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Preoperative Frailty and Adverse Outcomes Following Coronary Artery Bypass Grafting Surgery in US Veterans

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Preoperative frailty and adverse outcomes following coronary artery bypass grafting surgery in US veterans

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Abstract

Background: Contemporary guidelines emphasize the value of incorporating frailty into clinical decision-making regarding revascularization strategies for coronary artery disease. Yet, there are limited data describing the association between frailty and longer-term mortality among coronary artery bypass grafting (CABG) patients.

Methods: We conducted a retrospective cohort study (2016–2020, 40 VA medical centers) of US veterans nationwide that underwent coronary artery bypass grafting (CABG). Frailty was quantified by the Veterans Administration Frailty Index (VA-FI), which applies the cumulative deficit method to render a proportion of 30 pertinent diagnosis codes. Patients were classified as non-frail (VA-FI $\leq$ 0.1),

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pre-frail (0.1 < VA-FI ≤ 0.2), or frail (VA-FI > 0.2). We used Cox proportional hazards models to ascertain the association of frailty with all-cause mortality. Our primary study outcome was 5-year all-cause mortality; the co-primary outcome was days alive and out of the hospital within the first postoperative year.

Results: There were 13,554 CABG patients (median 69 years, 79% White, 1.5% women). The mean pre-operative VA-FI was 0.21 (SD: 0.11); 31% were pre-frail (VA-FI: 0.17) and 47% were frail (VA-FI: 0.31). Frail patients were older and had higher co-morbidity burdens than pre-frail and non-frail patients. Compared with non-frail patients (13.0% [11.4, 14.7]), there was a significant association between frail and pre-frail patients and increased cumulative 5-year all-cause mortality (frail: 24.8% [23.3, 26.1]; HR: 1.75 [95% CI 1.54, 2.00]; pre-frail 16.8% [95% CI 15.3, 18.4]; HR 1.2 [1.08,1.34]). Compared with non-frail patients (mean 362[SD 12]), pre-frail (mean 361 [SD 14]; $p < 0.01$) and frail patients (mean 358[SD 18]; $p < 0.01$) spent fewer days alive and out of the hospital in the first postoperative year.

Conclusions: Pre-frailty and frailty were prevalent among US veterans undergoing CABG and associated with worse mid-term outcomes. Given the high prevalence of frailty with attendant adverse outcomes, there may be an opportunity to improve outcomes by identifying and mitigating frailty before surgery.

KEYWORDS
coronary artery bypass grafting, coronary artery disease, frailty

INTRODUCTION

Coronary artery bypass grafting (CABG) may provide more durable long-term results than percutaneous intervention (PCI) in patients with complex multi-vessel coronary artery disease or distal/bifurcation left main stenosis.[1] CABG, even in high-risk patients, has a 1% to 2% postoperative mortality.[2] However, mid-term survival and quality of life depend more upon non-cardiac comorbidites, rather than coronary lesion complexity. As life expectancy has increased world-wide, CABG patients are now older and have a higher prevalence of rik factors like diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, and geriatric syndromes such as frailty.[3,4] Recent coronary revascularization guidelines, therefore, appropriately recommend a heart-team approach in choosing treatments for older patients with stable coronary artery disease.[3] Yet, frailty is a complex syndrome and may be independent of age.[5] In the past decade, frailty among US residents has increased across all age-groups.[6] Current practice recommendations are based on recent revascularization trials, from which frail patients are often excluded.[7] Prior evidence demonstrates increased perioperative mortality after CABG in frail patients.[8] A recent study from Canada reports

Key points

- In this observational cohort study of 13,554 US veterans prior to coronary artery bypass grafting (2016–2020), almost half were frail, while an additional 1/3rd were pre-frail.
- Compared with non-frail patients, the adjusted relative risk for 5-year mortality was 20% and 75% higher in pre-frail and frail patients, respectively.
- Frail (mean: 358 days) and pre-frail (mean: 360 days) patients also averaged fewer days alive and out of the hospital during their first postoperative year, respectively. Our study highlights the need to routinely assess for frailty prior to surgery, even in patients that are not considered "old."

Why does this paper matter?

Pre-operative frailty and pre-frailty prior to coronary artery bypass grafting, independent of age, are associated with higher 5-year mortality and lower 1-year out of hospital days.

increased 5-year mortality among frail CABG patients.[9] Yet, little is available on the impact of frailty in younger patients, and very little data from the US. We, thus, examined the association between pre-operative frailty and mid-term outcome in US veterans after CABG using the validated VA frailty index (VA-FI).[10,11] We also evaluated the association between frailty and hospital-free survival after CABG.

METHODS

Overview of data and development of the cohort

Using data from the largest integrated healthcare system in the US,[12] we linked inpatient, outpatient, and laboratory results to obtain an accurate longitudinal trajectory of events for each veteran in our study. The VASQIP (our primary data source), a registry managed by the national surgery office, contains rigorously defined, nurse-adjudicated variables from the pre-, intra- and postoperative periods for all patients receiving cardiac surgery at VA medical centers.[13] VASQIP data was supplemented with information from the corporate data warehouse (CDW), which contains data regarding their non-index inpatient and outpatient visits and vital status indicators.

Our retrospective study cohort consists of consecutive patients who underwent CABG from January 1 2016 through June 30 2020 at VA medical centers nationwide (CONSORT flowchart: Figure S1).

Calculation of the VA Frailty Index (VA-FI)

The VA-FI is based on the cumulative deficit approach (Rockwood et al.), which posits that health-related deficits accumulate over the lifetime.[14] VA-FI items (31 variables using claims data)[10,11] were selected such that all variables: (1) are related to health status; (2) increase with age; (3) do not reach a prevalence of 100% before 65 years; and (4) cover a range of systems such as cognition, function, and morbidity. Each patient's VA-FI score is the ratio of observed variables to the total number of included variables (i.e., 31) and is categorized using predefined thresholds as: non-frail (VA-FI ≤ 0.1), pre-frail ($0.1 <$ VA-FI ≤ 0.2), or frail (VA-FI > 0.2). The Risk Analysis Index (RAI) also measures frailty using 14 variables assessed either by patient survey or from the non-cardiac VASQIP registry.[15] While the RAI was recently implemented for non-cardiac surgery, RAI calculation requires variables not available in the VASQIP.[15,16] Moreover, the VA-FI score has been previously validated in patients with cardiovascular disease.[17] Therefore, although a variety of frailty measures exist, we chose the VA-FI for its robust validation and its calibration to VA-specific contexts.[15] As all patients in our cohort had coronary artery disease, we rescaled our score using 30 variables, as done in our earlier study.[18]

Outcomes

The primary endpoint was all-cause mortality, obtained from the Social Security Index, the Beneficiary Identification Records Locator Subsystem (BIRLS), and the Center for Medicare and Medicaid Services (CMS). We obtained the death date or censor date, with the vital status current until December 31, 2021.

Our co-primary outcome was days alive and out of hospital (DAOH) during the first postoperative year. Secondary outcomes studied were 30-day and 1-year mortality.

Covariates

Demographic, clinical, and laboratory data, most recent to the surgery date, were first obtained from the VASQIP. When data were unavailable in VASQIP, information was extracted from the prior clinical records or claims data (from the CDW) using the International Classification of Diseases 9th and 10th editions (ICD) or Common Procedure Terminology (CPT) codes. Demographics included age at surgery, sex, self-reported race, and ethnicity. Clinical factors obtained were hypertension, diabetes mellitus, dyslipidemia, obesity (body mass index ≥ 30 kg/m^2), heart failure, chronic kidney disease (estimated GFR < 60 mL/min/m^2), smoking status, prior myocardial infarction, prior open-heart surgery, prior PCI, left ventricular dysfunction (left ventricular systolic function <40%), and pre-operative intra-aortic balloon pump use. Patients were stratified into three age groups: <60, 60–80, >80 years. We obtained data regarding the extent of coronary artery disease (number of vessels with >70% stenosis), the presence of left main stenosis (defined as >50% luminal narrowing), the acuity of surgery, and concomitant valve replacement.

Statistical analyses

We compared baseline characteristics between the three groups (non-frail, pre-frail, and frail) using the X^2 test (categorical variables) or the Kruskal-Wallis test (continuous variables). We calculated the 5-year cumulative all-

cause mortality (using the Kaplan-Meier method) for the whole cohort and separately for each group. We tested the pairwise difference in the cumulative event rates with the log-rank test using the Bonferroni correction. To evaluate the association between frailty and all-cause mortality, we fit a multi-level Cox proportional hazards model using the frailty group as our exposure and included the following variables for adjustment: age at surgery, self-reported race, sex, smoking status, obesity, New York Heart Association functional class, left ventricular dysfunction, concomitant valve surgery, prior myocardial infarction, prior PCI, left main disease, and prior cardiac surgery. These variables were included as they are independent of the VA-FI score; covariates used to calculate the VA-FI score were not separately included in this model. As patients are clustered within VA medical centers, this was fit as a random effect in the model. To confirm the consistency of results, the main model was also repeated, excluding patients that underwent concomitant valve replacement and limiting the cohort to only those that underwent isolated CABG.

Results are reported as hazard ratios (HR) (95% confidence intervals [CI]). To explore the effect of frailty according to age, we fitted the same Cox model separately for each age group (< 60, 60–80, > 80 years). As a sensitivity analysis, we repeated the same model in important clinical sub-groups: race, diabetes mellitus, heart failure, peripheral arterial disease, and left main stenosis. We also explored the association between preoperative frailty and 5-year mortality by modeling the continuous VA-FI score as a restricted cubic spline (with knots at the 25th, 50th, and 75th percentiles of the VA-FI score) in the Cox model. Using predicted values from this model and a VA-FI score of 0.2 as the reference, we obtained and plotted the adjusted hazard ratio for the entire range of observed VA-FI scores (0.1–0.6).

For all patients, we calculated the number of DAOH during the first postoperative year. We initially compared DAOH between frailty groups with the Kruskal–Wallis test; then we performed pairwise comparisons between groups with multiplicity adjustment. To evaluate the risk of lower DAOH in frail patients, we obtained risk ratios (RR) using a multivariable poisson model with DAOH as the outcome variable offset for the survival time (truncated at 365 days) .

We studied early endpoints (30-day, 90-day, and 1-year mortality) using a hierarchical binomial regression model and a multi-level Cox proportional hazards model, respectively. Missing data was minimal (<1%), and we performed simple median/mode imputation. All hypothesis tests were two-tailed and reported at the 95% confidence level. R 4.2.1 (The R Foundation for Statistical Computing, Austria) and Stata 17 (The Stata Corporation, College Station, Texas) were used for statistical analyses.

Ethics, data availability statement

The Cleveland VA Medical Center (IRB # 16004-H03) approved this study and waived individual patient consent. Data collection and statistical analyses were performed between September 2021 and April 2022. The data are the property of the VA; hence, they cannot be made available to researchers outside the VA. The statistical scripts used in deriving the VA-FI score as well as all analyses are available for download at the corresponding author's GitHub account: https://github.com/svd09.

RESULTS

Overview of the cohort

The final study cohort included 13,554 consecutive patients from 40 medical centers who underwent CABG from January 1st, 2016, through June 30th, 2020. Among these, 1881 (13%) also underwent concomitant valve surgery. Their median age was 69 years (IQR-63,72), 191 (1.4%) were female, 79.4% were White, 11.4% were Black, and 9.3% were Hispanic. Baseline demographics are shown in Table 1. There were high rates of diabetes mellitus (55%), prior myocardial infarction (44%), chronic kidney disease (37%), and heart failure (23%). The majority underwent elective surgery (87%) with a low perioperative intra-aortic balloon pump (3%) use.

Prevalence of frailty

The mean preoperative frailty score was 0.21 (SD-0.11), with 4221 (31%) and 6362 (46%) patients categorized as pre-frail and frail, respectively. Among the diagnoses comprising the VA-FI score, hypertension (98%), diabetes mellitus (67%), and chronic kidney disease (CKD) (64%), were the most common (Table S1). The prevalence of the individual components of the VA-FI score varied between age groups (Figure S1). In young patients (< 60 years), depression and anxiety disorders were higher, while >80 year olds were more likely to have atrial fibrillation and peripheral arterial disease.

Compared with those who were non-frail, frail patients were older (median age, 69 vs. 66 years) and more likely to be female (1.7% vs. 0.9%). They were also sicker, with a higher prevalence of diabetes mellitus (67% vs. 29%), peripheral vascular disease (39% vs. 9%), and heart failure (32% vs. 10%) (Table 1). Frail patients had

TABLE 1 Clinical characteristics of 13,554 patients according to their frailty status that underwent CABG (2016–2020) at VA medical centers nationwide.

	Overall Cohort	Not frail group (0–0.1)	Pre-frail group (>0.1–0.2)	Frail group (>0.2)
	***N* = 13,554**	***N* = 2971**	***N* = 4221**	***N* = 6362**
Age (median [IQR])	69 (63,72)	66 (61,71)	68 (63,72)	69 (65,73)
Female sex	191 (1.4)	27 (0.9)	53 (1.3)	111 (1.7)
Self-reported race				
White	10,771 (79.4)	2291 (77.1)	3347 (79.2)	5133 (80.7)
Black	1546 (11.4)	341 (11.5)	510 (12.1)	695 (10.9)
Others	1241 (9.2)	339 (11.4)	367 (8.7)	535 (8.4)
NYHA functional class III/IV	6007 (44.3)	1167 (39.3)	1772 (42)	3068 (48.2)
Diabetes mellitus	7398 (54.6)	870 (29.3)	2265 (53.6)	4263 (67.0)
Heart failure	3109 (22.9)	322 (10.8)	745 (17.6)	2042 (32.1)
Hypertension	11,282 (83.2)	1313 (44.2)	3718 (88.0)	6251 (98.2)
Chronic kidney disease	4943 (36.5)	44 (1.5)	820 (19.4)	4079 (64.1)
Atrial fibrillation	3877 (28.6)	10 (0.3)	492 (11.6)	3375 (53.0)
COPD	3948 (29.1)	384 (12.9)	1037 (24.6)	2527 (39.7)
Peripheral vascular disease	3746 (27.6)	295 (9.9)	947 (22.4)	2504 (39.4)
Cerebrovascular Disease	2547 (18.8)	172 (5.8)	597 (14.1)	1778 (27.9)
VA PROM score (mean [SD])	1.65 (1.02)	1.57 (0.97)	1.62 (1)	1.7 (1.05)
Prior myocardial infarction	5897 (43.5)	1205 (40.6)	1789 (42.4)	2903 (45.6)
Prior Percutaneous intervention	531 (3.9)	155 (5.2)	191 (4.5)	185 (2.9)
Current smoker	2939 (21.7)	694 (23.4)	950 (22.5)	1295 (20.4)
Preoperative IABP use	403 (3)	102 (3.4)	144 (3.4)	157 (2.5)
Prior heart surgery	232 (1.7)	31 (1)	63 (1.5)	138 (2.2)
Hemoglobin (gm/dl) (median [IQR])	13.7 (12.4,14.7)	14.1 (13,15)	13.7 (12.6,14.7)	13.4 (12,14.5)
HbA1C (%) (mean [SD])	6.74	6.28	6.84	6.88
LDL-C concentration (median [IQR])	85 (63,114)	94 (70,126)	85 (64,114)	80 (60,108)
Surgery as an elective procedure	11,829 (87.2)	2554 (86)	3666 (86.6)	5609 (88.2)
Albumin (gm/dl) (mean [SD])	3.85 (0.5)	3.91 (0.46)	3.87 (0.46)	3.8 (0.54)
Creatinine (mg/dl) (mean [D])	1.22 (0.95)	1.07 (0.59)	1.16 (0.76)	1.32 (1.16)
Concomitant valve surgery	1881 (13.9)	334 (11.2)	573 (13.5)	975 (15.3)
Left ventricular systolic dysfunction	2458 (18.6)	468 (16.2)	722 (17.5)	1268 (20.4)
Extent of coronary artery disease				
Proximal LAD disease	10,601 (79.4)	2356 (80.8)	3294 (79)	4951 (79.1)
Circumflex disease (%)	8534 (65)	1871 (65.3)	2693 (65.6)	3969 (64.4)
Right coronary artery disease (%)	9178 (69.5)	2001 (69.5)	2872 (69.6)	4305 (69.5)
Triple vessel disease/LMCA disease	6647 (51.3)	1487 (52.7)	2095 (51.7)	3065 (50.4)

Note: This table presents the baseline clinical characteristics of our study cohort.

Abbreviations: CeVD, cerebrovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HbA1c, Hemoglobin A1c; IABP, intra-aortic balloon pump; LAD, left anterior descending; LDL-C, low density lipoprotein C; LMCA, left main coronary artery; NYHA, New York heart association; PCI, percutaneous intervention; VA PROM, VA projected risk of 30-day mortality.

TABLE 2 Incidence rate and hazard of 5-year all-cause mortality according to the frailty group.

30-day mortality	Cumulative Incidence (95% CI)	Odds ratio	*p*-value*
Not frail	1.51 (1.07, 1.95)	1.00 (reference)	
Pre-Frail	1.44 (1.08, 1.80)	0.85 (0.57, 1.25)	0.41
Frail	1.80 (1.48, 2.13)	0.91 (0.63, 1.30)	0.60
90-day mortality			
Not frail	2.32 (1.78, 2.86)	1.00 (Reference)	
Pre-frail	2.25 (1.80, 2.69)	0.96 (0.70, 1.32)	0.84
Frail	3.50 (3.05, 3.95)	1.52 (1.16, 2.02)	0.002
1-year mortality		Hazard Ratio	*p*-value*
Not Frail	3.47 (2.81, 4.13)	1.00 (reference)	
Pre-Frail	4.15 (3.54, 4.75)	1.08 (0.84, 1.38)	0.51
Frail	6.14 (5.55, 6.73)	1.43 (1.15, 1.79)	0.001
5-year mortality		Hazard Ratio	*p*-value*
Not Frail	13.04 (11.36, 14.68)	1.00 (reference)	
Pre-Frail	16.83 (15.28, 18.30)	1.20 (1.04, 1.39)	<0.001
Frail	24.75 (23.33, 26.13)	1.75 (1.54, 2.00)	< 0.001

Note: We analyzed the all-cause mortality at 30 days, 1 year and 5-years for 13,554 Veterans according to their preoperative frailty status. We present the crude cumulative event rates and the results of the adjusted regression models fit for each time point.
**p*-values are from the tests fit for pairwise comparison; therefore, each group is evaluated with the 'not frail' group as the comparator and we account for multiplicity using the Bonferroni correction.

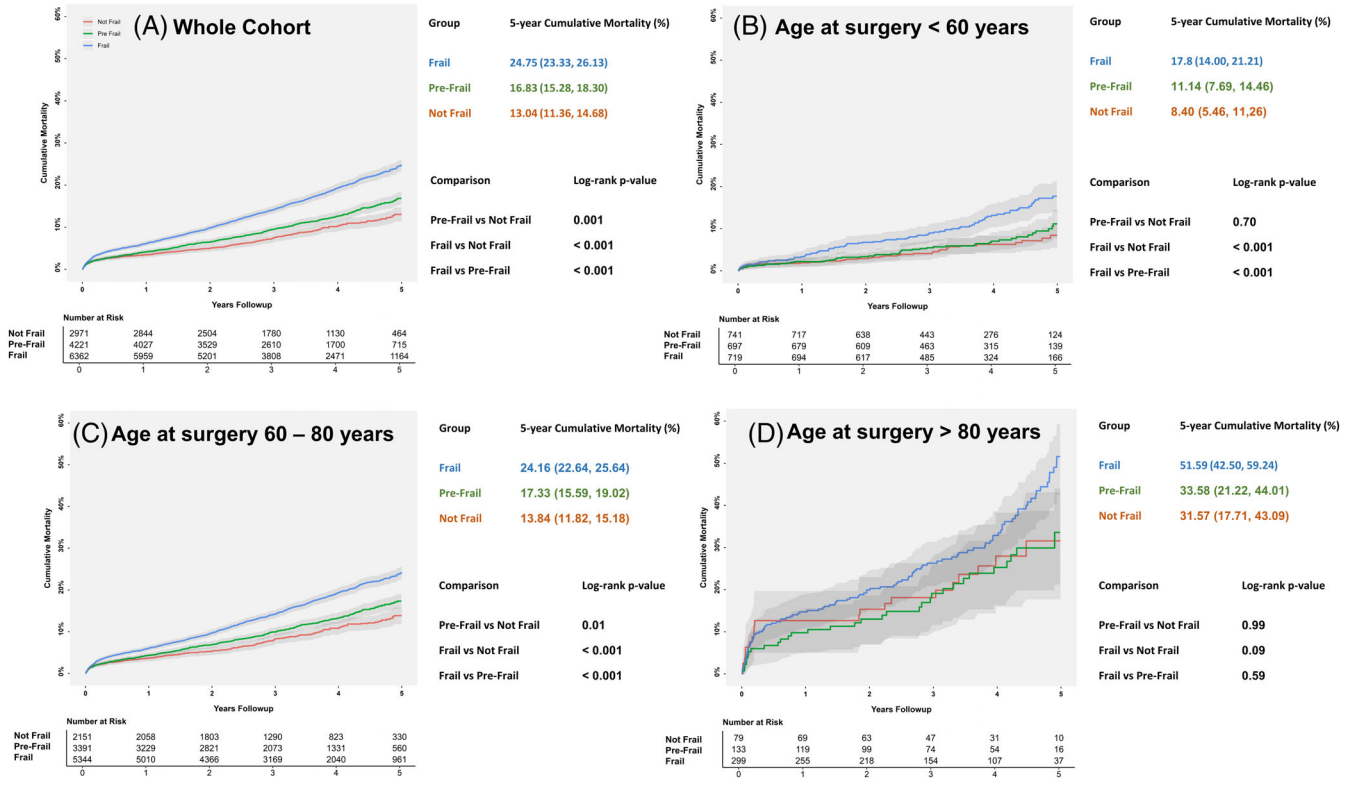
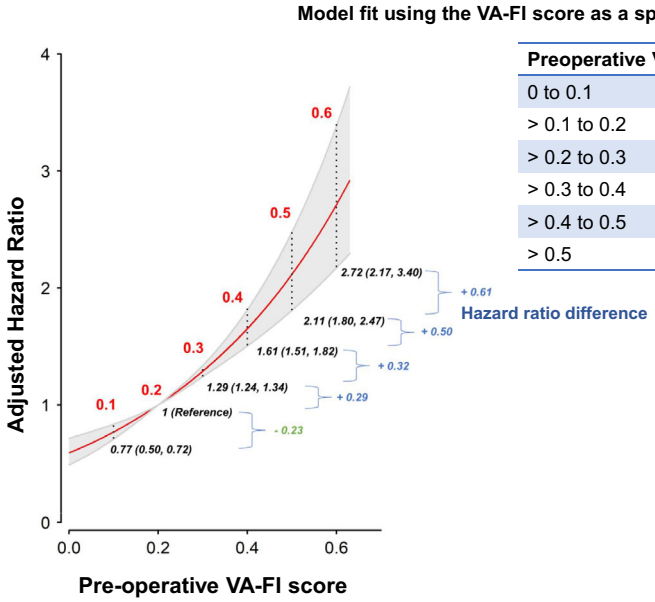


FIGURE 1 Cumulative mortality observed during the study period (overall, and for age groups <60 years, 60–80 years and >80 years) in the non frail, pre-frail and frail groups.



Preoperative VA-FI score	N = 13,554
0 to 0.1	2971 (21.9%)
> 0.1 to 0.2	4221 (31.1%)
> 0.2 to 0.3	3984 (29.3%)
> 0.3 to 0.4	1778 (13.1%)
> 0.4 to 0.5	488 (3.7%)
> 0.5	112 (0.9%)

FIGURE 2 Adjusted hazard ratios for 5-year mortality across the range of VA-FI scores. We fit a Cox proportional hazards model to evaluate the association between the patient's preoperative VA-FI score (fit on a continuous scale with restricted cubic splines) and 5-year all-cause mortality. As depicted in the figure, with an increasing VA-FI score, we observed an increase in the mortality risk. Considering a VA-FI = 0.2 as reference (HR = 1), every 0.1 increase in the VA-FI was associated with a non-linear increase in mortality. HR, hazard ratio; VA-FI, Veteran Affairs Frailty Index.

similar rates of elective surgery (88% vs. 86%) and triple vessel disease/left main disease (50% vs. 52%), however, were more likely to also receive concomitant valve surgery (15% vs. 11%) (Table 1).

Primary outcome

Over a median follow-up period of 3.48 years (IQR-2.37,4.62; maximum-5.9), the cumulative 5-year all-cause mortality for the whole cohort was 19.87% (18.96, 20.77). Compared with non-frail patients (13.04 [11.36, 14.68]%), the crude 5-year mortality was higher in pre-frail (16.83 [15.28, 18.36]%) and frail (24.75 [23.33, 26.13]%) patients (Table 2). As depicted in Figure 1, compared with the non-frail, the 5-year cumulative mortality was higher in the pre-frail and frail patients in the <60 year and 60–80 year age groups. In >80 year olds, the 5-year mortality was comparable across age groups.

In adjusted analyses, compared with the non-frail patients, the risk of 5-year mortality was higher among the pre-frail (HR 1.20; 95% CI-1.04,1.39) and frail (HR 1.75; 95% CI-1.54,2.00) (Table 2). These results were consistent (pre-frail HR 1.30 [95%CI 1.10, 1.53], frail HR 1.94 [95%CI 1.67,2.26]) after excluding patients that received concomitant valve replacement and limiting the cohort to those that underwent isolated CABG. Apart from frailty, concomitant valve surgery, left ventricular dysfunction, and prior cardiac surgery were other factors associated with increased risk for mortality (Table S2). We observed a higher risk of mortality as the VA-FI scores increased (Figure 2). Adjusted for other covariates and referenced to a VA-FI score of 0.2, a patient with a score of 0.3 and 0.4 had a 29% and 61% increased mortality risk (Figure 2). Among frail patients, although the absolute HR was highest in patients <60 years, the association between preoperative frailty and all-cause mortality was independent of age.(Figure 3 and Figure S3).

Co-primary outcome

Days alive out of the hospital (DAOH)

In the whole cohort, the mean DAOH was 362 (SD-15.9) days. Accounting for mortality, compared with non-frail patients (362 [12.2]), pre-frail patients (360.9 [14.2]), and frail patients (358 [18.1]) spent fewer days alive and out of the hospital over the first year after surgery. Compared with the non-frail group, pre-frail (RR 0.36; CI-0.17,0.77) and frail (RR 0.04; CI-0.02,0.08) were less likely to have more DAOH after surgery (Figure S4).

Secondary outcomes

30-day, 90-day and 1-year mortality

The 30-day mortality (1.63%) in our cohort was low and comparable in all groups: non-frail (25/2971; 1.51%),

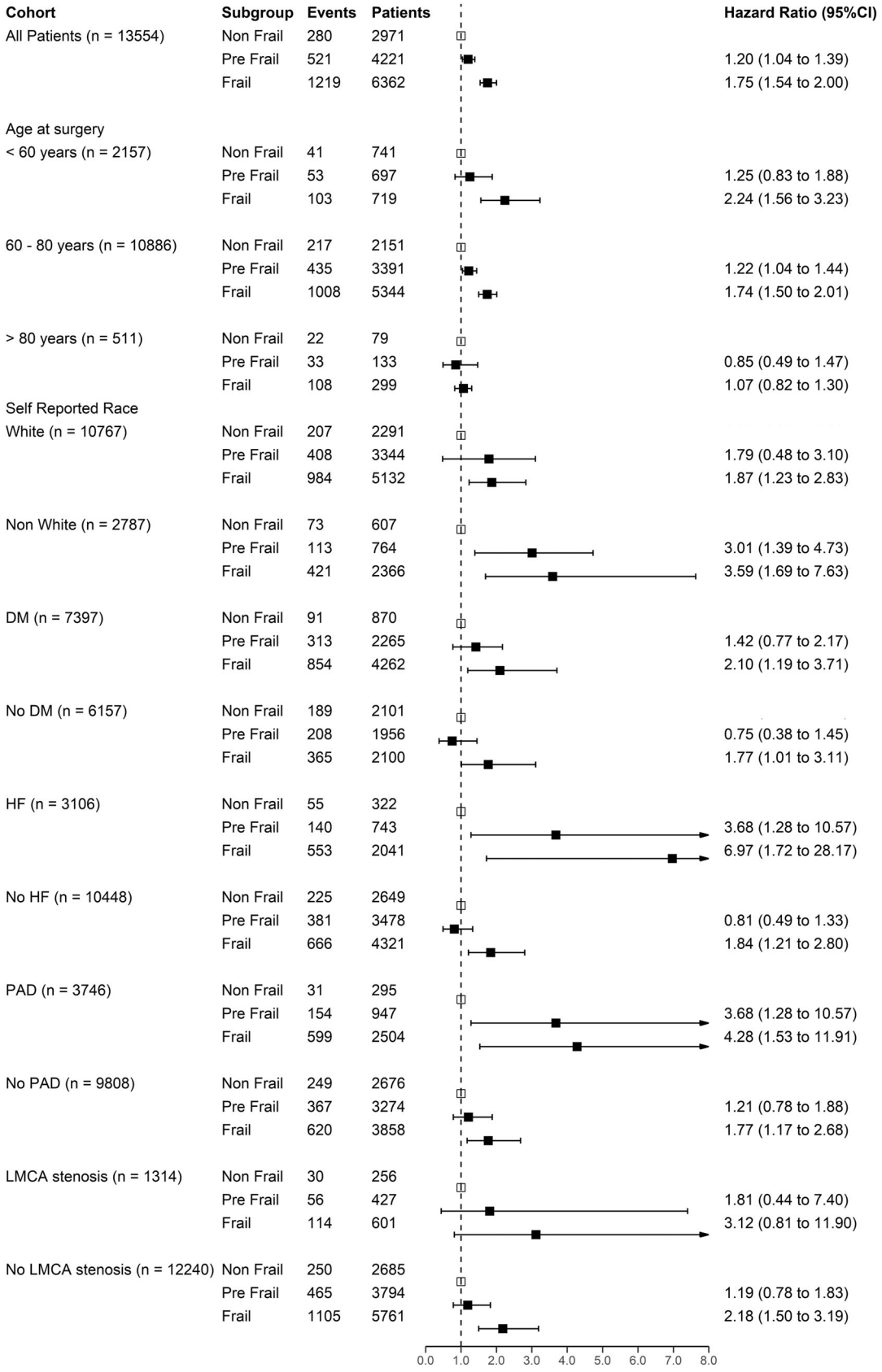


FIGURE 3 Plot of hazard ratios for the pre-frail and frail group (with the non-frail as reference) for all the exploratory subgroup analyses.

pre-frail (61/4221; 1.44%), and frail (115/6362; 1.80%). The adjusted odds for the odds of 30-day mortality (ref: non-frail) were similar in the pre-frail (OR 0.85-CI: 0.57, 1.25) and frail (OR 0.91-CI: 0.63, 1.30) (Table 2). However, compared with the non-frail group, 90-day mortality rates were higher in the frail group (cumulative incidence 3.50 [3.05, 3.95]%; OR 1.52 [1.16, 2.02]; $p = 0.002$). The overall 1-year cumulative mortality was 4.95% (4.57, 5.30), with an increasing incidence (3.47% non-frail, 4.15% pre-frail, and 6.14% frail) across the continuum of frailty (Table 2). Adjusting for covariates, the 1-year mortality risk (ref: non-frail) was higher among frail patients (HR 1.43; CI-1.15,1.79) (Table 2).

DISCUSSION

Synopsis of findings

Using contemporary national data on 13,554 US veterans who underwent CABG, we evaluated the adjusted association between preoperative frailty using the VA-FI score and 5-year mortality. We observed that pre-frailty and frailty were highly prevalent among US veterans prior to CABG and both of these conditions were associated with an increased 5-year mortality risk and fewer hospital-free days during the first postoperative year.

Our results in context

The 2021 coronary revascularization guidelines recommend that clinicians consider patient frailty when choosing optimal revascularization strategies, especially in older patients.[19] Prior research has amply demonstrated the negative association between frailty and surgical outcomes, with a large systematic review reporting a two-fold increase in peri-operative CABG mortality[9,20]; a prospective analysis of 500 patients (>60 years) undergoing isolated CABG even reports a 3-fold increase in all-cause mortality among frail patients.[21] However, little is available regarding the impact of frailty in younger patients (<60 years) undergoing surgery. Our study firstly supports prior evidence regarding the association between frailty and increased mid-term mortality in patients undergoing CABG and, secondly, demonstrates the consistent negative association between frailty and mortality, independent of age. Unlike prior studies, the early postoperative survival in frail patients was not lower in our cohort. This could be attributed to a selection bias, wherein only apparently healthier frail patients are selected for surgery, or it could also be the result of excellent perioperative care. While we do not have data on the quality of life after surgery, we do report that frail patients have fewer days alive and out of the hospital. Therefore, whilst mortality may be comparable, frail patients may have a poorer quality of life in the early postoperative period. Frail patients, then, will not derive the same benefit from surgery compared to their non-frail counterparts. These important conclusions should be considered in the shared decision-making process between clinicians and patients prior to surgery.

Unlike prior studies, the prevalence of pre-frailty and frailty was much higher in our cohort.[9,22] While others report 10% to 15% of patients as being frail, in our cohort of veterans, 40% of patients were classified as frail, with an additional 30% pre-frail, which may be explained by the following: First, our cohort was approximately 4 to 5 years older than contemporary studies.[9,22] Second, the VA-FI score contains many non-traditional cardiovascular risk factors, like anxiety and depression. Inclusion of these factors can increase the number of patients classified as frail (VA-FI >0.2), a cut-off used by many other frailty indices. However, we support our primary results by also using the VA-FI score on the continuous scale. Moreover, recent research demonstrates that these clinical conditions are often interrelated with pre-frailty and frailty.[23,24] It is, therefore, possible that scores like the Johns Hopkins Adjusted Clinical Groups (ACG) measure, used by Tran et al.[9] or the clinical frailty scale, used by Reichart et al.,[22] may underestimate the true prevalence of frailty. We agree that there is no clear "gold standard" definition for frailty; however, using any formal definition of frailty is better than an "eyeball test" of frailty that is highly inaccurate.[8] Irrespective of which frailty measure is used, the importance of such non-traditional risk factors is especially pertinent among veterans, as prior combat exposure makes them more likely to suffer from cognitive impairment and mental health conditions.[11,25,26]

Clinical Implications

Clinicians would agree that peri-procedural recovery after CABG is more prolonged than after PCI; however, CABG may provide more robust clinical benefits at 5 years and beyond.[27] As our study demonstrates fewer hospital-free days and higher mid-term mortality in frail patients, the key is identifying patients that will survive this early time period of 6 months to 1 year with an acceptable quality of life. A recent study reports that patients 2 weeks older than 80 were much less likely to receive CABG than those 2 weeks before their 80th birthday.[28] Such implicit bias is inevitable; we therefore recommend routine assessments of frailty prior to CABG,

irrespective of age. Consideration of life expectancy and life quality are important discussions prior to CABG, and frailty represents a lens through which life expectancy may be reestimated.[11,29] In this regard, an automated claims-based frailty index, such as the VA-FI (and others), can be readily incorporated into clinical practice and it would definitely improve risk stratification and outcomes.[11,30,31] Although frail patients have a 13% higher short-term mortality rate after PCI,[32,33] no randomized trials compare the outcomes of CABG versus PCI in frail patients. A recent cost-effectiveness analysis demonstrates that pre-procedural frailty screening was useful in choosing the appropriate intervention strategy.[34] Therefore, future prospective studies need to focus on this important issue, but till then, decision-making needs to be based on observational studies like ours.

Our study has important strengths, including the large sample size, length of follow-up, and well-validated measure of frailty. We used a longitudinal dataset with preoperative, intraoperative, and postoperative variables that are well curated and used robust analytic methods to address confounding. Among its limitations, ours is an observational study and therefore not randomized. The calculation of the VA-FI score was dependent on correct administrative coding. When relying on administrative data, there can be errors due to under- or overcoding. For example, dementia is often under-recognized and therefore under-coded in administrative data, especially at the early stages. Wherever possible, we used validated and previously published algorithms to identify deficits from claim data.[35] While we implemented multivariable regression with robust measured confounding control, differences observed between cohorts could be due to unmeasured confounding, especially those associated with lifestyle factors like diet and physical activity. We were able to obtain information regarding readmissions that occurred in the VA healthcare system and those paid for by the VA. We did not have data regarding those readmissions that occurred outside the VA under private insurance coverage. Finally, factors like the complexity of coronary stenosis and technical aspects of the CABG procedure that may impact the outcome were unavailable.

CONCLUSION

Pre-frailty and frailty were prevalent among US veterans undergoing CABG and associated with worse mid-term outcomes. Frail patients also spent fewer days alive and out of the hospital during their first postoperative year. Given the high prevalence of frailty and its attendant adverse outcomes, there may be opportunities to improve outcomes by identifying and mitigating frailty before surgery.

AUTHOR CONTRIBUTIONS

Ajar Kochar – substantial contributions to devising the study, interpreting the results, writing the manuscript and final approval of the version to be submitted. Salil V Deo – substantial contributions to devising the study, interpreting the results, writing the manuscript and final approval of the version to be submitted. Brian Charest – substantial contributions to the statistical analyses, interpreting the results and final approval of the version to be submitted. Fanny Peterman-Rocha – substantial contributions to interpreting the results, revising the article critically for important intellectual content and final approval of the version to be submitted. Yakov Elgudin – substantial contributions to interpreting the results, revising the article critically for important intellectual content and final approval of the version to be submitted. Danny Chu – substantial contributions to interpreting the results, revising the article critically for important intellectual content and final approval of the version to be submitted. Robert W Yeh – substantial contributions to interpreting the results, revising the article critically for important intellectual content and final approval of the version to be submitted. Sunil V Rao – substantial contributions to interpreting the results, revising the article critically for important intellectual content and final approval of the version to be submitted. Dae H Kim – substantial contributions to interpreting the results, revising the article critically for important intellectual content and final approval of the version to be submitted. Jane A Driver – substantial contributions to interpreting the results, revising the article critically for important intellectual content and final approval of the version to be submitted. Daniel E Hall – substantial contributions to interpreting the results, revising the article critically for important intellectual content and final approval of the version to be submitted. Ariela R Orkaby – substantial contributions to interpreting the results, writing and revising the article critically for important intellectual content and final approval of the version to be submitted.

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CONFLICT OF INTEREST STATEMENT

Dr Orkaby serves as consultant for Anthos Therapeutics. Dr. Hall serves as a consultant to FutureAssure, LLC. Other authors do not have any conflict of interests to disclose pertaining to this manuscript.

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The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr Deo had full access to the data in the study and both Drs Orkaby and Deo take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Data S1: The Supplementary appendix contains supplemental tables and figures that are referenced in our manuscript.

Supplementary Table S1. The prevalence of each component of the VA-FI score.

Supplementary Table S2. The multivariable Cox proportional hazards models for 5-year all-cause mortality.

Supplementary Figure S1. Flowchart outlining the cohort selection process.

Supplementary Figure S2. Heatmap presenting the prevalence for each component of the VA-FI score.

Supplementary Figure S3. Plot demonstrating the result of the interaction of preoperative frailty (on a continuous scale) and patients age group.

Supplementary Figure S4. A density histogram presenting days alive and out of the hospital (DAOH) during the first postoperative year for each group.

Supplementary Content. Code to calculate the VA-FI score.

STROBE Checklist for cohort studies.

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