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The Effect and Relationship of Frailty Indices on Survival After Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES This study sought to evaluate the ability of individual markers of frailty to predict outcomes after transcatheter aortic valve replacement (TAVR) and of their discriminatory value in different age groups.

BACKGROUND Appropriate patient selection for TAVR remains a dilemma, especially among the most elderly and potentially frail.

METHODS The study evaluated patients ≥65 years of age in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry, linked to Centers for Medicare and Medicaid administrative claims data, receiving elective TAVR from November 2011 to June 2016 (n = 36,242). Indices of frailty included anemia, albumin level, and 5-m walk speed. We performed Cox proportional hazards regression for 30-day and 1-year mortality, adjusting for risk factors known to be predictive of 30-day mortality in the Transcatheter Valve Therapy registry, as well as survival analysis.

RESULTS These indices are independently associated with mortality at 30 days and 1 year and provide incremental value in risk stratification for mortality, with low albumin providing the largest value (hazard ratio: 1.52). Those with low albumin and slower walking speed had longer lengths of stay and higher rates of bleeding and readmission ($p < 0.001$). Those with anemia also had higher rates of bleeding, readmission, and subsequent myocardial infarction ($p < 0.001$).

CONCLUSIONS This represents the largest study to date of the role of frailty indices after TAVR, further facilitating robust modeling and adjusting for a large number of confounders. These simple indices are easily attainable, and clinically relevant markers of frailty that may meaningfully stratify patients at risk for mortality after TAVR.
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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

CI = confidence interval

CMS = Centers for Medicare and Medicaid Services

HR = hazard ratio

IQR = interquartile range

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

TVT = Transcatheter Valve Therapy

Transcatheter aortic valve replacement (TAVR) is an effective and increasingly utilized treatment option for patients with severe aortic stenosis with elevated surgical risk (1,2). Despite predictably high procedural success rates (3), long-term outcomes may be poorer with advancing age and with markers of advanced frailty (3–7).

Despite societal guidelines recommending frailty assessment as part of the patient selection process before valve replacement (8), a consensus definition of frailty remains elusive and complicates efforts to standardize patient evaluation (9). Thus, among patients referred for TAVR, reproducibly identifying clinically relevant markers of frailty remains a dilemma.

SEE PAGE 232

Descriptions of frailty usually include measures of nutritional status and muscle wasting, as well as functional and cognitive impairment (10–14). Several markers of frailty in those undergoing TAVR have been identified in smaller cohorts (5,6,9,15,16) and have been associated with poorer outcomes. However, to date, these findings have not been validated in a larger population. Moreover, no prior study has evaluated whether the predictive power of frailty markers is inherent to the individual marker, independent of the age of the patient.

Although some identified markers of frailty are simple to obtain, others require more intensive effort. Likewise, while risk stratification tools have been proposed (9,16), they require inclusion of all components. Until now, the incremental predictive value of frailty markers for poorer outcomes have not been evaluated in a manner that would help guide an optimal workflow of frailty assessment during TAVR evaluation.

Herein, we evaluated the clinical significance of previously identified markers of frailty, and the incremental stepwise prognostic benefit of assessing these, in a large population of patients undergoing TAVR.

METHODS

SOCIETY OF THORACIC SURGEONS/AMERICAN COLLEGE OF CARDIOLOGY TRANSCATHETER VALVE THERAPY REGISTRY. By mandate, under the Centers for Medicare and Medicaid Services (CMS) National Coverage Determination requirement, all U.S. TAVR centers are required to participate in the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) registry (17). The STS/ACC TVT registry is a collaborative registry program that collects clinical data from consecutive TAVR cases across all U.S. TAVR sites. Centers participating in the registry gather clinical data using standardized definitions (17,18). The National Cardiovascular Data Registry warehouse and Duke Clinical Research Institute perform data quality checks to optimize data accuracy (3). The ACC has designated Chesapeake Research Review Incorporated as its internal review board; the TVT registry has submitted a protocol to this Institutional Review Board and has been granted a waiver of informed consent. To facilitate collection of long-term outcomes, the STS/ACC TVT registry has previously been linked to CMS claims data provided by CMS (19) using direct patient identifiers.

PATIENT SELECTION. We identified a cohort of all patients undergoing elective TAVR registered in the STS/ACC TVT registry from November 2011 to June 2016 with complete data who had not had a prior valve procedure (aortic, or otherwise). We excluded all patients who were <65 years of age, had prior aortic valve procedures (including surgical aortic valve replacement or repair, or balloon aortic valvuloplasty), had prior nonaortic valve procedures (mitral valve repair or replacement), or had cardiac arrest or cardiogenic shock within 24 h of TAVR procedure. We then linked this cohort with the CMS dataset to assess 30-day and 1-year clinical endpoints.

OUTCOMES. The primary outcome was all-cause mortality at 30 days and 1 year following TAVR. Secondary outcomes included a composite outcome comprising all-cause mortality and readmission for

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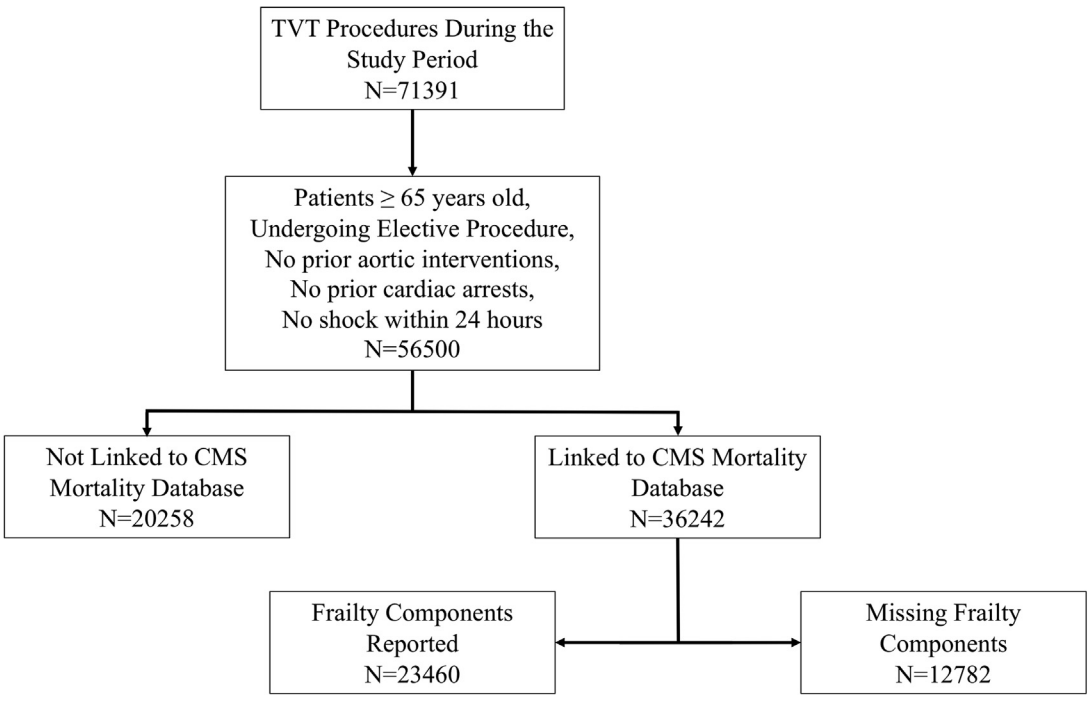
FIGURE 1 Ascertainment of the Study Population



Flow diagram outlining ascertainment of the study population. CMS = Centers for Medicaid and Medicare Services; TVT = Transcatheter Valve Registry.

heart failure at 30 days and 1 year following TAVR, the incidence of stroke, myocardial infarction, any bleeding complications, readmission for heart failure at 30 days and 1 year, and length of stay ≥3 days (20) for index admission. All 1-year outcomes were obtained through linkage to CMS claims data. As a result, 1-year outcomes of bleeding and stroke do not conform to Valve Academic Research Consortium-2 criteria (21).

MARKERS OF FRAILTY AND STUDY COHORT. Previously identified markers of frailty available in the STS/ACC TVT registry were serum albumin level, anemia (hemoglobin level), and performance on the 5-m walk test and were included in the model in an a priori fashion. Low serum albumin was defined as albumin level <3.5 mg/dl (15,16,22). Anemia was defined as a hemoglobin level <13 mg/dl for men and <12 mg/dl for women (6,16,23). A slow 5-m walk test was defined as completing the test in >6 s (walking speed of <0.83 m/s) or an inability to complete the test, including the inability to walk for any reason (walking speed of 0 m/s) (6,16,24). Walking speed above the 99th percentile was considered highly likely to be aberrant or invalid, and those patients were excluded from analysis.

STATISTICAL ANALYSIS. Presenting and baseline characteristics are reported as frequency and proportion for categorical variables and median (interquartile range [IQR]) for continuous variables. Statistical comparisons were generated using a chi-square test for categorical variables and a Wilcoxon test for continuous variables. Unadjusted and adjusted Cox proportional hazards 30-day and 1-year mortality models are reported. Factors adjusted for in the multivariate model are described in the Online Appendix. Age and each frailty marker were assessed to determine if an interaction existed. We included an age category of ≥90 years to evaluate nonagenarians as a specific group to evaluate for interactions between age and each frailty marker, as well as the total number of positive markers. To address within-center correlation for response, robust standard errors were used. Owing to the competing risk of death, for nonfatal endpoints the Fine-Gray test statistic is reported. The hazard ratios with 95% confidence intervals and p values are also presented. All modeling

TABLE 1 Baseline Clinical Data of the Entire Cohort (N = 56,500)

Frailty factors	
Total albumin, g/dl*	45,483; 3.8 (3.4–4.1)
Anemia†	34,954 (61.87)
Was the 5-m walk test performed?	36,380 (64.39)
Unable to walk	4,975 (8.81)
5-m speed <0.83 m/s	6,341 (11.22)
5-mr speed, m/s*	36,309; 1.53 (1.20–2.00)
Demographics	
Age, yrs*	56,500; 83 (78–88)
Female	27,085 (47.94)
Hispanic or Latino	2,062 (3.65)
Cardiac procedure history	
Permanent pacemaker	8,642 (15.30)
Previous ICD	2,457 (4.35)
Prior PCI	19,666 (34.81)
Prior CABG	15,569 (27.56)
Prior other cardiac surgery	2,153 (3.81)

Continued in the next column

TABLE 1 Continued

Medical history and risk factors	
STS Predicted Risk of Mortality	56,498; 6.00 (4.06–8.96)
TVT TAVR risk score	52,407; 3.41 (2.53–4.74)
Current/recent smoker	2,751 (4.87)
Hypertension	50,656 (89.66)
Diabetes mellitus	20,211 (35.77)
Prior MI	13,345 (23.62)
LVEF*	
<30%	3,247 (5.75)
30% and <45%	7,351 (13.01)
≥45% and <60%	17,998 (31.85)
≥60%	27,178 (48.10)
Heart failure within 2 weeks	43,325 (76.68)
NYHA functional class within 2 weeks*	
I	1,586 (2.81)
II	9,315 (16.49)
III	36,826 (65.18)
IV	8,237 (14.58)
Atrial fibrillation/flutter	23,088 (40.86)
Conduction defect	17,881 (31.65)
Currently on dialysis	1,806 (3.20)
Chronic lung disease*	
None	32,233 (57.05)
Mild	9,979 (17.66)
Moderate	7,335 (12.98)
Severe	6,577 (11.64)
Home oxygen	6,162 (10.91)
Transient ischemic attack	5,091 (9.01)
Prior stroke	6,547 (11.59)
Carotid stenosis	
None	35,141 (62.20)
Right	3,378 (5.98)
Left	3,186 (5.64)
Both	4,594 (8.13)
Not assessed	9,296 (16.45)
Peripheral arterial disease	16,542 (29.28)
Immunocompromise present	5,358 (9.48)
Baseline KCCQ-12 overall score*	47,519; 41.2 (25.0–60.4)
Home anticoagulant	1,805 (3.19)
Home dual antiplatelet therapy	692 (1.22)
Body surface area, m^2*	56,434; 1.84 (1.70–2.00)
Hostile chest	3,991 (7.06)
Porcelain aorta	2,961 (5.24)
Discharge factors	
Discharge status (alive)	54,832 (97.05)
Length of stay, days*	54,832; 4 (3–7)

Values are n; median (interquartile range), or n (%). All p values are based on Pearson chi-square tests for all categorical row variables unless otherwise specified. *The p values are based on chi-square rank-based group means score statistics for all continuous/ordinal row variables. †As defined in the Methods.

CABG = coronary artery bypass grafting; ICD = implantable cardioverter-defibrillator; KCCQ-12 = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TVT = Transcatheter Valve Therapy.

assumptions were tested and transformations of continuous variables were included when necessary. The correlation between risk factors was reviewed. Kaplan-Meier and cumulative incidence plots are reported for each component of frailty. SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina), was used for all analyses.

RESULTS

PATIENT POPULATION. We identified a total of 71,391 patients in the STS/ACC TVT registry from November 2011 to June 2016. Of these, 56,500 met the pre-specified inclusion criteria. After linking to the CMS database, we identified a final cohort of 36,242 patients with complete data for analysis (**Figure 1**) of the primary mortality endpoints and composite endpoints. Median follow-up time for all patients included in the survival analysis (n = 23,605) was 380 (IQR: 193 to 656) days. Median follow-up time among all those alive at 1 year (n = 19,959) was 405 (IQR: 240 to 709) days.

BASELINE PATIENT CHARACTERISTICS AND FRAILTY COMPONENTS. Baseline clinical factors, including frailty components, among those included in the total cohort, are reported in **Table 1**. Baseline characteristics describing each cohort, including those who had CMS data available, as well as each cohort categorized by the status of each evaluated marker of frailty, are available in Online Tables 1A to 1C. Compared with those for whom CMS data were not

available, there were no clinically significant differences in the distribution of baseline frailty makers (Online Table 2). Patients in the linked cohort were less likely to be Hispanic (2.7% vs. 5.3%; p < 0.0001); more likely to have a conduction deficit (Online Table 2) and a permanent cardiac pacemaker (16.0% vs. 14.1%; p < 0.0001), peripheral arterial disease (29.6% vs. 28.7%; p = 0.0368), or atrial fibrillation (41.5% vs. 39.7%; p < 0.0001); more likely to be on home oxygen (11.3% vs. 10.3; p = 0.0005); and more likely to be on dialysis (3.4% vs. 2.9%; p = 0.0067). Those in the linked cohort were more likely to be free of any carotid stenosis (62.5% vs. 61.6%; p = 0.0446) or chronic lung disease (56.7% vs. 57.7%; p = 0.0435), and less likely to be a current smoker (4.6% vs. 5.3%; p < 0.001), have diabetes (34.6% vs. 37.9%; p < 0.001), or have experienced a prior myocardial infarction (23.2% vs. 24.4%; p = 0.0015). Baseline characteristics that were found to be statistically, though not clinically, significantly different between the linked and unlinked cohorts included body surface area, prevalence of a porcelain aorta, New York Heart Association functional class, and length of stay on index admission for TAVR (Online Table 2).

PRIMARY ENDPOINTS. All-cause mortality at 30 days and 1 year. Unadjusted and adjusted mortality at 30 days stratified by each marker of frailty (low albumin, anemia, slow walking time) are reported in **Tables 2 and 3**, respectively. After stratifying for increasing number of positive makers of frailty, mortality at 30 days worsened with increasing positive markers in unadjusted analyses (**Figure 2**). Patients with all 3 positive markers of frailty were more likely to suffer mortality at 30 days in adjusted analyses (adjusted hazard ratio [HR]: 1.4; 95% confidence interval [CI]: 1.0 to 1.8; p < 0.041).

Survival at 1 year stratified by each marker of frailty is reported in **Figure 3**. Patients with any positive marker of frailty demonstrated poorer survival at 1 year, as compared with those with no positive markers (**Figures 3A to 3C**), and this relationship persisted in adjusted analyses (**Table 3**). After stratifying for increasing number of positive makers of frailty, survival was incrementally poorer at 1 year among those with increasing positive makers (**Central Illustration, Figure 3D**); this relationship persisted after adjustment (**Table 3**) (adjusted HR for those with 3 positive markers: 2.5; 95% CI: 2.1 to 3.0; p < 0.001).

Among the tested makers of frailty, low albumin was most associated with mortality at 30 days (adjusted HR: 1.3; 95% CI: 1.1 to 1.5; p < 0.001) and 1 year (adjusted HR: 1.5; 95% CI: 1.4 to 1.6; p < 0.001)

TABLE 2 Cumulative Incidence of Relevant Outcomes by Indices of Frailty

	Incidence at 30 Days	p Value	Incidence at 1 Year	p Value
Low albumin (n = 11,674)*				
Mortality	6.06 vs. 3.75	<0.0001	25.90 vs. 14.70	<0.0001
Stroke	2.25 vs. 2.45	0.12	4.91 vs. 5.40	0.24
Myocardial infarction	0.51 vs. 0.67	0.03	1.91 vs. 2.13	0.36
Any bleeding	13.30 vs. 11.10	<0.0001	26.30 vs. 20.10	<0.0001
Rehospitalization†	4.51 vs. 3.06	<0.0001	15.50 vs. 11.20	<0.0001
Need for new pacemaker	10.98 vs. 10.87	0.745		
Length of stay, days	6 (3-9) vs. 4 (3-6)	<0.0001		
Anemia (n = 34,954)*				
Mortality	4.79 vs. 3.76	<0.001	20.50 vs. 13.30	<0.0001
Stroke	2.28 vs. 2.43	0.36	5.04 vs. 5.52	0.19
Myocardial infarction	0.64 vs. 0.50	0.08	2.28 vs. 1.64	<0.0001
Any bleeding	12.40 vs. 10.00	<0.0001	24.70 vs. 16.00	<0.0001
Rehospitalization†	4.08 vs. 2.71	<0.0001	14.60 vs. 9.80	<0.0001
Need for new pacemaker	10.20 vs. 10.02	0.4912		
Length of stay, days	4 (3-7) vs. 4 (2-6)	<0.0001		
Slow walking speed (n = 6,341)*				
Mortality	4.55 vs. 3.22	<0.001	18.07 vs. 12.40	<0.0001
Stroke	2.56 vs. 2.05	<0.0001	5.70 vs. 4.99	<0.0001
Myocardial infarction	0.63 vs. 0.63	0.27	1.98 vs. 2.05	0.88
Any bleeding	11.80 vs. 9.46	<0.0001	22.20 vs. 17.30	<0.0001
Rehospitalization†	3.69 vs. 2.71	<0.0001	12.90 vs. 9.38	<0.0001
Need for new pacemaker	11.75 vs. 11.50	0.5617		
Length of stay, days	5 (3-8) vs. 4 (3-7)	<0.0001		

Values are % or median (interquartile range). Data represent the incidence compared with those without the positive marker being evaluated. *As defined in the Methods. †For acute congestive heart failure exacerbation.

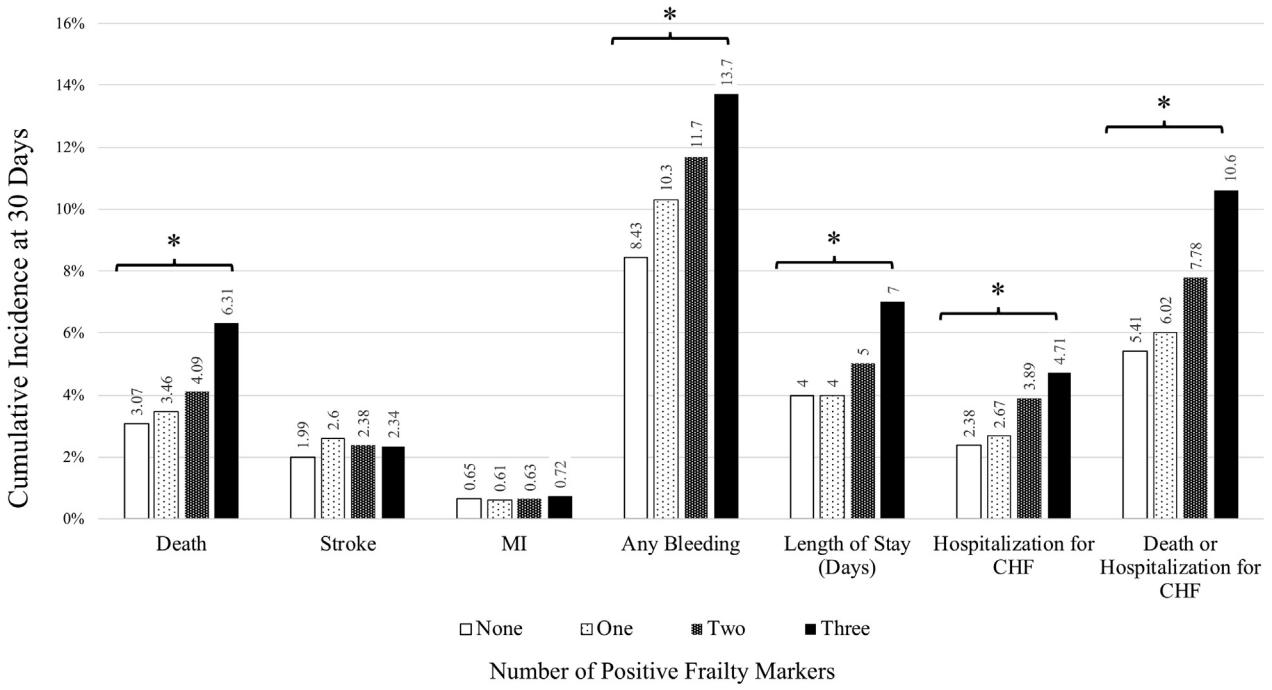
TABLE 3 Adjusted Hazard Ratios for Mortality at 30 Days and 1 Year

	Hazard Ratio (95% CI)	p Value
Model 1: Association between frailty markers and mortality at 1 yr		
Speed (≤0.83, >0.83)	1.36 (1.23-1.50)	<0.001
Albumin (≤3.4, >3.4)	1.52 (1.41-1.64)	<0.001
Anemia status	1.20 (1.11-1.31)	<0.001
Model 2: Association between number of positive frailty markers and mortality at 1 yr		
1 frailty marker	1.33 (1.12-1.56)	<0.001
2 frailty markers	1.73 (1.47-2.04)	<0.001
All 3 frailty markers	2.50 (2.08-3.01)	<0.001
Model 3: Association between frailty markers and mortality at 30 days		
Speed (≤0.83, >0.83)	1.21 (1.00-1.47)	0.05
Albumin (≤3.4, >3.4)	1.29 (1.12-1.48)	<0.001
Anemia status	0.97 (0.83-1.12)	0.651
Model 4: Association between number of positive frailty markers and mortality at 30 days		
1 frailty marker	0.94 (0.72-1.23)	0.669
2 frailty markers	0.99 (0.75-1.29)	0.919
All 3 frailty markers	1.36 (1.01-1.84)	0.041

The model included age, sex, body surface area, number of days from the initial TAVR performed, Hispanic descent, access site, lung disease, LVEF, prior myocardial infarction, platelet count, effective glomerular filtration rate, current dialysis, prior peripheral arterial disease, smoking status, diabetes, left main coronary artery stenosis ≥50%, proximal left anterior descending artery stenosis ≥70%, endocarditis, carotid stenosis, NYHA symptom class, conduction defect, home oxygen use, hostile chest, porcelain aorta, prior percutaneous coronary intervention, prior coronary artery bypass surgery, prior cardiac operators, aortic etiology, valve morphology, aortic insufficiency, tricuspid insufficiency, atrial fibrillation or flutter, presence of a cardiac pacemaker and previous ICD, and all 3 frailty markers (slow walking speed, low albumin, anemia).

CI = confidence interval; other abbreviations as in **Table 1**.

FIGURE 2 Incidence of Individual Outcomes at 30 Days by Increasing Number of Positive Frailty Markers



Incidence of individual outcomes at 30 days by increasing number of positive frailty markers. Length of stay is reported as median length of stay on index admission for transcatheter aortic valve replacement (TAVR). *p < 0.001. CHF = congestive heart failure; MI = myocardial infarction.

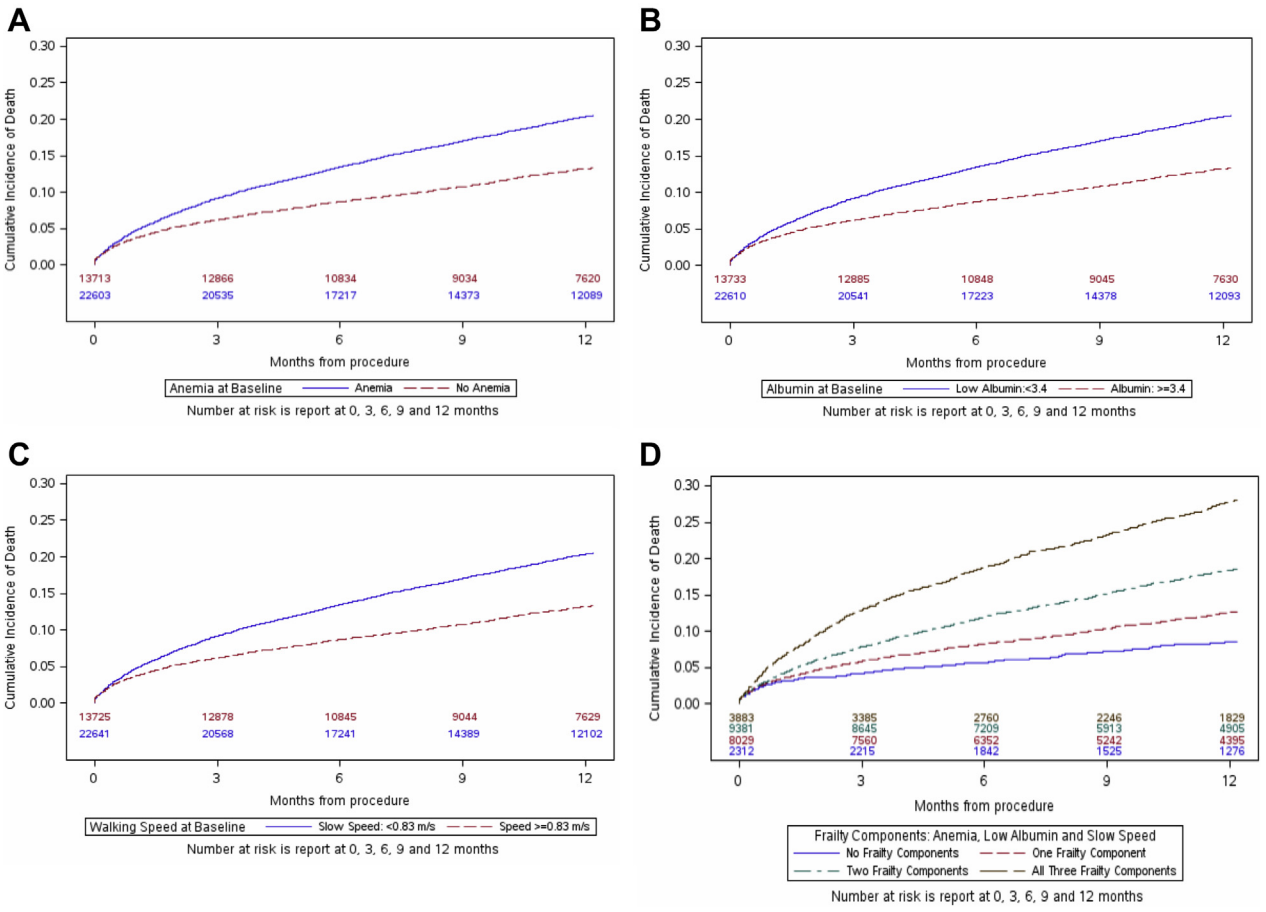
(Figure 3A). Those patients with anemia were more likely to experience mortality at 30 days (Table 2); however, this relationship did not persist after adjustment for known risk factors (adjusted HR: 1.0; 95% CI: 0.8 to 1.1; p = 0.651). Similarly, those patients with anemia were more likely to suffer mortality at 1 year in both unadjusted (Figure 3B) and adjusted analyses (adjusted HR: 1.2; 95% CI: 1.1 to 1.3; p < 0.001) compared with those without anemia. Patients with slow walking speed were more likely to suffer mortality at 30 days (adjusted HR: 1.2; 95% CI: 1.0 to 1.5; p = 0.050) and at 1 year (adjusted HR: 1.4; 95% CI: 1.2 to1.5; p < 0.001) (Figure 3C) compared to those with normal walking speeds.

Effect of decile of age. There was a significant interaction between decile of age and anemia status in the unadjusted model for mortality at 30 days (p = 0.0007). However, after adjustment for known confounders, this interaction did not persist. There were no significant interactions between decile of age and any marker of frailty in the unadjusted and adjusted analyses for 30-day and 1-year mortality (Online Table 3). Likewise, there was no significant interaction between decile of age and number of positive markers of frailty in the unadjusted and adjusted models for 30-day and 1-year mortality (Online Table 3).

Incremental contribution of individual markers of frailty for predicting mortality. Low albumin was the single strongest predictor of 30-day and 1-year mortality (adjusted 1-year HR: 1.5; 95% CI: 1.4 to 1.6; p < 0.001) followed by slow walking speed and anemia. Those with anemia, after controlling for albumin status, remained at increased risk of mortality at 1 year (adjusted HR: 1.2; 95% CI: 1.1 to 1.3; p < 0.001). Last, those with slower walking speeds remained at a high risk for the primary outcome at 1 year after adjusting for albumin and anemia status (adjusted HR: 1.4; 95% CI: 1.2 to 1.5; p < 0.001).

SECONDARY ENDPOINTS. Composite endpoint: All-cause mortality and rehospitalization for heart failure. The unadjusted incidence of the composite endpoint stratified by individual as well as increasing number of markers of frailty is reported in Table 4. Low albumin was associated with a higher rate of the composite endpoint of all-cause mortality or rehospitalization for heart failure at 30 days (10.2% vs. 6.7%; p < 0.0001) and 1 year (35.7% vs. 22.8%; p < 0.0001). Similarly,

FIGURE 3 **Survival Analysis for Each Marker of Frailty**



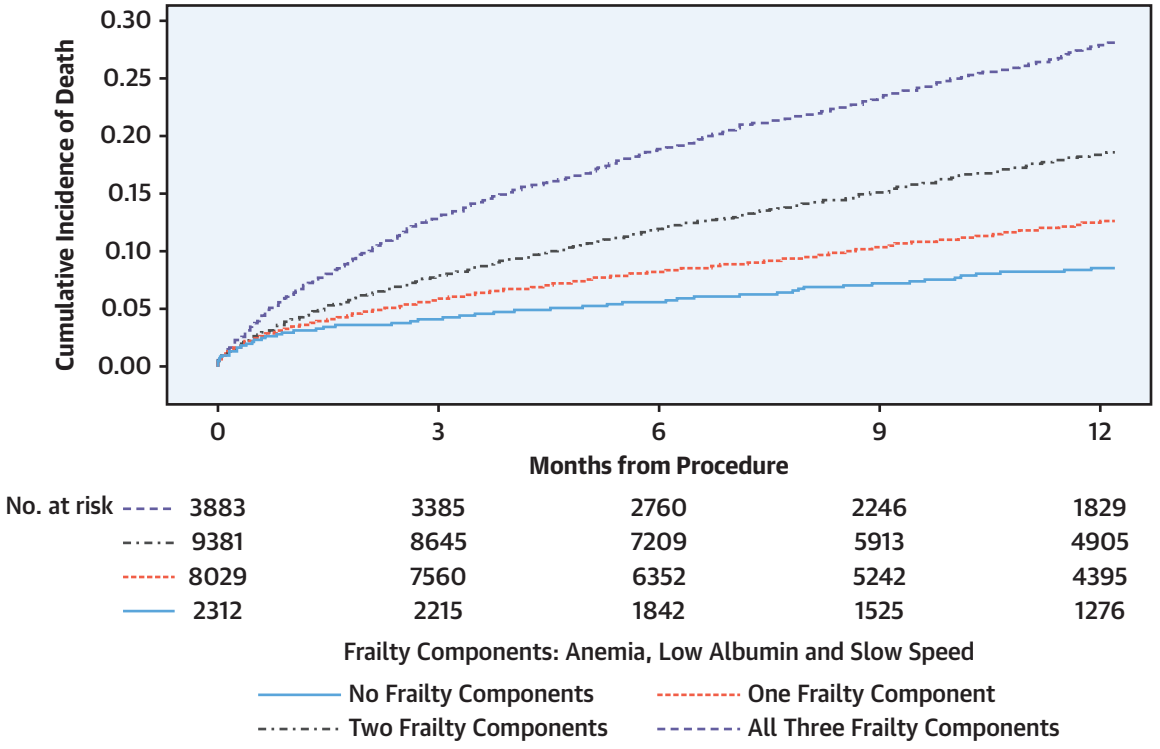
Survival analysis for each marker of frailty, **(A)** anemia (hemoglobin ≤13 g/dl for men, ≤12 g/dl for women) (adjusted hazard ratio [HR]: 1.20; 95% confidence interval [CI]: 1.11 to 1.31; $p < 0.001$), **(B)** low albumin (<3.4 g/dl) (adjusted HR: 1.52; 95% CI: 1.41 to 1.64; $p < 0.001$), **(C)** slower walking speeds (<0.83 m/s) (adjusted HR: 1.36; 95% CI: 1.23 to 1.50; $p < 0.001$), and **(D)** stratified for those with increasing number of positive markers of frailty (adjusted HR for those with 3 positive markers: 2.50; 95% CI: 2.08 to 3.01; $p < 0.001$). The number at risk in each group at each time point is denoted at the **bottom of the graph** in the color corresponding to the groups denoted in the legend.

there were higher rates of the composite outcome for those with either slower walking speeds or anemia (Table 4). Likewise, compared with patients with no positive frailty markers, patients with any positive frailty marker were more likely to experience the composite outcome at 30 days and 1 year in (Table 4). Survival free of the composite endpoint was poorer in patients with any frailty marker (Figures 4A to 4C) and incrementally poorer among those with increasing positive markers (Figure 4D). These relationships persisted after adjustment for known risk factors (Online Table 4).

Individual endpoints. Unadjusted rates of secondary endpoints at 30 days and 1 year stratified by individual markers of frailty are reported in Table 2.

Among those with low albumin at 30 days, there were higher rates of readmission for heart failure and any bleeding complication compared with those without low albumin (Table 2). There was no significant difference in the rates of stroke and myocardial infarction (Table 2). There was no difference in the incidence of need for a new pacemaker between these groups. Similarly, at 1 year, those with low albumin had higher rates of readmission for heart failure (15.5% vs. 11.2%; $p < 0.0001$) and any bleeding complication (26.3% vs. 20.1%; $p < 0.0001$), and similar rates of stroke (4.9% vs. 5.4%; $p = 0.24$) and myocardial infarction (1.9% vs. 2.1%; $p = 0.36$), compared with those without low albumin.

CENTRAL ILLUSTRATION **Survival of Patients Stratified by Varying Degrees of Frailty**



Kiani, S. et al. J Am Coll Cardiol Intv. 2020;13(2):219–31.

Survival analysis stratified for those with increasing number of positive markers of frailty, from those with none to all 3 frailty markers (adjusted hazard ratio for those with 3 positive markers: 2.50; 95% confidence interval: 2.08 to 3.01; $p < 0.001$). The number at risk in each group at each time point is denoted at the **bottom of the graph** in the color corresponding to the groups denoted in the legend.

Among those with slower walking speed, at 30 days, there was a higher rate of readmission for heart failure, any bleeding, and stroke compared with non-slow walkers and similar rates of myocardial infarction (Table 2) compared with those without slow walking speeds. There was no difference in the incidence of need for new pacemaker among those with slower walking speed compared with those without (Table 2). Similarly, at 1 year there was a higher rate of readmission for heart failure (12.9% vs. 9.4%; $p < 0.0001$), any bleeding (22.2% vs. 17.3%; $p < 0.0001$), and stroke (5.7% vs. 4.99%; $p < 0.0001$) compared with non-slow walkers. There was no significant difference at 1 year in rates of myocardial infarction (2.0% vs. 2.1%; $p = 0.88$) compared with non-slow walkers.

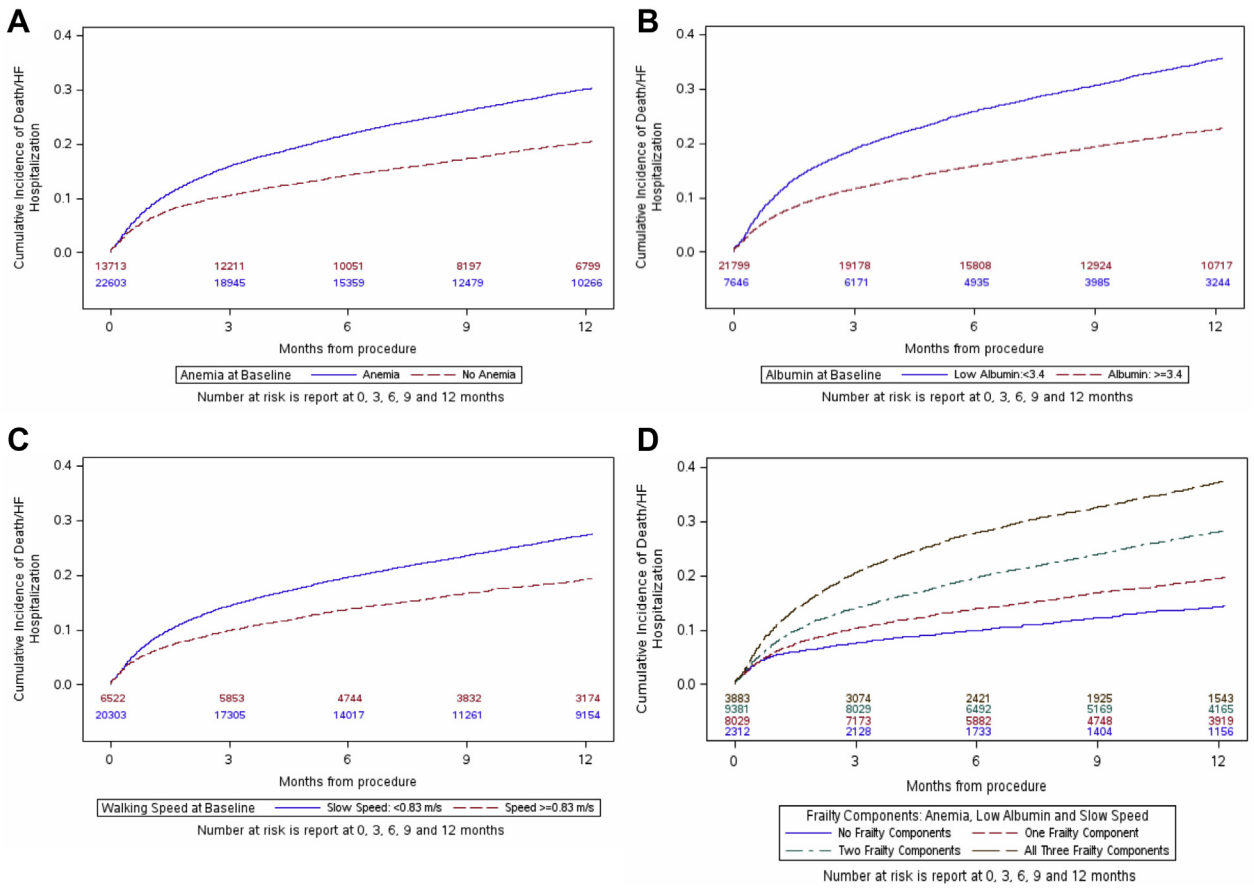
Length of stay on index admission for TAVR was incrementally higher among those with increasing markers of frailty (Figure 2). The rates of readmission for heart failure ($p < 0.001$) and any bleeding complication ($p < 0.001$) increased with the number of positive markers of frailty at 30 days (Figure 2) and 1 year (Figure 5). There was no significant difference

TABLE 4 **Unadjusted Composite Endpoints by Frailty Marker**

	Incidence (%)*	p Value
30 days†		
Low albumin	10.20 vs. 6.68	<0.0001
Anemia	8.61 vs. 6.34	<0.0001
Slow walking speed	8.01 vs. 5.84	<0.0001
1 yr†		
Low albumin	35.70 vs. 22.80	<0.0001
Anemia	30.30 vs. 20.50	<0.0001
Slow walking speed	27.60 vs. 19.40	<0.0001

Results are the unadjusted incidence compared with those without the positive index being evaluated. *Those patients with specified frailty marker vs. control subject (those without the specified marker). †Composite of all-cause mortality or admission for heart failure exacerbation.

FIGURE 4 **Survival Free of the Composite Endpoint of Mortality and Admission for Acute Decompensated Heart Failure**



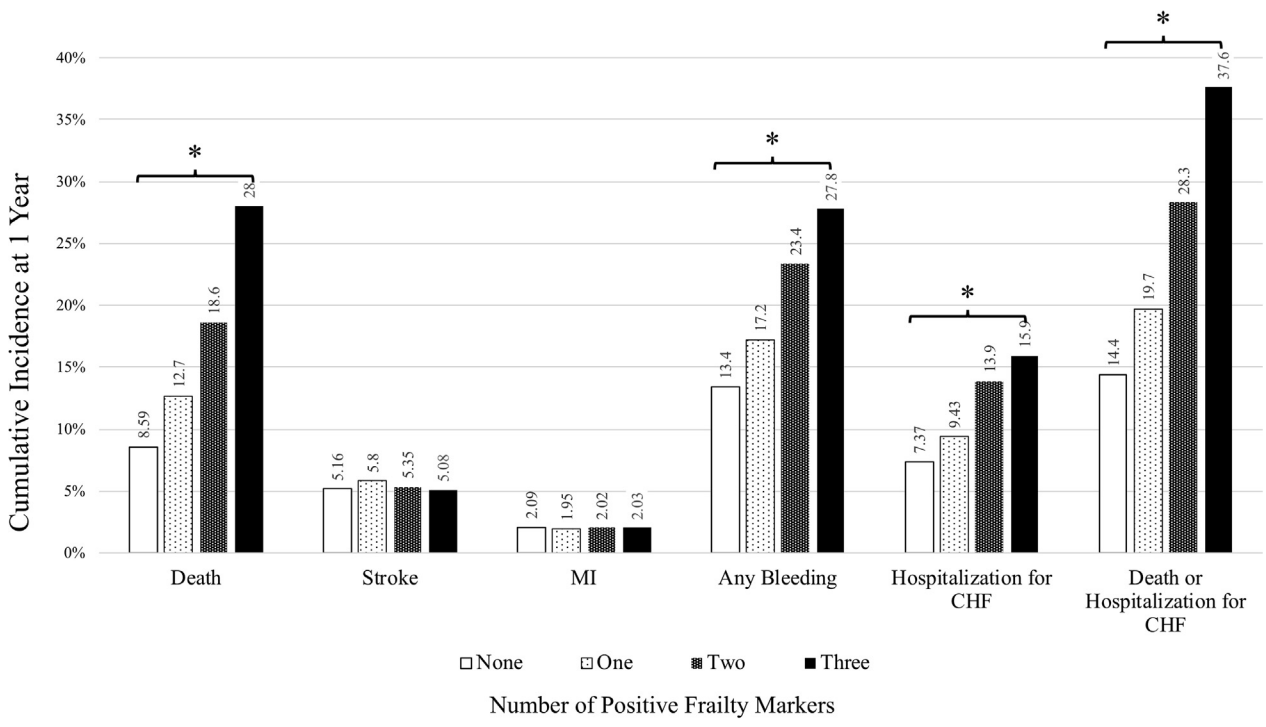
Survival analysis of the composite endpoint of mortality and admission for acute decompensated heart failure for each marker of frailty, **(A)** anemia (hemoglobin ≤13 g/dl for men, ≤12 g/dl for women), **(B)** low albumin (<3.4 g/dl), **(C)** slower walking speeds (<0.83 m/s), and **(D)** stratified for those with increasing number of positive markers of frailty. The number at risk in each group at each time point is denoted at the **bottom of the graph** in the color corresponding to the groups denoted in the legend.

in the rates of stroke at 30 days (p = 0.38) (Figure 2) and 1 year (p = 0.11) (Figure 5) and myocardial infarction at 30 days (p = 0.91) (Figure 2) and 1 year (p = 0.96) (Figure 5) among those with increasing number of positive markers of frailty.

DISCUSSION

Herein, we report outcomes of the largest study to date of frailty in patients undergoing TAVR. We observed that patients with positive markers of frailty have a significantly higher risk of all-cause mortality after TAVR than patients with fewer markers of frailty. Low albumin was the strongest predictor of all-cause mortality, while slow-walking speed on the 5-m walk test and anemia remained significant, though slightly weaker, independent predictors. Positive markers of frailty also correlated with an increased risk for TAVR related morbidity including bleeding and readmission for heart failure exacerbation at 30 days and 1 year. We also found a correlation between increasing number of positive frailty markers and an incremental increase in these adverse outcomes. This relationship persisted after adjusting for risk factors known to predict mortality in the TVT registry (25), as well as the STS Predicted Risk of Mortality (Online Table 5). Interestingly, no significant interaction between age and frailty was noted for any outcome. This suggests that the magnitude of the risks and poor outcomes associated with frailty in TAVR patients outweigh any potential advantage one might expect younger patients to have over older

FIGURE 5 Incidence of Individual Outcomes at 1 Year by Increasing Number of Positive Frailty Markers



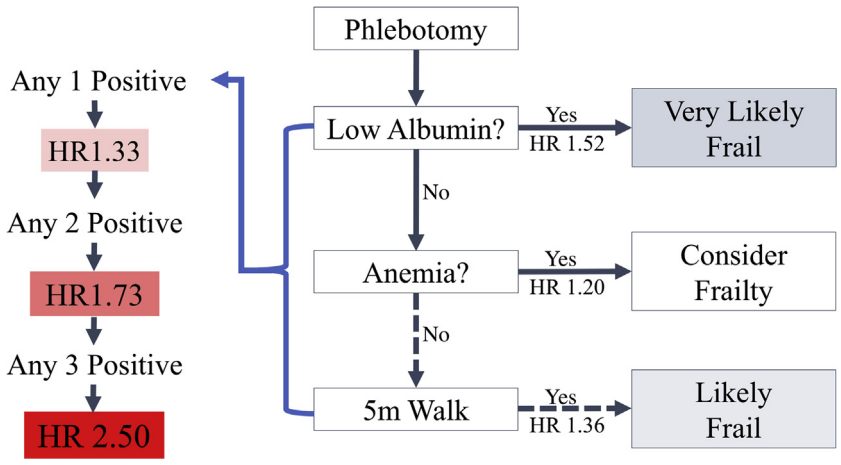
Incidence of individual outcomes at 1 year by increasing number of positive frailty markers. *$p < 0.001$. Abbreviations as in Figure 2.

patients undergoing the same major procedure. Given the predictive power demonstrated by frailty markers in this study, one can argue that screening for markers of frailty should be performed as part of any routine TAVR preprocedural assessment, regardless of age. Indeed, we recommend that these markers of frailty be included in subsequent iterations of risk scores for TAVR.

Low albumin, anemia, and slow walking speed have been previously shown to be associated with TAVR-related mortality both independently (22,24,26) as well as in context of other markers of frailty (5,6,9,15,16). Typical screening tools often require multiple metrics to be obtained simultaneously, which can be cumbersome and time consuming in a busy clinical environment. We evaluated the utility of a putative frailty screening workflow with the goal of simplifying the process and minimizing additional tasks in the clinical setting (**Figure 6**). Because low albumin was the strongest single predictor of frailty, we used this as a starting point. We then evaluated the incremental benefit of screening for anemia in addition to low-albumin, given that phlebotomy would have already been performed. After these 2 markers are screened for, next would be a 5-m walk test, which does require additional time and resources. Even when screening for frailty in the previous stepwise method, each marker incrementally improved the predictive power from those markers already evaluated.

Prior studies have evaluated subgroups of clinical trial populations or smaller cohorts with variable results. In 2 substudies of the PARTNER (Placement of Aortic Transcatheter Valve) trials, Green et al. (5,6) demonstrated an association between mortality at 1 year and increased frailty among high-risk patients. Likewise, Forcillo et al. (15), in a cohort of extreme-risk patients, demonstrated increased mortality among those with low albumin (though no association with other frailty factors), as well as an increased rate of a composite endpoint (mortality, stroke, new heart block requiring permanent pacemaker, major or life-threatening bleeding, acute renal failure, major vascular complication, and 30-day readmission rate) among frail patients at 30 days. Similarly, in a large cohort of patients in the United States, Kundi et al. (27) demonstrated increased mortality at 30 days and 1 year among patients with higher Hospital Frailty

FIGURE 6 Proposed Putative Frailty Screening Workflow



Proposed framework to identify markers of frailty in patients, leveraging metrics routinely obtained, when possible, to streamline in-clinic workflow. Hazard ratios (HRs) from the incremental predictive model adjusting for prespecified clinical factors included in the Transcatheter Valve Therapy registry risk model for mortality are shown. All HRs presented are statistically significant at the $p < 0.05$ level.

Risk Scores undergoing transcatheter valve therapies, including TAVR. Moreover, the utility of including indices of frailty in risk models to predict 30-day mortality after TAVR has been previously demonstrated (28). Indeed, prior work has also shown that the addition of an assessment of frailty to conventional risk scores (e.g., the STS 2) augmented their performance in predicting mortality at 30 days and 1 year after TAVR (29). The findings of our current study are consistent with those of prior reports and serve to clarify prior conflicting results in a large, real-world cohort.

Afilalo et al. (16) prospectively evaluated the incremental predictive value of several proposed frailty scales to predict outcomes following TAVR or surgical aortic valve replacement in a cohort of 1,020 patients from 14 centers and found an increased risk of mortality among frail patients at 1 year. Likewise, they demonstrated that the Essential Frailty Toolset (a risk score comprising albumin, anemia status, ability to perform chair raises, and cognitive status on the Mini-Mental State Exam) outperformed prior described frailty scores in predicting mortality as well as worsening disability. We demonstrated similar outcomes using albumin, anemia, and a 5-m walk test. We did not include a cognitive assessment as these data are not collected routinely in the TVT registry. Despite not including a cognitive assessment, these 3 markers performed comparably to the Essential Frailty Toolset in this particular cohort. Further, we demonstrated the incremental value of adding each marker of frailty to the prior in a stepwise manner that would streamline workflow in a busy clinical setting.

STUDY LIMITATIONS. First, the study was not prospective. However, because of a large sample size, we were able to perform robust modeling to adjust for several risk factors known to predict mortality in this cohort (25). Likewise, we obtained similar results when adjusting for the STS Predicted Risk of Mortality. Although statistically significant differences were reported for certain baseline factors, these differences were small and not clinically meaningful. Second, we did not include cognitive assessment in our model. Despite this, we demonstrated a significant association between the evaluated frailty factors and the outcomes of interest. Cognitive assessment is an important metric to ascertain in any patient in whom there is suspicion for impairment. However, cognitive evaluation can be cumbersome and time consuming to perform for providers. Although cognitive assessment remains an important component of patient work-up, our data suggest that it may not be necessary in the initial screening of patients undergoing TAVR for frailty. Third, to minimize confounders in our analysis, we chose to exclude patients with prior valve procedures and evaluate only those undergoing de novo TAVR. Because of this, our results may not be generalizable to the population of patients with prior valve surgery or those undergoing redo TAVR. Fourth, a subset of patients in our study population did have missing data, thus excluding them from our

analysis. However, we do not believe that the presence of absence of data is indicative of a relationship to frailty. There was no clinically significant difference in baseline clinical factors between those with or without frailty indices reported in the TVT registry at large (Online Table 6), as well as those with CMS-linked outcome data (Online Table 7). Although some of these statistical comparisons reached significance, this was due to a very large sample size and did not represent clinically meaningful differences. Therefore, we believe that the cohort used in the analysis is representative of the population of interest. Last, although our study demonstrates an increased risk of poor outcomes in patients with positive frailty markers, we did not evaluate whether these outcomes were modifiable. Poor nutrition and muscle wasting, anemia and functional impairment may often be treatable. Work-up for etiology and treatment of underlying causes is reasonable and should be undertaken in these patients in the periprocedural period. It seems reasonable to assume that improvements in these metrics may correlate with an improvement in symptoms. However, whether modifying these markers will lead to improved outcomes remains to be thoroughly investigated.

CONCLUSIONS

In short, our study is the largest evaluation of the role of frailty in patients undergoing TAVR to date. We demonstrated that frailty markers of low albumin, anemia, and slow walking speed are significant independent predictors of mortality and morbidity in patients undergoing TAVR. Low albumin was the strongest single predictor, and slow walking speed and anemia remained important predictors even after adjustment for other markers of frailty. Moreover, these markers have incremental value to predict mortality when used in concert. Whether or not modifying these risk factors will impact outcomes remains to be seen and is an area of potential future investigation. We also put forth a streamlined framework for screening patients for frailty during routine evaluation for TAVR. Taken together, these markers represent a simple, yet powerful, algorithm using factors that are already often ascertained in the routine evaluation for TAVR and can be used to further risk-stratify patients of any age, individualize therapy, and guide patient selection.

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PERSPECTIVES

WHAT IS KNOWN? Frailty is a global syndrome that renders patients more vulnerable to poorer outcomes after cardiovascular procedures.

WHAT IS NEW? Low albumin, anemia, and slow walking speed are markers of frailty that are significant independent predictors of mortality and morbidity in patients undergoing TAVR, and their presence should raise concern for the presence of frailty and prompt further investigation.

WHAT IS NEXT? Patients with positive indices of frailty should be counseled about their increased risk for poorer outcomes after TAVR. Further studies need to explore whether modification of these markers of frailty can reduce the risk of mortality after TAVR or whether they only serve as indirect markers of more profound clinical impairment.

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KEY WORDS patient selection, risk score, TAVR

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.