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ORIGINAL INVESTIGATIONS

Frailty in Older Adults Undergoing Aortic Valve Replacement

The FRAILTY-AVR Study

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ABSTRACT

BACKGROUND Frailty is a geriatric syndrome that diminishes the potential for functional recovery after a transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) procedure; however, its integration in clinical practice has been limited by a lack of consensus on how to measure it.

OBJECTIVES This study sought to compare the incremental predictive value of 7 different frailty scales to predict poor outcomes following TAVR or SAVR.

METHODS A prospective cohort of older adults undergoing TAVR or SAVR was assembled at 14 centers in 3 countries from 2012 to 2016. The following frailty scales were compared: Fried, Fried+, Rockwood, Short Physical Performance Battery, Bern, Columbia, and the Essential Frailty Toolset (EFT). Outcomes of interest were all-cause mortality and disability 1 year after the procedure.

RESULTS The cohort was composed of 1,020 patients with a median age of 82 years. Depending on the scale used, the prevalence of frailty ranged from 26% to 68%. Frailty as measured by the EFT was the strongest predictor of death at 1 year (adjusted odds ratio [OR]: 3.72; 95% confidence interval [CI]: 2.54 to 5.45) with a C-statistic improvement of 0.071 ($p < 0.001$) and integrated discrimination improvement of 0.067 ($p < 0.001$). Moreover, the EFT was the strongest predictor of worsening disability at 1 year (adjusted OR: 2.13; 95% CI: 1.57 to 2.87) and death at 30 days (adjusted OR: 3.29; 95% CI: 1.73 to 6.26).

CONCLUSIONS Frailty is a risk factor for death and disability following TAVR and SAVR. A brief 4-item scale encompassing lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia outperformed other frailty scales and is recommended for use in this setting. (Frailty Assessment Before Cardiac Surgery & Transcatheter Interventions; NCT01845207) (J Am Coll Cardiol 2017;70:689–700)
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ABBREVIATIONS AND ACRONYMS

ADL = activities of daily living

BIC = Bayesian information criterion

CFS = Clinical Frailty Scale

EFT = Essential Frailty Toolset

IADL = instrumental activities of daily living

IDI = integrated discrimination improvement

SAVR = surgical aortic valve replacement

SPPB = Short Physical Performance Battery

STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality

TAVR = transcatheter aortic valve replacement

Frailty is conceptually defined as a diminished capability to recover from pathological or iatrogenic stressors due to aging-related impairments (1). Frailty plays a pivotal role in defining the older patient's potential for recovery following a transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) procedure (2,3). Although the likelihood of short-term procedural success exceeds 95% (4), 2 of 5 patients in the PARTNER I (Placement of AoRTic TraNscathetER Valve Trial) and CoreValve Pivotal trials experienced poor health-related quality of life or death over the ensuing year (5). To optimize patient selection, national guidelines strongly recommend an objective evaluation of frailty, but they caution that the lack of a clear and agreed-upon assessment is a barrier limiting its use (6–8). This lack of consensus surrounding frailty assessment tools is a major reason why frailty is often not measured in clinical practice (9) and why it is reported to have divergent prevalence estimates and effect sizes across studies (10). Gait speed is the most commonly used test to screen for frailty; however, characterization of frailty with gait speed alone lacks specificity to discriminate between complex patients who may or may not experience poor outcomes following TAVR or SAVR (11,12).

To achieve better discrimination, multidomain frailty scales are preferred. The Fried scale reflects strength, mobility, weight loss, fatigue, and habitual activity, and is predictive of survival and quality of life after aortic valve procedures (13,14). The Rockwood Clinical Frailty Scale (CFS) broadly reflects the patient's functional abilities, and is predictive of survival after TAVR (15), whereas the Short Physical Performance Battery (SPPB) narrowly reflects the patient's lower-extremity muscle function (16). Additional TAVR-centric frailty scales have been derived (17–19), including our 4-item Essential Frailty Toolset (EFT) (**Central Illustration**).

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There has yet to be a head-to-head comparison of frailty scales, with each having been sparingly validated in individual studies and adopted at selected sites. Thus, we sought to compare the incremental predictive value of frailty scales in a prospective multicenter cohort of older adults undergoing TAVR or SAVR. Our overarching goal was to harmonize

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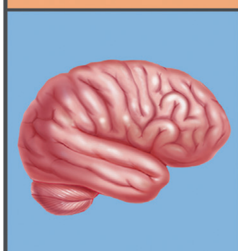
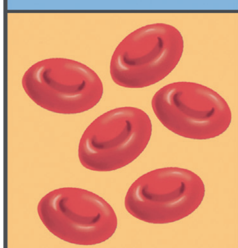
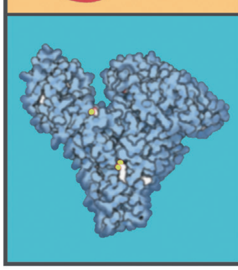
CENTRAL ILLUSTRATION Essential Frailty Toolset in Older Adults Undergoing Aortic Valve Replacement

	Five chair rises <15 seconds		0 Points
	Five chair rises ≥15 seconds		1 Point
	Unable to complete		2 Points
	No cognitive impairment		0 Points
	Cognitive impairment		1 Point
	Hemoglobin	≥13.0 g/dL ♂ ≥12.0 g/dL ♀	0 Points
	Hemoglobin	<13.0 g/dL ♂ <12.0 g/dL ♀	1 Point
	Serum albumin	≥3.5 g/dL	0 Points
	Serum albumin	<3.5 g/dL	1 Point

EFT Score	1-Year Mortality TAVR	SAVR
0-1	6%	3%
2	15%	7%
3	28%	16%
4	30%	38%
5	65%	50%

EFT Points: ________

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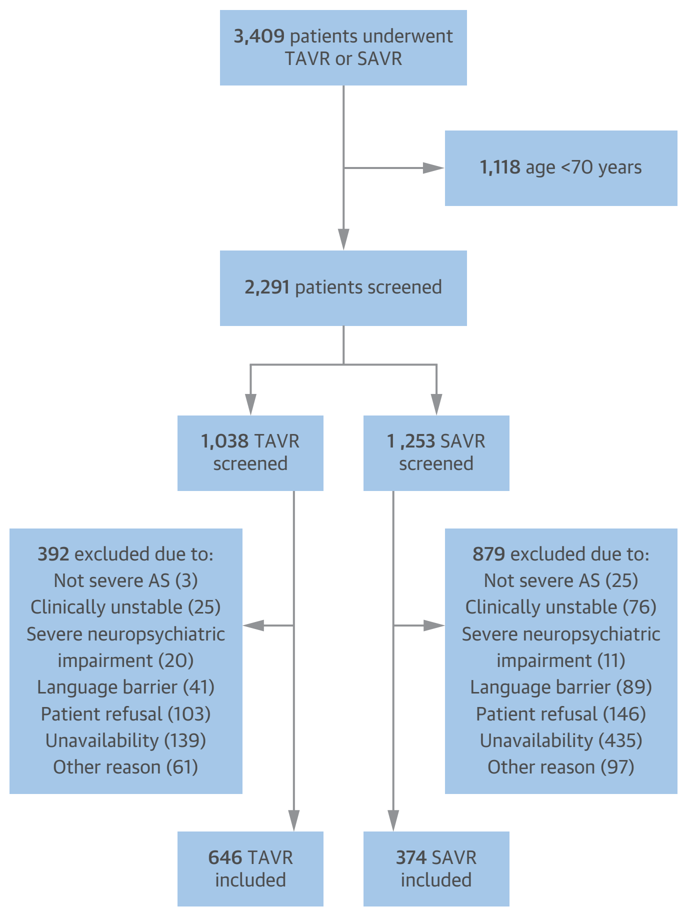
The EFT is scored 0 (least frail) to 5 (most frail) based on the following 4 items: pre-procedural anemia, hypoalbuminemia, lower-extremity muscle weakness defined as a time of ≥15 s or inability to complete five sit-to-stand repetitions without using arms, and cognitive impairment defined as a score of <24 on the Mini-Mental State Examination (which is highly unlikely if the patient is able to correctly recall 3 out of 3 words after a distractive task and may obviate the need for further cognitive testing). EFT = Essential Frailty Toolset; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

FIGURE 1 Flow Diagram



A total of 1,020 older adults were included in the cohort: 499 transfemoral TAVR; 147 nonfemoral TAVR; 179 isolated SAVR; and 195 combined SAVR with coronary artery bypass. The most common reason for nonenrollment was failure to arrange a study interview pre-procedure due to patient and/or researcher unavailability. No patient was lost to follow-up for the primary endpoint of 1-year all-cause mortality. AS = aortic stenosis; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

practice by providing clearer recommendations on how to best assess frailty, which would in turn be used to individualize care and improve outcomes in vulnerable patients.

METHODS

STUDY DESIGN. A prospective cohort of older adults undergoing TAVR or SAVR was assembled at 14 academic centers in Canada, the United States, and France. Consecutive patients were approached and invited to complete a comprehensive geriatric evaluation before the procedure. The evaluation included a series of physical performance tests and questionnaires focused on frailty, with the objective being to compare the predictive value of different frailty scales. After the procedure, trained observers reviewed medical records to ascertain adverse events and contacted the patients by telephone at 6 and 12 months to readminister questionnaires pertaining to physical functioning and disability. The Frailty Assessment Before Cardiac Surgery & Transcatheter Interventions study was registered (NCT01845207) and approved by the ethical review boards at the participating hospitals. All patients signed an informed consent form before participating. The paper was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (20).

PARTICIPANTS. Patients with symptomatic aortic stenosis were screened in aortic valve clinics and inpatient wards. Inclusion criteria were: age 70 years or older, undergoing TAVR or SAVR with or without concomitant revascularization between January 2012 and December 2015, and signed consent. Exclusion criteria were: need for emergency surgery, concomitant replacement or repair of another heart valve or the aorta, clinical instability (unstable vital signs, refractory ischemia, or acute decompensated heart failure), severe neuropsychiatric impairment, or prohibitive language barrier. Questionnaires were available in English and French.

FRAILTY ASSESSMENT. Seven frailty scales were compared (Online Table 1). The Fried scale consists of 5 items, with 3 of 5 required to diagnose frailty: 5-m gait speed, grip strength, weight loss, exhaustion, and inactivity (21). The Fried+ scale consists of the same items plus cognition assessed by the Mini-Mental State Examination (22) and mood by the Short-Form Geriatric Depression Scale (23), with 3 of 7 required to diagnose frailty. The Rockwood CFS is scored 1 to 9 based on a semiquantitative evaluation of the patient's symptoms, mobility, inactivity, exhaustion, and disability for basic activities of daily living (ADL) and instrumental activities of daily living (IADL) (24). The SPPB consists of 3 physical tests, with each scored 0 to 4 for a composite score of 0 to 12: gait speed, time to stand 5 times from a seated position without using arms, and ability to stand 10 s with the feet in tandem or side-by-side positions (25). The Bern scale consists of 6 items for a composite score of 0 to 7: gait speed, mobility, cognition, nutrition, ADL and IADL disability (17,18). The Columbia scale consists of 4 items, with each scored 0 to 3 for a composite score of 0 to 12: gait speed, grip strength, serum albumin, and ADL disability (19). The EFT consists of 4 items for a composite score of 0 to 5:

time to stand 5 times from a seated position without using arms (1 point if ≥15 s, 2 points if unable to complete), cognition (1 point if Mini-Mental State Examination score <24), hemoglobin (1 point if <13 g/dl in men or <12 g/dl in women), and serum albumin (1 point if <3.5 g/dl or if serum albumin was not measured then Mini-Nutritional Assessment score <8) (26).

COVARIATES. In addition to the measurements of frailty and disability, patients were asked about their living situation and social support. Habitual physical activity was assessed by the expanded Paffenbarger questionnaire (27). Medical records were used to extract cardiac and noncardiac comorbidities, procedural details, pre- and post-procedural laboratory results, echocardiography data, cardiac catheterization data, computed tomography data, and information on disposition and repeat hospitalizations. The Society of Thoracic Surgeons (STS) risk model was used to calculate the predicted risk of mortality (PROM) for each patient. Data definitions were based on the standards set forth by the STS Adult Cardiac Surgery Database and the Valve Academic Research Consortium (28). Observers were trained at the beginning of the study, and all data were reviewed centrally for quality and consistency.

OUTCOMES. The primary outcome was death from any cause at 12 months following the index procedure. Vital status was ascertained by a combination of medical records, death certificates, linkage to administrative data, and contact with the patients and their family members. The secondary outcomes were death from any cause at 30 days and a composite of death or worsening disability, defined as institutionalization or ≥2 new accrued disabilities in ADLs or IADLs at 12 months measured with the Older Americans Resources and Services questionnaire (29). Adverse events were adjudicated by local investigators, and any disagreements were resolved by consensus.

STATISTICAL APPROACH. Continuous variables are presented as median (interquartile range [IQR]) and compared using the Wilcoxon rank sum test. Categorical variables are presented as proportions and compared using the chi-square test. Frailty scales were primarily analyzed in their continuous form and secondarily in their dichotomous form based on a priori cutoffs. Multivariable logistic regression was used to determine the association between each frailty scale and all-cause mortality, adjusting for the type of procedure and either the STS-PROM or individual covariates. The individual covariates were selected based on a review of validated risk models and univariate analyses. To compare the incremental predictive value of each frailty scale, the following model performance statistics were calculated: C-statistic, Bayesian information criterion (BIC) and integrated discrimination improvement (IDI) (30). For the C-statistic and IDI, more positive values indicate improved discrimination. For the BIC, more negative values indicate improved prediction, with a change of −10 indicating *very strong* evidence of improvement (31). Study data were managed using REDCap electronic data capture tools hosted at the Lady Davis Institute's Centre for Clinical Epidemiology (32). Analyses were performed using the Stata release 14 software package (StataCorp, College Station, Texas).

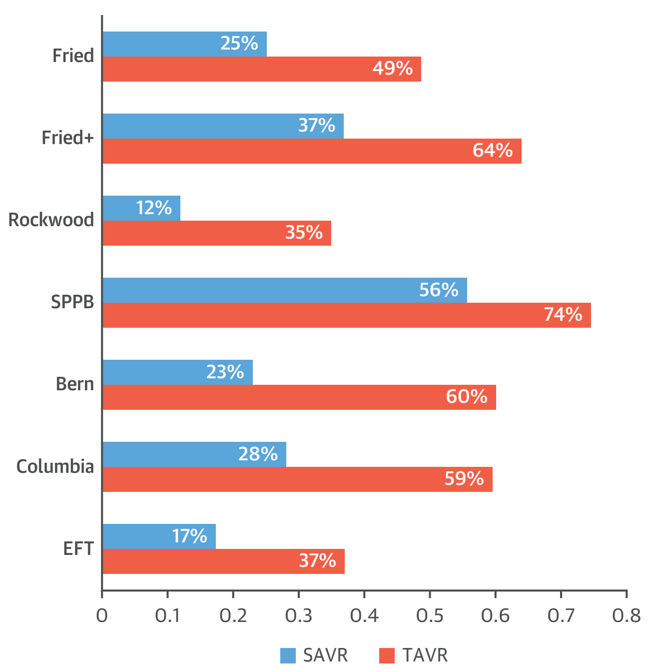
TABLE 1 Baseline Characteristics

	Total (N = 1,020)	Alive (n = 875)	Deceased (n = 145)	p Value
Age, yrs	82 (77–86)	81 (76–86)	85 (81–88)	<0.001
Female	421 (41)	356 (41)	65 (45)	0.35
BMI, kg/m^2	26.6 (23.6–30.1)	27.0 (23.9–30.5)	24.9 (22.0–27.5)	<0.001
Prior cardiac surgery	202 (20)	179 (20)	23 (16)	0.20
COPD	176 (17)	145 (17)	31 (21)	0.16
Home oxygen	17 (2)	10 (1)	7 (5)	0.001
Gastrointestinal bleed	56 (5)	41 (5)	15 (10)	0.006
Cirrhosis	11 (1)	8 (1)	3 (2)	0.21
Dialysis	12 (1)	6 (1)	6 (4)	<0.001
Osteoporosis	131 (13)	106 (12)	25 (17)	0.09
Cancer	151 (15)	121 (14)	30 (21)	0.03
Diabetes	281 (28)	239 (27)	42 (29)	0.68
PAD	160 (16)	131 (15)	29 (20)	0.12
Stroke	78 (8)	61 (7)	17 (12)	0.05
Myocardial infarction	223 (22)	186 (21)	37 (26)	0.25
Atrial fibrillation	339 (33)	268 (31)	71 (49)	<0.001
NYHA functional class III–IV	626 (61)	511 (58)	115 (79)	<0.001
LVEF, %	60.0 (50.0–65.0)	60.0 (50.0–65.0)	57.5 (45.0–62.5)	0.005
Aortic valve area, cm^2	0.73 (0.60–0.89)	0.75 (0.60–0.90)	0.70 (0.60–0.80)	0.08
Mean gradient, mm Hg	43 (36–54)	44 (36–54)	40 (32–50)	0.002
PASP, mm Hg	39 (31.0–48.0)	39 (30.1–47.0)	44 (35.0–52.0)	0.002
GFR, ml/min/1.73 m^2	59.0 (44.6–70.6)	60.0 (45.6–71.5)	50.2 (35.2–63.8)	<0.001
Hemoglobin, g/dl	12.3 (11.1–13.5)	12.5 (11.3–13.6)	11.4 (10.3–12.1)	<0.001
Albumin, g/dl	3.9 (3.6–4.2)	4.0 (3.6–4.3)	3.7 (3.4–4.0)	<0.001
STS-PROM, %*	4.3 (2.7–6.8)	4.0 (2.5–6.2)	6.8 (4.3–9.2)	<0.001
Procedure type				<0.001
TAVR transfemoral	499 (49)	415 (47)	84 (58)	
TAVR nonfemoral	147 (14)	112 (13)	35 (24)	
SAVR isolated	179 (18)	173 (20)	6 (4)	
SAVR with bypass	195 (19)	175 (20)	20 (14)	

Values are median (IQR) or n (%). *The STS-PROM was 5.3 (3.6 to 7.9) in transfemoral TAVR, 5.8 (3.8 to 8.9) in nonfemoral TAVR, 2.4 (1.7 to 3.7) in isolated SAVR, and 2.9 (2.1 to 4.8) in combined SAVR with bypass.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; IQR = interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PAD = peripheral arterial disease; PASP = pulmonary artery systolic pressure; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predicted Risk Of Mortality; TAVR = transcatheter aortic valve replacement.

FIGURE 2 Prevalence of Frailty According to Various Scales



The overall prevalence of frailty varied depending on the scale used, and was generally 2-fold higher in TAVR **(orange bars)** compared with SAVR **(blue bars)** patients. Frailty scales were dichotomized based on original cutoffs: Fried ≥3 of 5, Fried+ ≥3 of 7, Rockwood Clinical Frailty Scale ≥5 of 9, SPPB ≤8 of 12, Bern ≥3 of 7, Columbia ≥6 of 12, and EFT ≥3 of 5. EFT = Essential Frailty Toolset; SPPB = Short Physical Performance Battery; other abbreviations as in Figure 1.

RESULTS

The FRAILTY-AVR cohort consisted of 1,020 older adults, of whom 646 underwent TAVR and 374 underwent SAVR, 195 with and 179 without concomitant coronary artery bypass. The median age was 82 years (IQR: 77 to 86 years) with a range of 70 to 99 years and a distribution as follows: 38% age 70 to 79 years, 53% age 80 to 89 years, and 9% age 90 to 99 years. The median STS-PROM was 4.3% (IQR: 2.7% to 6.8%) in the overall cohort, 5.4% (IQR: 3.6% to 8.1%) in the TAVR group, and 2.7% (IQR: 2.0% to 4.1%) in the SAVR group. The flow diagram for enrollment is shown in Figure 1. In nonenrolled patients, the median age was 79 years (IQR: 74 to 83 years), with 42% women and 45% judged to have high predicted operative risk. The 1-year follow-up for vital status was complete in all patients.

A total of 145 (14%) deaths occurred during the first year, with a higher risk observed in patients undergoing TAVR via a nonfemoral approach (24%), followed by TAVR via a femoral approach (17%), SAVR with coronary artery bypass (10%), and SAVR without coronary artery bypass (3%). Baseline characteristics stratified by vital status are shown in Table 1. Nonsurvivors were older (age 85 years vs. 81 years; $p < 0.001$); had lower body mass index (24.9 kg/m^2 vs. 27.0 kg/m^2; $p < 0.001$), hemoglobin (11.4 g/dl vs. 12.5 g/dl; $p < 0.001$), serum albumin (3.7 g/dl vs. 4.0 g/dl; $p < 0.001$), left ventricular ejection fraction (57.5% vs. 60.0%; $p = 0.005$), and mean aortic gradient (40.0 mm Hg vs. 44.0 mm Hg; $p = 0.002$); had higher pulmonary arterial systolic pressure (44.0 mm Hg vs. 39.0 mm Hg; $p = 0.002$); and had a higher prevalence of atrial fibrillation (49% vs. 31%; $p < 0.001$), kidney disease (67% vs. 50%; $p < 0.001$), dialysis (4% vs. 1%; $p < 0.001$), home oxygen (5% vs. 1%; $p = 0.001$), prior gastrointestinal bleed (10% vs. 5%; $p = 0.006$), cancer (21% vs. 14%; $p = 0.03$), and stroke (12% vs. 7%; $p = 0.05$).

UNIVARIATE ASSOCIATIONS BETWEEN FRAILTY AND MORTALITY. The overall prevalence of frailty varied from 26% with the Rockwood CFS to 68% with the SPPB, and was approximately 2-fold higher in patients undergoing TAVR compared with SAVR (Figure 2). Nonsurvivors had higher levels of frailty with all scales tested, as shown in Table 2 and Figure 3. Nonsurvivors had slower 5-m gait speed (0.54 m/s vs. 0.76 m/s; $p < 0.001$); slower chair rise time (60.0 s vs. 19.0 s; $p < 0.001$); weaker handgrip strength (20.0 kg vs. 26.0 kg; $p < 0.001$); a higher number of disabilities (2 vs. 0; $p < 0.001$); and a higher prevalence of falls (31% vs. 19%; $p = 0.001$), cognitive impairment (37% vs. 14%; $p < 0.001$), depressed mood (43% vs. 30%; $p = 0.002$), diminished appetite (40% vs. 24%; $p < 0.001$), and living in an assisted facility at baseline (16% vs. 8%; $p = 0.002$).

MULTIVARIABLE MODELS FOR MORTALITY AND WORSENING DISABILITY. In multivariable analyses, the EFT demonstrated the strongest association with 1-year mortality (OR: 3.72; 95% confidence interval [CI]: 2.54 to 5.45) and contributed the greatest incremental value when added to a model containing the STS-PROM and procedure type (Table 3, Figure 4). Specifically, when the EFT was added, the C-statistic improved by 0.071, the BIC improved by −54, and the IDI was 0.067 ($p < 0.001$). In comparison, when the Fried scale was added, the C-statistic improved by 0.011, the BIC improved by −6, and the IDI was 0.012 ($p = 0.004$). The optimal model with the EFT and clinical risk factors had a final C-statistic of 0.813 (Table 4). Sensitivity analyses separating TAVR and SAVR cohorts yielded similar results (Online Tables 2 to 6).

Of 807 patients who survived and completed the disability questionnaire before and 1 year after the procedure, 160 (20%) worsened by at least 2 deficits and 647 (80%) improved or maintained a stable number of deficits; 41 previously autonomous older adults required placement in an assisted living facility. Thus, the incidence of death or worsening disability was 35% at 1 year. After adjustment, the EFT, relative to other frailty scales, demonstrated the strongest association with death or worsening disability (OR: 2.13; 95% CI: 1.57 to 2.87) and contributed the greatest incremental value, evidenced by a C-statistic improvement of 0.029, a BIC improvement of −23, and an IDI of 0.032 ($p < 0.0001$) (**Table 3**).

At 30 days, the observed incidence of death from all causes was slightly lower than the STS-PROM for SAVR (2.4% observed vs. 3.4% predicted) and TAVR (5.6% observed vs. 6.4% predicted). After adjustment, the EFT was associated with a 3-fold increase in 30-day mortality (OR: 3.29; 95% CI: 1.73 to 6.26) and contributed the greatest incremental value above the STS-PROM, evidenced by a C-statistic improvement of 0.064, a BIC improvement of −12, and an IDI of 0.0262 ($p < 0.0001$) (**Table 3**).

TABLE 2 Frailty Scales and Geriatric Domains

	Total (N = 1,020)	Alive (n = 875)	Deceased (n = 145)	p Value
Frailty scales				
Fried, 0 to 5	2 (1-3)	2 (1-3)	3 (2-4)	<0.001
Fried+, 0 to 7	3 (1-4)	3 (1-4)	4 (3-5)	<0.001
Rockwood, 1 to 9	4 (3-5)	4 (3-4)	4 (4-5)	<0.001
SPPB, 0 to 12*	7 (4-9)	7 (5-9)	5 (3-7)	<0.001
Bern, 0 to 7	2 (1-4)	2 (1-3)	3 (2-5)	<0.001
Columbia, 0 to 12	5 (3-8)	5 (3-7)	7 (6-9)	<0.001
EFT, 0 to 5	2 (1-3)	2 (1-2)	3 (2-4)	<0.001
Individual items				
Chair rise time, s	20.1 (14.9-60.0)	19.0 (14.3-47.9)	60.0 (17.7-60.0)	<0.001
Gait speed, m/s	0.72 (0.49-0.94)	0.76 (0.52-0.97)	0.54 (0.31-0.76)	<0.001
Grip strength, kg	25.0 (18.0-32.8)	26.0 (19.0-34.0)	20.0 (16.0-26.0)	<0.001
Poor balance	314 (31)	255 (29)	59 (41)	<0.001
Inactivity	554 (54)	451 (52)	103 (71)	<0.001
Exhaustion	424 (42)	354 (40)	70 (48)	0.08
Weight loss	179 (18)	146 (17)	33 (23)	0.07
Diminished appetite	268 (26)	210 (24)	58 (40)	<0.001
Depressed mood	325 (32)	263 (30)	62 (43)	0.002
Cognitive impairment†	179 (18)	125 (14)	54 (37)	<0.001
Hearing impairment	269 (26)	226 (26)	43 (30)	0.33
Visual impairment	388 (38)	323 (37)	65 (45)	0.07
Falls	213 (21)	168 (19)	45 (31)	0.001
Assisted living facility	91 (9)	68 (8)	23 (16)	0.002
ADL disability	255 (25)	200 (23)	55 (38)	<0.001
IADL disability	475 (47)	377 (43)	98 (68)	<0.001
Number of disabilities	1 (0-2)	0 (0-2)	2 (0-4)	<0.001

Values are median (IQR) or n (%). *For the SPPB, lower scores indicate greater frailty (whereas for all other scales, higher scores indicate greater frailty). To calculate median results reflective of the entire cohort, patients who were physically unable to complete the chair rise test were imputed as 60 s and those physically unable to complete the gait speed or grip strength tests were imputed as 0 m/s or 0 kg. †Cognitive impairment was defined as a Mini-Mental State Examination score <24, with 162 patients having scores between 18 to 23 (mild) and 17 patients having scores <18 (severe).

ADL = activities of daily living; EFT = Essential Frailty Toolset; IADL = instrumental activities of daily living; SPPB = Short Physical Performance Battery.

DISCUSSION

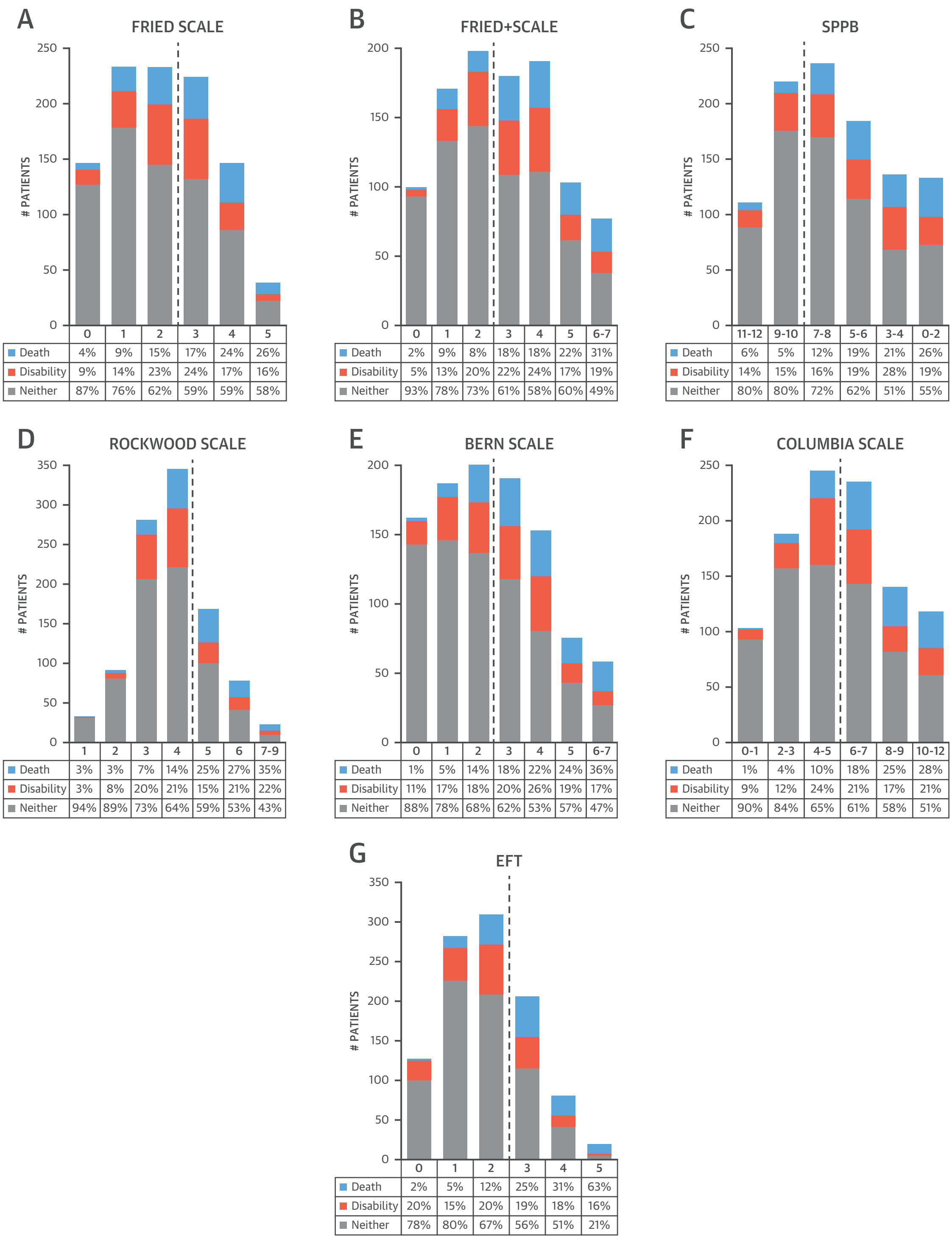
FRAILTY-AVR is the largest prospective study to date specifically designed to investigate frailty in older adults undergoing TAVR and SAVR. Our results can be summarized as follows:

1. When measured objectively with a validated scale, frailty adds incremental value above existing risk models to predict midterm mortality and progressive disability after an aortic valve procedure.
2. The prevalence of frailty varies significantly depending on the scale used to measure it, as does its predictive value.
3. The EFT outperformed other frailty scales to identify vulnerable older adults who are at higher risk of poor outcomes after TAVR or SAVR.
4. Although the likelihood of procedural success and short-term survival was very high, the incidence of subsequent functional decline and poor patient-centered outcomes at 1 year was 35% for the entire cohort and >50% for those who were frail.

Our study adds to the growing body of evidence on frailty in TAVR and SAVR (3). The most commonly cited tools to assess frailty are 5-m gait speed and the Fried scale, both of which have shown a predictive effect on mortality, but a modest C-statistic improvement of 0.004 when added to clinical risk models in population-based registries and clinical trial datasets (11,12). Given this limited improvement, multidomain scales were developed and adapted to the highly frail and complex TAVR population. Lower-extremity muscle weakness, malnutrition, and cognitive impairment played a prominent role in newer scales, which were shown in small studies of 100 to 244 patients to have a predictive effect on mortality and disability 6 to 12 months after TAVR (18,19,33). As various scales emerged, uncertainty grew as to which should be used in day-to-day clinical practice, and whether the effort to measure such scales was justified by meaningful improvements in discrimination (34).

The FRAILTY-AVR study has addressed this knowledge gap by comparing the incremental value of frailty scales in a well-powered sample across a broad spectrum of risk and procedure types. Among all

FIGURE 3 **Frailty Scales and 1-Year Outcomes**



A – FRIED SCALE

	0	1	2	3	4	5
Death	4%	9%	15%	17%	24%	26%
Disability	9%	14%	23%	24%	17%	16%
Neither	87%	76%	62%	59%	59%	58%

B – FRIED+SCALE

	0	1	2	3	4	5	6-7
Death	2%	9%	8%	18%	18%	22%	31%
Disability	5%	13%	20%	22%	24%	17%	19%
Neither	93%	78%	73%	61%	58%	60%	49%

C – SPPB

	11-12	9-10	7-8	5-6	3-4	0-2
Death	6%	5%	12%	19%	21%	26%
Disability	14%	15%	16%	19%	28%	19%
Neither	80%	80%	72%	62%	51%	55%

D – ROCKWOOD SCALE

	1	2	3	4	5	6	7-9
Death	3%	3%	7%	14%	25%	27%	35%
Disability	3%	8%	20%	21%	15%	21%	22%
Neither	94%	89%	73%	64%	59%	53%	43%

E – BERN SCALE

	0	1	2	3	4	5	6-7
Death	1%	5%	14%	18%	22%	24%	36%
Disability	11%	17%	18%	20%	26%	19%	17%
Neither	88%	78%	68%	62%	53%	57%	47%

F – COLUMBIA SCALE

	0-1	2-3	4-5	6-7	8-9	10-12
Death	1%	4%	10%	18%	25%	28%
Disability	9%	12%	24%	21%	17%	21%
Neither	90%	84%	65%	61%	58%	51%

G – EFT

	0	1	2	3	4	5
Death	2%	5%	12%	25%	31%	63%
Disability	20%	15%	20%	19%	18%	16%
Neither	78%	80%	67%	56%	51%	21%

For the 7 frailty scales compared **(A to G)**, the **bar heights** represent the number of patients in each frailty category, and **bar subdivisions** represent the number of patients experiencing death from any cause **(blue)**, worsening disability requiring institutionalization or assistance for at least 2 basic or instrumental activities of daily living **(orange)**, or neither (i.e., favorable outcomes) **(gray).** Abbreviations as in Figures 1 and 2.

TABLE 3 Incremental Value of Frailty Scales

Frailty Scales	Adjusted OR (95% CI)*	ΔC-Statistic	ΔBIC	IDI
Prediction of 1-yr mortality				
Fried	1.63 (1.12–2.37)	0.011 ($p = 0.35$)	−6	0.012 ($p = 0.004$)
Fried+	2.58 (1.68–3.97)	0.021 ($p = 0.13$)	−14	0.020 ($p < 0.001$)
Rockwood	2.40 (1.63–3.52)	0.030 ($p = 0.04$)	−19	0.027 ($p < 0.001$)
SPPB	2.96 (1.75–5.00)	0.021 ($p = 0.12$)	−16	0.023 ($p < 0.001$)
Bern	2.57 (1.69–3.91)	0.040 ($p = 0.01$)	−26	0.031 ($p < 0.001$)
Columbia	3.04 (1.98–4.66)	0.039 ($p = 0.01$)	−26	0.031 ($p < 0.001$)
EFT	3.72 (2.54–5.45)	0.071 ($p < 0.001$)	−54	0.067 ($p < 0.001$)
Prediction of 1-yr mortality or worsening disability				
Fried	1.49 (1.12–1.99)	0.013 ($p = 0.14$)	−9	0.015 ($p < 0.001$)
Fried+	2.10 (1.56–2.84)	0.022 ($p = 0.03$)	−19	0.025 ($p < 0.001$)
Rockwood	1.38 (1.00–1.88)	0.016 ($p = 0.09$)	−13	0.019 ($p < 0.001$)
SPPB	1.95 (1.41–2.71)	0.018 ($p = 0.07$)	−16	0.022 ($p < 0.001$)
Bern	1.90 (1.41–2.56)	0.025 ($p = 0.02$)	−17	0.024 ($p < 0.001$)
Columbia	1.77 (1.32–2.37)	0.021 ($p = 0.04$)	−16	0.023 ($p < 0.001$)
EFT	2.13 (1.57–2.87)	0.029 ($p = 0.01$)	−23	0.032 ($p < 0.001$)
Prediction of 30-day mortality				
Fried	1.45 (0.77–2.72)	0.008 ($p = 0.73$)	1	0.008 ($p = 0.003$)
Fried+	2.76 (1.28, 5.94)	0.020 ($p = 0.47$)	−3	0.013 ($p = 0.001$)
Rockwood	1.87 (0.99–3.54)	0.018 ($p = 0.48$)	1	0.007 ($p = 0.04$)
SPPB	4.07 (1.43–11.60)	0.023 ($p = 0.39$)	−3	0.013 ($p < 0.001$)
Bern	3.29 (1.53–7.07)	0.031 ($p = 0.25$)	−1	0.007 ($p = 0.02$)
Columbia	2.65 (1.28–5.49)	0.024 ($p = 0.36$)	0	0.007 ($p = 0.01$)
EFT	3.29 (1.73–6.26)	0.064 ($p = 0.07$)	−12	0.026 ($p < 0.001$)

*Multivariable logistic regression models were adjusted for the STS-PROM and the type of procedure performed (they were also adjusted for individual comorbidities in Online Table 6). Frailty scores were analyzed as continuous variables, although adjusted odds ratios in this table are presented in dichotomous form to facilitate between-scale comparisons. For the ΔC-statistic and IDI, positive values indicate improved discrimination; for the ΔBIC, negative values indicate improved prediction.

ΔBIC = change in Bayesian Information Criterion; CI = confidence interval; EFT = Essential Frailty Toolset; IDI = Integrated Discrimination Improvement; OR = odds ratio; SPPB = Short Physical Performance Battery; STS-PROM = Society of Thoracic Surgeon Predicted Risk of Mortality.

scales tested, the EFT was found to be the most robust predictor of outcomes, leading to the largest C-statistic improvement of 0.071. This improvement is clinically meaningful and comparable in magnitude to that of the STS-PROM added to a basic model containing the type of procedure performed. The EFT was also found to best predict therapeutic futility, as 8 of 10 patients with EFT scores of 5 of 5 experienced fatal or disabling outcomes (although the absolute number of such patients was low). Likewise, the majority of patients with CFS scores of ≥7 of 9 experienced fatal or disabling outcomes; no other frailty scale or trait was consistently predictive of futility. Our representative study population mirrored what would be encountered in real-world aortic valve clinics. Unlike previous studies, our assessment of frailty was comprehensive and was not confined to a post hoc analysis of variables available in an existing TAVR database. These design features minimized the risk of measurement and selection biases, and maximized the generalizability of our results.

The advantages of the EFT, beyond its predictive value, are that it is quick to perform, it does not require specialized equipment, and, importantly, its components have high interobserver reliability (35) and are actionable. Older adults with slow chair rise times have been shown to benefit from physical therapy and protein supplementation (36–38), a strategy that is currently being evaluated in the PERFORM-TAVR (Protein and Exercise to Reverse Frailty in OldeR Men and women undergoing TAVR) trial. Exercise has similarly been shown to improve cognitive function, either alone or in combination with pharmaceutical drugs (39). Nutritional intervention is recommended for older adults who are identified by low serum albumin or other markers to be at risk for malnutrition (40), with protein supplementation having measurable effects on mortality and morbidity (41). Last, therapy may be indicated for certain causes of anemia, such as iron deficiency, myelodysplastic syndrome, and deficiency of folate or vitamin B_{12}. From a mechanistic standpoint, all 4 components of the EFT have been correlated with higher circulating inflammatory markers, reflecting the biological link between inflammation and frailty (42,43).

In addition to the frailty markers tested, other risk factors for poor outcomes were found to be: atrial

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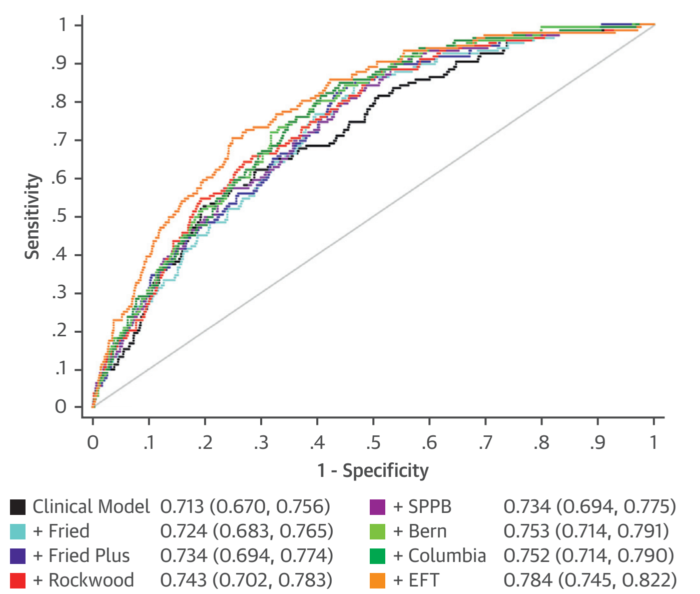
FIGURE 4 ROC Curves for Frailty Scales to Predict 1-Year Mortality



Each frailty scale was added to a clinical model containing the STS-PROM and the type of procedure performed (TAVR or SAVR). ROC curves were plotted, demonstrating that the greatest improvement in C-statistic to predict 1-year mortality was achieved with the EFT. The **inset figure legend** displays the C-statistic and 95% confidence interval for each scale. ROC = receiver operating characteristic; STS-PROM = Society of Thoracic Surgeon Predicted Risk of Mortality; other abbreviations as in Figures 1 and 2.

TABLE 4 Multivariable Model to Predict 1-Yr Mortality

	Adjusted OR (95% CI)
Age, per yr	1.03 (0.99-1.08)
Female	1.07 (0.70-1.62)
BMI, per kg/m^2	0.95 (0.91-0.98)
Atrial fibrillation	1.59 (1.06-2.41)
Home oxygen	3.33 (1.06-10.47)
Cancer	1.31 (0.79-2.19)
Prior stroke	0.93 (0.48-1.81)
Prior gastrointestinal bleed	1.47 (0.72-3.00)
GFR, per 10 ml/min/1.73 m^2	0.88 (0.78-0.99)
Mean aortic gradient, per 10 mm Hg	0.87 (0.75-1.01)
LVEF, per %	1.01 (0.99-1.02)
PASP ≥60 mm Hg	2.08 (1.19-3.63)
Procedure type	
TAVR transfemoral	1 (Referent)
TAVR nonfemoral	1.82 (1.09-3.05)
SAVR isolated	0.40 (0.16-1.01)
SAVR with bypass	1.39 (0.75-2.59)
Frailty*, ordinal (per EFT point)	1.87 (1.57-2.24)
dichotomous (EFT ≥3 of 5)	3.42 (2.29-5.12)

*The Essential Frailty Toolset (EFT) encompasses lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia, for a composite score of 0 to 5.

GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; other abbreviations as in Tables 1 and 3.

fibrillation, oxygen-dependent lung disease, and kidney disease (especially when dialysis-dependent). These 3 clinical risk factors are identical to those highlighted by Holmes et al. (4) as major predictors of 1-year mortality in the STS/American College of Cardiology Transcatheter Valve Therapies registry of 12,182 TAVR patients. Obesity was associated with worsening disability at 12 months and, paradoxically, was associated with lower all-cause mortality at 1 and 12 months (44). Thus, obese patients were more likely to survive, but were also more likely to develop progressive functional limitations and loss of autonomy after TAVR. Based on this observation, cardiac rehabilitation may be especially beneficial in frail obese patients to counteract their tendency toward functional decline and disability.

STUDY LIMITATIONS. First, as this was not a randomized trial, the TAVR and SAVR groups had differing risk profiles because high-risk patients were expectedly more likely to be referred for TAVR, according to institutional practices. Sensitivity analyses restricted to TAVR patients yielded similar results (Online Tables 2 to 6). Second, TAVR patients were logistically more likely to be screened and enrolled due to their requisite passage through centralized TAVR clinics. As SAVR patients represented a larger proportion of the nonenrolled patients and were generally younger, this (rather than selection bias) explains why the median age of nonenrolled patients was 3 years lower than that of enrolled patients. Third, the cognitive impairment domain of the EFT was assessed by the Mini-Mental State Examination, which can be time-consuming to administer. A modified version of the EFT using the shorter Mini-Cog Test (45) has since been adopted (cognitive impairment being highly likely if 0 of 3 words are correctly recalled after a distractive task, highly unlikely if all 3 words are correctly recalled, and arbitrated by a clock draw if 1 to 2 words are correctly recalled). Fourth, the EFT was derived using patients enrolled in the FRAILTY-AVR study before December 2014, which may have enhanced its predictive value in this study. Nevertheless, the predictive value of the EFT was only mildly attenuated when comparing patients included in the derivation subset with those enrolled afterward (C-statistic improvement of 0.06 to 0.07 vs. 0.05 to 0.06, respectively). Fifth, 68 surviving patients declined or could not be reached to complete the disability questionnaire at 1 year, so the reported incidence of death or progressive disability is conservative and may have been as high as 39% if these patients were assumed to have progressive disability. Of note, the development of new disabilities was not driven by post-procedural strokes, which were documented in only 2% of patients.

CONCLUSIONS

Frailty is a major risk factor for death and disability following TAVR and SAVR. In particular, the EFT adds incremental predictive value to identify vulnerable older adults and is recommended for use in this setting. The time and resources required to administer the EFT are minimal, and its components can be intervened upon before or after the procedure to optimize outcomes. Although the EFT is not all-encompassing, it is a well-rooted starting point to test for frailty, and to identify patients in whom further geriatric assessment should be considered to confirm the diagnosis of sarcopenia, malnutrition, dementia, depression, or disability. Further research is warranted to define the therapeutic and mechanistic implications of this frailty construct, and to validate its utility in other groups of patients with cardiovascular disease.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Frailty is a major risk factor for death and disability following either TAVR or SAVR. Assessment of frailty using a brief 4-item scale encompassing lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia adds incremental prognostic value.

TRANSLATIONAL OUTLOOK: Additional research is needed to explore the pathophysiology of frailty as it accompanies aging and to assess the effect of exercise and nutrition to reduce frailty and improve clinical outcomes among patients undergoing cardiovascular interventions.

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KEY WORDS aortic stenosis, disability, frailty, outcomes, surgical aortic valve replacement, survival, transcatheter aortic valve replacement

APPENDIX For supplemental tables, please see the online version of this article.