Original Article

Clinical Outcomes of Subcutaneous and Visceral Adipose Tissue Characteristics Assessed in Patients Underwent Transcatheter Aortic Valve Replacement

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ABSTRACT

Background: Adipose tissue (AT) characteristics are considered to be a marker for predicting clinical outcomes. This study aimed to investigate the prognostic value of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) computed tomography (CT) assessment in patients who underwent transcatheter aortic valve replacement (TAVR).

Methods: We used the Japanese multicentre registry data of 1372 patients (age: 84.5 ± 5.0 years, women: 70.6%) who underwent TAVR. The SAT and VAT were assessed according to the preprocedural CT

RÉSUMÉ

Introduction : Les caractéristiques du tissu adipeux (TA) sont considérées comme un marqueur de la prédiction des résultats cliniques. La présente étude avait pour objectif d'examiner la valeur pronostique de l'évaluation par tomodensitométrie (TDM) du tissu adipeux sous-cutané (TASC) et du tissu adipeux viscéral (TAV) des patients qui subissaient un remplacement valvulaire aortique par cathéter (RVAC).

Méthodes : Nous avons utilisé les données du registre multicentrique japonais de 1 372 patients (âge : 84,5 ± 5,0 ans, femmes : 70,6 %) qui subissaient un RVAC. Nous avons évalué le TASC et le TAV selon la

Obesity has been proven to be a major risk factor for cardiovascular disorders; however, several observational studies have reported that obesity offers a survival advantage in patients who have undergone cardiac surgery and catheter intervention.[1-4] A meta-analysis of patients who underwent transcatheter aortic valve replacement (TAVR) also identified

the paradoxical survival benefits of a higher body mass index (BMI) in patients defined as obese.[5] Obesity is a heterogeneous condition with individual variability in fat deposition and is associated with metabolic complications.[6] In addition to BMI distribution, fat-distribution studies have thus far focused on the absolute volume of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) in any given depot.[7,8] Several lines of evidence suggest that measurement of these fat characteristics by computed tomography (CT) is clinically important for evaluating the risk of mortality in elderly and patients with malignant disease.[9-12] Thus, quantitative (area) and qualitative (density) adipose tissue (AT) assessment with CT will be helpful when evaluating the relationship between prognosis and obesity. Because CT scans

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area and density. Baseline characteristics and clinical outcomes were compared based on the differences in AT characteristics. The independent associations with all-cause mortality after TAVR were evaluated according to the CT area and density of AT.

Results: Low-volume area of SAT and VAT was associated with worse clinical outcomes compared with high-volume area of SAT and VAT in patients who underwent TAVR (log-rank test $P = 0.016$ and $P = 0.014$). High CT density of SAT and VAT was associated with increasing mortality in comparison with low CT density of SAT and VAT (log-rank test $P < 0.001$ and $P = 0.007$). The Cox regression multivariate analysis demonstrated the independent association of increased all-cause mortality in the high SAT and VAT density (hazard ratio [HR]: 1.41, 95% confidence interval [CI]: 1.06-1.88, $P = 0.019$, and HR: 1.34, 95% CI: 1.03-1.76, $P = 0.031$, respectively), but not in the low SAT and VAT area (HR: 0.85, 95% CI: 0.74-1.29, $P = 0.85$, and HR: 0.78, 95% CI: 0.60-1.03, $P = 0.085$, respectively).

Conclusions: CT-derived AT characteristics, particularly the qualitative assessments, were useful for predicting the prognosis in patients after TAVR.

surface et la densité à la TDM préinterventionnelle. Nous avons comparé les caractéristiques initiales et les résultats cliniques en nous basant sur les différences dans les caractéristiques du TA. Nous avons évalué les associations indépendantes à la mortalité toutes causes confondues après le RVAC selon la surface et la densité du TA à la TDM.

Résultats : La surface de faible volume du TASC et du TAV était associée à de plus mauvais résultats cliniques que la surface de grand volume du TASC et du TAV chez les patients qui subissaient le RVAC (test logarithmique par rangs $P = 0,016$ et $P = 0,014$). La densité du TASC et du TAV à la TDM était associée à l'augmentation de la mortalité en comparaison d'une faible densité du TASC et du TAV à la TDM (test logarithmique par rangs $P < 0,001$ et $P = 0,007$). L'analyse multivariée selon le modèle de régression de Cox démontrait l'association indépendante de l'augmentation de la mortalité toutes causes confondues lors de densité élevée du TASC et du TAV (rapport de risque [RR] 1,41, intervalle de confiance [IC] à 95 %, 1,06-1,88, $P = 0,019$, et RR 1,34, IC à 95 %, 1,03-1,76, $P = 0,031$, respectivement), mais non lors de faible surface du TASC et du TAV (RR 0,85, IC à 95 %, 0,74-1,29, $P = 0,85$, et RR 0,78, IC à 95 % : 0,60-1,03, $P = 0,085$, respectivement).

Conclusions : Les caractéristiques du TA acquises par TDM, particulièrement les évaluations qualitatives, étaient utiles à la prédiction du pronostic des patients après le RVAC.

of the chest, abdomen, and pelvis are routinely performed in patients undergoing TAVR for preoperative planning, these images can be effectively used to obtain these non-cardiovascular tissue characteristics. A few reports have evaluated the prognostic impact of AT characteristics assessed by CT in patients who underwent TAVR.[13-15] However, there remains a paucity of data due to the relatively small sample sizes and lack of CT density information. The current study therefore aimed to investigate the clinical impact of CT-derived AT area and density information on the prognosis of patients who underwent TAVR using large-scale Japanese multicentre registry data.

Methods

The data were obtained from the Japanese **O**ptimized **C**ath**e**ter v**A**lvular i**N**tervention-**T**ranscatheter **A**ortic **V**alve

Implantation (OCEAN-TAVI) registry. Between October 2013 and July 2016, a total of 1391 patients were treated by the TAVR procedure in 12 centres. All patients were diagnosed with severe aortic stenosis on the basis of conventional echocardiographic findings. Preprocedural multidetector CT was performed to assess the appropriateness of TAVR procedures. Only 1 patient did not undergo CT examination due to severely reduced renal function. The CT data of 18 patients were not sufficient for the analysis due to a lack of whole images and/or poor image quality. Thus, the CT data of the remaining 1372 patients were analysed in this study. Clinical data, patient characteristics, laboratory data, echocardiographic data, procedural variables, length of hospital stay, and in-hospital and all-cause mortality rates before and after TAVR were examined. The detailed TAVR procedures were described previously.[16,17] The Edwards SAPIEN-XT/SAPIEN-3 (Edwards Lifesciences, Irvine,

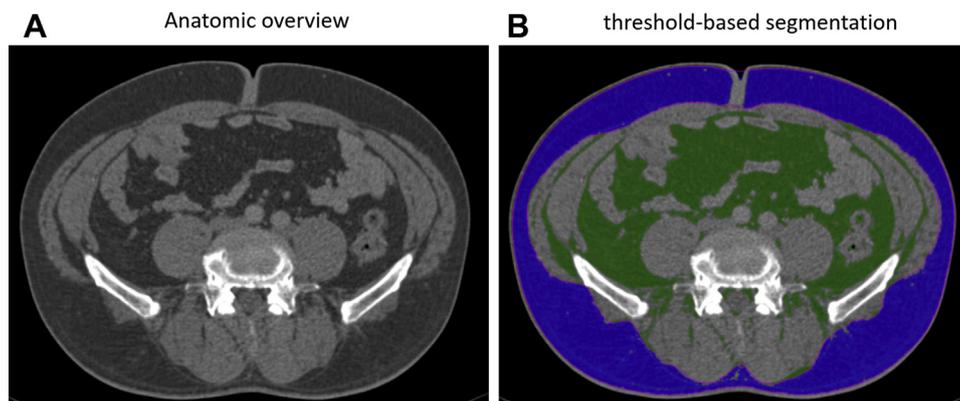**Figure 1.** Abdominal fat area measurements by computed tomography. (**A**) Anatomic overview and (**B**) threshold-based segmentation. Regions in blue and green indicate the subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), respectively. The SAT area is 190.0 cm^2, the SAT density is −96.42 Hounsfield units (HU), the VAT area is 147.5 cm^2, and the VAT density is −92.10 HU.

Table 1. Baseline characteristics of study patients

	Overall, N = 1373	SAT density			VAT density		
		Low, n = 544	High, n = 829	P value	Low, n = 850	High, n = 523	P value
Baseline clinical characteristics							
Age (y)	84.5 ± 5.1	83.6 ± 5.0	85.1 ± 5.0	< 0.001	84.0 ± 5.2	85.3 ± 4.8	< 0.001
< 80 (n)	186 (13.5%)	93 (17.1%)	93 (11.2%)	< 0.001	130 (15.3%)	56 (10.7%)	< 0.001
80-84 (n)	431 (31.4%)	205 (37.7%)	226 (27.3%)		300 (35.3%)	131 (25.0%)	
85-89 (n)	567 (41.3%)	192 (35.3%)	375 (45.2%)		320 (37.6%)	247 (47.2%)	
≥ 90 (n)	189 (13.8%)	54 (9.9%)	135 (16.3%)		100 (11.8%)	89 (17.0%)	
Male (n)	404 (29.4%)	206 (37.9%)	198 (23.9%)	< 0.001	311 (36.6%)	93 (17.8%)	< 0.001
Height (cm)	149.4 ± 9.1	151.4 ± 9.1	148.2 ± 8.8	< 0.001	151.0 ± 9.1	146.9 ± 8.5	< 0.001
Weight (kg)	49.5 ± 9.1	54.9 ± 9.7	46.3 ± 8.7	< 0.001	53.0 ± 9.8	44.3 ± 87.9	< 0.001
BSA (m²)	1.4 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	< 0.001	1.5 ± 0.2	1.3 ± 0.1	< 0.001
BMI (kg/m²)	22.2 ± 3.6	23.9 ± 3.4	21.0 ± 3.2	< 0.001	23.2 ± 3.5	20.5 ± 3.0	< 0.001
BMI < 20 (n)	388 (28.3%)	59 (10.8%)	329 (39.7%)	< 0.001	149 (17.5%)	239 (45.7%)	< 0.001
NYHA class, III or IV	684 (49.8%)	253 (46.5%)	431 (52.0%)	0.047	420 (49.4%)	264 (50.5%)	0.739
Logistic EuroSCORE (%)	12.8 (8.4 to 21.6)	12.0 (7.5 to 19.4)	13.3 (8.9 to 22.5)	< 0.001	12.4 (7.6 to 20.5)	13.6 (9.0 to 22.4)	0.003
EuroSCORE II (%)	3.8 (2.3 to 6.1)	3.6 (2.1 to 5.7)	3.8 (2.5 to 6.5)	0.004	3.7 (2.2 to 6.1)	3.9 (2.5 to 6.1)	0.138
STS score (%)	6.7 (4.7 to 9.8)	6.0 (4.0 to 8.9)	7.2 (5.2 to 10.4)	< 0.001	6.4 (4.3 to 9.5)	7.1 (5.2 to 10.0)	< 0.001
< 4%	226 (16.5%)	132 (24.3%)	94 (11.3%)	< 0.001	172 (20.2%)	54 (10.3%)	< 0.001
4-8%	641 (46.7%)	248 (45.6%)	393 (47.4%)		375 (44.1%)	266 (50.9%)	
> 8%	506 (36.9%)	164 (30.1%)	342 (41.3%)		303 (35.6%)	203 (38.8%)	
Clinical frailty scale	4.0 ± 1.3	3.8 ± 1.1	4.1 ± 1.3	< 0.001	3.8 ± 1.2	4.2 ± 1.3	< 0.001
Preprocedural laboratory data							
BNP (pg/mL)	272.6 (127.3 to 570.9)	209.8 (94.0 to 438.2)	344.6 (151.6 to 694.0)	< 0.001	233.1 (106.0 to 497.6)	364.6 (162.7 to 769.5)	< 0.001
Creatinine (mg/dL)	1.1 ± 0.6	1.1 ± 0.5	1.1 ± 0.6	0.997	1.1 ± 0.5	1.0 ± 0.6	0.065
Estimated GFR (mL/min)	50.8 ± 19.8	51.3 ± 19.6	50.6 ± 20.0	0.533	50.3 ± 19.5	51.7 ± 20.4	0.231
Haemoglobin (g/dL)	11.2 ± 1.6	11.6 ± 1.6	10.9 ± 1.6	< 0.001	11.4 ± 1.7	10.8 ± 1.5	< 0.001
Comorbidities							
Peripheral artery disease (n)	211 (15.4%)	76 (14.0%)	135 (16.3%)	0.252	125 (14.7%)	86 (16.4%)	0.397
Prior MI (n)	90 (6.6%)	39 (7.2%)	51 (6.2%)	0.504	61 (7.2%)	29 (5.5%)	0.262
Prior PCI (n)	353 (25.7%)	161 (29.6%)	192 (23.2%)	0.008	236 (27.8%)	117 (22.4%)	0.026
Prior CABG (n)	105 (7.6%)	51 (9.4%)	54 (6.5%)	0.061	77 (9.1%)	28 (5.4%)	0.012
Prior stroke (n)	160 (11.7%)	64 (11.8%)	96 (11.6%)	0.932	104 (12.2%)	56 (10.7%)	0.436
Diabetes mellitus (n)	291 (21.2%)	148 (27.2%)	143 (17.2%)	< 0.001	219 (25.8%)	72 (13.8%)	< 0.001
Hypertension (n)	1081 (78.8%)	445 (81.8%)	636 (76.7%)	0.026	690 (81.2%)	391 (74.8%)	0.005
Chronic kidney disease (n)	844 (61.5%)	334 (61.4%)	510 (61.5%)	1.0	532 (62.6%)	312 (59.7%)	0.279
Pulmonary disease (n)	303 (22.1%)	114 (21.0%)	189 (22.8%)	0.426	190 (22.4%)	113 (21.6%)	0.789
Liver disease (n)	44 (3.2%)	15 (2.8%)	29 (3.5%)	0.532	23 (2.7%)	21 (4.0%)	0.207
Active cancer (n)	69 (5.0%)	29 (5.3%)	40 (4.8%)	0.706	38 (4.5%)	31 (5.9%)	0.253
Echocardiographic data							
LVEF (%)	61.9 ± 13.1	62.3 ± 12.8	61.7 ± 13.3	0.402	61.9 ± 12.9	61.9 ± 13.4	0.99
AVA (cm²)	0.64 ± 0.17	0.66 ± 0.17	0.62 ± 0.17	< 0.001	0.65 ± 0.17	0.61 ± 0.17	< 0.001
Indexed AVA (cm²/m²)	0.45 ± 0.11	0.44 ± 0.11	0.45 ± 0.12	0.017	0.44 ± 0.11	0.46 ± 0.12	0.007
Peak velocity (m/s)	4.6 ± 0.8	4.5 ± 0.8	4.6 ± 0.8	0.129	4.5 ± 0.8	4.6 ± 0.8	0.006
Peak gradient (mm Hg)	86.1 ± 29.7	84.6 ± 28.1	87.0 ± 30.6	0.135	84.4 ± 28.7	88.8 ± 31.0	0.008
Mean gradient (mm Hg)	50.4 ± 18.2	49.5 ± 17.3	51.1 ± 18.8	0.103	49.5 ± 17.6	52.0 ± 19.1	0.014
AR ≥ grade 2 (n)	127 (9.2%)	41 (7.5%)	86 (10.4%)	0.086	81 (9.5%)	46 (8.8%)	0.702
MR ≥ grade 2 (n)	133 (9.7%)	45 (8.3%)	88 (10.6%)	0.162	81 (9.5%)	52 (9.9%)	0.851

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Computed tomography data

SAT area (cm²/m)	104.2 (60.6 to 152.0)	149.9 (112.9 to 190.6)	73.9 (41.3 to 110.0)	130.0 (91.7 to 174.1)	59.7 (31.3 to 94.1)	< 0.001
SAT density (HU)	−89.2 (−97.6 to −75.4)	−99.4 (−103.9 to −96.5)	−79.7 (−87.2 to −67.7)	−96.0 (−101.0 to −89.6)	−72.3 (−81.9 to −63.9)	< 0.001
VAT area (cm²/m)	91.8 (53.8 to 138.0)	137.6 (100.7 to 171.2)	64.8 (39.7 to 97.7)	123.7 (91.7 to 162.0)	49.4 (32.5 to 71.2)	< 0.001
VAT density (HU)	−78.8 (−87.0 to −69.6)	−87.9 (−93.0 to −83.3)	−71.6 (−78.0 to −65.3)	−84.9 (−90.6 to −79.8)	−66.9 (−71.1 to −62.9)	< 0.001

Values are numbers (%) or mean ± standard deviation, median with interquartile range.
AR, aortic regurgitation; AVA, aortic valve area; BMI, body mass index; BNP, B-type natriuretic peptide; BSA, body surface area; CABG, coronary artery bypass graft; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; HU, Hounsfield units; LVEF, left ventricle ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAT, subcutaneous adipose tissue; STS score, Society of Thoracic Surgeons Predictive Risk of Mortality; VAT, visceral adipose tissue.

CA) balloon-expandable prosthesis and the Medtronic CoreValve/Evoult-R System (Medtronic, Minneapolis, MN) self-expandable prosthesis were used during the study period. The size of the bioprosthesis was determined primarily using CT and echocardiographic findings. Information regarding the occurrence and/or causes of death was obtained from the treating hospital applicable or the patient's family member(s). The medical ethics committee in each hospital approved this study, and written informed consent was obtained from all patients before the TAVR procedure. The OCEAN-TAVI investigation was registered with the University Hospital Medical Information Network (no.: UMIN000020423).

Routine preprocedural CT was performed with patients placed in the decubitus dorsalis position. All the obtained CT images were transferred to a dedicated workstation (Aquarius iNtuition Viewer; TeraRecon Incorporated, Eindhoven, The Netherlands). The CT analyses were performed by experienced radiographic specialists. These investigators were blinded to the clinical outcomes after TAVR. CT images were examined by 120 kV and reconstructed using a cardiac standard filter with a slice thickness of 1.0-5.0 mm based on the individual centre protocol. VAT was defined as fat within the peritoneal cavity and SAT was defined as fat between skin and the underlying muscular layer, demarcated by manually tracing the inner border of the transversus abdominis muscle.[18] A representative case of CT analysis is provided in Figure 1. We semiautomatically measured the area (cm²) and mean attenuation (Hounsfield units [HU]) of the VAT and SAT at the level of the umbilicus. The SAT and VAT were segmented using fat-specific thresholds (−150 to −30 HU) according to the previous formula.[19,20] Inter- and intra-variability of the SAT/VAT area—and density values from 20 randomly chosen patients—confirmed the high reliability of analysed CT data (Supplemental Table S1). We analysed the threshold of the CT area and density for predicting mortality by a classification and regression tree (CART) survival model.[16] However, we could not obtain the cutoff values for both the SAT and VAT areas. Therefore, we determined that the cutoff values for the SAT and VAT areas were the median values according to sex. According to the CART survival model, the cutoff value of SAT density for predicting mortality was −90.7 HU in men and −94.3 HU in women. The VAT density threshold was −71.2 HU in men and −75.7 HU in women. The prognostic values of SAT and VAT calculated by the CT area and density were assessed for the entire cohort using this cutoff value.

All statistical analyses were performed using IBM SPSS statistics v23 (SPSS, Inc, Chicago, IL) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as the mean ± standard deviation and as medians with interquartile ranges. Group differences were tested using 1-way analyses of variance with subsequent Student's t test or using the Mann-Whitney test depending on the variable's distribution. The relationship between the CT density of AT and BMI was evaluated using Spearman's correlation analysis. The Kaplan-Meier method was used to generate event-free survival curves, and differences in mortality were assessed with the log-rank test. A univariate Cox regression analysis was performed to obtain the hazard ratio (HR) for midterm

Table 2. Relationships between AT of CT area and density and body characteristics/serum markers/age

Variable	SAT area		SAT density		VAT area		VAT density	
	ρ	P value	ρ	P value	ρ	P value	ρ	P value
SAT area (cm^2/m)	—	—	—	—	—	—	—	—
SAT density (HU)	−0.74	< 0.01	—	—	—	—	—	—
VAT area (cm^2/m)	0.74	< 0.01	−0.71	< 0.01	—	—	—	—
VAT density (HU)	−0.64	< 0.01	0.85	< 0.01	−0.76	< 0.01	—	—
BMI (kg/m^2)	0.59	< 0.01	−0.48	< 0.01	0.59	< 0.01	−0.47	< 0.01
Haemoglobin (g/dL)	0.16	< 0.01	−0.23	< 0.01	0.17	< 0.01	−0.23	< 0.01
LDL-C (mg/dL)	0.04	0.119	−0.002	0.927	−0.007	0.792	0.002	0.952
HDL-C (mg/dL)	−0.08	< 0.01	−0.19	< 0.01	−0.19	< 0.01	0.15	< 0.01
Albumin (g/dL)	0.13	< 0.01	−0.21	< 0.01	0.087	< 0.01	−0.19	< 0.01
Age (y)	−0.13	< 0.01	0.19	< 0.01	−0.11	< 0.01	0.17	< 0.01

AT, adipose tissue; BMI, body mass index; CT, computed tomography; HDL-C, high-density lipoprotein cholesterol; HU, Hounsfield units; LDL-C, low-density lipoprotein cholesterol; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

mortality during the follow-up period. Thereafter, a multivariate analysis was performed using the baseline clinical characteristics and other variables with a univariate P value of < 0.05 and clinically important factor including age to examine the independent associations of VAT and SAT area and density with midterm mortality. As a result, the variables included were the several considerable factors such as age, gender, BMI, prevalence of New York Heart Association class III/IV, surgical risk score, clinical frailty scale, B-type natrium peptide, creatinine value, haemoglobin, peripheral artery disease, prior myocardial infarction, prior stroke, pulmonary disease, liver disease, and procedural approach route differences. To consider the effect of study institution on the results, we performed a multivariate mixed effect Cox regression analysis with study institution as the random effect. All tests with 2-sided P values of < 0.05 were considered statistically significant.

Results

Baseline patient characteristics

The baseline characteristics related to SAT and VAT densities are presented in Table 1. The average age of the 1372 patients was 84.5 ± 5.0 years, and 70.6% of the patients were women. Patients were clinically followed beyond 1 year with the exception of 2 patients without survival information. As a result, the follow-up rate at 1 year was 99.9%. A total of 312 patients (men: 133 patients, women: 179 patients) died during a median follow-up period of 768 days (interquartile range: 665-1069 days). Based on the differences in the high and low AT densities, several significant clinical characteristic differences in age, gender, body characteristics including BMI, the prevalence of New York Heart Association class III/IV, surgical risk score, multiple comorbidities, and echocardiographic parameters were evaluated.

The relationship between the AT characteristics assessed by CT and body characteristics

The relationships between the CT area and the density of AT and clinical variables are presented in Table 2. The SAT area was positively correlated with the VAT area, and the SAT and VAT density were negatively correlated with the SAT and VAT area (all P < 0.05). In addition, there were strong correlations among all CT characteristics and BMI. The CT area was positively correlated and the CT density was negatively correlated with BMI (all P < 0.05).
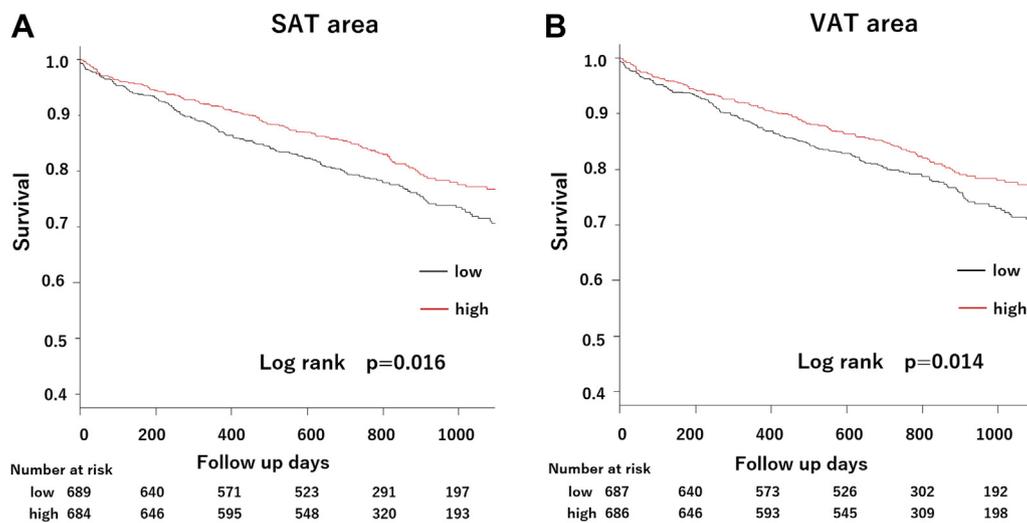

Figure 2. Kaplan-Meier all-cause survival rates according to adipose tissue area. The Kaplan-Meier all-cause survival rates according to the computed tomography area of (**A**) SAT and (**B**) VAT. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

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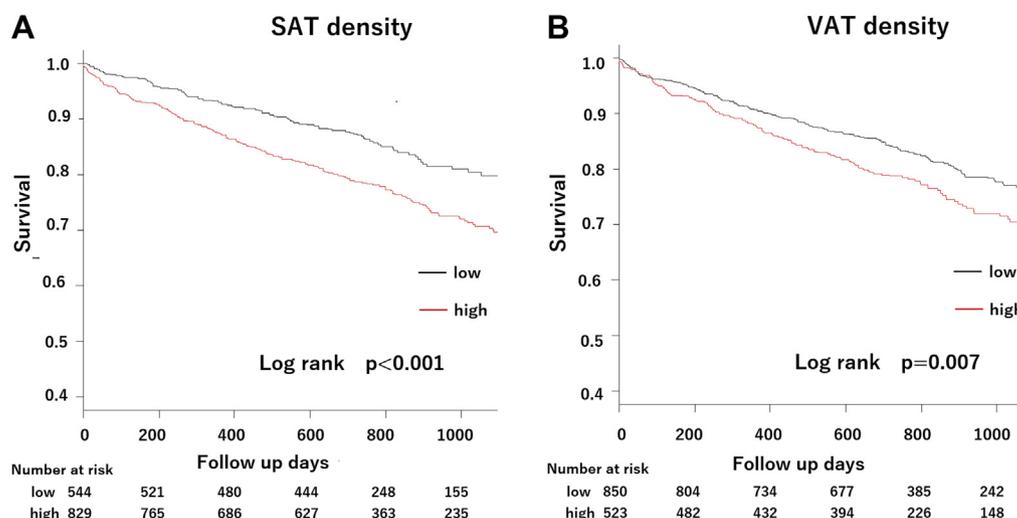Clinical Outcomes of Adipose Tissue After TAVR

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Figure 3. Kaplan-Meier all-cause survival rates according to adipose tissue density. Kaplan-Meier all-cause survival rates according to the computed tomography density of (**A**) SAT and (**B**) VAT. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Clinical outcomes of AT characteristics

The Kaplan-Meier survival rates according to the CT area of SAT and VAT are provided in Figure 2. The low-volume area of SAT and VAT was significantly associated with worse clinical outcomes compared with the high-volume area of SAT and VAT (log-rank test $P = 0.016$ and $P = 0.014$, respectively). The Kaplan-Meier survival rates according to the CT density of SAT and VAT are provided in Figure 3. Patients with the high CT density of SAT and VAT were significantly associated with increasing mortality after TAVR in comparison with those patients with the low CT density of SAT and VAT (log-rank test $P < 0.001$ and $P = 0.007$, respectively).

Prognostic value of AT characteristics after TAVR

The results of the Cox regression analysis are presented in Table 3. In the univariate analysis, improved clinical outcomes were found in patients with high SAT and VAT area compared with those with low SAT area (HR: 0.76, 95% confidence interval [CI]: 0.61-0.95, $P = 0.016$) and low VAT area (HR: 0.76, 95% CI: 0.60-0.95, $P = 0.014$). However, these results were attenuated in the multivariate analysis concerning the SAT area (HR: 0.85, 95% CI: 0.74-1.29, $P = 0.85$) and VAT area (HR: 0.78, 95% CI: 0.60-1.03, $P = 0.085$). In contrast, the clinical outcomes of patients with high SAT density compared with low SAT density were independently associated with increased risk of mortality after TAVR in the multivariate analysis (HR: 1.41, 95% CI: 1.06-1.88, $P = 0.019$). The results of increased risk of mortality after TAVR were not diminished in the patients with high VAT density than patients with low VAT density (HR: 1.34, 95% CI: 1.03-1.76, $P = 0.031$). Based on the findings from the Cox regression with cubic spline analysis, the nonuniform specific curve of expected HR for all-cause mortality was drawn in the CT area of SAT and VAT and the CT densities of SAT and VAT (Fig. 4). In addition, a multivariate mixed effect Cox regression analysis considering the centre differences showed results similar to the main ones (SAT area,

HR: 0.99, 95% CI: 0.75-1.32; VAT area, HR: 0.76, 95% CI: 0.58-1.00; SAT density, HR: 1.37, 95% CI: 1.02-1.83; and VAT density, HR: 1.38, 95% CI: 1.05-1.81, for all-cause mortality).

Discussion

This study demonstrated the additional prognostic value of CT assessment of AT according to routine preprocedural CT data in patients who underwent TAVR. A small AT area was associated with poorer clinical outcomes. Although obesity is related to significant mortality with increasing prevalence of cardiometabolic risk factors, the inverse relationship between body fat composition and poor prognosis is frequently referred to as the obesity paradox.[1-5] The concept of the obesity paradox has been widely confirmed in aging populations with or without cardiac disease.[1-5,21,22] Although BMI classification is useful for assessing the degree of obesity, BMI alone may misclassify patients with regard to the true amount of fat, particularly in underweight and normal weight populations.[23] Thus, CT analysis of AT offers an advantage over BMI for predicting mortality after TAVR.

In addition to the quantitative AT area reflecting the degree of obesity, the qualitative assessment determined by the CT density of AT enabled more accurate prediction of prognosis after TAVR. The importance of CT density as a qualitative assessment for predicting mortality has been reported in older patients.[9] This large-scale analysis revealed that patients with a higher CT density of AT had poorer clinical outcomes, which is in accordance with our current result. The reason for the impact of this adipose assessment on all-cause mortality remains unclear; the effects of hormones on physiology represent a possible explanation. Previous reports have reported that adipose density correlates with serum leptin levels.[9] In addition, serum leptin levels have been reported to be associated with all-cause mortality in older women, which is similar to the results of this study.[24] In the field of oncology, several studies have also confirmed that the AT characteristics, primarily high CT density and a small CT area of AT, were

Table 3. Cox regression analysis for the association between all-cause mortality and clinical findings

Explanatory variables	Univariate analysis			Multivariate analysis											
				Model 1			Model 2			Model 3			Model 4		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
CT measurement of AT															
High SAT area (for low)	0.76	0.61-0.95	0.016	0.99	0.75-1.32	0.96									
High SAT density (for low)	1.66	1.3-2.12	< 0.001				1.40	1.05-1.86	0.024						
High VAT area (for low)	0.76	0.6-0.95	0.014							0.79	0.60-1.04	0.098			
High VAT density (for low)	1.36	1.09-1.7	0.0075										1.32	1.01-1.72	0.042
Adjusting factors															
Age (per 1 category increase)*	1.02	1.0-1.05	0.059	1.01	0.98-1.03	0.59	1.01	0.98-1.03	0.65	1.01	0.98-1.03	0.66	1.01	0.98-1.03	0.6
Male (for female)	1.92	1.54-2.41	< 0.001	2.21	1.69-2.87	< 0.001	2.27	1.74-2.95	< 0.001	2.18	1.68-2.84	< 0.001	2.32	1.77-3.04	< 0.001
BMI (per 1 kg/m^2 increase)	0.95	0.92-0.98	0.0012	0.97	0.93-1.01	0.1	0.98	0.95-1.02	0.37	0.98	0.94-1.02	0.38	0.98	0.94-1.02	0.26
STS score (per 1.0 % increase)	1.03	1.02-1.04	< 0.001	1.00	0.99-1.02	0.51	1.00	0.99-1.02	0.6	1.00	0.99-1.02	0.43	1.00	0.99-1.02	0.58
NYHA class III/IV (for I/II)	1.57	1.25-1.96	< 0.001	1.23	0.95-1.59	0.12	1.25	0.97-1.62	0.09	1.25	0.97-1.62	0.088	1.27	0.98-1.64	0.074
Clinical frailty scale (per 1 group increment)	1.23	1.13-1.34	< 0.001	1.18	1.06-1.30	0.0015	1.17	1.06-1.29	0.002	1.18	1.07-1.30	0.0014	1.16	1.05-1.29	0.003
High BNP (> median)	1.60	1.26-2.04	< 0.001	1.20	0.93-1.55	0.17	1.16	0.89-1.50	0.27	1.20	0.93-1.55	0.16	1.18	0.91-1.52	0.21
Creatinine (per 1.0 mg/dL increase)	1.77	1.58-1.99	< 0.001	1.60	1.36-1.88	< 0.001	1.59	1.36-1.87	< 0.001	1.59	1.36-1.86	< 0.001	1.59	1.35-1.86	< 0.001
Haemoglobin (per 1.0 g/dL increase)	0.82	0.77-0.88	< 0.001	0.89	0.82-0.96	0.0045	0.89	0.82-0.97	0.0085	0.89	0.82-0.96	0.0048	0.89	0.82-0.97	0.0054
Peripheral artery disease	1.66	1.27-2.16	< 0.001	1.12	0.81-1.54	0.49	1.12	0.82-1.55	0.48	1.12	0.81-1.54	0.5	1.12	0.81-1.54	0.5
Prior MI	1.67	0.16-2.41	0.006	1.30	0.86-1.98	0.21	1.27	0.83-1.94	0.27	1.33	0.87-2.02	0.19	1.30	0.85-1.98	0.22
Prior PCI	1.21	0.95-1.55	0.13	—			—			—			—		
Prior CABG	1.30	0.89-1.89	0.18	—			—			—			—		
Prior stroke	1.45	1.07-1.98	0.017	1.16	0.84-1.62	0.37	1.16	0.83-1.61	0.38	1.19	0.85-1.65	0.31	1.19	0.85-1.65	0.31
Diabetes mellitus	1.15	0.89-1.5	0.28	—			—			—			—		
Hypertension	1.11	0.84-1.46	0.48	—			—			—			—		
Pulmonary disease	1.34	1.05-1.73	0.021	1.33	1.01-1.75	0.042	1.31	1.00-1.73	0.054	1.35	1.02-1.77	0.034	1.33	1.01-1.75	0.042
Liver disease	2.85	1.85-4.41	< 0.001	2.78	1.67-4.65	< 0.001	2.79	1.67-4.66	< 0.001	2.79	1.67-4.66	< 0.001	2.81	1.68-4.70	< 0.001
Active cancer	1.45	0.94-2.23	0.094	—			—			—			—		
LVEF (per 10% increase)	0.99	0.98-1.00	0.15	—			—			—			—		
MR ≥ grade 2	1.82	1.32-2.51	< 0.001	1.77	1.24-2.51	0.0015	1.74	1.23-2.48	0.002	1.75	1.23-2.49	0.0017	1.74	1.22-2.47	0.0021
Transfemoral (for nontransfemoral)	0.67	0.52-0.87	0.0021	0.85	0.63-1.13	0.26	0.85	0.64-1.13	0.27	0.85	0.64-1.14	0.28	0.85	0.64-1.14	0.28

AT, adipose tissue; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CI, confidence interval; CT, computed tomography; HR, hazard ratio; LVEF, left ventricle ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAT, subcutaneous adipose tissue; STS score, Society of Thoracic Surgeons Predictive Risk of Mortality; VAT, visceral adipose tissue.

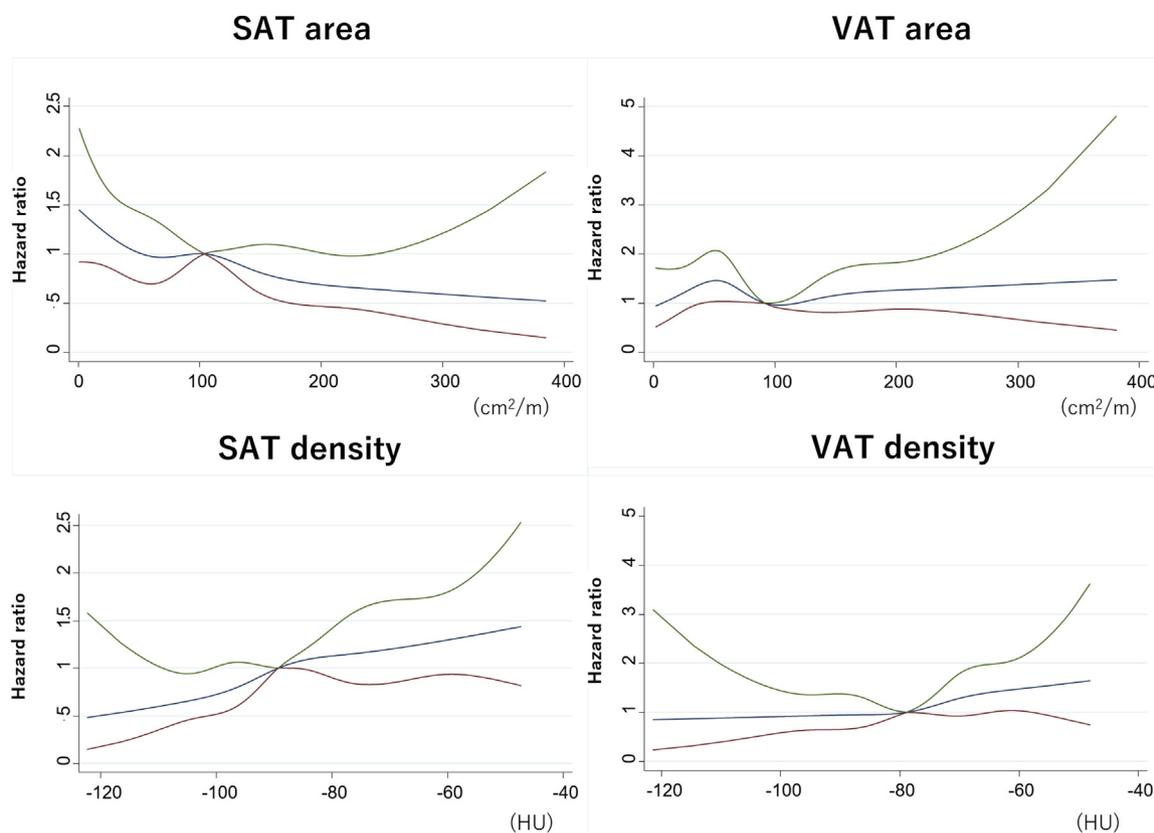*Categorized as age < 80 years, 80-84 years, 85-89 years, and ≥ 90 years.

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SAT area

VAT area

SAT density

VAT density

Figure 4. The spline curve of hazard ratio for all-cause mortality in each computed tomography measurement. The relationship between individual characteristics of adipose tissue and hazard ratio (HR) and all-cause mortality. The blue line shows the expected HR based on the spline analysis. The green and red lines show the 95% confidence interval for HR. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

associated with late adverse clinical outcomes.[10-12] Thus, CT qualitative assessments are considered to be important for estimating the life expectancy of patients with malignant disease. In our TAVR cohort, the average age of the patients was > 80 years and multiple comorbidities were present. The CT density of AT may be a surrogate marker for predicting mortality in elderly and fragile patients with advanced disease. In contrast, a previous study indicated that a lower CT density of AT was associated with incremental cardiometabolic risk in a younger population.[25] The average CT area and density of AT according to sex slightly differed between the previous study and our current study.[25] Age, ethnic, and sex differences should be taken into account when considering the impact of AT on clinical outcomes. Our current findings in a cohort of TAVR patients, which mainly comprised elderly patients with multiple comorbidities, may not be simply generalizable to the general population.

Although evidence supports the importance of AT assessments, the complex nature of the relationship between AT characteristics and clinical outcome after TAVR remains a topic of debate. Some clinical articles have noted the correlation between AT and clinical outcome after TAVR.[13-15] These studies reported that the fat area alone was not related to clinical outcomes[13] and that a small SAT area alone (the VAT area was not mentioned) was associated with a poor outcome.[14] Another study suggested the significant correlation of both small SAT and VAT areas with poor prognosis, and reported that the highest quartile of the CT density in

SAT (but not in VAT) was an independent factor for increased mortality after TAVR.[15] Our data are in partial agreement with the results of previous studies. However, the CT area of AT differed between sexes and likely weakened the prognostic predictive value compared with CT density. The current study applied a cutoff value of CT density according to a survival CART.[16] These statistical approaches highlight the importance of CT density assessments of both SAT and VAT in conjunction with the CT area for predicting mortality after TAVR.

Several limitations of this study should be discussed. First, this study was of a retrospective design, and a small number of patients (n = 19) were excluded from the initial analysis because of a lack of CT images and/or poor image quality. Thus, some selection bias was inevitable. Second, the study population comprised homogeneous Japanese elderly patients. The distributions of AT in this cohort were likely different from those of the general population. As we discussed, the volume and density of AT were different from those of younger patients and the western TAVR cohort.[13,15,25] Again, the age- and race-specific differences should be confirmed by further study. Third, several confounding factors were considered in the Cox regression model. However, some potentially important variables were not included in the current model. Fourth, preprocedural CT was performed at individual centres, and therefore, the AT data were obtained from several different multidetector CT systems. The reconstruction of CT images used a cardiac standard filter

with the slice thickness according to the individual centre's protocol. Therefore, central differences in the CT area and density of AT were observed (Supplemental Table S2). However, the worse prognosis of each CT characteristic was not diminished in the 3 subdivisions adjusting for the treated number of patients (Supplemental Fig. S1). Fifth, we measured the AT at the level of the umbilicus. We applied the measurement approaches used in the previous research.[19,20] The location can cause errors in patients with central obesity or panniculus, although the proportion of patients with obesity (BMI > 30) was low in this study (n = 29, 2.2%). The other paper also evaluated the consistent CT landmark for AT measurement at the L4 level.[15]

In conclusion, this study revealed the prognostic value of both SAT and VAT characteristics in patients who underwent TAVR. The clinical outcomes could be stratified by the CT area of the SAT and VAT. The AT area alone was powerless for predicting prognosis compared with the CT density. Beyond the quantitative fat area, CT density provided an additional diagnostic value regardless of sex. Detailed CT analysis, particularly qualitative assessment of AT, may help to determine the subsequent risk in patients undergoing TAVR. In routine practice, CT scanning is performed before TAVR. The AT measurements and conventional CT analysis would be useful for defining important frailty parameters, such as VAT and SAT densities, which are predictive of poor outcomes after TAVR. They may support decision-making on TAVR indications for too sick or too frail patients.

Disclosures

M.Y., N.T., T.N., S.S., K.M., and Y.W. are clinical proctors for Edwards Lifesciences and Medtronic. M.A., M.T., K.T., A.H., and K.H. are clinical proctors of Edwards Lifesciences. HU is a clinical proctor for Medtronic. The rest of the authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.09.019.