Prognostic Impact of Computed Tomography-Derived Abdominal Fat Area on Transcatheter Aortic Valve Implantation

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Background: Obesity has previously been identified as an indicator of good prognosis in patients undergoing transcatheter aortic valve implantation (TAVI), an association known as the “obesity paradox”. We investigated whether abdominal total fat area (TFA), visceral fat area (VFA), or subcutaneous fat area (SFA) are prognostic indicators of long-term clinical outcome in patients undergoing TAVI.

Methods and Results: We retrospectively analyzed 100 consecutive patients who underwent TAVI between December 2013 and April 2017. TFA, VFA, and SFA were measured from routine pre-procedural computed tomography (CT). Patients were divided into 2 groups according to median TFA, VFA, or SFA, and we investigated the association of abdominal fat area with adverse clinical events, including all-cause death and re-hospitalization due to worsening heart failure. At a median follow-up of 665 days, patients with higher SFA had significantly lower incidence of the composite outcome and all-cause death compared with patients with lower SFA (15.0% vs. 37.7%, $P=0.025$; and 8.9% vs. 23.7%, $P=0.047$, respectively). In contrast, patients with higher TFA or VFA did not show significant reduction in the incidences of the composite outcome or all-cause mortality.

Conclusions: CT-derived SFA had prognostic value in patients undergoing TAVI.

Key Words: Computed tomography; Obesity paradox; Subcutaneous fat area; Transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) is a widely accepted therapeutic option for symptomatic severe aortic valve stenosis (AS), especially in high-risk patients such as elderly or frail patients, and those with multiple comorbidities. Given that patients in this group have a higher intrinsic risk, TAVI has been reported to be associated with a relatively high rate of long-term mortality and re-hospitalization due to heart failure.¹ Therefore, it is important to identify patients at higher risk who may not benefit from this procedure.

Recently, body mass index (BMI) has been identified as an important prognostic indicator in patients undergoing TAVI. The “obesity paradox” refers to the paradoxical finding that higher BMI is an indicator of good prognosis not only in patients undergoing TAVI but also in patients with various diseases including diabetes, renal disease, stroke, and other cardiovascular diseases.^{2–15} BMI, however, is of potentially limited clinical value due to its inability to differentiate between fat mass and lean body mass, and

there have been no reports on the individual prognostic value of body fat.

The aim of the present study was therefore to evaluate the effect of abdominal fat on long-term clinical outcomes in patients undergoing TAVI. To clarify this, we focused on abdominal fat area, including the visceral fat area (VFA) and subcutaneous fat area (SFA) evaluated on computed tomography (CT), and evaluated their individual effects on long-term clinical outcomes such as all-cause mortality and re-hospitalization due to worsening heart failure in patients undergoing TAVI.

Methods

Subjects

This was a retrospective study of 100 consecutive patients with severe AS undergoing TAVI between December 2013 and April 2017 at Mitsui Memorial Hospital in Tokyo, Japan.

Received June 21, 2018; revised manuscript received August 13, 2018; accepted September 4, 2018; released online October 5, 2018
Time for primary review: 40 days

Division of Cardiology (T.O., K. Koseki, T.N., K.N., D.T., T.T., Y.S., K.S., H.K., K.Y., K. Komiyama, J.A., K.T.), Division of Cardiovascular Surgery (A.O., S.M.), Division of Anesthesia (M.Y.), Mitsui Memorial Hospital, Tokyo; Division of General Internal Medicine, Nakahara Medical Clinic, Kawasaki (S.K.), Japan

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Figure 1. Measurement of intra-abdominal fat area using multi-detector computed tomography data. Regions in red and blue indicate visceral fat area and subcutaneous fat area, respectively.

The multidisciplinary heart team discussed all cases, and a consensus was achieved regarding the therapeutic strategy in each case. TAVI was performed in a hybrid operating room under general anesthesia using balloon-expandable or self-expandable transcatheter aortic valves. All patients provided written informed consent prior to study enrollment and the identities of these patients have been protected.

Measurement of VFA and SFA

All patients underwent routine pre-procedural CT, which was performed with a 320-row multi-detector CT (Aquilion ONE, Canon Medical Systems, Tochigi, Japan) with patients placed in the decubitus dorsalis position. The images obtained were transferred to a dedicated workstation (Ziostation2, Ziosoft, Tokyo, Japan), in which the total fat area (TFA), VFA, and SFA were semi-automatically measured at the level of the umbilicus (**Figure 1**).

Endpoints and Follow-up

The occurrence of clinical events was recorded from admission and outpatient medical records or by telephone interview. All patient follow-up data were collected by March 2018. The median follow-up period was 665 days (IQR, 390–956 days). Endpoints were composite outcomes of all-cause mortality and re-hospitalization due to worsening heart failure. For patients who had multiple cardiac events during the study period, the time until the first event was used in the calculations.

Statistical Analysis

Categorical data are represented as frequencies and percentages and the differences between groups were evaluated with the chi-squared test. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Non-normally distributed variables are expressed as median (IQR) and were compared between groups using the Mann-Whitney U-test. Normally distributed variables are expressed as mean $\pm$ SD and were compared between groups using Student's t-test. Spearman's rank correlation coefficients (r) were calculated to assess the link and the degree of association between BMI and abdominal fat area. Event-free survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% CI for the composite outcome and all-cause mortality. Because this was an observational study and differences in

baseline characteristics could significantly affect outcome, sensitivity analysis was performed to adjust for confounders using 2 Cox regression models. The first model was adjusted for age and gender, both of which should be considered for abdominal fat area. In the second model, we selected covariates that were different ($P<0.1$) between patients with and without the composite outcome. In this model, we used a stepwise-backward selection with a probability to remove the effect from the regression at $P>0.05$. Throughout the present study, $P<0.05$ was considered significant. Statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics According to Composite Outcome

Baseline patient characteristics are listed in **Table 1**. During the follow-up period, 34 patients experienced clinical events, including 20 cases of all-cause mortality and 20 cases of re-hospitalization due to worsening heart failure.

The composite outcome was observed in patients who had a significantly higher prevalence of atrial fibrillation, significantly lower hemoglobin, and significantly higher brain natriuretic peptide. There were no differences in body weight, BMI, waist circumference (WC), or body surface area (BSA) between patients who reached the composite outcome and those who did not. In terms of CT-derived abdominal fat area, SFA was numerically lower in patients who reached the composite outcome, whereas VFA was similar between patients who reached the composite outcome and those who did not.

Baseline Characteristics According to SFA

We divided all patients into 2 groups according to median SFA: the low-SFA group (SFA $<92.6\text{ cm}^2$, $n=50$) and the high-SFA group (SFA $\geq 92.6\text{ cm}^2$, $n=50$). Baseline characteristics are listed in **Table 2**. As expected, the low-SFA group had lower body weight, WC, BMI, BSA, TFA, and VFA. There were no significant differences in other baseline characteristics, including age, gender, clinical status, concomitant diseases, previous medical history, laboratory data, echocardiographic data, and procedures.

BMI and Abdominal Fat Area

We assessed the correlation between BMI and abdominal fat area (**Figure 2**). BMI had a positive and statistically

Table 1. Baseline Patient Characteristics vs. Composite Outcome

	All patients (n=100)	Composite outcome (+) (n=34)	Composite outcome (-) (n=66)	P-value
Age (years)	84 (81–88)	84 (80–89)	85 (81–87)	0.813
Female	69 (69.0)	25 (73.5)	44 (66.7)	0.649
Height (cm)	151.2±8.2	150.4±8.8	151.6±7.9	0.515
Weight (kg)	50.4±9.7	49.7±8.7	50.7±10.2	0.618
WC (cm)	79.5 (71.8–87.3)	78.7 (72.5–84.1)	80.5 (71.4–87.6)	0.485
BMI (kg/m²)	22.0±4.0	21.8±4.6	22.0±3.8	0.800
BSA (m²)	1.45±0.15	1.44±0.14	1.46±0.16	0.527
CT-derived abdominal fat area (cm²)				
TFA	174.4 (56.4–255.2)	131.6 (52.2–237.3)	183.8 (62.6–264.2)	0.291
SFA	92.6 (32.9–144.0)	61.7 (35.0–126.45)	100.1 (32.2–148.8)	0.188
VFA	63.0 (23.3–107.9)	64.7 (14.0–108.8)	63.0 (29.5–106.9)	0.678
Logistic EuroSCORE (%)	10.43 (7.01–17.47)	13.57 (8.48–21.27)	10.11 (6.96–15.21)	0.075
STS score: mortality (%)	5.26 (3.96–7.10)	5.00 (3.76–7.54)	5.44 (3.97–6.91)	0.949
NYHA functional class III/IV	38 (38.0)	14 (41.2)	24 (36.4)	0.668
Concomitant disease				
Hypertension	69 (69.0)	25 (73.5)	44 (66.7)	0.649
Diabetes	25 (25.0)	6 (17.6)	19 (28.8)	0.330
Dyslipidemia	57 (57.0)	17 (50.0)	40 (60.6)	0.394
CKD (eGFR <60 mL/min/1.73 m ²)	35 (35.0)	13 (38.2)	22 (33.3)	0.662
COPD	10 (10.0)	5 (14.7)	5 (7.6)	0.301
Atrial fibrillation	27 (27.0)	14 (41.2)	13 (19.7)	0.032
Previous history				
Previous MI	2 (2.0)	0 (0.0)	2 (3.0)	0.547
Prior stroke	14 (14.0)	8 (23.5)	6 (9.1)	0.068
Previous PAD	2 (2.0)	0 (0.0)	2 (3.0)	0.547
Laboratory data (before procedure)				
Hemoglobin (g/dL)	10.9 (9.7–12.3)	10.0 (9.2–11.1)	11.4 (10.2–12.5)	0.006
WBC (/μL)	4,900 (4,100–6,600)	4,500 (3,900–6,470)	5,100 (4,300–6,600)	0.118
Platelet count (10 ⁴ /μL)	18.7 (14.5–21.4)	17.1 (13.8–21.3)	18.9 (14.7–21.4)	0.291
eGFR (mL/min/1.73 m ²)	54.6 (38.6–64.4)	48.9 (38.9–64.6)	56.2 (37.1–64.2)	0.603
ALB (g/dL)	4.1 (3.7–4.3)	3.9 (3.6–4.3)	4.2 (3.7–4.4)	0.065
T-CHO (mg/dL)	176.0 (151.5–195.0)	164.5 (147.5–188.8)	177.5 (153.5–195.8)	0.522
Na (mEq/L)	139 (137–142)	139 (136–141)	140 (137–142)	0.206
K (mEq/L)	4.4 (4.0–4.8)	4.4 (4.1–4.8)	4.4 (3.9–4.8)	0.461
BNP (pg/mL)	183.7 (115.3–446.3)	333.5 (151.1–561.1)	164.9 (112.2–363.8)	0.049
Echocardiographic data				
Before procedure				
LVEF (%)	65.2±14.5	63.6±14.0	66.1±14.8	0.425
LVEF ≤35%	6 (6.0)	1 (2.9)	5 (7.7)	0.661
Calculated AVA (cm ²)	0.65±0.18	0.67±0.19	0.65±0.18	0.617
Mean aortic gradient (mmHg)	58.6±18.4	54.6±19.5	60.7±17.6	0.117
Peak jet velocity (m/s)	4.78±0.77	4.58±0.83	4.88±0.72	0.061
Aortic regurgitation ≥moderate	12 (12.0)	5 (14.7)	7 (10.8)	0.747
Procedural data				
Trans-femoral approach	87 (87.0)	28 (82.4)	59 (89.4)	0.356
Balloon-expandable valves (XT/S3)	86 (86.0)	31 (91.2)	55 (83.3)	0.371
After procedure				
Calculated AVA (cm ²)	1.63±0.43	1.52±0.39	1.68±0.45	0.099
Mean aortic gradient (mmHg)	11.8±5.2	11.2±5.1	12.0±5.3	0.481
Peak jet velocity (m/s)	2.17±0.42	2.09±0.42	2.20±0.42	0.206
Aortic regurgitation ≥moderate	4 (4.0)	1 (2.9)	3 (4.6)	1.000

Data given as mean±SD, median (IQR) or n (%). ALB, albumin; AVA, aortic valve area; BNP, brain natriuretic peptide; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; K, potassium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; Na, sodium; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; S3, SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA); SFA, subcutaneous fat area; STS, Society of Thoracic Surgeons; T-CHO, total cholesterol; TFA, total fat area; VFA, visceral fat area; WBC, white blood cell count; WC, waist circumference; XT, SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA).

	Low-SFA group (n=50)	High-SFA group (n=50)	P-value
Age (years)	85 (81–89)	84 (80–87)	0.189
Female	30 (60)	39 (78)	0.083
Height (cm)	151.8±9.2	150.6±7.1	0.445
Weight (kg)	44.7±8.1	56.1±7.6	<0.001
WC (cm)	71.6 (67.1–76.2)	86.9 (81.7–91.1)	<0.001
BMI (kg/m²)	19.3±2.5	24.6±3.5	<0.001
BSA (m²)	1.39±0.16	1.52±0.12	<0.001
CT-derived abdominal fat area (cm²)			
TFA	55.7 (19.4–115.3)	250.9 (198.0–322.0)	<0.001
SFA	31.4 (10.1–59.3)	144.9 (117.7–193.9)	<0.001
VFA	23.0 (8.9–53.9)	96.5 (63.6–135.4)	<0.001
Logistic EuroSCORE (%)	10.11 (6.59–17.60)	10.74 (7.48–16.62)	0.893
STS score: mortality (%)	5.86 (3.91–7.29)	4.81 (3.97–7.01)	0.279
NYHA functional class III/IV	18 (36)	20 (40)	0.837
Concomitant disease			
Hypertension	36 (72)	33 (66)	0.666
Diabetes	11 (22)	14 (28)	0.645
Dyslipidemia	25 (50)	32 (64)	0.225
CKD (eGFR <60 mL/min/1.73 m ²)	16 (32)	19 (38)	0.675
COPD	4 (8)	6 (12)	0.741
Atrial fibrillation	15 (30)	12 (24)	0.653
Previous history			
Previous MI	1 (2)	1 (2)	1.000
Prior stroke	9 (18)	5 (10)	0.388
Previous PAD	1 (2)	1 (2)	1.000
Laboratory data (before procedure)			
Hemoglobin (g/dL)	10.8 (9.4–12.5)	11.1 (10.0–12.2)	0.809
WBC (/μL)	4,700 (4,030–6,570)	4,950 (4,120–6,750)	0.748
Platelet count (10 ⁴ /μL)	18.7 (14.5–21.4)	18.5 (14.3–21.9)	0.937
eGFR (mL/min/1.73 m ²)	55.5 (39.8–65.7)	53.2 (35.8–62.1)	0.252
ALB (g/dL)	4.0 (3.7–4.4)	4.1 (3.7–4.3)	0.616
T-CHO (mg/dL)	179.5 (153.5–196.0)	176.0 (150.5–185.8)	0.756
Na (mEq/L)	139 (135–141)	140 (137–142)	0.315
K (mEq/L)	4.5 (4.2–4.9)	4.4 (4.0–4.6)	0.241
BNP (pg/mL)	210.6 (127.5–436.0)	163.7 (104.5–441.3)	0.632
Echocardiographic data			
Before procedure			
LVEF (%)	65.2±14.6	65.2±14.5	0.977
LVEF ≤35%	2 (4)	4 (8)	0.436
Calculated AVA (cm ²)	0.65±0.17	0.66±0.19	0.817
Mean aortic gradient (mmHg)	57.8±19.0	59.4±18.0	0.662
Peak jet velocity (m/s)	4.74±0.79	4.18±0.75	0.628
Aortic regurgitation ≥moderate	7 (14)	5 (10)	0.760
Procedural data			
Trans-femoral approach	41 (82)	46 (92)	0.234
Balloon-expandable valves (XT/S3)	44 (88)	42 (84)	0.774
After procedure			
Calculated AVA (cm ²)	1.56±0.44	1.69±0.43	0.174
Mean aortic gradient (mmHg)	11.4±5.0	12.1±5.4	0.557
Peak jet velocity (m/s)	2.16±0.43	2.17±0.41	0.927
Aortic regurgitation ≥moderate	4 (8)	0 (0)	0.117

Data given as mean±SD, median (IQR) or n (%). Abbreviations as in Table 1.

Figure 2. Body mass index (BMI) vs. total fat area (TFA), visceral fat area (VFA), and subcutaneous fat area (SFA).

Figure 3. Kaplan-Meier analysis for the composite outcome, including all-cause mortality and re-hospitalization due to worsening heart failure and all-cause mortality according to median (A) subcutaneous fat area (SFA), (B) visceral fat area (VFA), and (C) total fat area (TFA).

significant correlation with TFA ($r=0.832$, $P<0.001$), VFA ($r=0.747$, $P<0.001$), and SFA ($r=0.807$, $P<0.001$).

Abdominal Fat Area and Long-Term Clinical Outcome

Cumulative incidence of the composite outcome and all-cause mortality were compared between patients with lower and higher SFA, VFA, or TFA. The Kaplan-Meier survival curves for the composite outcome and all-cause mortality are shown in **Figure 3**. During a median follow-up period of 665 days, lower SFA was significantly associated with higher cumulative incidence of the composite outcome

(37.7% vs. 15.0%, $P=0.025$) and all-cause mortality (23.7% vs. 8.9%, $P=0.047$). In contrast, lower VFA had no significant effect on the cumulative incidence of composite outcome (29.5% vs. 23.6%, $P=0.692$) or all-cause mortality (16.7% vs. 16.2%, $P=0.66$). Consequently, lower TFA had a tendency to be associated with a higher cumulative incidence of the composite outcome (31.2% vs. 21.7%, $P=0.218$) and all-cause mortality (19.2% vs. 13.7%, $P=0.175$). Statistical significance, however, was not observed. Similarly, lower BMI, lower BSA, and lower WC were not significantly associated with the composite outcome. For

Figure 4. Kaplan-Meier analysis for the composite outcome, including all-cause mortality and re-hospitalization due to worsening heart failure and all-cause mortality according to median (A) body mass index (BMI), (B) body surface area (BSA), and (C) waist circumference.

Table 3. Cox Proportional Hazard Analysis for the Composite Outcome

	Univariate		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Lower SFA	2.18 (1.08–4.40)	0.029	2.12 (1.04–4.34)	0.039	2.77 (1.27–6.02)	0.010
Age	1.03 (0.97–1.09)	0.390	1.01 (0.95–1.08)	0.727	Not included	
Female	0.82 (0.38–1.76)	0.611	0.83 (0.38–1.80)	0.639	Not included	
Logistic EuroSCORE	1.02 (0.98–1.06)	0.418			Dropped	
Atrial fibrillation	2.06 (1.03–4.10)	0.040			Dropped	
Prior stroke	2.34 (1.05–5.24)	0.039			2.65 (1.13–6.18)	0.025
Hemoglobin (g/dL)	0.74 (0.59–0.93)	0.010			0.73 (0.57–0.92)	0.009
ALB (g/dL)	0.49 (0.24–0.98)	0.045			Dropped	
BNP (pg/mL)	1.00 (1.00–1.00)	0.010			Dropped	
Post-procedure AVA	0.53 (0.23–1.20)	0.128			Dropped	

Model 1, adjusted for age and gender. Model 2, adjusted for Logistic EuroSCORE, atrial fibrillation, prior stroke, hemoglobin, ALB, BNP, calculated post-procedure AVA, using stepwise-backward selection. Abbreviations as in Table 1.

all-cause mortality, only lower BMI was associated with higher cumulative incidence (23.6% vs. 9.0%, $P=0.041$; Figure 4).

The results of the Cox regression analysis for the cumulative incidence of the composite outcome are given in Table 3. On Cox univariate analysis, the HR for the composite outcome or all-cause mortality were 2.18 (95% CI: 1.08–4.40, $P=0.029$) and 2.56 (95% CI: 0.98–6.67, $P=0.055$) for the lower SFA group, respectively. After adjusting for age and gender, lower SFA was independently associated with higher risk of the composite outcome (HR,

2.12; 95% CI: 1.04–4.34, $P=0.039$). Likewise, on stepwise Cox regression modeling, there was an increased risk of the composite outcome in the lower SFA group (HR, 2.77; 95% CI: 1.27–6.02, $P=0.010$).

Discussion

The present study has demonstrated that SFA was significantly associated with long-term clinical outcome in patients undergoing TAVI, whereas VFA and TFA were not. To the best of our knowledge, this is the first study to evaluate

the relationship between abdominal fat area and long-term clinical outcomes in patients undergoing TAVI.

Pre-procedural CT is currently considered the gold standard for the evaluation of patients undergoing TAVI, and is now widely used as a routine pre-procedural evaluation at a number of institutions.^{16–19} Therefore, SFA, which can be easily measured on pre-procedural CT,^{20–22} could be a simple and useful prognostic indicator in patients undergoing TAVI.

Previous studies using BMI as a measure of obesity have demonstrated an obesity paradox in patients undergoing TAVI, as well as in patients undergoing percutaneous coronary intervention (PCI) or surgical aortic valve replacement (SAVR).^{9–11} BMI, however, is a non-specific parameter that is potentially limited by the inability to differentiate between fat mass and lean body mass. Moreover, although BMI has a positive correlation with abdominal fat area, BMI cannot differentiate visceral fat mass from subcutaneous fat mass. Therefore, it has been unclear what component of BMI affects clinical outcome in patients undergoing TAVI. The present study suggests that not visceral fat but subcutaneous fat has prognostic value in patients undergoing TAVI.

Possible explanations for the obesity paradox have been discussed in previous studies. Given that obesity measured by BMI includes both lean body mass and fat mass, higher lean body mass, which consists of skeletal muscle mass, was suggested to be one of the reasons for the obesity paradox. Namely, lower skeletal muscle mass is correlated with frailty and was suggested to be associated with early poor outcome and high-resource utilization after TAVI.²³ The present study, however, suggests that fat mass, especially subcutaneous fat mass, might also have prognostic value. This provides another possible mechanism for the obesity paradox in patients undergoing TAVI. First, the aging population of patients who tend to undergo TAVI might be different from other populations in which the obesity paradox has been previously suggested. In the present study, the median VFA and SFA for all patients were 63.0 cm² (IQR, 23.2–107.9 cm²) and 92.6 cm² (IQR, 32.9–144.0 cm²), respectively, which are far lower than the average reported in previous studies.^{24,25} This suggests that the aging population of patients undergoing TAVI may have lower baseline body fat. Therefore, lower SFA in this population might suggest excessive body fat loss, which indicates malnutrition, multi-organ dysfunction, or multiple comorbidities including occult malignancy. These factors have been identified as significant predictors of mortality in other populations,^{26–29} and could therefore be applicable to the present situation. In this context, this mechanism seems to be applicable not only to TAVI patients but also to general elderly patients. To our knowledge, however, there are no studies limited to elderly patients that evaluate the prognostic impact of abdominal fat area. Moreover, subcutaneous fat has been demonstrated to have cardiovascular benefits due to secretion of adiponectin, which has anti-inflammatory, insulin-sensitizing, and anti-atherogenic effects.³⁰ These cardiovascular benefits could be another mechanism contributing to the aforementioned findings.

Study Limitations

This study had several limitations worth noting. A major limitation of the study was that it was a retrospective, single-center study with a small sample size. Furthermore, the clinical events were not adjudicated by an independent

clinical event committee. Therefore, the results should be interpreted cautiously until verified in further studies. To our knowledge, however, this study is the first to report on the prognostic value of CT-derived SFA. As noted, SFA can be easily measured in patients undergoing TAVI, and is a more specific parameter of obesity than BMI, which has been previously established as a useful prognostic indicator in patients undergoing TAVI. Therefore, despite the limitations of the study, the present findings provide a novel prognostic indicator in patients undergoing TAVI, and may provide new insights into the concept of the obesity paradox. Further studies are needed to validate the current results and also to determine whether these findings are reproducible in other populations.

Conclusions

In patients undergoing TAVI, CT-derived SFA was an independent predictor of long-term adverse clinical outcome, whereas VFA was not. This simple and practical marker might be useful for predicting long-term clinical outcome in patients undergoing TAVI.

Disclosures

K.T. receives honoraria from Canon Medical Systems, Edwards Lifesciences, and Medtronic. M.Y. receives honoraria from Edwards Lifesciences. The other authors declare no conflicts of interest.

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