

ORIGINAL RESEARCH

Midterm Outcomes of Underweight Patients Undergoing Transcatheter Aortic Valve Implantation



Insight From the LAPLACE-TAVR Registry

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ABSTRACT

BACKGROUND Obesity is a major risk factor for cardiovascular disease; however, a paradoxical effect of obesity has been reported in patients with heart failure or myocardial infarction. Although several studies have suggested the same obesity paradox in patients undergoing transcatheter aortic valve replacement (TAVR), they included a limited number of underweight patients.

OBJECTIVES This study aimed to clarify the effect of being underweight on TAVR outcomes.

METHODS We retrospectively analyzed 1,693 consecutive patients undergoing TAVR between 2010 and 2020. The patients were categorized according to body mass index: underweight (<18.5 kg/m²; n = 242), normal weight (18.5 to 25 kg/m²; n = 1,055), and overweight (>25 kg/m²; n = 396). We compared midterm outcomes after TAVR among the 3 groups; all clinical events were in accordance with the Valve Academic Research Consortium-2 criteria.

RESULTS Underweight patients were more likely to be women and have severe heart failure symptoms, peripheral artery disease, anemia, hypoalbuminemia, and pulmonary dysfunction. They also had lower ejection fractions, smaller aortic valve areas, and higher surgical risk scores. Device failure, life-threatening bleeding, major vascular complications, and 30-day mortality occurred more frequently in underweight patients. The midterm survival rate of the underweight group was inferior to those of the other 2 groups ($P < 0.0001$; average follow-up, 717 days). In the multivariate analysis, underweight was associated with noncardiovascular mortality (HR: 1.78; 95% CI: 1.16-2.75) but not cardiovascular mortality (HR: 1.28; 95% CI: 0.58-1.88) after TAVR.

CONCLUSIONS Underweight patients had a worse midterm prognosis, demonstrating the obesity paradox in this TAVR population. (Outcomes of transcatheter aortic valve implantation in Japanese patients with aortic stenosis: multi-center registry; [UMIN00031133](https://doi.org/10.1016/j.jaccasi.2022.08.014)) (JACC: Asia 2023;3:78-89) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Obesity is a well-known major risk factor for cardiovascular (CV) disease¹; however, overweight patients show better outcomes following percutaneous coronary intervention² and open-heart surgery.³ In heart failure, the higher the body mass index (BMI), the lower the mortality rate.^{4,5} This phenomenon is known as the obesity paradox. Explanations for the obesity paradox in patients with heart failure include better tolerability for guideline-directed medical therapy and increased metabolic reserve toward a catabolic state of heart failure.⁶ The obesity paradox has also been reported in transcatheter aortic valve replacement (TAVR).⁷⁻¹² In previous TAVR studies, overweight and/or obese patients had better prognosis than normal-weight patients, whereas underweight patients were not included or numerically limited. The East Asian population undergoing TAVR has a lower mean BMI than those in Western Europe and North America,¹³ and the true impact of a lower BMI on TAVR outcomes remains unclear. Here we sought to investigate whether underweight is associated with all-cause, CV, and non-CV mortality following TAVR using data from a multicenter registry.

MATERIALS AND METHODS

STUDY DESIGN. We analyzed the data from a prospective multicenter registry, the LAPLACE (aLiAnce for exPLoring cLinical prospects of AortiC valve disease)-TAVR registry, which comprises the Sakakibara Heart Institute, Juntendo University Hospital, Mie University Hospital, Yamagata University Hospital, Hirosaki University Graduate School of Medicine, and Kawasaki Saiwai Hospital. We investigated 1,693 consecutive patients who underwent TAVR between April 2010 and July 2020. Data from all patients were prospectively collected in our dedicated database and retrospectively analyzed. Patient consent was obtained using an opt-out style or written informed consent. The institutional review board of each hospital approved the study protocol. This study was conducted in accordance with the Declaration of Helsinki and the other ethical guidelines for medical research involving humans. This registry was registered in the clinical research database (UMIN000031133).

TAVR PROCEDURE. The indications for TAVR were severe aortic stenosis (AS) or bioprosthetic valve failure, and decisions were made by each hospital's multidisciplinary heart team. We selected TAVR or other therapeutic options based on age, comorbidities, frailty, and patient preference. Procedural details were previously reported.^{14,15}

BMI AND CLASSIFICATION. We divided the patients into 3 groups by BMI, defined as weight in kilograms divided by the square of height in meters. Height and body weight were measured at the time of TAVR. BMI was classified based on the World Health Organization criteria¹⁶ and defined as underweight (<18.5 kg/m²), normal weight (18.5-25 kg/m²), and overweight (>25 kg/m²). The background and procedural characteristics and outcomes after TAVR were compared among the 3 groups. Owing to the small sample size of obese patients (n = 62 [3.7%]), they were included in the overweight group.

STUDY ENDPOINTS. The primary endpoint of this study was all-cause mortality after TAVR. The secondary endpoints were as follows: 1) 30-day mortality; 2) early combined endpoints at 30 days; 3) CV mortality after TAVR; and 4) non-CV mortality after TAVR. Clinical events were defined according to Valve Academic Research Consortium (VARC)-2 criteria.¹⁷ The combined endpoint included all-cause mortality, all strokes, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction, major vascular complications, and valve-related dysfunction requiring repeat procedures. Mortality cause was classified as CV or non-CV according to VARC-2 criteria. Pneumonia was considered a respiratory disease. We followed the patients until August 2020 by outpatient visits, telephone interviews, or postcards.

STATISTICAL ANALYSIS. Categorical variables are expressed as number (%). Continuous variables are presented as mean ± SD, and normality was confirmed using the Shapiro-Wilk test. The chi-square test or Fisher exact test, if appropriate, was used to compare categorical variables. Normally distributed continuous variables were compared using Student's *t*-test, whereas non-normally distributed variables were compared using the Mann-Whitney *U* test. One-way analysis of variance was used to compare the continuous variables among the 3 groups. The Kaplan-Meier method was used to evaluate postprocedural survival

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

BMI = body mass index

CV = cardiovascular

TAVR = transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

TABLE 1 Baseline Characteristics					
	Total (N = 1,693)	Underweight (n = 242)	Normal weight (n = 1,055)	Overweight (n = 396)	P Value
Demographic data					
Age (y)	84.2 ± 5.4	84.4 ± 6.3	84.6 ± 5.1	83.2 ± 5.4	<0.0001
Women	1,123 (66)	184 (76)	663 (63)	276 (70)	0.0001
Height (cm)	151.1 ± 9.3	150.5 ± 8.9	151.5 ± 9.5	150.4 ± 9.1	0.072
Body weight (kg)	51.5 ± 10.5	39.0 ± 5.5	50.2 ± 7.6	62.6 ± 8.8	<0.0001
BMI (kg/m ²)	22.5 ± 3.8	17.2 ± 1.2	21.8 ± 1.8	27.7 ± 2.6	<0.0001
BSA (m ²)	1.5 ± 0.2	1.3 ± 0.1	1.4 ± 0.2	1.6 ± 0.2	<0.0001
NYHA functional class III or IV	846 (50)	159 (66)	496 (47)	191 (48)	<0.0001
Comorbidity					
Hypertension	1,314 (78)	151 (62)	815 (77)	348 (88)	<0.0001
Diabetes mellitus	383 (23)	37 (15)	241 (23)	105 (27)	0.004
Dyslipidemia	936 (55)	119 (49)	550 (52)	267 (67)	<0.0001
Cancer: previous or active	318 (19)	54 (27)	203 (19)	61 (15)	0.079
Previous stroke	205 (12)	19 (7.9)	138 (13)	48 (12)	0.080
COPD	159 (9.4)	27 (11)	100 (9.5)	32 (8.0)	0.42
Steroids use	107 (6.3)	18 (7.4)	64 (6.1)	25 (6.3)	0.85
AF/AFL	419 (25)	59 (24)	260 (25)	100 (25)	0.96
CAS	145 (8.6)	24 (9.9)	91 (8.6)	30 (7.6)	0.36
PAD	260 (15)	54 (22)	162 (15)	44 (11)	0.0007
Residual CAD	511 (30)	66 (27)	338 (32)	107 (27)	0.10
Previous MI	92 (5.4)	15 (6.2)	59 (5.6)	18 (4.5)	0.63
PMI/ICD	111 (6.6)	19 (7.9)	74 (7.0)	18 (4.5)	0.16
EuroSCORE II (%)	6.3 ± 7.2	7.7 ± 8.4	6.4 ± 7.2	5.3 ± 5.9	<0.0001
STS score (%)	7.0 ± 4.9	8.3 ± 5.6	7.1 ± 4.9	5.7 ± 3.9	<0.0001
Laboratory data					
Hemoglobin (g/dL)	11.5 ± 1.6	11.0 ± 1.5	11.5 ± 1.6	12.0 ± 1.6	<0.0001
Platelet (×10 ⁴ /μL)	18.3 ± 6.9	18.3 ± 7.0	18.3 ± 7.2	18.5 ± 6.3	0.34
eGFR (mL/1.73 m ² /min)	53.5 ± 18.8	57.0 ± 20.2	53.1 ± 18.2	52.5 ± 19.1	0.007
Albumin (g/dL)	3.7 ± 0.5	3.6 ± 0.5	3.8 ± 0.5	3.8 ± 0.4	<0.0001
NT-pro BNP (pg/mL)	3,188 ± 9,058	4,279 ± 7,583	3,516 ± 10,687	1,628 ± 2,509	<0.0001
%FVC (%)	85.1 ± 20.7	77.0 ± 22.0	86.5 ± 20.9	85.9 ± 18.3	<0.0001
Echocardiographic data					
Ejection fraction (%)	61.2 ± 10.5	59.3 ± 13.1	60.8 ± 10.4	63.4 ± 8.2	<0.0001
AVA (cm ²)	0.68 ± 0.19	0.61 ± 0.19	0.68 ± 0.19	0.71 ± 0.17	<0.0001
AV mean pressure gradient (mm Hg)	50.1 ± 18.9	49.1 ± 20.6	50.7 ± 19.2	49.1 ± 17.0	0.37
Values are mean ± SD or n (%) unless otherwise indicated.					
AF = atrial fibrillation; AFL = atrial flutter; AV = aortic valve; AVA = aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; CAS = carotid artery stenosis; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FVC = forced vital capacity; ICD = implantable cardioverter defibrillator; MI = myocardial infarction; NT-pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PAD = peripheral artery disease; PMI = pacemaker implantation; STS = Society of Thoracic Surgeons.					

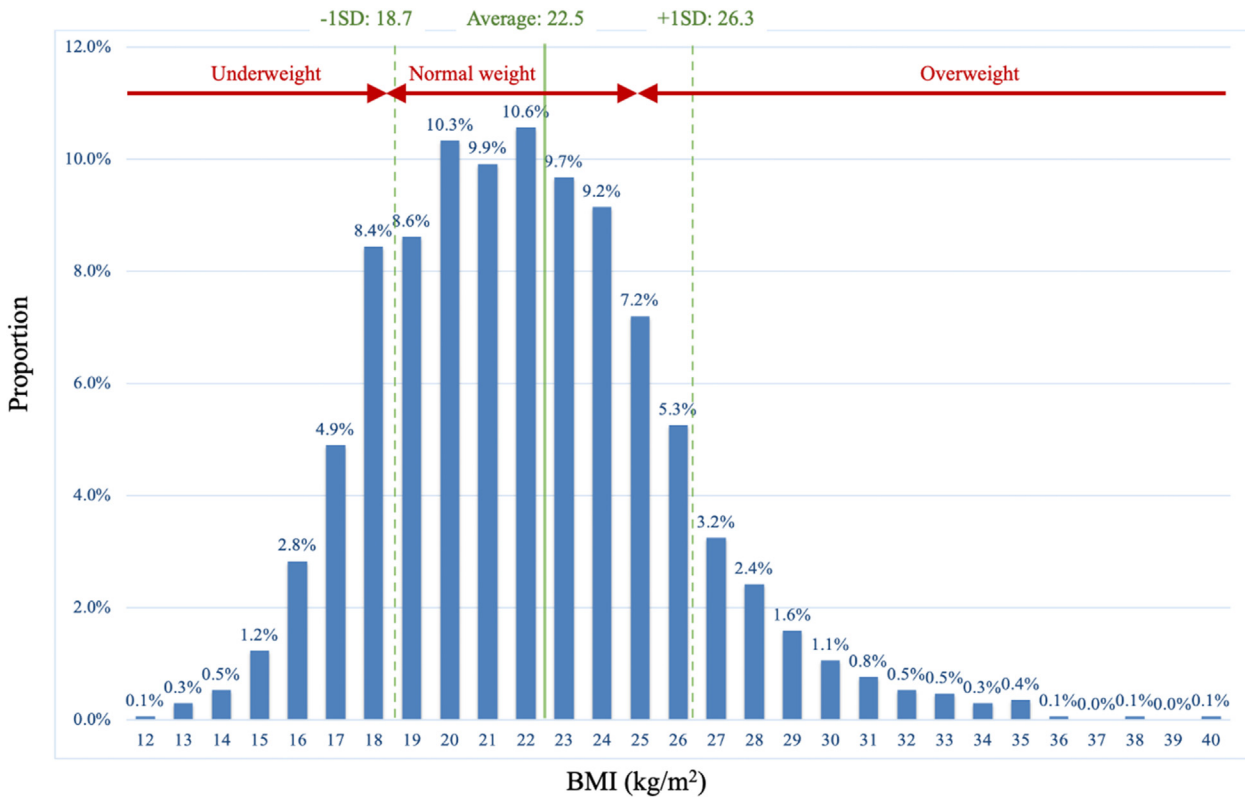
using the log-rank test. The prognostic value of the clinical variables was tested using Cox proportional hazard analysis. Variables tested in the multivariate analysis were selected based on the *P* value in the univariate analysis, clinical plausibility, and multicollinearity. Differences were considered statistically significant at values of *P* < 0.05. These analyses were performed using JMP version 16.2.0 statistical software.

RESULTS

PATIENT BASELINE CHARACTERISTICS. The mean age of the population was 84.2 years; 69% of them

were women. There were 242 underweight patients (14.3%), 1,055 normal-weight patients (62.3%), and 396 overweight patients (23.4%) (Table 1, Figure 1, Supplemental Figure 1). Underweight patients were more likely to be women (76% vs 63% vs 70%, *P* = 0.0001) and have severe heart failure symptoms (New York Heart Association functional class III/IV: 66% vs 47% vs 48%, *P* < 0.0001) or peripheral artery disease (22% vs 15% vs 11%, *P* = 0.0007) than normal-weight and overweight patients, respectively. Previous or active cancer tended to be more prevalent in the underweight group (27% vs 19% vs 15%, *P* = 0.079). The underweight group had lower mean levels of hemoglobin (11.0 ± 1.5 vs 11.5 ± 1.6 vs

FIGURE 1 BMI Distribution of Patients Undergoing Transcatheter Aortic Valve Implantation



From the average body mass index (BMI) of 22.5 kg/m², patients present normal distribution of their BMI.

12.0 ± 1.6 g/dL, $P < 0.0001$), albumin (3.6 ± 0.5 vs 3.8 ± 0.5 vs 3.8 ± 0.4, $P < 0.0001$), and % forced vital capacity (77.0% ± 22.0% vs 86.5% ± 20.9% vs 85.9% ± 18.3%, $P < 0.0001$) and a higher N-terminal pro-brain natriuretic peptide level (4,279 ± 7,583 pg/mL vs 3,516 ± 10,687 pg/mL vs 1,628 ± 2,509 pg/mL, $P < 0.0001$). The systolic function of the underweight group was the lowest (ejection fraction, 59.3% ± 13.1% vs 60.8% ± 10.4% vs 63.4% ± 8.2%, $P < 0.0001$) with more advanced AS (aortic valve area, 0.61 ± 0.19 cm² vs 0.68 ± 0.19 cm² vs 0.71 ± 0.17 cm², $P < 0.0001$). The estimated surgical risk was the highest in the underweight group (European System for Cardiac Operative Risk Evaluation II: 7.7% ± 8.4% vs 6.4% ± 7.2% vs 5.3% ± 5.9%, $P < 0.0001$; and Society of Thoracic Surgeons score: 8.3% ± 5.6% vs 7.1% ± 4.9% vs 5.7% ± 3.9%, $P < 0.0001$).

PROCEDURAL DETAILS AND 30-DAY OUTCOMES.

The underweight group was less commonly treated with the transfemoral approach (88% vs 94% vs 95%,

$P = 0.0009$) with longer procedural time (95.4 ± 54.1 vs 88.4 ± 61.1 vs 82.0 ± 37.6, $P = 0.0005$) (Table 2). The underweight group had the longest mean stay in the cardiac care unit (2.2 ± 3.1 days vs 1.9 ± 3.0 days vs 1.8 ± 2.4 days, $P < 0.0001$), lowest device success rate (95% vs 98% vs 98%, $P = 0.006$), and lowest home discharge rate (85% vs 92% vs 93%, $P = 0.0006$).

The 30-day mortality rate of the underweight group was the highest, but the difference was not statistically significant (1.7% vs 0.9% vs 0.3%, $P = 0.18$). The combined endpoint at 30 days occurred more frequently in the underweight group (11% vs 7.6% vs 5.3%, $P = 0.027$) because of more frequent life-threatening bleeding (3.7% vs 2.2% vs 0.7%, $P = 0.036$), major vascular complications (3.3% vs 2.9% vs 0.5%, $P = 0.018$), and valve-related complications (0.8% vs 0.2% vs 0%, $P < 0.0001$).

CLINICAL OUTCOMES. The mean follow-up period was 717 days (median 585 [IQR: 233-1,029] days).

TABLE 2 Procedure Details and 30-Day Outcome

	Total (N = 1,693)	Underweight (n = 242)	Normal Weight (n = 1,055)	Overweight (n = 396)	P Value
Procedural details					
General anesthesia	701 (41)	112 (46)	425 (40)	164 (41)	0.24
TF approach	1,581 (93)	213 (88)	991 (94)	377 (95)	0.0009
Surgical cut-down	278 (16)	41 (17)	164 (16)	73 (18)	0.48
Procedure time (min)	88.2 ± 55.6	95.4 ± 54.1	88.4 ± 61.1	82.0 ± 37.6	0.0005
Radiation time (min)	23.5 ± 15.0	23.9 ± 11.1	24.0 ± 17.4	22.3 ± 9.3	0.40
Contrast material (mL)	73.1 ± 47.1	78.6 ± 47.0	73.0 ± 48.5	70.0 ± 43.1	0.047
Device success	1,653 (98)	230 (95)	1,033 (98)	390 (98)	0.006
New-onset AF	80 (4.7)	11 (4.5)	51 (4.8)	18 (4.5)	0.97
Postprocedural PMI	142 (8.4)	24 (9.9)	87 (8.2)	31 (7.8)	0.61
PPM	161 (9.5)	8 (3.3)	88 (8.3)	65 (16)	<0.0001
CCU duration (d)	1.9 ± 2.9	2.2 ± 3.1	1.9 ± 3.0	1.8 ± 2.4	<0.0001
Median (d)	1 (1-2)	2 (1-2)	1 (1-2)	1 (1-2)	-
Discharge home	1,542 (91)	205 (85)	968 (92)	369 (93)	0.0006
30-day outcome					
All-cause death	15 (0.9)	4 (1.7)	10 (0.9)	1 (0.3)	0.18
Stroke	50 (3.0)	10 (4.1)	28 (2.7)	12 (3.0)	0.47
Life-threatening bleeding	35 (2.1)	9 (3.7)	23 (2.2)	3 (0.7)	0.036
AKI stage 2 or 3	32 (1.9)	5 (2.1)	20 (1.9)	7 (1.8)	0.97
Coronary obstruction	7 (0.4)	2 (1.3)	3 (0.3)	2 (0.5)	0.44
Major vascular complication	41 (2.4)	8 (3.3)	31 (2.9)	2 (0.5)	0.018
Valve-related dysfunction	7 (0.4)	5 (0.8)	2 (0.2)	0 (0)	<0.0001
30-day combined endpoint	129 (7.6)	27 (11)	81 (7.6)	21 (5.3)	0.027

Values are n (%) or mean ± SD unless otherwise indicated.
AF = atrial fibrillation; AKI = acute kidney injury; CCU = cardiac care unit; PMI = pacemaker implantation; PPM = prosthesis patient mismatch; TF = transfemoral.

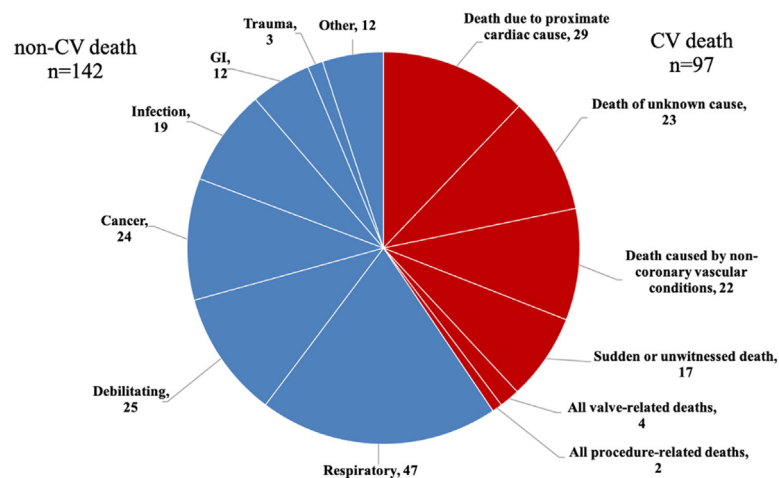
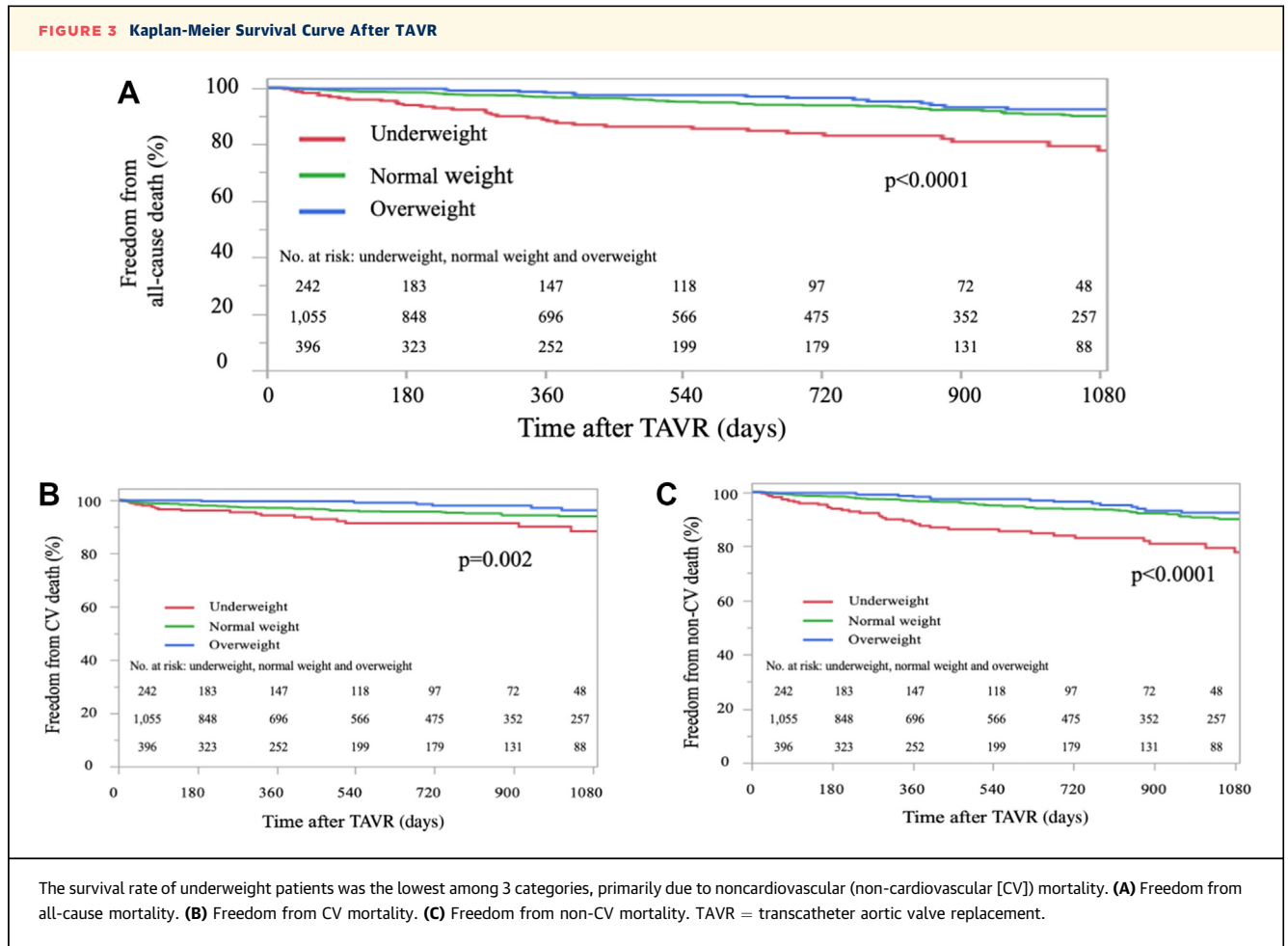
FIGURE 2 Post-Transcatheter Aortic Valve Implantation Mortality Details

Figure shows the proportion of cardiovascular (CV) and noncardiovascular deaths, and their details. GI = gastrointestinal.



There were 239 all-cause deaths (14%) during this period, 41% of which were of CV causes (Figure 2). Freedom from all-cause mortality of the underweight group was lower than that of the other 2 groups on the Kaplan-Meier curve ($P < 0.0001$) (Figure 3A). Independent predictors of all-cause mortality were as follows (Table 3): female sex (HR: 0.50; 95% CI: 0.37-0.66; $P < 0.0001$), underweight (HR: 1.66; 95% CI: 1.17-2.36; $P = 0.0047$), steroid user (HR: 1.63; 95% CI: 1.01-2.62; $P = 0.046$), atrial fibrillation/atrial flutter (HR: 2.17; 95% CI: 1.62-2.92; $P < 0.0001$), Society of Thoracic Surgeons score (HR: 1.04 per 1% increase; 95% CI: 1.00-1.07; $P = 0.049$), albumin (HR: 0.41 per 1-g/dL increase; 95% CI: 0.30-0.57; $P < 0.0001$), device success (HR: 0.47; 95% CI: 0.26-0.84; $P = 0.010$), and 30-day combined endpoint (HR: 2.16; 95% CI: 1.49-3.13; $P < 0.0001$). Regarding causes of death, freedom from both CV and non-CV deaths was lower in the underweight group than in the other 2 groups

(Figures 3B and 3C). In the multivariate analysis, underweight was independently associated with non-CV mortality (HR: 1.78; 95% CI: 1.16-2.75; $P = 0.009$) (Table 5) but not CV mortality after TAVR (HR: 1.28; 95% CI: 0.58-1.88; $P = 0.37$) (Table 4).

The median value of BMI in the underweight group was 17.6 kg/m², and the survival of extreme underweight patients (BMI < 17.6 kg/m²) was similar to that of nonextreme underweight patients (17.6 < BMI < 18.5 kg/m²) ($P = 0.77$) (Supplemental Figure 2).

DISCUSSION

We analyzed the effect of underweight on TAVR outcomes (Central Illustration). Overall, 242 of 1,693 patients (14.3%) were underweight, with a BMI of < 18.5 kg/m². The baseline characteristics of the underweight group were different in several respects compared with the other groups. Despite a similar

TABLE 3 Univariate and Multivariate Analysis for All-Cause Mortality After TAVR

	Univariate			Multivariate		
	HR	95% CI	P Value	HR	95% CI	P Value
Age (per 1-y increase)	1.03	1.002-1.06	0.028	1.02	0.99-1.05	0.17
Woman	0.56	0.43-0.73	<0.0001	0.50	0.37-0.66	<0.0001
Underweight	2.10	1.57-2.81	<0.0001	1.66	1.17-2.36	0.005
Overweight	0.56	0.39-0.81	0.0009	0.71	0.47-1.07	0.10
Hypertension	0.68	0.51-0.91	0.039	0.96	0.69-1.35	0.97
Diabetes mellitus	1.01	0.75-1.37	0.93			
Cancer: previous or active	1.67	1.25-2.22	0.0008	1.37	0.99-1.91	0.060
Previous stroke	1.17	0.79-1.75	0.45			
COPD	1.39	0.92-2.11	0.13			
Steroids use	1.60	1.04-2.47	0.044	1.63	1.01-2.62	0.046
AF/AFL	2.31	1.78-3.01	<0.0001	2.17	1.62-2.92	<0.0001
CAS	1.34	0.89-2.02	0.17			
PAD	1.78	1.30-2.37	0.0006	1.41	0.99-1.99	0.052
Residual CAD	1.22	0.93-1.60	0.16			
Previous MI	1.13	0.68-1.88	0.64			
PMI/ICD	1.07	0.63-1.80	0.81			
EuroSCORE II (per 1% increase)	1.03	1.02-1.05	<0.0001	0.99	0.98-1.00	0.86
STS score (per 1% increase)	1.07	1.06-1.09	<0.0001	1.04	1.00-1.07	0.049
eGFR (per 1-mL/1.73 m ² /min increase)	0.99	0.98-0.99	0.015	0.99	0.99-1.00	0.17
Albumin (per 1-g/dL increase)	0.30	0.23-0.40	<0.0001	0.41	0.30-0.57	<0.0001
Ejection fraction (per 1% increase)	0.98	0.97-0.99	0.004	1.01	0.99-1.03	0.078
AV mean pressure gradient (per 1-mm Hg increase)	0.99	0.99-1.001	0.12			
TF approach	0.55	0.39-0.77	0.0008	0.77	0.53-1.13	0.18
Device success	0.29	0.18-0.48	<0.0001	0.47	0.26-0.84	0.010
New-onset AF	1.36	0.82-2.27	0.25			
Postprocedural PMI	1.09	0.72-1.66	0.68			
PPM	0.80	0.52-1.24	0.58			
30-day combined endpoint	2.89	2.07-4.03	<0.0001	2.16	1.49-3.13	<0.0001

TAVR = transcatheter aortic valve replacement; other abbreviations as in Tables 1 and 2.

30-day mortality rate, underweight patients had higher all-cause mortality (non-CV causes) than the other 2 groups.

The strengths of this study were its number of underweight patients, long duration of patient follow-up, and cause of death analysis.

UNDERWEIGHT GROUP IN TAVR. According to World Health Organization criteria, underweight was defined as a BMI of <18.5 kg/m².¹⁶ Previous studies included only 0% to 9% of underweight patients undergoing TAVR (Table 6).^{7-9,18} Compared with patients in Western countries, many Japanese patients undergoing TAVR have a lower BMI.¹³ The average BMI of our patients was 22.5, and 242 of the overall 1,693 (14.3%) patients were classified as underweight. In contrast, the average BMI of Western patients is 26 to 27 kg/m².¹³ Some studies have revised the criteria of underweight upward to a BMI of <20 kg/m²,^{10-12,19} the criterion for frailty defined by the VARC-2. Even if

the cutoff for underweight was a BMI of <20 kg/m², only 6% to 9% of patients in Western countries would meet it (Table 6).^{10-12,19} Thus, the true prognostic impact of a lower BMI after TAVR, the left side of the BMI mortality curve, has not been fully elucidated. Different criteria for underweight might be needed for different populations. As an alternative to BMI, lean body mass was reportedly an excellent prognostic indicator after TAVR,²⁰ but it requires complicated calculations. The modified BMI, which is calculated as BMI multiplied by serum albumin value, is also reportedly useful for stratifying prognosis after TAVR.²¹

Similar to previous reports,^{8-12,18,19} the underweight group in our study had a higher prevalence of female sex and New York Heart Association functional class III/IV, and it was associated with a smaller mean aortic valve area, a lower mean ejection fraction, and higher operative scores. We might have

TABLE 4 Univariate and Multivariate Analysis for CV Death After TAVR

	Univariate			Multivariate		
	HR	95% CI	P Value	HR	95% CI	P Value
Age (per 1-y increase)	1.02	0.98-1.06	0.35			
Woman	0.58	0.38-0.86	0.009	0.54	0.35-0.85	0.007
Underweight	1.83	1.14-2.94	0.019	1.28	0.58-1.88	0.37
Overweight	0.36	0.18-0.71	0.0008	0.46	0.23-0.94	0.032
Hypertension	0.99	0.60-1.64	0.98			
Diabetes mellitus	0.85	0.51-1.40	0.50			
Cancer: previous or active	1.85	1.19-2.86	0.009			
Previous stroke	1.49	0.85-2.64	0.19			
COPD	1.61	0.88-2.95	0.15			
Steroids use	0.50	0.16-1.58	0.19			
AF/AFL	2.95	1.97-4.43	<0.0001	2.97	1.89-4.67	<0.0001
CAS	1.09	0.55-2.17	0.81			
PAD	2.38	1.53-3.70	0.0003	1.89	1.13-3.07	0.014
Residual CAD	1.43	0.94-2.17	0.10			
Previous MI	1.62	0.82-3.23	0.19			
PMI/ICD	1.23	0.57-2.66	0.61			
EuroSCOREII (per 1% increase)	1.04	1.02-1.06	0.0001	1.02	0.99-1.05	0.16
STS score (per 1% increase)	1.07	1.04-1.10	<0.0001	1.003	0.95-1.06	0.91
eGFR (per 1-mL/1.73 m ² /min increase)	0.99	0.98-1.01	0.45			
Albumin (per 1-g/dL increase)	0.37	0.24-0.58	<0.0001	0.59	0.35-0.97	0.039
Ejection fraction (per 1% increase)	0.97	0.96-0.99	0.0009	1.006	0.98-1.03	0.58
AV mean pressure gradient (per 1-mm Hg increase)	0.99	0.99-1.01	0.69			
TF approach	0.75	0.43-1.32	0.33			
Device success	0.40	0.16-1.00	0.081			
New-onset AF	1.30	0.57-2.97	0.56			
Postprocedural PMI	0.92	0.46-1.84	0.82			
PPM	0.78	0.39-1.57	0.76			
30-day combined endpoint	3.52	2.14-5.79	<0.0001	2.70	1.51-4.81	0.0008

CV = cardiovascular; other abbreviations as in Tables 1 to 3.

hesitated to use curative therapy for AS in underweight patients because of their frailty and high operative risk.

PROCEDURAL DETAILS OF TAVR IN THE UNDERWEIGHT GROUP. In the underweight group, the non-transfemoral approach was used more frequently and the incidence of vascular and bleeding complications was higher, similar to previous reports.^{8,9,11,12,18} A low BMI is associated with a small body surface area, and the small vessel size of a small body may be responsible for the higher incidence of the nontransfemoral approach and vascular complications. In addition, the non-transfemoral approach itself is associated with vascular complications.²² The higher percentage of the nontransfemoral approach and procedural complications in the underweight group probably led to a longer mean procedural time, extended postoperative intensive care unit stay, and lower home discharge rates. The latter 2 indices were

associated with poor outcomes after TAVR.^{23,24} To reduce vascular and bleeding complications and improve the prognosis of underweight patients, a lower-profile transcatheter heart valve is needed. Nontransthoracic approaches, including the trans-subclavian and transaxillary, are promising therapeutic options in the underweight group for whom the transfemoral approach is unsuitable.²² The rate of 30-day mortality in the present study was much lower than that in the previous studies (Table 6). The possible rationale for this result includes more recent TAVR procedures included in the current research: higher percentage of transfemoral approach and the second-generation valve used, and more accumulated experience about TAVR planning.

NEGATIVE PROGNOSTIC EFFECT OF UNDERWEIGHT AND SUSPECTED REASONS. We followed patients undergoing TAVR for approximately 2 years, the longest follow-up duration of studies to

TABLE 5 Univariate and Multivariate Analysis for Non-CV Death After TAVR

	Univariate			Multivariate		
	HR	95% CI	P Value	HR	95% CI	P Value
Age (per 1-y increase)	1.04	1.00-1.07	0.039	1.03	0.99-1.07	0.090
Woman	0.57	0.41-0.80	0.002	0.52	0.36-0.76	0.0005
Underweight	2.29	1.58-3.33	<0.0001	1.78	1.16-2.75	0.009
Overweight	0.69	0.45-1.07	0.087			
Hypertension	0.54	0.38-0.77	0.004	0.68	0.45-1.01	0.15
Diabetes mellitus	1.12	0.77-1.64	0.56			
Cancer: previous or active	1.52	1.04-2.22	0.37	1.32	0.86-2.03	0.20
Previous stroke	0.96	0.55-1.67	0.89			
COPD	1.35	0.77-2.35	0.31			
Steroids use	2.54	1.59-4.05	0.0004	2.31	1.37-3.90	0.002
AF/AFL	1.76	1.24-2.50	0.002	1.51	1.03-2.21	0.033
CAS	1.64	0.99-2.70	0.066			
PAD	1.44	0.95-2.18	0.96			
Residual CAD	1.19	0.83-1.69	0.34			
Previous MI	0.69	0.31-1.57	0.35			
PMI/ICD	0.81	0.38-1.74	0.58			
EuroSCOREII (per 1% increase)	1.03	1.001-1.04	0.012	0.97	0.94-1.00	0.052
STS score (per 1% increase)	1.08	1.06-1.10	<0.0001	1.07	1.03-1.11	0.002
eGFR (per 1-mL/1.73 m ² /min increase)	0.99	0.98-0.99	0.008	0.99	0.99-1.01	0.37
Albumin (per 1-g/dL increase)	0.24	0.17-0.35	<0.0001	0.33	0.21-0.50	<0.0001
Ejection fraction (per 1% increase)	0.99	0.97-1.01	0.18			
AV mean pressure gradient (per 1-mm Hg increase)	0.99	0.98-0.99	0.045	0.99	0.99-1.01	0.38
TF approach	0.49	0.32-0.75	0.002	0.68	0.42-1.09	0.11
Device success	0.27	0.15-0.50	0.0005	0.48	0.23-1.01	0.054
New-onset AF	1.26	0.64-2.48	0.51			
Postprocedural PMI	1.14	0.66-1.94	0.65			
PPM	0.82	0.47-1.44	0.77			
30-day combined endpoint	2.47	1.58-3.87	0.0004	1.80	1.10-2.94	0.019

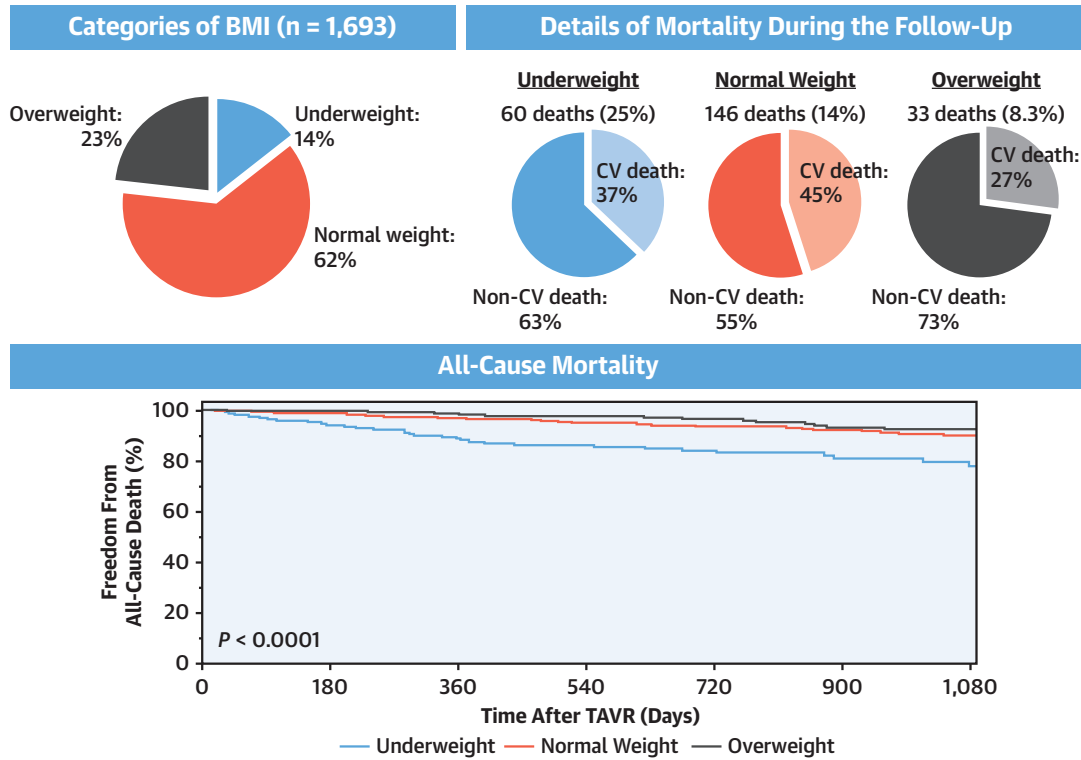
Abbreviations as in Tables 1 to 3.

date.^{9,11,12,18,19} Despite similar 30-day mortality rates, the underweight group had worse midterm outcomes in our analysis. Although the details of mortality were not analyzed in previous studies, our data showed that non-CV causes of mortality dominated, and the most common causes were respiratory disease, debilitation, and cancer. A low BMI is an important criterion for the diagnosis of frailty, which is associated with postdischarge mortality in patients hospitalized for pneumonia.²⁵ The underweight group had worse lung function, and the therapeutic delay of AS in the underweight group might have accelerated the decline in lung function, a manifestation of physical frailty.²⁶ Respiratory diseases, including interstitial pneumonitis, chronic obstructive pulmonary disease, and malignancy, could reduce body weight, and the association between a low BMI and respiratory and malignant diseases may involve an inverse causal relationship. The mean serum albumin level was lower in the underweight group and a negative prognostic factor after TAVR.²⁷ Albumin is a major

body protein, and hypoalbuminemia reflects low nutritional status, physical function, and immune function. Timely therapeutic intervention for AS is warranted to improve the outcomes of the underweight group. Physical and nutritional interventions for frailty should also improve the outcomes of underweight patients.²⁸

STUDY LIMITATIONS. First, it was an observational study, and possible confounding factors related to outcomes might not have been fully analyzed. Second, it used a BMI of <18.5 kg/m² as the criterion for underweight. The distribution of BMI differs among populations, and a cutoff value of 18.5 kg/m² may limit the generalizability of our results. Third, although it was not an objective of our study, physical indices other than BMI (ie, lean body mass, muscle mass, adipose distribution) might be more effective for stratifying the outcomes of patients undergoing TAVR. The temporal trends of body weight or BMI should be relevant to the prognosis after TAVR; however, our database had lacked the information.

CENTRAL ILLUSTRATION Prevalence and Outcomes of Underweight Patients Undergoing Transcatheter Aortic Valve Replacement



Tezuka T, et al. JACC: Asia. 2023;3(1):78-89.

Fourteen percent of study patients (n = 1,693) were underweight, and presented the worst survival after transcatheter aortic valve replacement (TAVR). Most mortalities were attributed to non-cardiovascular (CV) causes.

TABLE 6 Backgrounds and Outcome of Underweight Patients in the Previous and Current Studies

	Boukhris et al ⁹ (n = 412)	Yamamoto et al ⁹ (n = 3,072)	Sharma et al ¹⁸ (n = 31,929)	Voigtländer et al ¹² (n = 16,865)	Tezuka et al (n = 1,693)
Year of TAVR	2009-2019	2010-2011	2011-2015	2011-2014	2010-2020
Country	Canada	France	USA	Germany	Japan
UW patients, n (%)	35 (8.5) ^a	95 (3.1) ^b	806 (2.5) ^b	956 (5.7) ^a	242 (14.3) ^b
Age (y)	80	84	85	83	84
Women	66	79	71	75	76
BSA (m ²)	NA	1.4	1.5	NA	1.3
Hypertension	83	57	80	NA	62
PAD	26	15	32	NA	22
eGFR (mL/1.73 m ² /min)	39	NA	64	NA	57
Albumin (g/dL)	3.6	NA	3.6	NA	3.6
Ejection fraction (%)	61	54	56	NA	59
STS score (%)	6.7	NA	9.0	8.7	8.3
TF approach	63	78	53	71	88
30-d mortality	8.6	17	11	7.6	1.7
1-y mortality	11	32	35	27	NA

Values are % unless otherwise noted. ^aBody mass index <20 kg/m². ^bBody mass index <18.5 kg/m².
 UW = underweight patients; other abbreviations as in Tables 1 to 3.

CONCLUSIONS

The underweight group had worse midterm survival among patients undergoing TAVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Although the obesity paradox has been reported in TAVR, underweight patients were not included or numerically limited. The East Asian population undergoing TAVR has a lower mean BMI than those in Western Europe and North America. From the present analysis, underweight patients had a worse midterm prognosis, demonstrating the obesity paradox in this TAVR population.

TRANSLATIONAL OUTLOOK: Timely therapeutic intervention for AS is warranted to improve the outcomes of the underweight group. Physical and nutritional interventions for frailty should also improve the outcomes of underweight patients.

REFERENCES

- Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373:1083-1096.
- Jamaly S, Redfors B, Omerovic E, Carlsson L, Karason K. Prognostic significance of BMI after PCI treatment in ST-elevation myocardial infarction: a cohort study from the Swedish Coronary Angiography and Angioplasty Registry. *Open Heart*. 2021;8:e001479.
- Vaduganathan M, Lee R, Beckham AJ, et al. Relation of body mass index to late survival after valvular heart surgery. *Am J Cardiol*. 2012;110:1667-1678.
- Shah R, Gayat E, Januzzi JL Jr, et al. Body mass index and mortality in acutely decompensated heart failure across the world: a global obesity paradox. *J Am Coll Cardiol*. 2014;63:778-785.
- Khalid U, Ather S, Bavishi C, et al. Pre-morbid body mass index and mortality after incident heart failure: the ARIC Study. *J Am Coll Cardiol*. 2014;64:2743-2749.
- Elagizi A, Carbone S, Lavie CJ, Mehra MR, Ventura HO. Implications of obesity across the heart failure continuum. *Prog Cardiovasc Dis*. 2020;63:561-569.
- González-Ferreiro R, Muñoz-García AJ, López-Otero D, et al. Prognostic value of body mass index in transcatheter aortic valve implantation: A "J"-shaped curve. *Int J Cardiol*. 2017;232:342-347.
- van der Boon RM, Chieffo A, Dumonteil N, et al. Effect of body mass index on short- and long-term outcomes after transcatheter aortic valve implantation. *Am J Cardiol*. 2013;111:231-236.
- Yamamoto M, Mouillet G, Oguri A, et al. Effect of body mass index on 30- and 365-day complication and survival rates of transcatheter aortic valve implantation (from the French Aortic National CoreValve and Edwards 2 [FRANCE 2] registry). *Am J Cardiol*. 2013;112:1932-1937.
- Yamamoto M, Hayashida K, Watanabe Y, et al. Effect of body mass index <20 kg/m² on events in patients who underwent transcatheter aortic valve replacement. *Am J Cardiol*. 2015;115:227-233.
- Koifman E, Kiramijyan S, Negi SI, et al. Body mass index association with survival in severe aortic stenosis patients undergoing transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2016;88:118-124.
- Voigtländer L, Twerenbold R, Schäfer U, et al. Prognostic impact of underweight (body mass index <20 kg/m²) in patients with severe aortic valve stenosis undergoing transcatheter aortic valve implantation or surgical aortic valve replacement (from the German Aortic Valve Registry [GARY]). *Am J Cardiol*. 2020;129:79-86.
- Lee CH, Inohara T, Hayashida K, Park DW. Transcatheter aortic valve replacement in Asia: present status and future perspectives. *JACC: Asia*. 2021;1:279-293.
- Yokoyama H, Tobaru T, Muto Y, et al. Long-term outcomes in Japanese nonagenarians undergoing transcatheter aortic valve implantation: a multi-center analysis. *Clin Cardiol*. 2019;42:605-611.
- Saji M, Tobaru T, Higuchi R, et al. Usefulness of the transcatheter aortic valve replacement risk score to determine mid-term outcomes. *Circ J*. 2019;83:1755-1761.
- Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894(i-xii):1-253. PMID: 11234459.
- Kappetein AP, Head SJ, Génèreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60:1438-1454.
- Sharma A, Lavie CJ, Elmariah S, et al. Relationship of body mass index with outcomes after transcatheter aortic valve replacement: results from the National Cardiovascular Data-STS/ACC TVT Registry. *Mayo Clin Proc*. 2020;95:57-68.
- Boukhris M, Forcillo J, Potvin J, et al. Does "obesity paradox" apply for patients undergoing transcatheter aortic valve replacement? *Cardiovasc Revasc Med*. 2022;38:1-8.
- Hioki H, Watanabe Y, Kozuma K, et al. Risk stratification using lean body mass in patients undergoing transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2018;92:1365-1373.
- Driggin E, Gupta A, Madhavan MV, et al. Relation between modified body mass index and adverse outcomes after aortic valve implantation. *Am J Cardiol*. 2021;153:94-100.
- Chandrasekhar J, Hibbert B, Ruel M, Lam BK, Labinaz M, Glover C. Transfemoral vs non-transfemoral access for transcatheter aortic valve

implantation: a systematic review and meta-analysis. *Can J Cardiol*. 2015;31:1427-1438.

23. Muto Y, Higuchi R, Yoshihisa A, et al. Prevalence, predictors, and mid-term outcomes of non-home discharge after transcatheter aortic valve implantation. *Circ Rep*. 2020;2:617-624.

24. Higuchi R, Takayama M, Hagiya K, et al. Prolonged intensive care unit stay following transcatheter aortic valve replacement. *J Intensive Care Med*. 2020;35:154-160.

25. Kundi H, Wadhwa RK, Strom JB, et al. Association of frailty with 30-day outcomes for acute

myocardial infarction, heart failure, and pneumonia among elderly adults. *JAMA Cardiol*. 2019;4:1084-1091.

26. Vaz Fragoso CA, Enright PL, McAvay G, Van Ness PH, Gill TM. Frailty and respiratory impairment in older persons. *Am J Med*. 2012;125:79-86.

27. Yamamoto M, Shimura T, Kano S, et al. Prognostic value of hypoalbuminemia after transcatheter aortic valve implantation (from the Japanese Multicenter OCEAN-TAVI Registry). *Am J Cardiol*. 2017;119:770-777.

28. Ijaz N, Buta B, Xue QL, et al. Interventions for frailty among older adults with cardiovascular disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2022;79:482-503.

KEY WORDS body mass index, obesity paradox, transcatheter aortic valve replacement

APPENDIX For supplemental figures, please see the online version of this paper.