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The Association Between Preoperative Frailty and Postoperative Delirium After Cardiac Surgery

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Abstract

Delirium is common after cardiac surgery, and preoperative identification of high-risk patients could guide prevention strategies. We prospectively measured frailty in 55 patients before cardiac surgery and assessed postoperative delirium using a validated chart review. The prevalence of frailty was 30.9%. Frail patients had a higher incidence of delirium (47.1%) compared with non-frail patients (2.6%; $p < 0.001$). In multivariable models, the relative risk (RR) of delirium was at least 2.1-fold higher in frail compared with non-frail patients (RR 18.3, 95% CI 2.1, 161.8, $p = 0.009$). Frailty may identify patients who would benefit from delirium-prevention strategies because of increased baseline risk for delirium.

Introduction

Delirium after cardiac surgery is a common¹ and costly complication, that increases the risk of morbidity,² mortality,³ and cognitive decline.⁴ Effective treatment of delirium is difficult,⁵ so prevention is critical. However, widespread prevention efforts in low-risk patients may have negative consequences, including increased resource utilization⁵ or medication side effects.⁶ Thus identifying high-risk patients is critical to target delirium-prevention strategies.

Frailty assessment is commonly used to characterize the most vulnerable subset of older adults with decreased reserve across multiple organ systems.⁷ The most widely used

physiologic definition of frailty (Fried criteria)⁸ incorporates assessment of gait, strength, weight loss, exhaustion, and activity and is thought to identify older adults at elevated risk for poor outcomes. In community-based cohort studies, frailty has been associated with falls,⁹ disability,¹⁰ institutionalization,¹¹ and death,¹¹ while after surgery, frailty has been associated with increased postoperative complications and length of stay.¹² Since delirium is thought to result from the interplay of an acute insult on a vulnerable patient,⁵ we hypothesized that patients with preoperative frailty (a validated geriatric marker of patient vulnerability) would be at higher risk for delirium after cardiac surgery.

Methods

IRB/Consent

This study was approved by the Johns Hopkins IRB (Baltimore, MD) and written informed consent was obtained from all participants.

Patients

This prospective observational pilot study enrolled patients between July 2010-April 2013 at a tertiary care hospital. Inclusion criteria were age >55 years-old and undergoing only coronary artery bypass graft (CABG) surgery. Exclusion criteria were emergency surgery, reoperations, acute illness besides coronary disease, or preoperative inotropic/vasoactive medication usage. Sample size was initially calculated for the primary question of demonstrating a difference in length of stay based on serum levels of a protein active in cellular senescence. As shown in Appendix 1, during enrollment, 262 patients were screened, 178 patients were eligible, 60 patients enrolled and 55 patients completed the study (3 withdrew, 1 had unplanned valve surgery, 1 had no staff availability).

Frailty Assessment

Trained research coordinators performed frailty assessments during the preoperative clinic visit (median 1 day, range 1-14 days prior to surgery) using the well-validated scale from Fried et al.⁸ (Appendix 2) evaluating 5 domains: (1) *shrinking*, defined as unintentional weight loss of 10 pounds in the last year; (2) *weakness*, determined by grip-strength, adjusted for gender and body mass index; (3) *exhaustion*, determined by two questions from the modified 10-item Center for Epidemiological Studies-Depression scale;¹³ (4) *low physical activity*, determined by the modified Minnesota Leisure Time Activities Questionnaire;¹⁴ and (5) *slowed walking speed*, as measured at normal pace over 15 feet. Each domain yielded a score of 0 or 1 based on cutoffs previously described,⁸ with frail patients defined as a total score of 3. Patients with scores of 0 (non-frail) and 1-2 (potentially pre-frail) were categorized together as the non-frail group.

Outcome Assessment

Delirium was assessed using a rigorous and validated chart-review method, which was the most validated method feasible at the time of this study.¹⁵ This method has the advantage of allowing assessment of the entire hospital course¹⁶ (including nights and weekends of an often long hospitalization [median 6 days, range 27 days in this sample]). It likely preferentially identifies hyperactive delirium,¹⁶ the subtype that has been associated with

danger to self,¹⁷ more falls,¹⁸ and worse outcomes in some studies.¹⁹ According to the methodology of Inouye et al.,¹⁵ a research abstractor (trained in delirium assessment by a psychiatrist with recognized expertise in delirium) searched all sections of the entire medical record for any mention of key terms, with evidence of acute onset or change, to support a delirium diagnosis based on the following question: "Is there any evidence from the chart of acute confusional state (e.g. delirium, mental status change, inattention, disorientation, hallucinations, agitation, inappropriate behavior, etc.)?" These data were recorded on a specific data form. A 3-person panel with active involvement/training in delirium research reviewed abstractions to determine the final diagnosis. Other organ-specific complications were assessed using Society for Thoracic Surgeons database criteria,^a with a composite outcome defined as any neurologic, cardiac, pulmonary, renal, infectious, or vascular complication.

Covariates

Demographics, co-morbidities, medications, and functional capacity information were collected at baseline. Postoperative complications were prospectively collected, as described in Table 1.

Data Analysis

Statistical analyses were conducted using Stata v.12 (StataCorp, College Station, TX). There were no missing exposure/outcome data or loss to follow-up. Patient and surgical characteristics were compared using Student's t-tests, rank-sum tests (for non-normally distributed data), chi-squared tests, and Fisher's exact tests (for comparisons with event frequency ≤ 5). Generalized linear models using the log link and Poisson distribution were used to determine the association between frailty and delirium. Age, stroke, depression, and Charlson score were *a priori* included in the final model based on potential associations with frailty^{11,12} and delirium.¹ We also conducted a sensitivity analysis using propensity scores incorporated into the main regression model.²⁰ Specifically, we calculated a propensity score using logistic regression to predict frailty status based on age, sex, alcohol, activities of daily living, instrumental activities of daily living, peripheral vascular disease, cerebrovascular disease, depression, albumin, and Charlson score.

Results

Among 55 enrolled patients, 17 (30.9%) were frail. As shown in Table 2, frail patients were generally older, more likely to have ever smoked, had a higher prevalence of steroid and statin use, and had higher baseline Charlson scores compared with non-frail patients. After surgery, frail patients had a higher incidence of composite complications and intensive care unit length of stay. (Table 1)

Nine patients (16.4%) developed postoperative delirium. As shown in Figure 1, the incidence of delirium was higher in frail compared with non-frail patients (47.1% vs. 2.6%; $p < 0.001$). In a multivariable model adjusted for age, prior stroke, depression, and quintile of

^aSociety of Thoracic Surgeons. 2008. Adult cardiac surgery database data collection form version 2.61. http://www.sts.org/sites/default/files/documents/pdf/ndb/STS_Quality_Module_DCF_18_Dec_08.pdf, Accessed 02/15/2011.

Charlson score (Table 3), the risk of delirium was increased by more than 2.1-fold in frail compared with non-frail patients (Relative Risk [RR] 18.3; 95% Confidence Interval [CI] 2.1, 161.8; $p=0.01$). A similar result was seen in propensity score-adjusted models (RR 15.8; 95%CI 1.8, 137.2; $p=0.012$). Additionally, inferences were unchanged if all covariates associated with frailty in Table 2 at a significance level of $p<0.05$ were added to the multivariable model. Among individual domains of frailty in the multivariable model, only weight loss (RR 8.3; 95%CI 1.8, 37.2; $p=0.01$) was associated with delirium.

Discussion

We identified frailty in 30.9% of patients presenting for CABG surgery, with a significantly higher incidence of delirium among frail compared with non-frail patients.

Our results extend the results of two prior studies with similar findings. The first study was limited to noncardiac surgery,²¹ in which patients had different baseline comorbidities and perioperative insults, so the results may not have been generalizable to cardiac surgery. The second well-done study²² in cardiac surgery patients used (among other frailty definitions) a modified version of the well-validated Fried frailty scale,⁸ and included low cognitive status and depressed mood as frailty criteria. Although the modified criteria have not been as well validated as the original Fried criteria, the inclusion of cognitive and mood questions may have strengthened the observed association between frailty and delirium. The results of our study demonstrate that the physical decline captured by the original validated Fried criteria is in and of itself associated with an increased risk for delirium after cardiac surgery. However, since we did not administer formal cognitive testing, we cannot characterize the exact role of cognition in modifying or mediating the frailty/delirium association.

Although the mechanism for our findings is unclear, geriatricians view frailty as a syndrome characterized by reduced ability to withstand stressors,⁷ and delirium may be one manifestation of this. From the pathophysiology perspective, a leading hypothesis for the etiology of delirium is neuroinflammation,^{5,23} which can occur both peripherally and centrally after surgery, with the central component perhaps predominant.²⁴⁻²⁶ Frail patients have increased peripheral inflammation at baseline,²⁷ which may be heightened by an inflammatory insult such as cardiopulmonary bypass. In the setting of a potentially disrupted blood-brain barrier,²⁸ resulting neuroinflammation may increase the risk for delirium in frail patients. Indeed in mouse models, the neurological effects of inflammation have been shown to be greater in mice with preexisting neurodegenerative disease.²⁹ Alternatively, the central neuroinflammatory response may be greater in frail patients, although this hypothesis has not been tested. Although reducing neuroinflammation may be a potential avenue for prevention or treatment of delirium, a 2014 trial³⁰ of the antiinflammatory steroid dexamethasone administered prior to cardiac surgery did not show any benefit for delirium prevention, with the caveat that steroid administration itself may be a risk factor for delirium.

There are several important limitations of this study. First, we used a validated delirium assessment method, but compared to the well-known Confusion Assessment Method,³¹ the sensitivity has been shown to be 74% and specificity 83%.¹⁵ With an incidence of delirium

in our study of 16.4%, misclassification error may be present, although the error would need to be quite large to obviate the results of this study. Second, our findings may only reflect hyperactive delirium that is clinically apparent on chart review, not hypoactive delirium which can be more difficult to diagnose but is also associated with increased mortality.³² Third, the small sample size predisposes to wide CIs and limits inclusion of potentially important confounding variables in our analysis. We did use propensity score adjustment, but a larger sample size would allow for more precise estimates. A many eligible patients were not approached or refused consent, thus introducing the risk of selection bias and limiting generalizability of the results. Nonetheless, the findings of this study are provocative in showing a link between preoperative frailty and risk for postoperative delirium. Further studies are needed to confirm this association using in-person delirium assessments as well as to examine whether a targeted delirium prevention strategy for frail patients may improve outcomes after CABG surgery.

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Appendix 1

Patient Flowchart

Appendix 2

Appendix 2

Instrument to Assess Frailty.

Domain	Definition
Shrinking (weight loss)	Shrinking is defined through self-report as an unintentional weight loss of 10 pounds in the last year. This information was obtained by asking the patient.
Decreased grip strength (weakness)	Weakness will be assessed by grip strength, and measured directly with a hand-held JAMAR dynamometer (Sammons Preston Rolyan). Three serial tests of maximum grip strength with the dominant hand will be performed, and a mean of the 3 values will be adjusted by gender and body mass index (BMI). Weakness will be defined as adjusted grip strength in the lowest 20 th percentile of a community-dwelling population of adults 65 years of age and older. Men will meet the criteria for weakness if their BMI and grip strength are 24 and 29 kg; 24.1–26 and 30 kg; 26.1–28 and 31 kg; >28 and 32 kg, respectively. Women will meet the criteria for weakness if their BMI and grip strength are 23 and 17 kg; 23.1–26 and 17.3 kg; 26.1–29 and 18 kg; and >29 and 21 kg, respectively.
Exhaustion	Exhaustion will be measured by responses by the patient to the following 2 statements from the modified 10-item Center for Epidemiological Studies-Depression scale: “I felt that everything I did was an effort” and “I could not get going.” Subjects will be asked, “How often in the last week did you feel this way?” Potential responses are: 0 = rarely or none of the time (<1 day); 1 = some or a little of the time (1–2 days); 2 = a moderate amount of the time (3–4 days); and 3 = most of the time. Subjects answering either statement with response 2 or 3 will meet the criteria for exhaustion.
Low activity	Physical activities will be ascertained for the 2 weeks before this assessment using the short version of the Minnesota Leisure Time Activities Questionnaire, which includes frequency and duration. The patient will be asked about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. Weekly tasks will be converted to equivalent kilocalories of expenditure, and individuals reporting a weekly kilocalorie expenditure in the lowest 20 th percentile for their gender (men, <383 kcal/week; women, <270 kcal/week) will be classified as having low physical activity.
Slowed walking speed	Slowness will be measured by averaging 3 trials of the patient walking 15 feet at a normal pace. Individuals with a walking speed <20 th percentile, adjusted for gender and height, will be scored as having slow walking speed. Men will meet criteria if height and walk time are 173 cm and 7 seconds, or >173 cm and 6 seconds, respectively. Women will meet criteria if height and walk time are 159 cm and 7 seconds, or >159 cm and 6 seconds, respectively.

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Figure 1.

The incidence of delirium after cardiac surgery among frail compared with non-frail patients. Among 38 non-frail patients, 1 patient developed delirium, while among 17 frail patients, 8 patients developed delirium.

Table 1Complications Among Frail and Non-Frail Patients after Cardiac Surgery^a

	Non-Frail N=38	Frail N=17	P-Value ^b
Neurologic, ^c n (%)	0 (0)	1 (5.9)	0.31
Cardiac, ^d n (%)	4 (10.5)	5 (29.4)	0.12
Pulmonary, ^e n (%)	1 (2.6)	2 (11.8)	0.22
Renal, ^f n (%)	4 (10.5)	1 (5.9)	1.0
Infection, ^g n (%)	1 (2.6)	1 (5.9)	0.53
Vascular, ^h n (%)	0 (0)	0 (0)	N/A
Composite Complications, ⁱ n (%)	9 (23.7)	9 (52.9)	0.03
Reoperation, n (%)	1 (2.6)	1 (5.9)	0.53
ICU Length of Stay (hours), med (IQR)	27.5 (23-52)	51 (27-75)	0.04
ICU readmission, n (%)	1 (2.8)	1 (5.9)	0.54
Hospital Length of Stay (days), med (IQR)	6 (5-7)	7 (6-8)	0.13
Hospital readmission, n (%)	5 (13.9)	2 (11.8)	1.0
30-day mortality, n (%)	2 (5.6)	0 (0)	1.0

Abbreviations: ICU= Intensive Care Unit

^aAll complications as listed below are defined by Society of Thoracic Surgeons database criteria. (<http://www.sts.org/sites/default/files/documents/STSAAdultCVDDataSpecificationsV2.81.pdf>, accessed 12/8/14)

^bP-values were obtained using the chi squared test for the “composite complications” variable, Fisher’s exact tests for all other dichotomous variables (all with event frequencies ≤ 5), and rank sum tests for continuous variables, which were non-normally distributed.

^cNeurologic complications include postoperative cerebrovascular accident, transient ischemic attack, or coma

^dCardiac complications include heart block, cardiac arrest, cardiac tamponade, perioperative myocardial infarction, atrial fibrillation, or aortic dissection

^ePulmonary complications include reintubation, prolonged ventilation, pulmonary embolism, or pneumonia

^fRenal complications include acute renal failure or new renal replacement therapy

^gInfection complications include deep sternal wound infection, leg or arm wound infections, or septicemia

^hVascular complications include iliac/femoral artery dissections or acute limb ischemia

ⁱComposite measure of complications was defined as the presence of any of the following complications as defined above (neurologic, cardiac, pulmonary, renal, infectious, or vascular)

Table 2**Baseline Patient Characteristics^a**

	Non-Frail N=38	Frail N=17	P-Value^b
Age (mean±SD)	64.7±5.6	67.7±8.4	0.12
Female, n (%)	8 (21.0)	6 (35.3)	0.26
Race			0.78
Caucasian, n (%)	32 (84.2)	15 (88.2)	
African American, n (%)	4 (10.5)	1 (5.9)	
Asian, n (%)	1 (2.6)	0 (0)	
Other, n (%)	1 (2.6)	1 (5.9)	
ADL, ^c median (IQR)	0 (0-0)	0 (0-0)	0.65
IADL, ^d median (IQR)	0 (0-0)	0 (0-0)	0.61
Cerebrovascular disease, n (%)	2 (5.3)	1 (5.9)	1.0
Dementia, ^e n (%)	0 (0)	1 (5.9)	0.31
Congestive heart failure, n (%)	1 (2.6)	1 (5.9)	0.53
Hypertension, n (%)	32 (84.2)	14 (82.4)	0.86
Peripheral vascular disease, n (%)	4 (10.5)	6 (35.3)	0.054
Chronic pulmonary disease, n (%)	4 (10.5)	5 (29.4)	0.12
Chronic renal insufficiency, n (%)	3 (7.9)	0 (0)	0.54
Depression, n (%)	2 (5.3)	3 (17.7)	0.17
Diabetes, n (%)	11 (29.0)	8 (47.0)	0.19
Severe liver disease, n (%)	1 (2.6)	0 (0)	1.0
Smoking status			0.01
Never, n (%)	16 (42.1)	3 (17.7)	
Previous, n (%)	0 (0)	3 (17.7)	
Current, n (%)	22 (57.9)	11 (64.7)	
Any alcohol use, n (%)	22 (57.9)	5 (29.4)	0.08
Charlson score, med (IQR)	1.5 (0-2)	3 (1-3)	0.06
Creatinine mg/dL, mean±SD	1.13±0.9	1.05±0.3	0.71
Hemoglobin g/dL, mean±SD	13.3±1.9	13.5±1.5	0.72
Medications			
Beta-adrenergic receptor blockers, n (%)	24 (63.2)	15 (88.3)	0.06
Angiotensin Converting Enzyme Inhibitors, n (%)	25 (65.8)	8 (47.1)	0.19
Diuretic, n (%)	13 (34.2)	7 (41.2)	0.62
Calcium Channel Blocker, n (%)	13 (34.2)	4 (23.5)	0.54
Anti-arrhythmic, n (%)	2 (5.3)	2 (11.8)	0.58
Warfarin, n (%)	0 (0)	1 (5.9)	0.31
HMG-Coenzyme A Reductase Inhibitors, n (%)	24 (63.2)	16 (94.1)	0.02
Steroids, n (%)	2 (5.3)	5 (29.4)	0.02
Insulin, n (%)	3 (7.9)	5 (29.4)	0.09

Abbreviations: SD=standard deviation; IQR= inter-quartile range; ADL=activities of daily living; IADL= Instrumental activities of daily living

^aBaseline information on patient characteristics was obtained from review of the medical record and patient interview.

^bP-values were calculated with t-tests for normally distributed continuous variables, rank sum tests for non-normally distributed continuous variables, Fisher's exact tests for dichotomous variables with event frequencies ≤ 5 , and chi squared tests for other dichotomous variables ("gender", "diabetes", "hypertension", "beta-adrenergic receptor blocker", "angiotensin converting enzyme inhibitors", "diuretic", and "HMG-coenzyme A reductase inhibitors").

^cTotal score on Activities of Daily Living scale (range 0-6) with "0" as independent

^dTotal score on Instrumental Activities of Daily Living scale (range 0-23) with "0" as independent

^eDementia is classified based on self or family-reported history, or from the medical record

Table 3

Risk of Delirium among Frail Compared with Non-Frail Patients in Adjusted Models

	Relative Risk for Delirium ^a	95% CI	P-Value
Frailty ^b	18.3	2.1-161.8	0.009
Age (in decades)	1.1	0.5-2.7	0.81
History of stroke	1.8	0.2-17.6	0.61
History of depression	0.67	0.1-5.9	0.72
Quintile of Charlson comorbidity index score	0.96	0.6-1.7	0.89

^aRelative risk of delirium was determined with generalized linear models using the log link and poisson distribution.

^bThere were no significant interactions between frailty and each of the other co-variables, when each of the other covariates were added to the model as an interaction term with frailty. Thus, the most parsimonious model is presented.