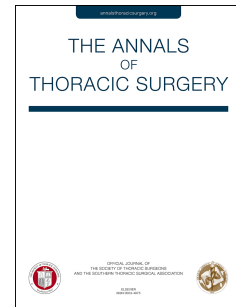


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The Pragmatic Impact of Frailty on Outcomes of Coronary Artery Bypass Grafting

Running head: Frailty in Coronary Bypass Grafting

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Abstract

Background: Although not formalized into current risk assessment models, frailty has been associated with negative postoperative outcomes in many specialties. Using administrative coding, we evaluated the impact of frailty on in-hospital mortality, complications and resource use in a nationally representative cohort of patients undergoing isolated coronary artery bypass grafting (CABG).

Methods: Patients ≥ 18 years who underwent isolated CABG across the United States were identified using the 2005-2016 National Inpatient Sample. Frailty was defined using a derivative of the validated Johns Hopkins Adjusted Clinical Groups frailty-defining diagnosis indicator. Mortality, length of stay, inflation-adjusted costs, and postoperative complications were evaluated using multi-level multivariable regression.

Results: Of an estimated 2,137,618 patients undergoing isolated CABG, 85,879 (4.0%) were considered frail. The proportion of frail patients increased over the study period (NP-trend=0.002), while annual mortality rates declined (NP-trend<0.001). Frail patients were older (68.9 ± 10.7 years vs. 65.0 ± 10.6 years, $P < 0.001$), and more commonly female (32.8% vs. 26.2%, $P < 0.001$). After adjustment, frailty was associated with increased odds of in-hospital mortality (adjusted odds ratio, AOR 2.49, 95% confidence interval, 95% CI: 2.30-2.70, $P < 0.001$), major complications (AOR 2.55, 95% CI: 2.39-2.71, $P < 0.001$), increased length of stay (AOR 1.40, 95% CI: 1.09-2.11, $P < 0.001$), and costs (AOR 1.03, 95% CI: 1.02-1.07, $P < 0.001$).

Conclusions: Frailty as identified by administrative coding serves as strong independent predictor of death and complications following CABG. Incorporation of frailty into risk models may aid in counseling patients about operative risk and benchmarking outcomes.

Abstract Word Count: 236

Keywords

Coronary Artery Bypass Graft Surgery, CABG, Frailty, National Inpatient Sample, NIS

Abbreviations

AOR: Adjusted Odds Ratio

CABG: Coronary Artery Bypass Graft

CI: Confidence Intervals

HCUP: Healthcare Cost and Utilization Project

ICD-9/10: International Classification of Diseases, Ninth/Tenth Edition:

HVH: High-Volume Hospitals

LVH: Low-Volume Hospitals

NIS: National Inpatient Sample

MVH: Medium-Volume Hospitals

Risk assessment in surgical therapies remains paramount to adequate patient counseling, intervention choice and performance assessment. With more than two hundred thousand coronary artery bypass (CABG) operations annually in the US, highly accurate models have been developed to aid in surgical decision-making as well as determination of risk adjusted outcomes¹⁻⁵. The Society of Thoracic Surgeons risk of mortality score is a validated tool that is widely utilized and undergoes regular re-calibration based on new data. Despite incorporation of many clinical variables, however, such risk scores are only able to partially predict mortality and adverse outcomes^{6,7}. While chronological age is a major driver of risk in nearly all models, one can surmise the wide variation in the physiologic fitness of patients within the same age group. Colloquially known as the “eye-ball test”, frailty has more recently been utilized to quantify the overall condition of patients⁷.

While a universally accepted definition is currently lacking, frailty is generally considered to be a measure of resilience to stressors and accumulation of comorbidities. A large body of literature has examined the impact of frailty on outcomes of hospitalizations for several surgical and medical diagnoses and found it to negatively impact index outcomes^{8,9}. A recent study by Afilalo assessed gait speed as a measure of frailty and found it to predict mortality and re-hospitalization in a cohort of 8,000 cardiac surgical patients^{10,11}. Due to the variability in the available measures of frailty, the Johns Hopkins group recently introduced the Adjusted Clinical Groups Score¹²⁻¹⁶. This system uses a cluster of coding-based diagnoses from the medical record to derive a binary frailty variable. We examined the impact of frailty as measured by the Johns Hopkins score on outcomes of coronary artery bypass grafting in the US. We hypothesized that frailty would be independently associated with increased mortality, complications and resource use.

Patients and Methods

Patient and hospital information from January 2005 to December 2016 was extracted from the National Inpatient Sample (NIS). As part of the Healthcare Cost and Utilization Project

(HCUP), the NIS is the largest publicly available, all-payer database and is maintained by Agency for Healthcare Research and Quality¹⁷. The NIS records de-identified patient and hospital information from all nonfederal hospitals across 45 states and allows for estimation of 97% of all hospital admissions in the United States¹⁷. In 2012, the NIS algorithm changed from sampling all patients in 20% of hospitals to 20% of patients in all participating hospitals. Appropriate trend and discharge weights provided by HCUP were utilized to account for this change. Using specialized methodology, HCUP releases inpatient charges that are all encompassing and not assigned to cost-categories. Cost to charge ratio files, also provided by HCUP, were used to derive total hospitalization costs and further adjusted for inflation. The need for full review of the study protocol and informed consent was waived by the institutional review board at the University of California, Los Angeles.

All statistical analyses were performed using Stata 15.1 and Stata 16.1 (StataCorp, College Station, TX). Categorical variables are presented as count with percentage and continuous variables as mean with standard deviation. Temporal trends were assessed using a non-parametric test for trend¹⁸. Pearson χ^2 tests and t-tests were used to compare categorical and continuous variables, respectively. We used stepwise backwards elimination to select variables, as well as retention of clinically relevant variables, for model selection. Continuous variables with non-normal distributions were log-transformed, and interaction terms tested and retained in models if significant. Statistical significance was set at $\alpha \leq 0.05$.

All adult patients (>18 years) who underwent isolated CABG were identified using the International Classification of Diseases, Ninth and Tenth Edition (ICD-9, ICD-10) relevant codes (Supplemental Table 1). Patients undergoing concomitant valve operations during index hospitalization as well as those with missing key data, including costs, mortality, and LOS, were excluded from the study (Figure 1). Available diagnostic coding was used to tabulate various patient comorbidities and complications (Supplemental Table 1). Hospital demographics were used as recorded in the NIS. All NIS derived variables including elective status used data

definitions from the NIS data dictionary¹⁷. The previously validated Elixhauser Comorbidity Index was used to characterize severity of patient comorbidity¹⁹. Patients were considered frail using the Johns Hopkins Adjusted Clinical Groups (ACG) indicator, previously described in detail elsewhere^{19,20}. Briefly, this binary designation classifies patients as frail (*Frail*) if any of the frailty-defining ICD codes in ten ACG domains were present at discharge (Supplemental Table 2)²⁰. Subset analyses were performed to assess the impact of center volume on outcomes of isolated CABG within the *Frail* and *Non-frail* cohorts. Hospitals were stratified into low-, medium-, and high-volume tertiles (LVH, MVH, HVH, respectively) based on annual isolated CABG caseload. The primary outcome of the study was to assess the impact of frailty on mortality and complications following isolated CABG. Secondary outcomes included length of stay, and hospitalization costs as well as trends in mortality and proportion of frailty in this cohort.

Results

Of an estimated 2,137,618 patients undergoing isolated CABG during the study period, 85,879 (4.0%) were considered *Frail*. Although the overall annual isolated CABG volume decreased significantly during the study period (Figure 2), the proportion of *Frail* patients increased (2.2% in 2005 to 5.4% in 2016, NP-trend=0.002). In-hospital mortality declined for both the *Frail* and overall isolated CABG cohorts over the study period (8.5% to 5.2%, NP-trend<0.001 and 2.3% to 1.9%, NP-trend<0.001, respectively).

Comparison of patient and hospital characteristics are displayed in Table 1. Compared to *Non-frail*, *Frail* patients were significantly older (68.9 years $\pm$ 10.7 vs. 65.0 years $\pm$ 10.6, $P<0.001$), more likely to be female (32.8% vs. 26.2%, $P<0.001$), and of Black race (9.1% vs. 6.7%, $P<0.001$). While a higher proportion of *Non-frail* patients had private insurance (35.0% vs. 18.4%, $P<0.001$), the majority of *Frail* were insured by Medicare (68.4% vs. 51.7%, $P<0.001$). The South had the highest proportion of isolated CABGs performed in both the *Non-frail* (44.6%) and *Frail* (43.5%) cohorts. Compared to *Non-frail*, patients in the *Frail* cohort had lower rates of hypertension (60.4% vs. 77.0%), obesity (9.8% vs. 17.3%), and diabetes (39.6% vs.

35.6%), but a higher prevalence of congestive heart failure (40.7% vs. 22.2%), liver (5.5% vs. 1.9%) and chronic kidney disease (22.1% vs. 12.3%, $P<0.001$ for all). On univariate analysis and *Non-frail* as reference, the *Frail* faced increased mortality (6.9% vs. 1.8%, $P<0.001$), costs (\$74,100 $\pm$ 61,000 vs. \$41,800 $\pm$ 26,000, $P<0.001$), and longer LOS (18.2 $\pm$ 15.7 days vs. 9.0 $\pm$ 6.1 days, $P<0.001$). Furthermore, *Frail* patients incurred higher rates of respiratory, cardiac, renal and overall complications compared to the *Non-frail*, as shown in Table 2.

Multivariable logistic regression was used to identify factors associated with mortality, complications, LOS, and hospitalization costs after adjustment for patient and hospital level factors (Table 3). After adjustment, frailty was independently associated with significantly elevated odds of mortality (AOR 2.49, 95% CI: 2.30-2.70, $P<0.001$) and overall complications (AOR 2.55, 95% CI: 2.39-2.71, $P<0.001$, Figure 3). Additionally, *Frail* patients experienced higher odds of renal (AOR 2.77, 95% CI: 2.63-2.92, $P<0.001$), respiratory (AOR 2.39, 95% CI: 2.26-2.53, $P<0.001$), and cerebrovascular complications (AOR 2.51, 95% CI: 2.30-2.73, $P<0.001$) with *Non-Frail* as reference. Furthermore, frailty was independently associated with greater costs (AOR 1.03, 95% CI: 1.02-1.07, $P<0.001$) and longer LOS (AOR 1.40, 95% CI: 1.09-2.11, $P<0.001$). On subset analysis accounting for CABG volume and using LVH as the reference, HVH status was associated with significantly reduced odds of mortality (AOR 0.72, 95% CI: 0.65-0.79, $P<0.001$) in the *Non-Frail* cohort but not in *Frail* group (AOR 1.01, 95% CI: 0.82-1.25, $P=0.88$).

Comment

The concept of frailty has recently received renewed interest in the surgical world. Imprecisely defined, frailty appears to represent a constellation of physical and physiological derangements that reduce the ability to appropriately recover from stressors. While several available tools are utilized to assess various domains of frailty, none have reached universal adoption in part owing to resource barriers. Meanwhile, commonly used risk calculators such as the Society of Thoracic Surgeons risk of mortality score and European System for Cardiac

Operative Risk Evaluation do not consider frailty parameters in their algorithms^{5,20}. We utilized a parsimonious, binary, and ICD-based frailty assessment tool in a nationally representative cohort of isolated CABG patients and made several important observations. While the number of CABG operations has declined over the past decade, the prevalence of frailty in this group has increased significantly affecting nearly 5% of patients in 2016. After adjusting for patient and hospital characteristics, frailty was independently associated with a 2- and 3-fold increase in the odds of mortality and complications. Patients considered frail also had a longer length of stay and costs at index hospitalization. Our findings have important implications for patient counseling, choice of intervention as well as policy and reimbursement algorithms.

In the present study, we observed a decline in overall CABG volume and an increasing prevalence of frailty in this cohort. Many explanations for the reduction of CABG cases across the US have been offered in previous studies and include the success of percutaneous coronary interventions as well as increased adoption of guideline based medical therapy¹. Although one might expect frail patients to be directed away from CABG given the lower peri-procedural risk of percutaneous coronary interventions, we observed an increase in the proportion of frail patients undergoing isolated CABG. Our findings may, in part, be explained by anatomic considerations in frail patients who may suffer from more advanced illnesses such as renal disease, not adequately captured in our database. In fact, Alkhouli and colleagues recently reported a moderate increase in the number of elderly patients and doubling in the proportion of patients with an Elixhauser score of 3 or greater²². More accurate coding practices in recent years, may also contribute the increasing prevalence of frailty in studies utilizing administrative databases. The value of quality improvement programs aimed at optimizing care in frail cardiac surgical candidates deserves further investigation.

While surgeons have subjectively assessed the patient's ability to withstand operations of various magnitudes, formalization of frailty assessment has been challenging. Absence of a universal definition and the constellation of findings present in frailty make it difficult for

practitioners to readily screen patients for this condition. Nonetheless, there is agreement that frailty reduces the patients' ability to appropriately respond to stressors including surgery. In the present work, we adjusted for known perioperative risk factors and found frailty to increase the odds of mortality nearly three-fold following CABG. Our findings suggest the presence of other non-traditional patient characteristics that influence operative outcomes. Interestingly, frail patients have previously been noted to have anemia as well as higher levels of factor VIII, D-dimer, C-reactive protein, leukocytes, fibrinogen, and inflammatory cytokines such as interleukin-6^{11,24,25}. While we were unable to assess such laboratory values, we used a measure of frailty that is binary and uses risk factors already captured in administrative databases. Results of the present study suggest the need to incorporate frailty into existing accepted risk scores. This will further allow for improved counseling of patients using objective measures and aid in determining alternate strategies that may reduce perioperative risk.

Frailty as identified in the present study appears to adversely impact complications and resource use. Those considered frail had a nearly 3-fold increase in the odds of overall complications, including respiratory, cerebrovascular, and renal. Beyond the index stay, such complications have the potential to significantly reduce a patient's functional status and quality of life. Addition of routine frailty screening may provide patients with a more realistic outlook on their recovery and therefore improve the informed consent process. On a systems level, we found frailty to increase healthcare costs and rates of non-home discharge, creating an additional burden on patients and payers alike. Therefore, streamlined identification of frailty such as described herein, can be utilized to better inform episodic payments, particularly if bundled.

The present study has several important limitations including those inherent to its retrospective design. First, the administrative nature of NIS prevents the ability to assess granular laboratory and physiologic data. Furthermore, our binary characterization was unable to capture the severity of frailty that may be obtained through other exams. Third, we were

unable to validate frailty through other methods and relied on previously published data on the Johns Hopkins Adjusted Clinical Groups algorithm. The accuracy of coding in the NIS is dependent on individual hospital and physician practices. Nonetheless, we used the largest available nationally representative database to derive the cohorts and performed robust analysis methods in order to reduce bias. Finally, cost analysis is limited to index hospitalization and does not include post discharge expenditures.

In conclusion, addition of frailty scores obtained from administrative billing data appear to enhance the predictive power of existing models in predicting mortality and adverse outcomes following isolated CABG. This metric may be readily incorporated into existing risk scores and be utilized to better inform patients of the expected surgical risks in the frail. Such assessments can inform optimal revascularization strategies and provide further insights into value-based care for frail patients.

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Table 1: Patient and Hospital characteristics of those undergoing Isolated CABG, stratified by frailty status. *Other race includes Asian, Native American, and other races as defined by NIS.

†Other payer includes Self-Pay, Uninsured, and Other as defined by NIS.

	<i>Non-Frail (N=2,137,618)</i>	<i>Frail (N=85,879)</i>	P-Value
Age, years (mean $\pm$ SD)	65.0 $\pm$ 10.6	68.9 $\pm$ 10.7	<0.001
Female n(%)	560,985 (26.2)	28,184 (32.8)	<0.001
Race n(%)			<0.001
White	1,416,295 (79.6)	57,894 (77.0)	
Black	119,295 (6.7)	6,810 (9.1)	
Hispanic	124,660 (7.0)	5,566 (7.4)	
Other*	119,511 (6.7)	4,879 (6.4)	
Income Quartile n(%)			<0.001
Lowest	571,950 (27.4)	26,140 (31.1)	
2nd Quartile	573,565 (27.5)	22,966 (27.3)	
3rd Quartile	517,598 (24.7)	19,924 (23.7)	
Highest	424,934 (20.4)	15,050 (17.9)	
Primary Payer n(%)			<0.001
Medicare	1,103,992 (51.7)	58,614 (68.4)	
Private Insurance	746,706 (35.0)	6,155 (18.4)	
Medicaid	128,422 (6.0)	15,657 (18.3)	
Other†	154,781 (7.3)	5,309 (6.2)	
Elective Operation n(%)	985,659 (46.2)	29,043 (33.9)	<0.001
Transferred from Outside Facility n(%)	285,930 (19.3)	17,128 (24.8)	<0.001
Elixhauser Index Score, (mean $\pm$ SD)	2.9 $\pm$ 1.8	3.8 $\pm$ 2.1	<0.001

Comorbidities n(%)

Atrial Fibrillation	572,458 (26.8)	267,68 (31.2)	<0.001
Congestive Heart Failure	474,571 (22.2)	34,913 (40.7)	<0.001
Valvular Disease	228,797 (10.7)	10,160 (11.8)	0.002
Peripheral Vascular Disease	278,790 (13.0)	11698 (13.6)	0.04
Hypertension	1,646,618 (77.0)	51,887 (60.4)	<0.001
Chronic Obstructive Pulmonary Disorder	318,787 (14.9)	14,681 (17.1)	<0.001
Liver Disease	39,744 (1.9)	4,689 (5.5)	<0.001
Diabetes	846,458 (39.6)	30,533 (35.6)	<0.001
Obesity	369,988 (17.3)	8,388 (9.8)	<0.001
Chronic Kidney Disease	262,451 (12.3)	18,938 (22.1)	<0.001
Dialysis Dependence	13,661 (0.06)	1,096 (1.3)	<0.001
Coagulopathy	262,789 (12.3)	16,538 (19.3)	<0.001

CABG Volume Tertiles n(%)

0.03

Low Volume Hospitals	719,345 (33.7)	30,966 (36.1)
Medium Volume Hospitals	725,487 (33.9)	26,903 (31.3)
High Volume Hospitals	692,530 (32.4)	28,009 (32.6)

Hospital Bed Size n(%)

0.02

Small	164,044 (7.7)	5,681 (6.6)
Medium	443,517 (20.8)	16,821 (19.7)
Large	1,519,826 (71.4)	63,014 (73.7)

Hospital Teaching Status n(%)

0.01

Rural	77,538 (3.6)	3,730 (4.4)
Urban Non-teaching	753,510 (35.4)	26,970 (31.5)

Urban Teaching	1,295,339 (61.1)	54,816 (64.1)	
Region n(%)			0.34
Northeast	312,444 (14.6)	12,917 (15.0)	
Midwest	528,405 (24.7)	22,403 (26.1)	
South	953,865 (44.6)	37,331 (43.5)	
West	342,648 (16.0)	13,228 (15.4)	

Table 2: Univariate comparison of outcomes following Isolated CABG in *Frail* and *Non-Frail* cohorts.

	<i>Non-Frail</i> (N=2,137,618)	<i>Frail</i> (N=85,879)	P-Value
Mortality n(%)	38,471 (1.8)	5,897 (6.9)	<0.001
Complications n(%)			
Respiratory	583,182 (27.3)	46,506 (54.2)	<0.001
Cerebrovascular	38,855 (1.8)	6,321 (7.3)	<0.001
Cardiac	662,998 (31.0)	33,822 (39.4)	<0.001
Renal	149,540 (7.0)	19,478 (22.7)	<0.001
Overall	1,132,304 (53.0)	66,866 (77.9)	<0.001
Costs (\$)	41,800±26,000	74,100±61,000	<0.001
Length of Stay (Days)	9.0±6.1	18.2±15.7	<0.001

Table 3: Logistic regression for in-hospital mortality following isolated CABG. . *Other race includes Asian, Native American, and other races as defined by NIS. C-statistic=0.76.

	Adjusted Odds Ratio	95% Confidence Interval	P-value
Frail	2.49	2.30-2.70	<0.001
Female	1.42	1.34-1.50	<0.001
Age	1.04	1.03-1.05	<0.001
Race			
White	Reference		
Black	1.14	1.03-1.26	0.01
Hispanic	0.99	0.82-0.96	0.98
Other*	1.19	1.07-1.33	0.001
Income Quartiles			
Lowest	Reference		
2 nd Quartile	0.93	0.86-1.00	0.06
3 rd Quartile	0.89	0.82-0.96	0.002
Highest	0.81	0.74-0.89	<0.001
Year of Operation	1.00	0.99-1.02	0.24
Elective Status			
Non-Elective	Reference		
Elective	0.60	0.56-0.64	<0.001
Transferred from Outside Facility			
Not Transferred	Reference		
Transferred	1.14	1.07-1.22	0.001
Elixhauser Index Score (per 1-point increment)	1.15	1.13-1.18	<0.001

Atrial Fibrillation	0.66	0.62-0.71	<0.001
Chronic Obstructive Pulmonary Disorder	0.76	0.70-0.83	<0.001
Dialysis Dependence	1.68	1.36-2.07	<0.001
Obesity	0.58	0.53-0.64	<0.001
Diabetes	0.49	0.46-0.53	<0.001
Peripheral Vascular Disease	1.27	1.18-1.37	<0.001
Valvular Disease	0.77	0.70-0.84	<0.001
Congestive Heart Failure	1.84	1.73-1.95	<0.001
Coagulopathy	1.44	1.34-1.53	<0.001
CABG Volume Tertiles			
Low Volume Hospitals	Reference		
Medium Volume Hospitals	0.89	0.83-0.95	0.001
High Volume Hospitals	0.76	0.71-0.82	<0.001
Hospital Teaching Status			
Rural	Reference		
Urban Non-teaching	1.14	0.98-1.33	0.08
Urban Teaching	1.22	1.05-1.43	0.01
Hospital Region			
Northeast	Reference		
Midwest	1.14	1.03-1.27	0.01
South	1.29	1.17-1.41	<0.001
West	1.23	1.10-1.37	<0.001

Figure Legends

Figure 1: Consort Diagram of Study Cohort. Exclusion Criteria groups may have overlap of patient admissions.

Figure 2: Annual Trends of Isolated CABG Volume and Proportion of Frail Patients. *Non-parametric test of trend, $p < 0.05$.

Figure 3: Adjusted Odds Ratios for Mortality and Complications among *Frail* relative to *Non-Frail* cohort. Logistic models are adjusted for patient, disease, and hospital characteristics. Dashed line at 1 represents reference (*Non-Frail* cohort).

