; female: 73.6%) composed the final analytic sample.

2. Assessment of Pre-operative Dementia Status and Incident Delirium:

Preoperative “probable dementia” was diagnosed if the patient had: 1) no delirium by Confusion Assessment Method (CAM) and either 2a) Mini Mental State Examination (MMSE) (21) score < 24 or 2b) clinical diagnosis of dementia by a geriatrician during the pre-hip fracture repair evaluation. Postoperative delirium was assessed using CAM combined with MMSE on postoperative day 2 (POD2) about 10:00 AM by the study geriatrician or a trained research nurse.

3. Mortality Data and Other Covariates:

Primary outcome of mortality was obtained through hospital reports, obituaries, National Death Index, and Social Security Death Index. The socio-demographic variables investigated were: 1) age (in years); 2) race (white or non-white); and 3) gender. Self-reported smoking and alcohol use variables were scored as either current or former/never. Body-mass index (BMI) was calculated from a person’s height and weight measured on hospital admission.

Each patient was rated preoperatively for clinical severity by the anesthesiologist based on the American Society of Anesthesiologists physical status (ASA-PS) classification rating system (1 to 5; where 1 = normal healthy patient, and 5 = moribund patient not expected to survive without operation) (22) and for comorbidity at admission based on chart review using the Charlson Comorbidity Index (CCI) (23), a weighted index that accounts for the number and severity of comorbid conditions. Lag time to surgery was measured in hours from the patient’s arrival time in the emergency department (ED) to the start time of the surgery. Intraoperative variables were obtained from the anesthesiology record and postoperative note recorded by the attending orthopedic surgeon. Types of hip fracture and surgery, types of anesthesia (spinal or general anesthesia), duration of surgery (in minutes), and amount of red blood cell (RBC) transfusion perioperatively (< 3 units of RBC transfusion = 0; 3 units = 1) were obtained.

4. Statistical Analysis

Statistical analysis was performed by SPSS 21. Initial unadjusted survival analysis relied on the two-group comparison of the Kaplan-Meier survival curves of the cohort based on delirium or dementia status with significance determined by the log-rank test. Time 0 was defined as the date of surgery, and subjects were censored at the time of death or the end of the one-year follow-up period, whichever occurred earlier. Then, in order to explore the differential and potentially additive effects of delirium and dementia, we categorized the cohort into the following four groups: no dementia or delirium group (NDD; n = 248), delirium-only group (Del; n = 73), probable dementia only group (Dem; n = 68), and delirium superimposed on dementia group (DSD; n = 77). We compared these groups with respect to baseline socio-demographic and clinical prognostic factors, using the chi-square test for categorical variables and analysis of variance for continuous variables. To adjust the estimated effect of group membership on mortality for the possible differences in the distribution of other prognostic factors among the four groups, we used the multivariable Cox proportional hazards model with the pertinent prognostic covariates selected a priori based on available literature: age, gender, clinical severity (measured by ASA PS), comorbidity (measured by CCI), time from ED to surgery and surgery duration. Then, using

the NDD group as the reference category, we estimated the relative risks associated with each of the three other categories by including the corresponding dummy variables in the Cox model.

Results:

Overall one-year mortality after hip fracture repair was 23.4%, and mortality was higher among hip fracture repair patients with history of probable dementia only than in those without (33.8% vs. 18.7%; Pearson χ^2 $p = 0.001$). Subjects with postoperative delirium were at increased risk of mortality at one and six months relative to those without delirium (one month: 10% vs. 4.1%, Pearson χ^2 $p = 0.012$; six months: 17.3% vs. 13.0%, $p = 0.003$) independent of dementia status. At one year, postoperative delirium was associated with higher mortality in patients with pre-surgical probable dementia (26.5% vs. 40.5%; Pearson χ^2 $p = 0.056$) but not in those without dementia (17.3% vs. 23.3%; Pearson χ^2 $p = 0.237$). The Kaplan-Meier survival analysis (Figure 1) also demonstrates poorer survival among DSD subjects (log-rank test $p = 0.041$), but delirium did not predict one-year survival among those without dementia (log rank test: $p = 0.891$).

Several significant baseline differences were identified in the sample when stratified by the aforementioned four groups based on cognitive status (Table 1). Subjects with probable dementia only were more likely to be female (84%) than were other cognitive categories though the only statistically-significant difference on Tukey Honestly Significant Difference test was versus delirium-only subjects ($p = 0.026$). Those with probable dementia had lower MMSE scores than those without (18.8 versus 26.8, independent samples t-test $p < 0.001$), which was expected because probable dementia was defined in part by MMSE score at baseline. Patients with DSD had the greatest number of comorbidities (5.5)—significantly more than NDD (3.7, independent samples t-test $p < 0.001$) and probable-dementia only (4.4, $p = 0.033$) subjects but insignificantly more than delirium-only subjects (4.9, $p = 0.17$).

Table 2 provides univariate and multivariate proportional hazards models for one-year mortality. Before adjustments, probable dementia alone (HR, 2.19; 95% CI, 1.49, 3.20) and delirium only (HR, 1.84; 95% CI 1.26, 2.69) were significantly associated with higher odds of one-year mortality. However, relative to NDD subjects, both univariate and multivariate analysis revealed that the HRs for neither the delirium-only group (adjusted HR, 1.42; 95% CI, 0.8, 2.52) nor the probable-dementia only group (adjusted HR, 1.12; 95% CI, 0.64, 1.95) differ significantly from the reference NDD group. Patients with DSD were at a nearly two-fold increased mortality risk during the one-year follow up (adjusted HR, 1.71; 95% CI, 1.06, 2.77).

Discussion:

This study emphasizes the importance of early recognition and prevention of delirium in patients with dementia after hip surgery. We found that post-surgical delirium decreases one-year survival of hip fracture repair patients by way of effect modification with pre-surgical probable dementia. Postoperative delirium alone predicted higher one- and six-month mortality risk relative to NDD and probable dementia alone subjects, but neither probable

dementia nor delirium alone was associated with one-year mortality after correcting for covariates.

Previous studies have investigated the predictive role of preoperative cognitive impairment (24–28), postoperative delirium (29) or both (30–33) relative to hip fracture surgery, but definitions of dementia in particular have varied widely across studies making direct comparisons between studies difficult. In general, studies find dementia, independent of severity, as predictive of mortality in this population (14), but those that stratify based on severity reveal a step-wise effect—those with more severe dementia have higher mortality rates (24, 30). But it is also true that those with more severe dementia are at higher risk of developing delirium after hip fracture surgery (30). On the other hand, delirium itself in both non-demented elderly (29) and when evaluated in cohorts that include demented subjects (30, 32) is not necessarily an independent predictor of mortality among hip fracture subjects, though may be additive when considered alongside baseline dementia (31).

This current study, then, attempts to refine the predictive values of baseline probable dementia and postoperative delirium by investigating whether either condition alone or together influenced outcomes. In other words, this analysis assesses for effect modification. As described previously, Cox regression analysis of all survival data from this current cohort yielded a mean 4.1 years of follow up per patient. Neither baseline cognitive impairment nor delirium survived as significant predictors of mortality in multivariate analysis (34). Similarly, when considering only one-year survival, neither probable dementia nor delirium alone was independently associated with increased mortality. Delirium does, however, appear to modify the relationship between probable dementia and one-year survival. This may be due to the inherent vulnerability of those who developed delirium, the pathogenic insults of delirium or its causes, or some combination of these. The survival slope of subjects with delirium alone suggests that the severity of acute illness contributed to early mortality but, after this early period of increased physiological vulnerability, survival in this population began to approximate that of the NDD cohort.

Despite the poor outcomes and high prevalence of DSD, this clinical scenario remains a relatively neglected area of investigation. Most importantly, delirium is often preventable even in patients with dementia, although the approaches for this population may take different forms. An intervention study by Inouye *et al.* suggests that, although persons with dementia are more vulnerable to delirium, they may be more responsive to preventive strategies such as orientation, therapeutic activities, mobility and avoidance of psychoactive drugs (35). Additionally, a randomized controlled trial by Marcantonio *et al.* of 126 elderly hip fracture patients found geriatric consultation reduced post-operative delirium.(36) The majority of patients in our present study received geriatric consultation both pre and post-operatively. This may explain in part why the 32% rate of delirium in this present study is nearly the same rate as those who received geriatric consultation in the study by Marcantonio *et al.* (36). Many delirium-prevention studies continue to exclude persons with dementia or neglect to report results separately for persons with dementia, and the impact of delirium prevention—particularly among those with dementia—on long-term mortality remains unclear.

Strengths of this study include its prospective design and evaluation of both baseline cognitive status as well as the postoperative cognitive complication of delirium. Subjects were assessed for delirium by a geriatrician or trained research nurse specifically rather than based on delirium reports per routine care. The present analysis also accounts for baseline socio-demographics, medical morbidity, and surgical duration.

The probable dementia criterion deserves comment. Because no measures of functional status were employed in this study, dementia was diagnosed based on either a formal assessment by a geriatrician, which necessarily included functional assessment by history, or based on MMSE score. A subset of those ruled in as probable dementia based on MMSE score alone may not have met clinical criteria for dementia thus introducing heterogeneity to the probable dementia group in this study. That is, non-demented subjects may have been included as probable dementia, but it is unlikely that subjects with dementia were miscategorized because it is less likely that a patient with significant dementia would score 25 or above on the MMSE. Thus, this study likely presents an over-inclusive group of probable dementia patients, which may also explain in part why probable dementia only was not independently predictive of one-year mortality.

Postoperative delirium assessments were conducted on postoperative day (POD) 2, when postoperative delirium incidence and inflammatory mediators peak (37). In fact, more than 90% of postoperative delirium may occur on the first three postoperative days (38). Assessment for delirium on other postoperative days would have detected additional cases, but how many delirium cases were missed in demented versus non-demented subjects is not known. The fact that a few-minute delirium assessment on POD 2 alone can predict survival over the following year is nevertheless remarkable. Also, whether further cases of delirium identified on days other than POD 2 would alter this predictive value deserves further investigation. One final statistical limitation is the potential for type I error inherent in the number of number of significance tests performed while employing an alpha of 0.05.

Conclusions:

We demonstrated that postoperative delirium in combination with preoperative dementia predicts greater one-year mortality after hip fracture repair patients. Delirium alone was associated with higher mortality one and six months after surgery relative to subjects with NDD and probable dementia alone, but this finding was no longer significant at one year.

As increasing number of older adults are diagnosed with dementia in earlier stages, attention to preventable and treatable problems like delirium will be critical. Future research should strive to elucidate the relationship between delirium and dementia and to discover whether delirium prevention in persons with dementia affects long-term survival, health care use, and quality of life. Simultaneously, assertive rehabilitation, dietary consultation, cognitive enhancing interventions, and efforts to bolster socialization and behavioral activation should be considered in future studies to evaluate the potential not only to improve survival but also to enhance quality of life (39).

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Figure 1.
Kaplan-Meier Survival Curves of One-Year Mortality Stratified by Cognitive Status

Table 1:Characteristics and Post-surgical Mortality Stratified by Cognitive Status ($n = 466$) *

Variables*	No delirium or dementia ($n = 248$)	Delirium only ($n = 73$)	Probable dementia ($n = 68$)	Delirium superimposed on dementia ($n = 77$)	p value* (χ^2 or ANOVA)
Socio-demographics					
Female	188 (75.8)	46 (63)	57 (83.8)	52 (67.5)	0.019
White	212 (85.5)	68 (93.2)	52 (76.5)	68 (88.3)	0.075
Current smoking	38 (15.3)	8 (11)	8 (11.8)	13 (16.9)	0.650
Current alcohol use	31 (12.5)	5 (6.8)	3 (4.4)	11 (14.3)	0.121
Pre-operative MMSE, mean (SD)	27.1 (2.8)	25.8 (3.4)	19.2 (4)	18 (5.3)	< 0.001
BMI, mean (SD)	24.7 (56)	22.9 (4.9)	22.2 (5.3)	24.1 (6)	0.012
Medical history					
Medical comorbidities (#)	3.7 (2.5)	4.9 (2.8)	4.4 (3.1)	5.5 (2.8)	< 0.001
Heart failure	33 (13.3)	20 (27.4)	9 (13.2)	16 (20.8)	0.023
Cerebrovascular disease or accident	29 (11.7)	15 (20.5)	14 (20.6)	21 (27.3)	0.007
Diabetes mellitus	52 (21)	14 (19.2)	17 (25)	15 (19.5)	0.823
Chronic obstructive pulmonary disease	46 (18.5)	15 (20.5)	15 (22.1)	15 (19.5)	0.924
Cancer	37 (14.9)	8 (11)	6 (8.8)	14 (18.2)	0.337
Depression	30 (12.1)	10 (13.7)	13 (19.1)	15 (19.5)	0.275
CCI, mean (SD)	3.9 (3.1)	4.4 (3.0)	5.9 (2.2)	6.4 (1.7)	0.002
Pre-op prescription meds, mean # (SD)	2.7 (2.8)	3.6 (3.4)	3.6 (4.5)	2.7 (2.8)	0.055
Pre-operative variables					
Type of fracture					
Femoral neck	101 (40.1)	31 (42.5)	29 (42.6)	36 (46.8)	0.475
Intertrochanteric	97 (39.1)	34 (46.6)	25 (36.8)	31 (40.3)	
Other	50 (20.2)	8 (11.0)	25 (20.6)	10 (13.0)	
ASAS-PS 4	21 (8.5)	14 (19.2)	12 (17.6)	15 (19.5)	0.012
ED to surgery (hours), mean (SD)	23.7 (27)	28.5 (29.9)	22.5 (31.8)	33.4 (40.2)	0.067
Intraoperative variables					
Type of surgery					
Hemiarthroplasty	90 (36.3)	38 (52.1)	23 (33.8)	32 (41.6)	0.072
Screw and side plate	39 (15.7)	16 (21.9)	13 (19.1)	15 (19.5)	
Intramedullary hip screw	68 (27.4)	11 (1.1)	17 (25.0)	12 (15.6)	
Cannulated screw	30 (12.1)	5 (6.8)	6 (8.8)	12 (15.6)	
Other					
Surgery duration (minutes), mean (SD)	104.9 (66.5)	132.3 (62.1)	104.1 (70.3)	113.8 (61.8)	0.014
Transfusion 3 units of RBC	26 (10.5)	19 (26)	12 (17.6)	11 (14.3)	0.009
Post-surgical mortality					
One-month follow up	9 (3.6)	8 (11.0)	3 (4.4)	8 (10.4)	0.035
Six-month follow up	30 (12.1)	15 (20.5)	11 (16.2)	21 (27.3)	0.013
One-year follow up	43 (17.3)	17 (23.3)	18 (26.5)	31 (40.3)	0.001

* All values n (%) unless otherwise specified. Presented p values for categorical variables are χ^2 test of independence and ANOVA for continuous variables.

Abbreviations: ASA-PS, American Society of Anesthesiologists, Physical Status; CCI, Charlson Comorbidity Index; SD, standard deviation

Bold: statistically significant at an alpha of 0.05

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Table 2:

Proportional Hazards Analysis of One-Year Mortality

Covariates	Univariate	Multivariate
Age	1.05 (1.02, 1.08)	1.03 (0.99, 1.06)
Male sex	1.39 (0.93, 2.07)	1.19 (0.78, 1.80)
Charlson Comorbidity Index	1.28 (1.19, 1.37)	1.22 (1.28, 1.33)
Surgery duration	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)
Cognitive variables	Univariate	
Delirium *	1.84 (1.26, 2.69)	N/A
Probable dementia **	2.19 (1.49, 3.20)	N/A
Cognitive status group	Univariate	Multivariate[†]
No delirium or dementia	<i>Reference</i>	<i>Reference</i>
Delirium alone	1.46 (0.83, 2.55)	1.42 (0.80, 2.52)
Probable dementia alone	1.59 (0.92, 2.75)	1.12 (0.64, 1.95)
Delirium superimposed on dementia	2.69 (1.70, 4.28)	1.71 (1.06, 2.77)

* Independent of preoperative probable dementia status

** Independent of posmiddleleerative delirium status

[†] Multivariate model presents hazard ratios for each cognitive status group relative to NDD group, corrected for age, sex, CCI, and surgery duration. Wald chi-square values for the three cognitive status comparators are Wald (df = 1) = 1.4, p = 0.231; (1) = 0.1, p = 0.703; (1) 4.8, p = 0.028; respectively.