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Malnutrition and Mortality in Frail and Non-Frail Older Adults Undergoing Aortic Valve Replacement

Running Title: *Goldfarb et al.; Malnutrition in TAVR and SAVR*

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Abstract

Background—Older adults undergoing aortic valve replacement are at risk for malnutrition. The association between pre-procedural nutritional status and midterm mortality has yet to be determined.

Methods—The FRAILTY-AVR prospective multi-center international cohort study was conducted between 2012-2017 in 14 centers in 3 countries. Patients ≥70 years of age who underwent transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) were eligible. The Mini Nutritional Assessment-Short Form (MNA-SF) was assessed by trained observers pre-procedure, with scores ≤7 of 14 considered malnourished and 8-11 of 14 considered at-risk for malnutrition. The Short Performance Physical Battery (SPPB) was simultaneously assessed to measure physical frailty, with scores ≤5 of 12 considered severely frail and 6-8 of 12 considered mildly frail. The primary outcome was 1-year all-cause mortality and the secondary outcome was 30-day composite mortality or major morbidity. Multivariable regression models were used to adjust for potential confounders.

Results—There were 1,158 patients (727 TAVR and 431 SAVR) with 45% females, a mean age of 81.3 years, a mean body mass index of 27.5 kg/m2, and a mean Society of Thoracic Surgeons-Predicted Risk of Mortality (STS-PROM) of 5.1%. Overall, 8.7% of patients were classified as malnourished and 32.8% were at-risk for malnutrition. MNA-SF scores were moderately correlated with SPPB scores (Spearman R=0.31, P<0.001). There were 126 deaths in the TAVR group (19.1 per 100 patient-years) and 30 deaths in the SAVR group (7.5 per 100 patient-years). Malnourished patients had a nearly 3-fold higher crude risk of 1-year mortality compared with those with normal nutritional status (28% vs 10%, P<0.001). After adjustment for frailty, STS-PROM, and procedure type, pre-procedural nutritional status was a significant predictor of 1-year mortality (OR 1.08 per MNA-SF point, 95% CI 1.01-1.16) and of the 30-day composite safety endpoint (OR 1.06 per MNA-SF point, 95% CI 1.00 to 1.12).

Conclusions—Pre-procedural nutritional status is associated with mortality in older adults following aortic valve replacement. Clinical trials are needed to determine whether pre- and post-procedural nutritional interventions can improve clinical outcomes in these vulnerable patients.

Key Words: malnutrition; aortic valve replacement; older adults; mortality

Clinical Perspective

What is new?

- Older adults undergoing aortic valve replacement have a high prevalence of malnutrition.
- Malnutrition is associated with higher 1-year mortality and 30-day adverse events following aortic valve replacement via a transcatheter or surgical approach.
- While malnutrition and frailty are inter-related, integration of nutritional assessment results in improved predictive value for frail patients.

What are the clinical implications?

- Pre-procedural nutritional screening can identify patients at risk for poor outcomes following aortic valve replacement.
- Further research is needed to determine whether malnourished older adults would benefit from nutritional supplementation before or after undergoing aortic valve replacement.

Introduction

Malnutrition is common in older adults undergoing cardiac surgery, with 20-40% being affected or at-risk.[1, 2] Malnutrition is a risk factor leading to the development of frailty, disability, and death.[3, 4] Among patients undergoing general surgery, malnutrition is associated with delayed wound healing, postoperative complications, prolonged hospital length of stay, hospital readmission, and death.[5] However, among patients undergoing cardiac surgery including surgical aortic valve replacement (SAVR), the association between malnutrition and outcomes is less certain;[6-8] and among patients undergoing transcatheter aortic valve replacement (TAVR) – a population with high degrees of frailty, malnutrition has yet to be specifically studied.

The evaluation of nutritional status is challenging in older adults, in part because body weight and traditional markers of malnutrition are not reliable indicators, and as a result, malnutrition is often overlooked. To facilitate the identification of malnutrition in older patients, the Mini Nutritional Assessment-Short Form (MNA-SF) is a pragmatic, clinically-oriented instrument that has a geriatric focus and has been validated for use in cardiac surgery.[1, 2, 9, 10]

In addition to the prognostic value of identifying malnutrition, there is potentially actionable therapeutic value for implementing nutritional interventions that have been shown to be effective in preventing morbidity and mortality.[11] While nutritional guidelines recommend screening for nutrition risk in all hospitalized older adults, they acknowledge that this is based on low levels of evidence stemming from small uncontrolled studies.[12] Likewise, an international consensus statement on nutrition in cardiac surgery concluded that "valid and reliable data are urgently needed to improve the so-far non-standardized clinical practice of nutrition screening."[13]

Thus, our objective was to assess the prevalence and prognostic association between malnutrition screening using the MNA-SF and short and midterm outcomes in a large multicenter cohort of older adults undergoing transcatheter or surgical aortic valve replacement (TAVR, SAVR).

Methods

Study Population

FRAILTY-AVR is a prospective cohort study conducted at 14 centers in Canada, the United States, and France, between 2012-2017. Patients ≥70 years of age who underwent TAVR or SAVR with or without coronary artery bypass grafting were enrolled. A comprehensive assessment of frailty and geriatric domains, including the MNA-SF, was performed before the procedure. Patients were followed for vital status and functional outcomes at 6 and 12 months after the procedure. Exclusion criteria were language barriers and moderate-to-severe neuropsychiatric impairments precluding informed consent, emergent surgery, unstable vital signs, and multi-valve surgery or replacement of the aorta. Ethical review boards at the participating hospitals approved this study and subjects provided informed consent to participate. The analytic methods and study materials have been explained in greater detail in the original manuscript;[14] the data has not been made publicly available at the present time but the analytical methods and study materials may be provided upon request.

Nutritional Screening

Prior to TAVR or SAVR, a trained research assistant administered the MNA-SF according to its standardized protocol.[9] The MNA-SF was chosen because, amongst four nutritional screening tools compared in older adults undergoing cardiac surgery, it was shown to have the highest

sensitivity for detecting malnutrition (85%), it was predictive of postoperative complications and length of stay,[1, 2] and it was easier to administer than other more comprehensive nutritional screening tools.[9, 10] The MNA-SF has been shown to have similar accuracy to its longer-version.[15]

The six MNA-SF domains encompass questions relating to (1) food intake, (2) weight loss, (3) basic mobility, and (4) disease acuity, as well as measurements relating to (5) body mass index and (6) cognitive or mood impairment. Rather than relying on self-report, cognitive function was assessed using the Mini Mental Status Examination, and mood was assessed using the Geriatric Depression Scale Short Form.[16, 17] Patients were grouped based on their composite MNA-SF score: normal nutritional status (scores 12-14), at-risk of malnutrition (scores 8-11), and malnutrition (scores 0-7).[18] These cut-points were selected *a priori* and were previously validated in hospitalized multimorbid older adults.[19, 20]

Measurements

During the same session as the MNA-SF, a trained research assistant administered the Short Physical Performance Battery (SPPB) to assess physical frailty.[21] Patients were grouped as follows: not frail (scores 9-12), mildly frail (scores 6-8), severely frail (scores 0-5). The Fried frailty scale was also administered.[22] Operative risk was represented using the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) that captures patient age, sex, comorbidities, and cardiac status.[23] Following TAVR or SAVR, electronic medical records were reviewed for demographic, comorbid, procedural, and postprocedural data, including complications, disposition, and last known vital status.

Outcomes

The primary outcome was 1-year all-cause mortality ascertained by electronic medical records, telephone contact with the patients and their next of kin, and linkage with administrative data sources. No patient was lost to follow-up for the 1-year mortality endpoint. The secondary outcome was 30-day mortality or major morbidity defined according to the Valve Academic Research Consortium-2 (VARC-2) composite safety endpoint as any of the following: all-cause mortality, reoperation, acute kidney injury, major bleed, or major vascular complication.[24] Individual components of the composite safety endpoint and postprocedural resource use were evaluated.

Statistical Analysis

Continuous data were presented as means ± standard deviations. Categorical data were presented as counts and percentages. The Cuzick test was used to detect bivariate differences across MNA-SF groups. Spearman's rank test was used to detect bivariate correlations between the MNA-SF and frailty scores. For the multivariable analysis, logistic regression was used to determine the association between MNA-SF and 1-year mortality after adjusting for operative risk (STS-PROM), physical frailty (SPPB), and type of procedure performed (TAVR vs. SAVR). Cox regression and Kaplan–Meier curves were used for survival analysis. STATA version 14 was used for all analyses (College Station, TX, USA).

Four sensitivity analyses were performed. First, the logistic regression model was adjusted for individual covariates found to be associated with MNA-SF (age, sex, stroke, chronic kidney disease, chronic lung disease, anemia, pulmonary hypertension, mean aortic gradient, left ventricular ejection fraction) instead of the composite STS-PROM. Second, the logistic regression model was adjusted for the Fried frailty scale instead of the SPPB. Next, an indicator

variable was analyzed to capture the effect of co-prevalent malnutrition and frailty. Finally, serum albumin was added to the logistic regression model and to a modified version of the MNA-SF score (empirically adding 2 points for serum albumin ≥4.0 g/dL, 1 point for 3.0-3.9 g/dL, and 0 points for <3.0 g/dL). Since measurement of serum albumin was not mandated in the original study protocol, multiple imputations were used to impute missing values.

Results

Baseline Characteristics

A total of 1,158 patients (727 TAVR, 431 SAVR) were included with a mean age of 81.3 ± 6.1 years and 481 (41.5%) females. The mean MNA-SF score was 11.5 ± 2.5 points out of 14, with 101 (8.7%) patients being malnourished, 380 (32.8%) being at-risk for malnutrition, and 677 (58.5%) having normal nutritional status, as shown in Figure 1. Baseline characteristics by MNA-SF group are shown in Table 1 and further sub-stratified by procedure type in Table S1. Patients in the malnourished group were older, more likely to be female, more likely to undergo TAVR, more likely to have prior stroke, chronic kidney disease, chronic lung disease, anemia, lower left ventricular ejection fraction, and higher STS-PROM. Serum albumin, which is not included in the MNA-SF but is a non-specific biomarker of nutritional status, was lower in the malnourished group.

Geriatric Domains

MNA-SF scores were moderately correlated with SPPB scores (R=0.31, P<0.001). The overlap between malnutrition and frailty was most apparent in the group with MNA-SF scores of 0-7, in which 53/101 were severely frail and 37/101 were mildly frail, and 11/101 were not frail (Figure 2). The combination of malnutrition and severe frailty was associated with the highest incidence

rate of mortality (Figure 2). Indicators of upper and lower extremity weakness were prevalent in the malnourished group, who were more likely to report falls (26% vs. 15%, P<0.001) and disabilities for basic and instrumental activities of daily living (77% vs. 42%, P<0.001). These geriatric characteristics stratified by MNA-SF group are shown in Table 1.

Unadjusted Analysis of Postoperative Outcomes

The primary outcome of 1-year all-cause mortality occurred in 28 (27.7%) patients in the malnourished group, 62 (16.3%) in the at-risk group, and 66 (9.7%) in the normal group (P<0.001) as shown in Table 2 and further sub-stratified by procedure type in Table S2. Kaplan-Meier curves are displayed in Figure 3. MNA-SF subdomains that were associated with increased 1-year mortality were appetite loss, decreased mobility, neuropsychiatric impairment, and low body mass index (Table S3). The secondary outcome of 30-day composite safety events occurred in 25 (24.8%) patients in the malnourished group, 110 (28.9%) in the at-risk group, and 150 (22.2%) in the normal group (P=0.08) as shown in Table 2. Malnourished patients had a longer LOS in the intensive care unit (P=0.03) and were more likely to require discharge to rehabilitation or convalescence facilities (P=0.002).

Adjusted Analysis of Postoperative Outcomes

In the multivariable logistic regression model adjusting for STS-PROM, SPPB, and procedure type, preprocedural nutritional status was a significant predictor of 1-year mortality (OR 1.07 per MNA-SF point, 95% CI 0.99, 1.15) and for 30-day composite safety events (OR 1.06 per MNA-SF point, 95% CI 1.00, 1.12), as shown in Table 3. The association between nutritional status and mortality was similar in the multivariable Cox regression model (hazard ratio 1.07 per MNA-SF point, 95% CI 1.01, 1.13) (Table S4).

Sensitivity Analyses

Preprocedural nutritional status remained a significant predictor of 1-year mortality when the logistic regression model was adjusted for individual comorbidities (OR 1.10, 95% CI 1.02, 1.18; Table S5), and when it was adjusted for the Fried scale instead of the SPPB scale (OR 1.10, 95% CI 1.03, 1.19; Table S6). When MNA-SF was analyzed as a categorical variable, the malnourished group had a higher risk of adjusted mortality (OR 1.76, 95% CI 1.02, 3.07) but not the at-risk group (OR 1.26, 95% CI 0.85, 1.87) as compared to those in normal group. When the MNA-SF and SPPB were analyzed as a combined indicator variable, the co-prevalence of malnutrition and frailty was associated with an incrementally higher risk of 1-year mortality (OR 3.21, 95% CI 1.66, 6.21; Table S7) as compared to either alone. For serum albumin, 744 patients had a pre-procedural value and 414 had a value imputed. When albumin was added to the multivariable model, the odds ratio for the MNA-SF was unchanged albeit with wider confidence intervals owing to the loss of statistical power (OR 1.07, 95% CI 0.99, 1.15; Table S8). When albumin was incorporated into the MNA-SF score, this enhanced MNA-SF (range 0-16 points) was predictive of 1-year mortality (OR 1.11, 95% CI 1.04, 1.19; Table S9).

Discussion

To our knowledge, this is the first study to systematically screen for malnutrition and demonstrate that it predicts poor outcomes following TAVR and SAVR. The findings of this study can be summarized as follows: 1) Patients can be easily screened for the presence or absence of malnutrition; 2) Malnutrition is a risk factor for midterm mortality and to a lesser extent short-term mortality and major morbidity post-procedure; 3) The risk associated with malnutrition persists even after adjusting for physical function and other potential confounders.

In addition, those that screened positive for malnutrition were more likely to be discharged to healthcare facilities (rehabilitation, convalescence). Lastly, signs of malnutrition were correlated with the phenotype of frailty and the presence of disability for activities of daily living, reaffirming the overlap between these geriatric syndromes.

Poor nutritional status has been shown to be risk factor for mortality in older adults living in the community,[25] living in nursing homes,[15] undergoing hip surgery,[26, 27] and hospitalized for acute decompensated heart failure.[28-30] In patients undergoing TAVR, there have been no prior studies specifically assessing the prevalence of malnutrition. In patients undergoing open cardiac surgery, Lomivorotov et al. observed a prevalence of 1% for malnutrition and 19% for at risk MNA-SF, while Chermesh et al. observed a prevalence of 18% for high-risk and 2% for moderate-risk malnutrition scores.[1, 2, 31, 32] Cumulatively, these studies suggested that 20% of open cardiac surgery patients were either positive or at risk for malnutrition.

The lower rate of malnutrition in the aforementioned studies compared to ours can be explained by the markedly younger age (mean 60-65 vs. 81 years) and lower-risk nature of their patients. Notwithstanding this difference, their studies and ours similarly showed that malnutrition was associated with a higher rate of postoperative 30-day mortality and major morbidity, although their multivariable models only adjusted for the EuroSCORE and did not account for other confounders such as frailty. Our study has added value in that it carefully considered the presence of concomitant frailty and demonstrated an independent effect of malnutrition on both 30-day and 1-year outcomes, and it included a larger sample size of older higher-risk patients such as those undergoing TAVR whose nutritional risk had not previously been investigated despite manifesting a very high burden of frailty.

Malnutrition and frailty are connected at the epidemiological and pathophysiological levels, since sarcopenia is a core element in the phenotype of frailty.[33] Malnourished patients are more likely to be frail at baseline, and to develop progressive worsening frailty; whereas patients that consume a balanced diet rich in protein and antioxidants are less likely to exhibit shrinking muscle mass and decreasing muscle strength over time.[3] In the community, 68% of malnourished older adults were found to be frail – fourfold higher than normally nourished – but only 8% of frail older adults were found to be malnourished; speaking to the multiple mechanisms by which frailty may arise in an individual.[34] In this study, 74% of malnourished patients were found to be frail by Fried's scale – threefold higher than normally nourished – but only 17% of frail patients were found to be malnourished.

In spite of the expected overlap between malnutrition and frailty, the correlation between nutritional status and physical frailty in our study was found to be modest. While few malnourished patients had normal frailty scores, there were two distinct types of patients within this subgroup – one with mildly impaired frailty scores (SPPB 6-8, functionally independent) and another with severely impaired frailty scores (SPPB 0-5, ADL disability). The combination of malnutrition and severe frailty was synergistically associated with the highest risk of mortality.

Frailty may be an intermediate step in the pathway between malnutrition and mortality. Malnutrition leads to an impaired host immune response and a pro-inflammatory state, which are key mechanisms in the pathogenesis of physical frailty.[35] Reduced handgrip strength, a marker of physical frailty, predicts poor nutritional status.[36, 37] Anemia, elevated C-reactive protein, inadequate food intake, and reduced mobility are prevalent in both malnourished and frail older adults.[38]

Our study raises the question of whether pre- and postoperative interventions should be recommended in malnourished cardiac patients to improve postoperative outcomes. Nutritional deficiencies are actionable and malnutrition is potentially a modifiable target. Malnourished older adults have shown the capacity to respond to protein supplementation with increased post-absorptive protein synthesis rates resulting in increased lean body mass,[39, 40] although these effects can be attenuated during the catabolic perioperative period.[41]

Interventions to improve nutritional status are associated with improved outcomes. A multicentre randomized controlled trial of 650 malnourished older adults hospitalized with acute cardiovascular and respiratory conditions reported that patients receiving a high-protein oral nutritional supplement achieved better nutritional status as measured by a Subjective Global Assessment and a substantial reduction in 90-day mortality rate (4.8% vs. 9.7%; P=0.02) as compared to placebo. A recent Cochrane review of 12 trials encompassing 6683 participants concluded that nutritional support interventions reduced all-cause mortality in malnourished or nutritionally at-risk adults (risk ratio 0.78; 95% CI 0.66, 0.92; P=0.004).[42] While a number of these trials examined patients undergoing surgical procedures, none were focused on older patients undergoing cardiac surgery or TAVR.

Given the evidence available at this time, preoperative nutritional support may be considered in the malnourished patient when elective surgery can be safely postponed for one week or more.[43] In addition, there may be a role for more intensive postoperative nutritional support in the malnourished or at-risk patient. An ongoing clinical trial is investigating the feasibility and value of a multidisciplinary strategy involving nutritional support for preprocedural optimization ("prehab") in older adults prior to elective cardiac surgery.[44]

There are limitations to our study. First, the MNA-SF is a screening tool that should ideally (time-permitting) be followed by confirmatory testing to establish the diagnosis of malnutrition. While many of our patients were evaluated by a clinical dietician before and/or after their procedure, the evaluation was not systematically captured or codified for the purposes of this study. Second, nutritional supplements and interventions prescribed by clinical providers could not be recorded, and therefore, their impact could not be assessed or adjusted for in our regression models. In light of this potential residual confounder, our observed results are likely to be conservative because (allegedly) beneficial nutritional interventions are typically used in malnourished patients. Third, our study was not powered to assess statistical interactions between malnutrition and frailty. However, we did present the continuous correlation and categorical overlap between nutritional status and physical frailty, and observed a rising incidence rate of all-cause mortality when both were perturbed.

Conclusions

Older adults with signs and symptoms of malnutrition, identified using the MNA-SF, had a nearly 3-fold increase in mortality one year following aortic valve replacement. While nutritional status was inter-related with physical frailty, the predictive effect of malnutrition was incremental to commonly used frailty scales. Since 4 of 10 older adults scored positive or at-risk for malnutrition before TAVR or SAVR, the scope of the problem affects a large number of patients and signifies an opportunity to help patients achieve better nutritional status and outcomes. Clinical trials are needed to validate the beneficial clinical impact of targeted nutritional interventions in malnourished or at-risk older adults undergoing TAVR or SAVR.

Disclosures

None

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Table 1. Baseline Characteristics by Nutritional Status

	Normal MNA 12-14 N=677	At-risk MNA 8-11 N=380	Malnutrition MNA 0-7 N=101	P-value
Age	80.7 ± 6.2	81.6 ± 5.8	83.4 ± 5.9	<0.001
Female	250 (37%)	178 (47%)	53 (52%)	<0.001
Body mass index, kg/m2	28.5 ± 5	26.8 ± 5.9	23.7 ± 5.4	<0.001
Weight, kg	79.0 ± 16.3	73.2 ± 17.7	65.1 ± 16.5	<0.001
Weight loss over past year, kg	0.1 ± 0.4	3.7 ± 5.3	8.7 ± 5.9	<0.001
Diabetes	184 (27%)	113 (30%)	24 (24%)	0.97
Coronary artery disease	415 (61%)	231 (61%)	63 (62%)	0.95
Prior stroke	41 (6%)	33 (9%)	12 (12%)	0.02
Peripheral arterial disease	93 (14%)	61 (16%)	15 (15%)	0.44
Chronic kidney disease	328 (48%)	205 (54%)	67 (66%)	<0.001
Chronic lung disease	97 (14%)	76 (20%)	22 (22%)	0.008
Gastrointestinal disease	132 (19%)	84 (22%)	27 (27%)	0.08
Cancer	99 (15%)	61 (16%)	15 (15%)	0.70
Left ventricular ejection fraction, %	57.9 ± 11.4	54.9 ± 12.7	49.7 ± 15.3	<0.001
Mean aortic gradient, mmHg	47.2 ± 15.8	44.1 ± 15.8	44.9 ± 15.3	0.004
Pulmonary artery pressure, mmHg	40.2 ± 14	41.1 ± 15.4	45.2 ± 14.5	0.009
Hemoglobin, g/L	125.7 ± 17	120.1 ± 16.7	114.6 ± 17.5	<0.001
Serum albumin, g/L	39.6 ± 4.9	38.2 ± 4.8	36.3 ± 4.8	<0.001
STS-PROM, %	4.4 ± 3.2	5.8 ± 3.9	7.9 ± 5.4	<0.001
TAVR	388 (57%)	263 (69%)	76 (75%)	<0.001
SAVR	289 (43%)	117 (31%)	25 (25%)	<0.001
Geriatric Domains				
SPPB, out of 12	7.4 ± 3.0	6.1 ± 3.3	4.9 ± 3.1	<0.001
Fried frailty scale	172 (25%)	188 (49%)	73 (74%)	<0.001
Falls	104 (15%)	91 (24%)	26 (26%)	<0.001
Gait speed, m/sec	0.8 ± 0.3	0.6 ± 0.3	0.5 ± 0.4	<0.001
Grip strength, kg	27.5 ± 10.4	24.0 ± 10.4	20.9 ± 9.9	<0.001
Cognitive impairment	90 (13%)	75 (20%)	29 (29%)	<0.001
Depressed mood	115 (17%)	166 (44%)	69 (68%)	<0.001
ADL disabilities, out of 7	0.3 ± 0.7	0.6 ± 1.3	1.3 ± 1.7	<0.001
IADL disabilities, out of 7	0.8 ± 1.3	1.3 ± 1.7	2.2 ± 2	<0.001

Abbreviations: ADL, basic activities of daily living; IADL, instrumental activities of daily living; MNA, mini nutritional assessment; 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.

Table 2. Outcomes by Nutritional Status

	Normal MNA 12-14 N=677	**At-risk MNA 8-11 N=380**	**Malnutrition MNA 0-7 N=101**	**P-value**
1-year mortality	66 (10%)	62 (17%)	28 (29%)	<0.001
30-day mortality	23 (3%)	23 (6%)	6 (6%)	0.05
30-day composite endpoint *	150 (22%)	110 (29%)	25 (25%)	0.08
Reoperation	55 (8%)	46 (12%)	11 (11%)	0.07
Stroke	15 (2%)	7 (2%)	5 (5%)	0.31
Acute kidney injury	46 (7%)	43 (11%)	7 (7%)	0.15
Major bleeding complication	81 (12%)	56 (15%)	8 (8%)	0.91
Major vascular complication	23 (3%)	23 (6%)	3 (3%)	0.33
ICU length of stay, hours	72.6 ± 91.6	81.6 ± 108.9	91.3 ± 135.4	0.03
Hospital length of stay, days	8.5 ± 8.9	9.1 ± 11.8	10.5 ± 12.1	0.25
Discharge to facility	196 (29%)	134 (35%)	43 (43%)	0.002

Abbreviations: ICU, intensive care unit; MNA, mini nutritional assessment.
* Composite endpoint refers to VARC composite safety endpoint: all-cause death, stroke, acute kidney injury, reoperation, major bleeding or vascular complication.

Table 3. Multivariable Logistic Regression Analysis

	1-year mortality *Odds Ratio (95% CI)*	**30-day composite endpoint** *Odds Ratio (95% CI)*
Malnutrition, per 1-point ↓ MNA	1.08 (1.01, 1.16)	1.06 (1.001, 1.12)
Frailty, per 1-point ↓ SPPB	1.14 (1.07, 1.20)	1.03 (0.98, 1.07)
STS-PROM, per %	1.10 (1.05, 1.15)	1.02 (0.99, 1.06)
Procedure, TAVR (vs. SAVR)	1.63 (1.04, 2.57)	0.81 (0.60, 1.09)

Abbreviations: CI, confidence interval; MNA, mini nutritional assessment; 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.

Figure Legends

Figure 1. Mini Nutritional Assessment Subdomains

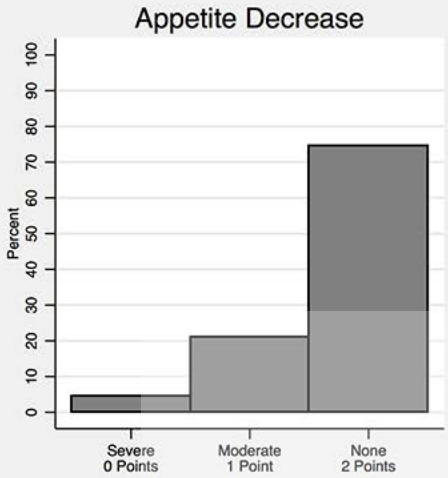
The Mini Nutritional Assessment Short Form (MNA-SF) score was calculated by summing the points for each of the six subdomains, with the worst total score being 0 points and the best total score being 14 points.

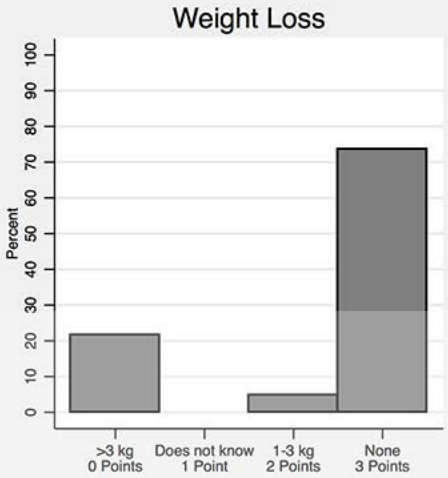
Figure 2. Relationship Between Nutrition and Physical Frailty

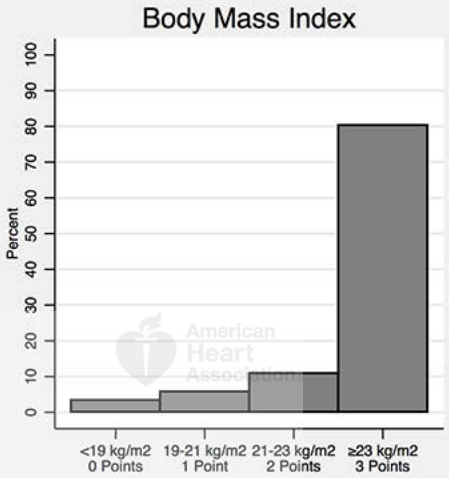
The prevalence of frailty was increased in malnourished patients, and the combination of frailty and malnutrition was associated with the highest risk of post-procedural mortality. Abbreviations: PY, person-years; SPPB, short physical performance battery.

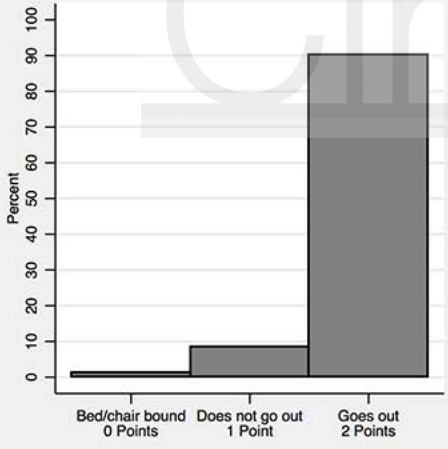
Figure 3. Kaplan-Meier Curves for All-Cause Mortality by Nutritional Status

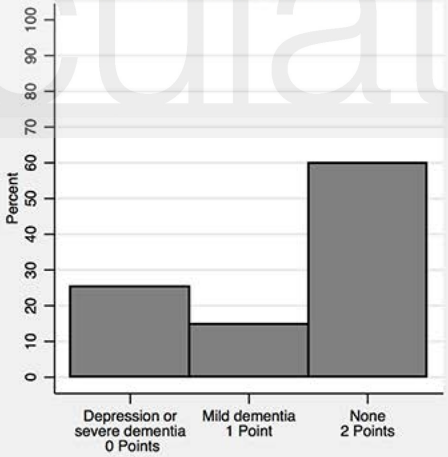
Malnourished patients had decreased survival following transcatheter aortic valve replacement (Panel A) and surgical aortic valve replacement (Panel B). Abbreviations: SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

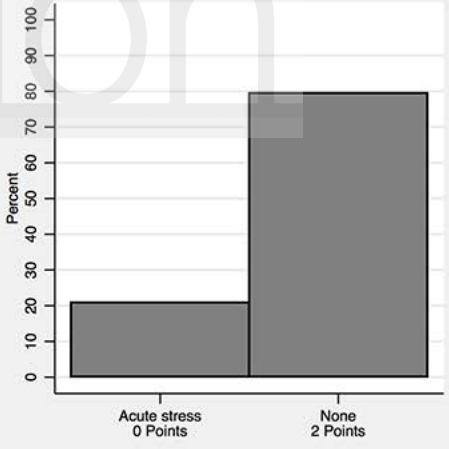


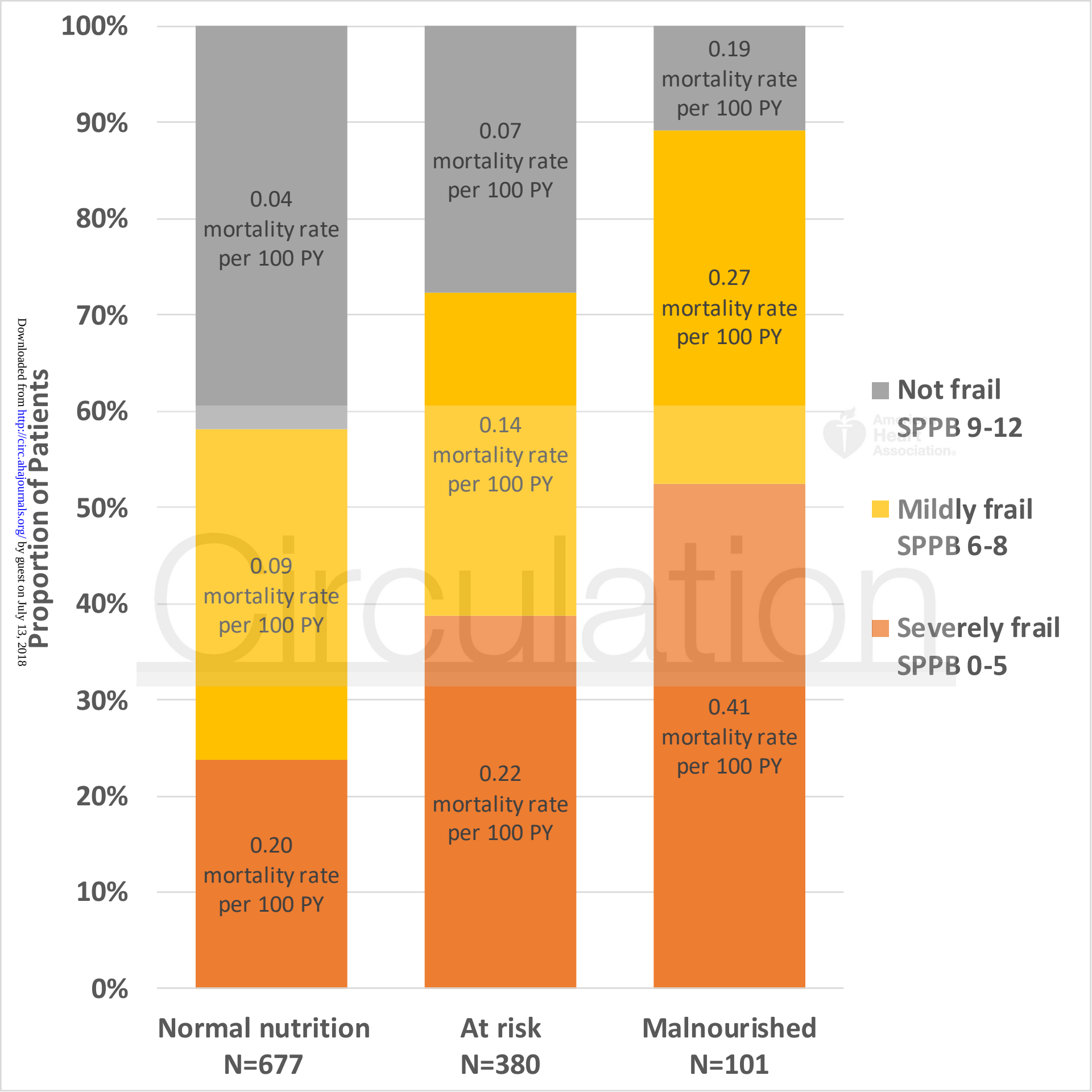


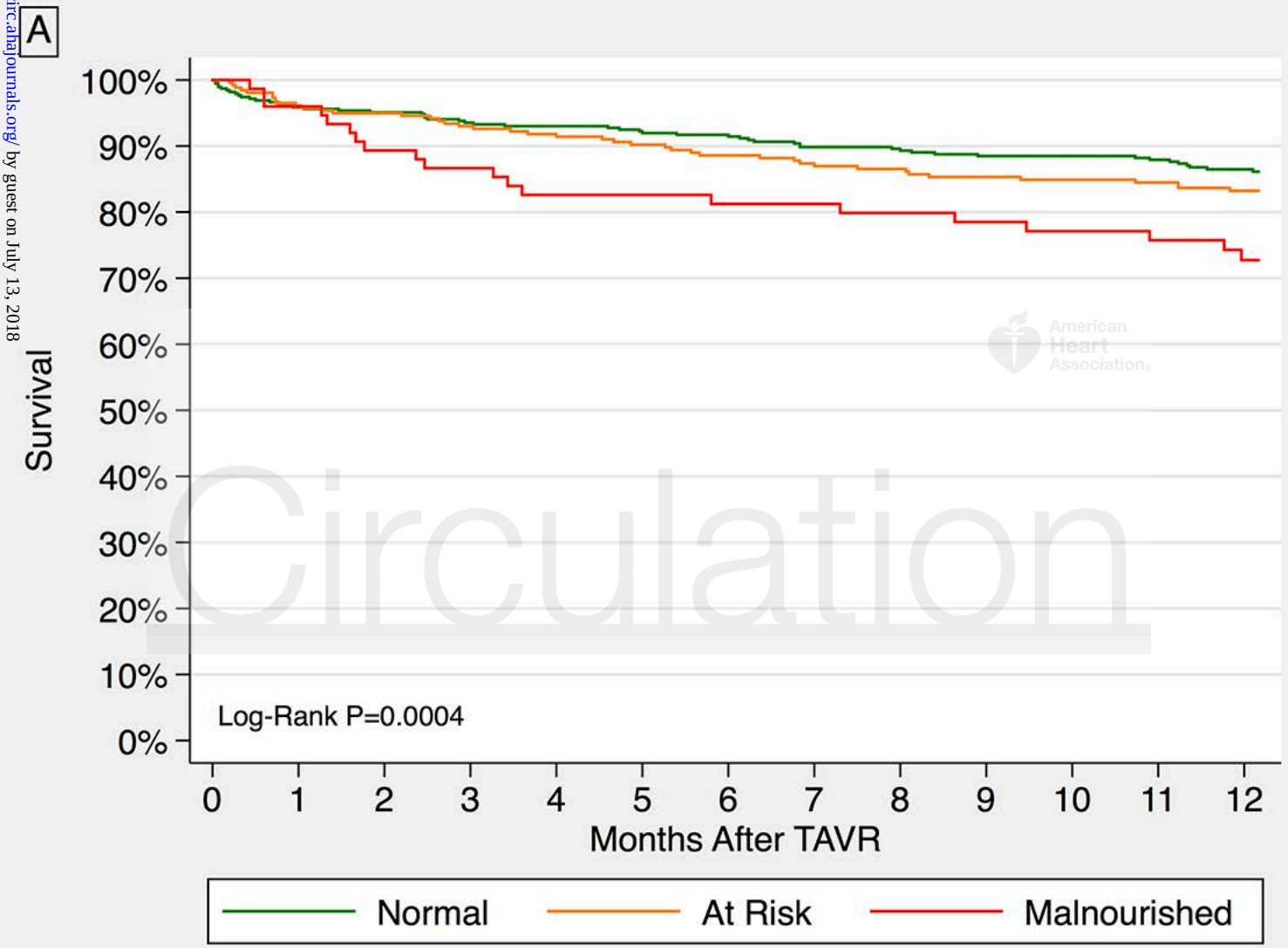


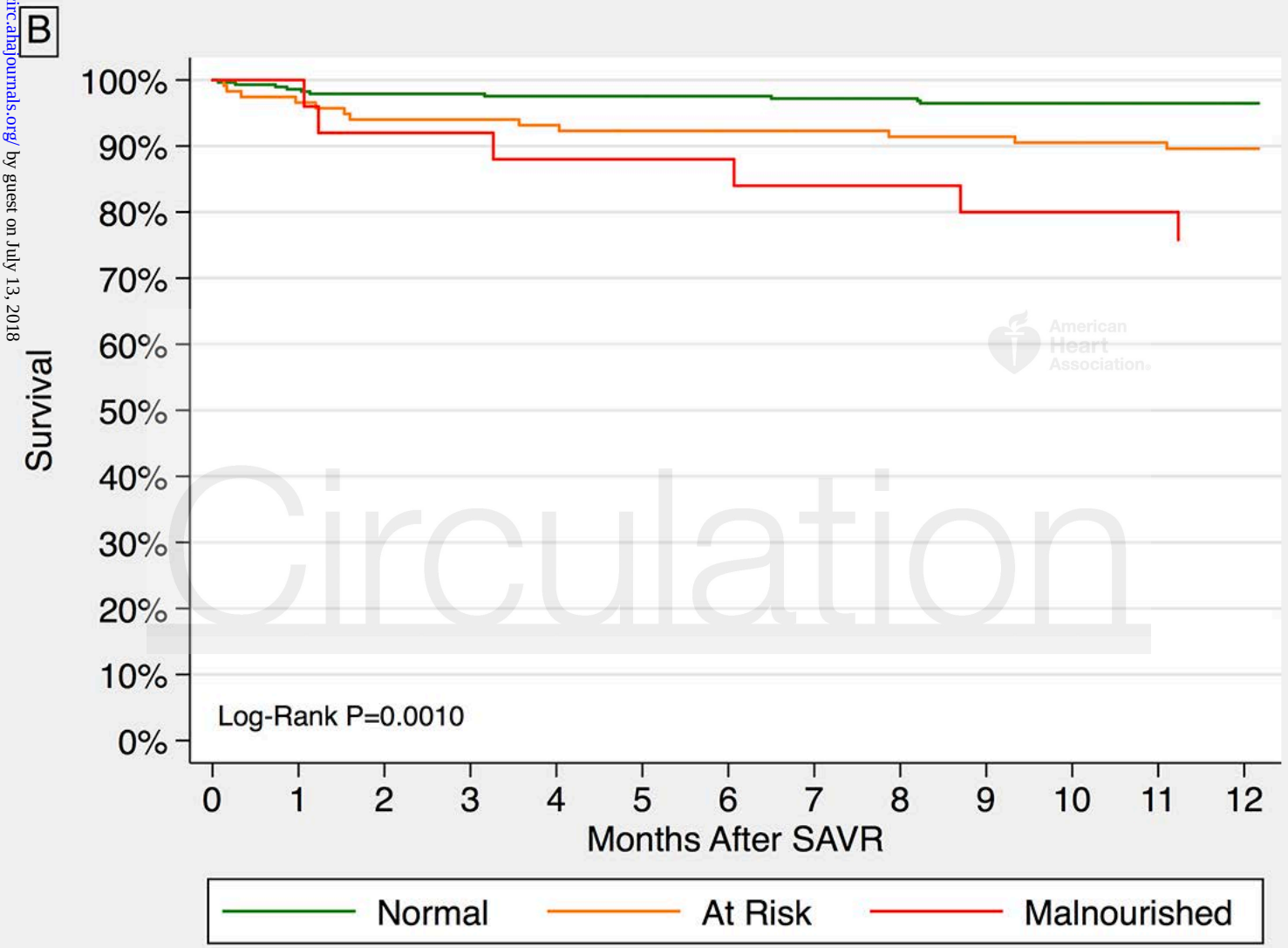












Malnutrition and Mortality in Frail and Non-Frail Older Adults Undergoing Aortic Valve Replacement

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on behalf of the FRAILTY-AVR Investigators

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SUPPLEMENTAL MATERIAL

Supplemental Tables

Table S1 [TAVR]. Baseline Characteristics by Nutritional Status in TAVR Patients

	Normal MNA 12-14 N=388	**At-risk MNA 8-11 N=263**	**Malnutrition MNA 0-7 N=76**	**P-value**
Clinical Domains				
Age	83.4 ± 5.6	83.1 ± 5.6	84.8 ± 5.5	0.40
Female	164 (42%)	127 (48%)	40 (53%)	0.05
BMI, kg/m2	27.9 ± 5.1	26.2 ± 5.5	23 ± 4.9	<0.001
Weight, kg	76.3 ± 16.5	71.3 ± 17	62.7 ± 14.5	<0.001
Weight loss over past year, kg	0.1 ± 0.4	3.8 ± 5.4	8.9 ± 6	<0.001
Diabetes	103 (27%)	69 (26%)	17 (22%)	0.54
Coronary artery disease	229 (59%)	152 (58%)	49 (64%)	0.61
Prior stroke	26 (7%)	27 (10%)	11 (14%)	0.02
Peripheral arterial disease	68 (18%)	49 (19%)	11 (14%)	0.77
Chronic kidney disease	218 (56%)	147 (56%)	56 (74%)	0.04
Chronic lung disease	68 (18%)	58 (22%)	18 (24%)	0.10
Gastrointestinal disease	75 (19%)	56 (21%)	19 (25%)	0.26
Cancer	63 (16%)	44 (17%)	14 (18%)	0.67
Left ventricular ejection fraction, %	57.1 ± 11.7	54.8 ± 12.5	48.4 ± 15.1	<0.001
Mean aortic gradient, mmHg	48.5 ± 16.5	45.1 ± 16.1	44.8 ± 14.2	0.01
Pulmonary artery pressure, mmHg	42.6 ± 15.2	41.9 ± 15.6	47.4 ± 14.6	0.07
Hemoglobin, g/L	122.5 ± 16.1	118.3 ± 16.6	112.4 ± 16.8	<0.001
Serum albumin, g/L	39 ± 4.6	38.2 ± 4.7	36.1 ± 4.9	<0.001
STS-PROM, %	5.4 ± 3.5	6.5 ± 4.2	9.0 ± 5.6	<0.001
Non-femoral access	89 (23%)	64 (24%)	14 (18%)	0.64
Geriatric Domains				
SPPB, out of 12	6.8 ± 3	5.8 ± 3.4	4.8 ± 3.2	<0.001
Fried frailty scale	127 (33%)	141 (54%)	60 (79%)	<0.001
Falls	68 (18%)	64 (24%)	22 (29%)	0.007
Gait speed, m/sec	0.7 ± 0.3	0.6 ± 0.3	0.4 ± 0.4	<0.001
Grip strength, kg	25 ± 9.6	23 ± 10.4	20.1 ± 9.9	<0.001
Cognitive impairment	68 (18%)	61 (23%)	24 (32%)	0.003
Depressed mood	74 (19%)	109 (42%)	50 (66%)	<0.001
ADL/IADL disabilities, out of 14	1.4 ± 1.9	2.4 ± 2.9	4.0 ± 3.4	<0.001

Abbreviations: ADL/IADL, basic and instrumental activities of daily living; BMI, body mass index; MNA, mini nutritional assessment; SPPB, short performance physical battery; STS-PROM, Society of Thoracic Surgery predicted risk of mortality.

Table S1 [SAVR]. Baseline Characteristics by Nutritional Status in SAVR Patients

	Normal MNA 12-14 N=289	**At-risk MNA 8-11 N=117**	**Malnutrition MNA 0-7 N=25**	**P-value**
Clinical Domains				
Age	77.1 ± 4.9	78.4 ± 4.7	79.2 ± 5.1	0.003
Female	86 (30%)	51 (44%)	13 (52%)	0.001
BMI, kg/m2	29.2 ± 4.8	28.1 ± 6.4	25.8 ± 6.3	<0.001
Weight, kg	82.7 ± 15.3	77.5 ± 18.6	72.3 ± 20.5	<0.001
Weight loss over past year, kg	0.1 ± 0.5	3.5 ± 5	8.1 ± 5.6	<0.001
Diabetes	81 (28%)	44 (38%)	7 (28%)	0.23
Coronary artery disease	186 (64%)	79 (68%)	14 (56%)	0.85
Prior stroke	15 (5%)	6 (5%)	1 (4%)	0.85
Peripheral arterial disease	25 (9%)	12 (10%)	4 (16%)	0.26
Chronic kidney disease	110 (38%)	58 (50%)	11 (44%)	0.08
Chronic lung disease	29 (10%)	18 (15%)	4 (16%)	0.12
Gastrointestinal disease	57 (20%)	28 (24%)	8 (32%)	0.12
Cancer	36 (12%)	17 (15%)	1 (4%)	0.64
Left ventricular ejection fraction, %	59 ± 10.8	55 ± 13.3	53.6 ± 15.4	0.002
Mean aortic gradient, mmHg	45.5 ± 14.8	41.7 ± 14.9	45.3 ± 18.5	0.05
Pulmonary artery pressure, mmHg	36.1 ± 10.3	38.4 ± 14.5	38.4 ± 12	0.53
Hemoglobin, g/L	130.1 ± 17.1	124 ± 16.4	121.3 ± 18.2	<0.001
Serum albumin, g/L	40.3 ± 5.2	38.2 ± 5.1	36.9 ± 4.5	<0.001
STS-PROM, %	3 ± 1.8	4.1 ± 2.2	4.4 ± 2.5	<0.001
Concomitant CABG	158 (55%)	64 (55%)	8 (32%)	0.14
Geriatric Domains				
SPPB, out of 12	8.3 ± 2.6	6.7 ± 3.1	5.3 ± 2.9	<0.001
Fried frailty scale	45 (16%)	47 (40%)	14 (56%)	<0.001
Falls	36 (12%)	27 (23%)	4 (16%)	0.04
Gait speed, m/sec	0.9 ± 0.3	0.7 ± 0.3	0.6 ± 0.3	<0.001
Grip strength, kg	30.9 ± 10.6	26.4 ± 10	23.4 ± 9.5	<0.001
Cognitive impairment	22 (8%)	14 (12%)	5 (20%)	0.03
Depressed mood	41 (14%)	57 (49%)	19 (76%)	<0.001
ADL/IADL disabilities, out of 14	0.5 ± 1	1.1 ± 1.6	2.1 ± 2.8	<0.001

Abbreviations: ADL/IADL, basic and instrumental activities of daily living; BMI, body mass index; CABG, coronary artery bypass graft; MNA, mini nutritional assessment; SPPB, short performance physical battery; STS-PROM, Society of Thoracic Surgery predicted risk of mortality.

Table S2 [TAVR]. Outcomes by Nutritional Status in TAVR Patients

	Normal MNA 12-14 N=388	**At-risk MNA 8-11 N=263**	**Malnutrition MNA 0-7 N=76**	**P-value**
1-year mortality	54 (15%)	50 (20%)	22 (30%)	0.002
30-day mortality	17 (4%)	18 (7%)	4 (5%)	0.36
30-day composite endpoint *	83 (21%)	74 (28%)	19 (25%)	0.14
Reoperation	32 (8%)	34 (13%)	8 (11%)	0.16
Stroke	5 (1%)	6 (2%)	5 (7%)	0.01
Acute kidney injury	31 (8%)	29 (11%)	5 (7%)	0.71
Major bleed	36 (9%)	26 (10%)	5 (7%)	0.67
Major vascular complication	18 (5%)	23 (9%)	2 (3%)	0.57
ICU length of stay, hours	83.8 ± 97.6	86.2 ± 117.1	98.4 ± 147.7	0.88
Hospital length of stay, days	7.1 ± 7.7	7.6 ± 9.8	9.3 ± 10.7	0.07
Discharge to facility	104 (27%)	87 (33%)	33 (43%)	0.003

Abbreviations: ICU, intensive care unit; MNA, mini nutritional assessment; TAVR, transcatheter aortic valve replacement.

* Composite endpoint refers to VARC composite safety endpoint: all-cause death, stroke, acute kidney injury, reoperation, major bleeding or vascular complication.

Table S2 [SAVR]. Outcomes by Nutritional Status in SAVR Patients

	Normal MNA 12-14 N=289	**At-risk MNA 8-11 N=117**	**Malnutrition MNA 0-7 N=25**	**P-value**
1-year mortality	12 (4%)	12 (11%)	6 (25%)	<0.001
30-day mortality	6 (2%)	5 (4%)	2 (8%)	0.06
30-day composite endpoint *	67 (23%)	36 (31%)	6 (24%)	0.28
Reoperation	23 (8%)	12 (10%)	3 (12%)	0.35
Stroke	10 (3%)	1 (1%)	0 (0%)	0.09
Acute kidney injury	15 (5%)	14 (12%)	2 (8%)	0.06
Major bleeding complication	45 (16%)	30 (26%)	3 (12%)	0.22
Major vascular complication	5 (2%)	0 (0%)	1 (4%)	0.82
ICU length of stay, hours	58.7 ± 81.5	72.6 ± 90.1	73.9 ± 99.5	0.02
Hospital length of stay, days	10.4 ± 10	12.6 ± 14.8	14 ± 15.2	0.02
Discharge to facility	92 (32%)	47 (40%)	10 (40%)	0.11

Abbreviations: ICU, intensive care unit; MNA, mini nutritional assessment; SAVR, surgical aortic valve replacement.

* Composite endpoint refers to VARC composite safety endpoint: all-cause death, stroke, acute kidney injury, reoperation, major bleeding or vascular complication.

Table S3. Mini Nutritional Assessment Subdomains and 1-Year Mortality

MNA Subdomains	**1-year mortality** *Odds Ratio (95% CI)*	**P-value**
Neuropsychological problem	2.73 (1.88, 3.95)	<0.001
Mobility impairment	1.72 (1.05, 2.82)	0.03
Appetite decline	1.69 (1.13, 2.52)	0.01
Low body mass index, per 1-kg/m2 ↓	1.09 (1.05, 1.13)	<0.001
Weight loss	0.98 (0.94, 1.02)	0.29
Acute stressor	0.83 (0.55, 1.24)	0.36

Abbreviations: CI, confidence interval; MNA, mini nutritional assessment; SAVR, surgical aortic valve replacement; SPPB, short performance physical battery; STS-PROM, Society of Thoracic Surgery predicted risk of mortality; TAVR, transcatheter aortic valve replacement.

Table S4. Cox Proportional Hazards Model for 1-Year Mortality

	Mortality *Hazard Ratio (95% CI)*	**P-value**
Malnutrition, per 1-point ↓ MNA	1.07 (1.01, 1.13)	0.02
Frailty, per 1-point ↓ SPPB	1.12 (1.07, 1.17)	<0.001
STS-PROM, per %	1.08 (1.05, 1.11)	<0.001
Procedure, TAVR (vs. SAVR)	1.65 (1.11, 2.44)	0.01

Abbreviations: CI, confidence interval; MNA, mini nutritional assessment; SAVR, surgical aortic valve replacement; SPPB, short performance physical battery; STS-PROM, Society of Thoracic Surgery predicted risk of mortality; TAVR, transcatheter aortic valve replacement.

Table S5. Multivariable Logistic Regression Model Adjusted for Individual Covariates

	1-year mortality *Odds Ratio (95% CI)*
Malnutrition, per 1-point ↓ MNA	1.10 (1.18, 1.02)
Frailty, per 1-point ↓ SPPB	1.13 (1.20, 1.06)
Age, per year	1.05 (1.01, 1.09)
Female sex	1.03 (0.55, 1.94)
Prior stroke	0.99 (0.66, 1.48)
Chronic kidney disease	1.27 (0.86, 1.88)
Chronic lung disease	1.13 (0.71, 1.81)
Anemia	2.05 (1.21, 3.47)
Pulmonary hypertension >60 mmHg	2.25 (1.48, 3.41)
Mean aortic gradient, per mmHg	0.98 (0.97, 1.00)
LVEF, per %	1.00 (0.99, 1.02)
Concomitant CABG	2.64 (1.20, 5.81)
Procedure, TAVR (vs. SAVR)	2.88 (1.38, 5.99)

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; LVEF, left ventricular ejection fraction; MNA, mini nutritional assessment; SAVR, surgical aortic valve replacement; SPPB, short performance physical battery; STS-PROM, Society of Thoracic Surgery predicted risk of mortality; TAVR, transcatheter aortic valve replacement.

Table S6. Multivariable Logistic Regression Model Adjusted for the Fried Frailty Scale

	1-year mortality *Odds Ratio (95% CI)*	**P-value**
Malnutrition, per 1-point ↓ MNA	1.10 (1.03, 1.19)	0.006
Frailty, per 1-point ↑ Fried score	1.30 (0.89, 1.91)	0.18
STS-PROM, per %	1.10 (1.06, 1.15)	<0.001
Procedure, TAVR (vs. SAVR)	1.77 (1.13, 2.78)	0.01

Abbreviations: CI, confidence interval; MNA, mini nutritional assessment; 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.

Table S7. Multivariable Logistic Regression Model with the MNA-SPPB Indicator Variable

	1-year mortality *Odds Ratio (95% CI)*	**P-value**
MNA-SPPB indicator variable Normal nutrition & Not frail Normal nutrition & Frail Malnutrition & Not frail Malnutrition & Frail	 1.00 (Referent) 2.08 (1.40, 3.07) 1.89 (0.86, 4.17) 3.21 (1.66, 6.21)	<0.001
STS-PROM, per %	1.11 (1.06, 1.15)	<0.001
Procedure, TAVR (vs. SAVR)	1.70 (1.07, 2.65)	0.02

Abbreviations: CI, confidence interval; MNA, mini nutritional assessment; 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.

Legend: The number of patients deceased/alive at 1 year was 63/624 in the normal nutrition and not frail group, 65/237 in the normal nutrition and frail group, 10/35 in the malnourished and not frail group, and 18/35 in the malnourished and frail group.

Table S8. Multivariable Logistic Regression Model Adjusted for Albumin

	1-year mortality *Odds Ratio (95% CI)*	**P-value**
Malnutrition, per 1-point ↓ MNA	1.07 (0.99, 1.15)	0.07
Frailty, per 1-point ↓ SPPB	1.12 (1.06, 1.15)	<0.001
STS-PROM, per %	1.09 (1.05, 1.14)	<0.001
Procedure, TAVR (vs. SAVR)	1.66 (1.05, 2.64)	0.03
Albumin, per g/dL	0.53 (0.35, 0.81)	0.003

Abbreviations: CI, confidence interval; MNA, mini nutritional assessment; 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.

Table S9. Multivariable Logistic Regression Model with the Modified MNA-Albumin Score

	1-year mortality *Odds Ratio (95% CI)*	**P-value**
Malnutrition, per 1-point ↓ MNA-Albumin*	1.11 (1.04,1.19)	0.002
Frailty, per 1-point ↓ SPPB	1.12 (1.06, 1.19)	<0.001
STS-PROM, per %	1.10 (1.05, 1.14)	<0.001
Procedure, TAVR (vs. SAVR)	1.65 (1.04, 2.61)	0.03

Abbreviations: CI, confidence interval; MNA, mini nutritional assessment; 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.

* The modified MNA-Albumin score (range 0 to 16) was calculated by adding the following points to the standard MNA score: 2 points for serum albumin ≥4.0 g/dL, 1 point for 3.0-3.9 g/dL, and 0 points for <3.0 g/dL.