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Significance of Adipose Tissue Quantity and Distribution on Obesity Paradox in Heart Failure

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Abstract

Obesity is a predictor of the development of systolic and diastolic heart failure (HF), but once established, patients with HF and obesity have better outcomes than their leaner counterparts, a phenomenon termed the “obesity paradox.” We sought to investigate the impact of adipose tissue quantity and distribution, measured by way of computed tomography, on outcomes in patients with HF. Patients admitted for acute decompensated HF between January 2017 to December 2018 were retrospectively analyzed. Body composition measurements were made on computed tomography of the abdomen/pelvis. Visceral, subcutaneous, and intermuscular adipose tissues were measured at the mid-third lumbar vertebra, along with skeletal muscle and waist circumference. Paracardial (pericardial and epicardial) adipose tissue was measured at the mid-eight thoracic vertebra. Visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI), along with skeletal muscle index, were indexed for patient height. A total of 200 patients were included, 44.5% female. Body mass index and waist circumference did not significantly predict outcomes. Patients with high SATI (highest sex-stratified tertile) had significantly better survival (hazard ratio 0.58, 95% confidence interval 0.39 to 0.87, p = 0.009), whereas high VATI was nonsignificant. Patients were further divided into 4 groups based on both VATI and SATI. One- and 4-year mortality risks were lowest in those with low VATI high SATI compared with the other groups; this persisted after multivariable adjustment for covariates, including albumin and skeletal muscle index. In conclusion, the “obesity paradox” appears to be largely driven by subcutaneous adipose tissue, independent of nutrition or skeletal muscle.

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Declaration of Competing Interest

Dr. Martens has received consultancy fees from Astra-Zeneca, Abbott, Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Novartis, Novo Nordisk, and Vifor Pharma. Dr. Estep is a consultant and medical advisor for Abbott and Medtronic Inc. Dr. Tang served as a consultant for Sequana Medical, Cardiol Therapeutics, Genomics plc, Zehna Therapeutics, Renovacor, WhiteSwell, Kiniksa Pharmaceuticals, Boston Scientific, CardiaTec Biosciences, and has received an honorarium from Springer Nature and American Board of Internal Medicine. The remaining authors have no competing interests to declare.

Keywords

heart failure; obesity; adipose tissue; computed tomography; body composition

Obesity is a predictor of the development of both systolic and diastolic heart failure (HF), largely because of its role as a significant risk factor for metabolic abnormalities, hypertension, and coronary artery disease.[1] This is particularly concerning with the overweight/obesity pandemic affecting 70% of the US population, with projected increases in the next 30 years.[2] However, studies have shown patients with HF and obesity to have relatively better outcomes than their leaner counterparts, a phenomenon termed the “obesity paradox.” The reason for this is unclear, with proposed mechanisms indicating protective cytokines, less cachexia, more muscle mass and strength, and more metabolic reserve.[1]

Adipose tissue is primarily divided into 2 types, white adipose tissue and brown adipose tissue. The former is a source of energy and protection, whereas the latter generates heat as its basic function.[2] White adipose tissue is further separated into visceral and subcutaneous, which confer negative and neutral/positive metabolic effects, respectively.[2] The quantity and deposition of adipose tissue fluctuate significantly and depend on age, gender, race, genetics, and environment. Studies have hypothesized that subcutaneous adipose tissue (SAT) acts as an initial physiologic metabolic sink for excess triglycerides, but it has a finite expansion capacity, called the “personal fat threshold,” beyond which there is expansion of the pro-inflammatory visceral and ectopic (liver, pancreas, heart, and skeletal muscle) adipose tissues, leading to metabolic disturbances and consequences.[3]

Body mass index (BMI) has traditionally been used to define obesity, but it does not evaluate actual body composition, often leading to misclassification.[4] Waist circumference is a better measure of obesity, given its strong association with visceral adipose tissue (VAT).[3] However, neither of these tools differentiates between VAT and SAT with their known differential impact on cardiovascular disease outcomes.[5] Dual-energy x-ray absorptiometry and bioimpedance analysis are more accurate methods of adipose tissue evaluation, but computed tomography (CT) and magnetic resonance imaging remain the gold standard for body composition assessment despite their lack of cutoffs for obesity and sarcopenia.[5,6] Herein, we investigate the impact of adipose tissue quantity and distribution as measured from CT images on outcomes in vulnerable patients with HF, particularly those admitted to the hospital for acute decompensation where such imaging studies are commonly performed. We hypothesized that the obesity paradox is largely driven by SAT and that its protective effect is decreased in those with higher visceral and ectopic (heart and skeletal muscle) adipose tissue deposition.

Methods

Consecutive patients admitted to the Cleveland Clinic between January 2017 to December 2018 for a primary diagnosis of acute decompensated HF were retrospectively identified. Acute decompensated HF was defined as an admission lasting >24 hours with signs and symptoms of congestion requiring intravenous diuretics. Patients with a history of HF or de novo HF were eligible irrespective of their admission left ventricular ejection fraction (EF).

Inclusion criterion was the presence of CT imaging of the abdomen/pelvis with or without contrast 1 month before the discharge date. Both contrast and noncontrast studies were eligible as previous research has shown body composition measurement to be minimally affected by contrast enhancement.[7] Exclusion criteria were primarily driven by issues with image extraction, quality, or significant tissue being cut off the image border. HF was classified based on the latest transthoracic echocardiogram before admission into reduced (≤40%), mildly reduced (41% to 49%), and preserved (≥50%) EF. This study was approved by the Cleveland Clinic Institutional Review Board, and written informed consent was waived as all procedures were performed as part of routine clinical care.

Body composition measurements were made on CT axial images using the commercially available software, Slice-O-Matic (Version 5.0, Tomovision, Quebec, Canada) and Automatic Body composition Analyzer using Computed tomography image Segmentation plus module (ABACS+, Voronoi Health Analytics, Vancouver, British Columbia, Canada). This semi-automated segmentation tool tags tissues using its knowledge of muscle shapes at the specific level and previously validated Hounsfield unit ranges of −29 to 150 for skeletal muscle, −150 to −50 for visceral and paracardial (pericardial and epicardial) adipose tissues, and −190 to −30 for subcutaneous and intermuscular adipose tissues (Figure 1).[8] Total adipose tissue was obtained by adding all adipose tissue measurements. Manual waist circumference measurements were also performed. All measurements were made at the mid-third lumbar vertebra, except for paracardial adipose tissue (PAT), measured at the mid-eight thoracic vertebra. Two observers made measurements blinded to patient history and outcomes. Before initiation, both observers were trained by a board-certified radiologist and the software developers (approximately 5 hours each). The observers each made measurements on 100 patients, with a board-certified radiologist confirming accuracy (initial 20 measurements).

Interobserver variability was assessed on 10 randomly selected patients. Intraclass correlation coefficient scores, on a scale of 0 to 1, were generated to assess interobserver variability; a score >0.90 was considered excellent reliability, 0.75 to 0.9 good, 0.5 to 0.75 moderate, and <0.5 poor. Interobserver agreements for VAT (0.998, 95% confidence interval [CI] 0.991 to 0.999), SAT (0.990, 95% CI 0.958 to 0.997), intermuscular adipose tissue (0.973, 95% CI 0.889 to 0.993), PAT (0.981, 95% CI 0.923 to 0.995), and skeletal muscle area (0.996, 95% CI 0.986 to 0.999) were all excellent.

After measurement of raw values, total adipose tissue index (TATI), VAT index (VATI), SAT index (SATI), and skeletal muscle index (SMI) were calculated by dividing each value by the square of the patient's height to normalize for body size.[9] No adjustment was made to PAT. The degree of myosteatosis (skeletal muscle fat infiltration) was assessed by calculating the intermuscular adipose tissue percentage (IMAT%) with the formula: IMAT (cm^2) / (SMA (cm^2) + IMAT [cm^2]) × 100.[10] Traditional obesity criteria for BMI (≥30.0 kg/m^2) and waist circumference (≥102 cm in men and ≥88 cm in women) were used.[3] Sex-stratified tertile cutoffs (Table 1) were also used to stratify high (highest tertile) and low (middle and lowest tertiles) TATI, VATI, SATI, and SMI. Finally, patients were differentiated into 4 groups based on high VATI low SATI, low VATI high SATI, high VATI and SATI, and low VATI and SATI.

Student's *t* test and analysis of variance were used for continuous normally distributed variables (reported as mean ± SD), and the Mann-Whitney *U* and Kruskal-Wallis tests for non-normally distributed variables (reported as median and 25th to 75th percentiles). Distributional histograms were used to assess the normality of distribution. Chi-square test was used for categorical variables, reported as numbers (percentages). The primary outcome of interest was all-cause mortality, as documented in the electronic health record. Using the log-rank test, Kaplan-Meier analysis was used to determine the time to event with group comparison. Cox-proportional hazard models were used for covariate correction in time-to-event analysis. Univariable predictors with a $p < 0.100$ on the initial screen were transferred to the step-forward multivariable confirmation. Linear regression models were also utilized, with non-normally distributed dependent variables undergoing log transformation as appropriate. A $p \leq 0.050$ indicated a statistically significant difference. All statistical analyses were performed using R by way of Jamovi (version 2.2.5) and SPSS (version 25, SPSS Inc., Chicago, Illinois).

Results

Of the 271 patients who met inclusion criteria, 71 were excluded (Figure 2), and 200 patients were included, with 69.0% of the CT scans obtained during the hospitalization. Opportunistic CT indications included abdominal pain or gastrointestinal symptoms (33.5%), known cancer work-up (20.5%), suspected infection (17.5%), suspected cancer workup (10.5%), peri-operative imaging (10.5%), suspected thrombosis or bleeding (5.5%), and trauma (2.0%). Most had HF with preserved EF (HFpEF) (49.0%), followed by HF with reduced EF (39.5%) and HF with mildly reduced EF (11.5%). The median study follow-up time was 23.9 (4.2 to 48.0) months. The average length of stay was 7 (4–15) days, with 122 (61.0%) deaths. Comparison between the genders showed similar TATI, whereas women had more SATI and IMAT% but less VATI, PAT, and SMI than men (Table 1). As expected, comparing HF types showed HFpEF patients to be more female and Caucasian (Table 2). Patients with HFpEF had higher TATI, SATI, and ectopic fat (PAT and IMAT%) but lower N-terminal pro–B-type natriuretic peptide (NT-proBNP), whereas VATI and SMI did not differ between the 3 HF groups.

Compared with nonobesity, patients with obesity by BMI (hazard ratio [HR] 0.85, 95% CI 0.58 to 1.26, $p = 0.418$, $p = 0.410$ by log-rank test) and waist circumference ($p = 0.096$ by log-rank test; Figure 3) were nonsignificantly different in all-cause mortality risks, albeit numerically lower. When stratified by TATI, however, fewer deaths occurred in the upper one-third of patients than in the lower two-thirds ($p = 0.032$ by log-rank test; Figure 3). In contrast, stratification by VATI was nonsignificant ($p = 0.080$ by log-rank test; Figure 3), but stratification by SATI showed a significantly lower death rate in the upper one-third of patients ($p = 0.008$ by log-rank test; Figure 3).

Table 3 compares different parameters between the 4 groups based on (1) high VATI low SATI (11.0%); (2) low VATI high SATI (11.0%); (3) high VATI and SATI (22.5%); and (4) low VATI and SATI (55.5%). Those with high VATI and SATI had the highest waist circumference, body surface area, BMI, ectopic fat (PAT and IMAT%), SMI, low-density lipoprotein cholesterol (LDL-C), and albumin; they also had the lowest NT-proBNP. On

direct comparison of the high VATI low SATI and low VATI high SATI groups, there were statistically significant differences in age (p = 0.022), BMI (p = 0.021), hyperlipidemia (p = 0.031), and discharge to a facility (p = 0.050); notably, there were no significant differences in waist circumference, ectopic fat (PAT and IMAT%), or NT-proBNP. There were 11 (50.0%) deaths in the high VATI low SATI group, 8 (36.4%) in the low VATI high SATI group, 24 (53.3%) in the high VATI and SATI group, and 79 (71.2%) in the low VATI and SATI (control) group. Long-term survival (median follow-up time 23.9 [4.2 to 48.0] months) was highest in the low VATI high SATI group (Figure 4). The univariable and multivariable Cox-proportional HRs for the groups for all-cause mortality are listed in Table 4.

To assess the impact of cancer on outcomes, 91 patients with confirmed cancer (39 metastatic) were excluded. Patients without cancer (n = 109) were stratified by new VATI (>66.6 cm^2/m^2 in men and 46.8 cm^2/m^2 in women) and SATI (>84.3 cm^2/m^2 in men and 108.6 cm^2/m^2 in women) sex-stratified tertile cutoffs. During a median follow-up of 33.7 (6.2 to 48.0) months, patients in the upper one-third of SATI (37 of 109) again had a lower death rate (HR 0.46, 95% CI 0.25 to 0.83, p = 0.011) compared with those in the lower two-third (72 of 109); stratification by VATI remained nonsignificant (HR 0.73, 95% CI 0.41 to 1.28, p = 0.272). Patients were further differentiated into 4 groups, with those in the low VATI high SATI group (16 of 109) having the highest survival (HR 0.41, 95% CI 0.17 to 0.97, p = 0.043) compared with the low VATI and SATI group (56 of 109). This was followed by the high VATI and SATI group (21 of 109) (HR 0.46, 95% CI 0.21 to 1.00, p = 0.049), whereas the high VATI low SATI (16 of 109) group did not significantly differ in survival (HR 0.82, 95% CI 0.40 to 1.71, p = 0.603) from the low VATI and SATI group.

The relation between ectopic adipose tissues and predictive covariates was assessed using multivariable linear regression. An adjusted linear model showed significant independent associations between PAT and male gender, Caucasian race, VATI, IMAT%, SMI, and left ventricular EF (Figure 5). Similarly, IMAT% was significantly associated with age, Caucasian race, SATI, PAT, and SMI (Figure 5). A multivariable Cox regression model found SATI (HR 0.99, 95% CI 0.99 to 1.00, p = 0.035) and IMAT% (HR 1.05, 95% CI 1.02 to 1.08, p <0.001) to be statistically significant predictors of all-cause mortality whereas Caucasian race, VATI, and PAT were not.

Predictors of LDL-C were also assessed, with VATI being the only covariate to independently predict LDL-C (Figure 5). Furthermore, predictors of NT-proBNP were evaluated with the finding that SMI and left ventricular EF were independently and inversely associated with NT-proBNP, whereas none of the adipose tissue depots showed significance, including VATI, SATI, PAT, and IMAT% (Figure 5).

Discussion

Leveraging semiautomated measurements of the quality and distribution of adipose tissue from CT images in patients hospitalized with acute decompensated HF, we observed several novel insights into the complex relation between obesity and prognosis. First, BMI and waist circumference did not predict adiposity type or outcomes, indicating the prognostic importance of adipose tissue depot-specific evaluation and definitions of obesity. Second,

high SAT independently predicted better outcomes, whereas VAT did not, suggesting that SAT may play a more prominent role in the “obesity paradox.” Third, IMAT% predicted higher mortality whereas PAT did not, likely because of the relation of the former to SMI for sarcopenia prediction rather than obesity. Finally, NT-proBNP is better predicted by SMI rather than adiposity. These findings indicate the need to consider adipose tissue type and skeletal muscle mass when risk-stratifying patients with HF.

Despite its limitations, BMI continues to be utilized to define obesity in studies and is recommended by most clinical guidelines.[3] To address this, surrogate anthropometric indexes of VAT have been proposed, with waist circumference being the most widely used, given its strong correlation.[3] However, neither of these simple definitions of obesity could differentiate outcomes in our sample. Furthermore, waist circumference did not differ between patients with high VATI low SATI and low VATI high SATI, demonstrating its inability to distinguish between the 2 adipose tissue types. This was remedied through direct measurements of adiposity. Stratification by high SATI predicted better outcomes whereas high VATI did not reach significance, indicating SAT as the likely major player in the “obesity paradox.” Studies have shown major differences in the metabolic activity of VAT and SAT, where VAT leads to increased inflammatory cytokines, such as tumor necrosis factor a and interleukin-6,[11,12] whereas SAT produces leptin, a hormone with many metabolic benefits.[13] Visceral and ectopic adipose tissues are also known risk factors for cardiovascular disease based on large cohort studies of the Framingham Heart Study and the Jackson Heart Study.[14,15] Therefore, the better outcomes we observed in these patients may be from higher SAT expansion capacity leading to less deposition of the metabolically toxic visceral and ectopic adipose tissues.

Expanding on body composition analysis, skeletal muscle is another major tissue compartment with different functions and outcome effects, indicating the need to consider it along with adipose tissue when studying the “obesity paradox.” The significance of high SAT for better survival persisted in our comparison of the 4 groups where low VATI high SATI was the only group to have significantly better outcomes after adjustment for age, race, gender, peripheral arterial disease, chronic obstructive pulmonary disease, albumin, PAT, SMI, and IMAT%. This significance, despite the inclusion of SMI and albumin, and the lack of difference in these variables on direct comparison of the high VATI low SATI and low VATI high SATI groups, indicate that SAT itself is associated with lower mortality, possibly because of its metabolic and endocrine effects, rather than being driven by higher muscle mass or better nutrition in patients with obesity.

On stratification of our sample by gender, we found female patients to have higher SATI than men, similar to patterns found in the general population.[16] They also had lower VATI and PAT, consistent with our regression model showing VATI as an independent predictor of PAT with a positive correlation. Furthermore, lower SMI and higher IMAT% were seen, indicating lower muscle mass and higher myosteatosis, respectively. This was again consistent with the published literature[17] and our regression model showing SMI as an independent predictor of IMAT% with a negative correlation. Despite these differences, women and men did not differ in all-cause mortality.

We observed that those with HFpEF had higher TATI, SATI, PAT, and IMAT%. VATI was higher and SMI lower, but these did not reach significance. This is consistent with recent studies showing HFpEF to be associated with diffuse adiposity,[18,19] although they also found higher SMI in these patients. Previous studies have shown VAT to increase the risk of and predict incident hospitalized HFpEF, whereas SAT showed no predictability for either HF type.[20] PAT has also been shown to be higher in patients with HFpEF compared with matched controls and has deleterious pro-inflammatory effects in addition to advancing diastolic dysfunction and causing poor exercise capacity because of profound hemodynamic derangements.[19]

Finally, we studied the predictors of NT-proBNP, demonstrating strong inverse associations with SMI and left ventricular EF. Although low NT-proBNP has classically been associated with obesity as defined by way of BMI,[21] recent literature shows SMI to play a more prominent part in predicting NT-proBNP. This was demonstrated in a recent analysis where a strong inverse relation was seen between SMI on cardiac magnetic resonance imaging and NT-proBNP (standardized beta = −0.19, p = 0.0012), but adipose tissue depots did not remain significant.[18] Although the mechanism for this is unclear, the influence of gender steroid hormones has been postulated.[22]

The biggest strength of our study was using gold-standard CT imaging to define body composition, including adipose tissue and skeletal muscle, and using this data to adjust covariates, which may alter outcomes through different mechanisms. The limitations include the selection of patients with opportunistic imaging obtained for various reasons, which may introduce confounders, but attempts were made to address this in the analyses. Also, we excluded several patients as described and included a minority of patients whose images of their bodies were cut off the image border, but tissue loss was considered minimal by subjective evaluation. This was necessary to avoid the exclusion of most patients with obesity. In addition, given the lack of validated definitions, we used tertile sex-stratified cutoffs for different tissues. Furthermore, the sample was obtained from patients hospitalized for acute decompensated HF, which may alter study variables; however, data such as weight and creatinine were obtained from the last values before discharge to ensure euvolemia and homeostasis. Finally, we did not have a consistent capture of rehospitalization data in our Electronic Health Record to investigate the impact of adipose tissue quantity and distribution on other HF-specific outcomes.

Taken together, although overweight and obesity have protective effects on HF, different adipose tissue depots are known to have different metabolic effects and impacts on prognosis. There has been a paucity of literature assessing the impact of adipose tissue distribution on HF outcomes, primarily relying on inaccurate surrogates such as BMI or waist circumference. Our data indicate that SAT plays a larger role in the better outcomes in patients with HF, whereas those with low VAT and SAT have the worst outcomes. This data highlights the need for more extensive studies assessing the impact of adipose tissue type on the “obesity paradox” and developing targeted interventions to minimize deleterious adipose tissues while preserving protective types.

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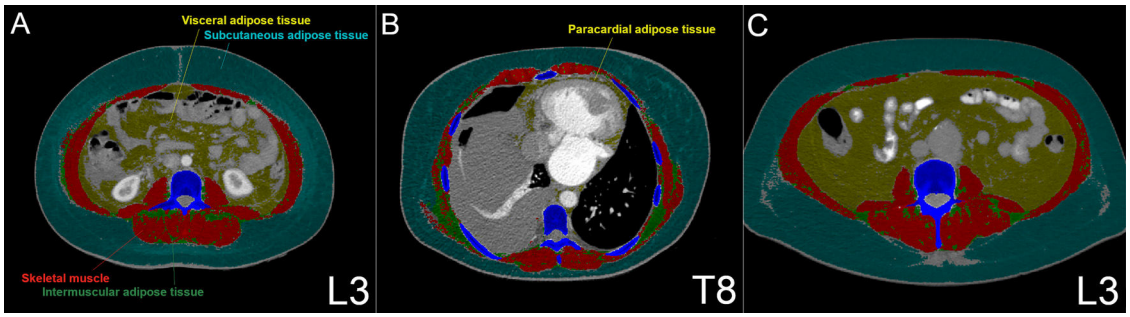

Figure 1.

Body composition analysis. After patient identification and extraction of CT images, the raw files were uploaded into Slice-O-Matic, where sagittal views were reproduced from axial slices. The thoracic vertebrae were manually identified by locating the most cranial vertebra with protruding ribs attached anteriorly to the sternum, identified as the first thoracic vertebra, and counting down. The lumbar vertebrae were manually identified by locating the sacrum and counting up to the last thoracic vertebra with protruding ribs, with the highest lumbar-like vertebra considered the first lumbar vertebra. After identifying the vertebral levels on sagittal view, automated measurements of total skeletal muscle, intermuscular adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue cross-sectional areas were made at the mid-vertebral body of the third lumbar vertebra using ABACS+ *(A)*; in addition, manual waist circumference measurements were performed using the Snake tool. Similar automated measurements were made at the mid-eighth thoracic vertebra, with the visceral adipose tissue measurement representing paracardial (pericardial and epicardial) adipose tissue cross-sectional area given the lack of visceral adipose tissue at this level *(B)*. As mentioned in the text, a minority of patients had their bodies cut off the image border but were included if tissue loss was considered minimal by subjective evaluation; this was to avoid the exclusion of most patients with obesity whose bodies are commonly cut off the image border (*C* is an example).

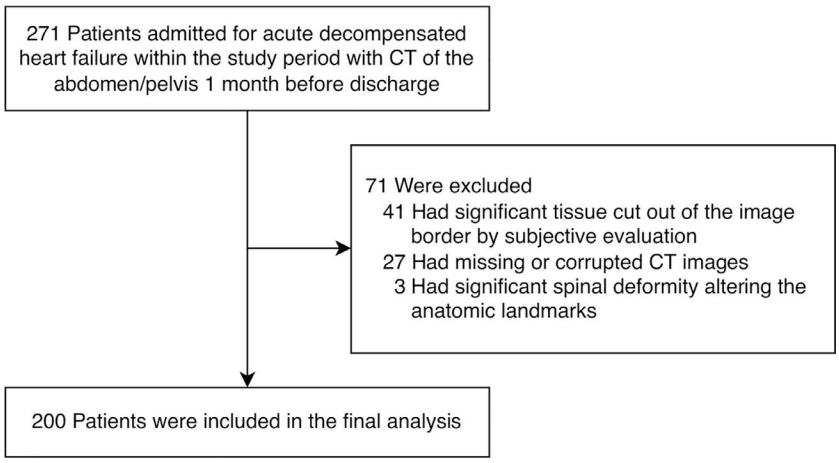

Figure 2.
Study population. Patient selection based on inclusion and exclusion criteria.

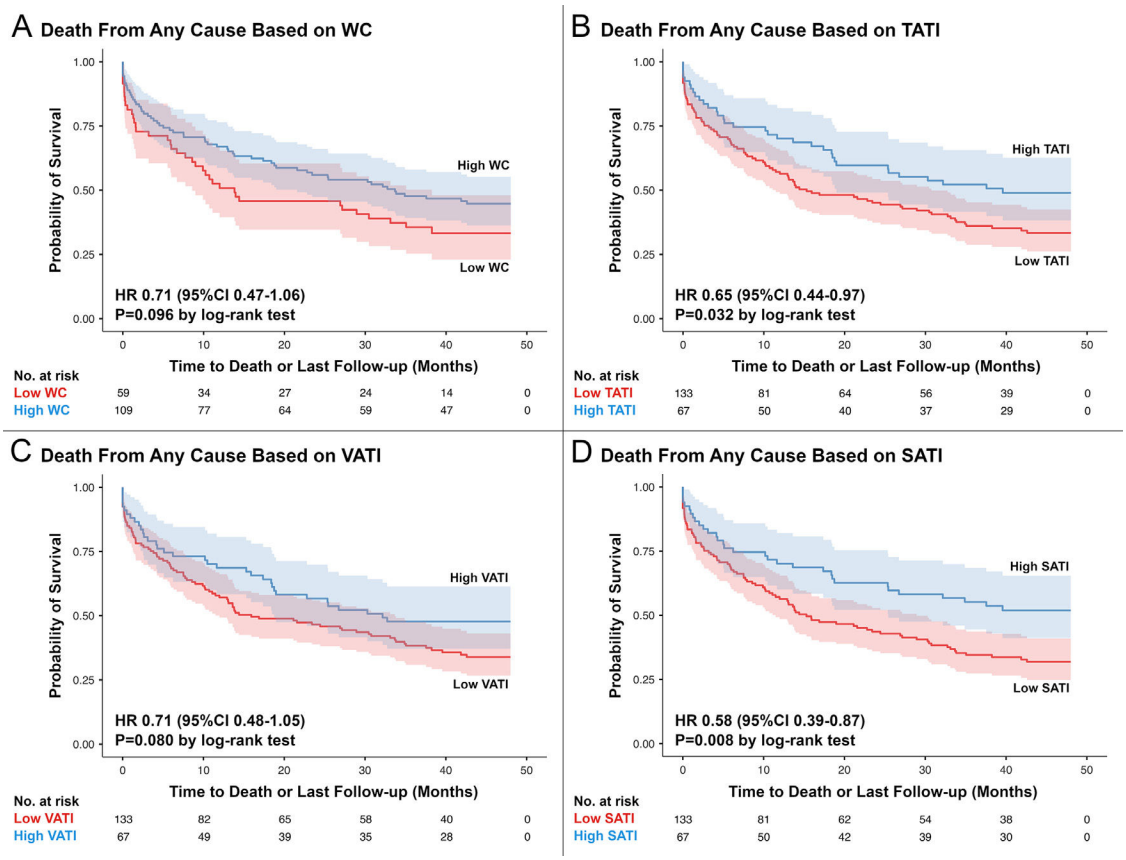

Figure 3.

Clinical outcomes based on different obesity definitions. Stratification by WC (A) and TATI (B) was nonsignificant, but stratification by VATI (C) and SATI (D) showed significantly higher survival in the upper one-third of patients. WC = waist circumference.

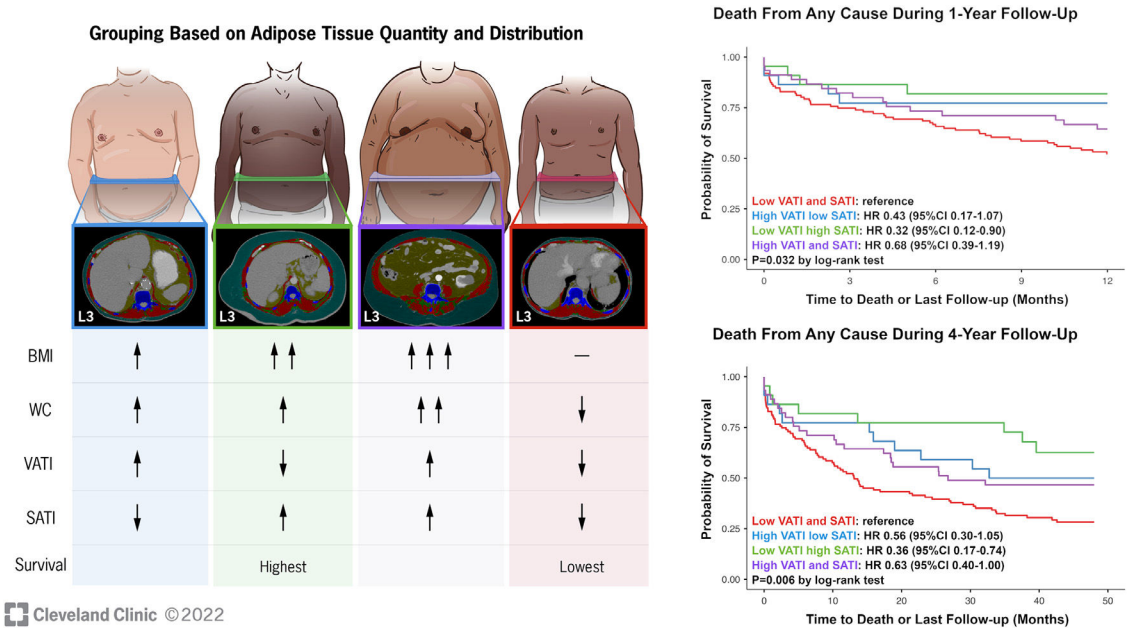

Figure 4.

Outcomes based on different adipose tissue quantity and distribution. Kaplan-Meier curves demonstrating best survival in patients with low VATI high SATI during 1- and 4-year follow-up periods. WC = waist circumference.

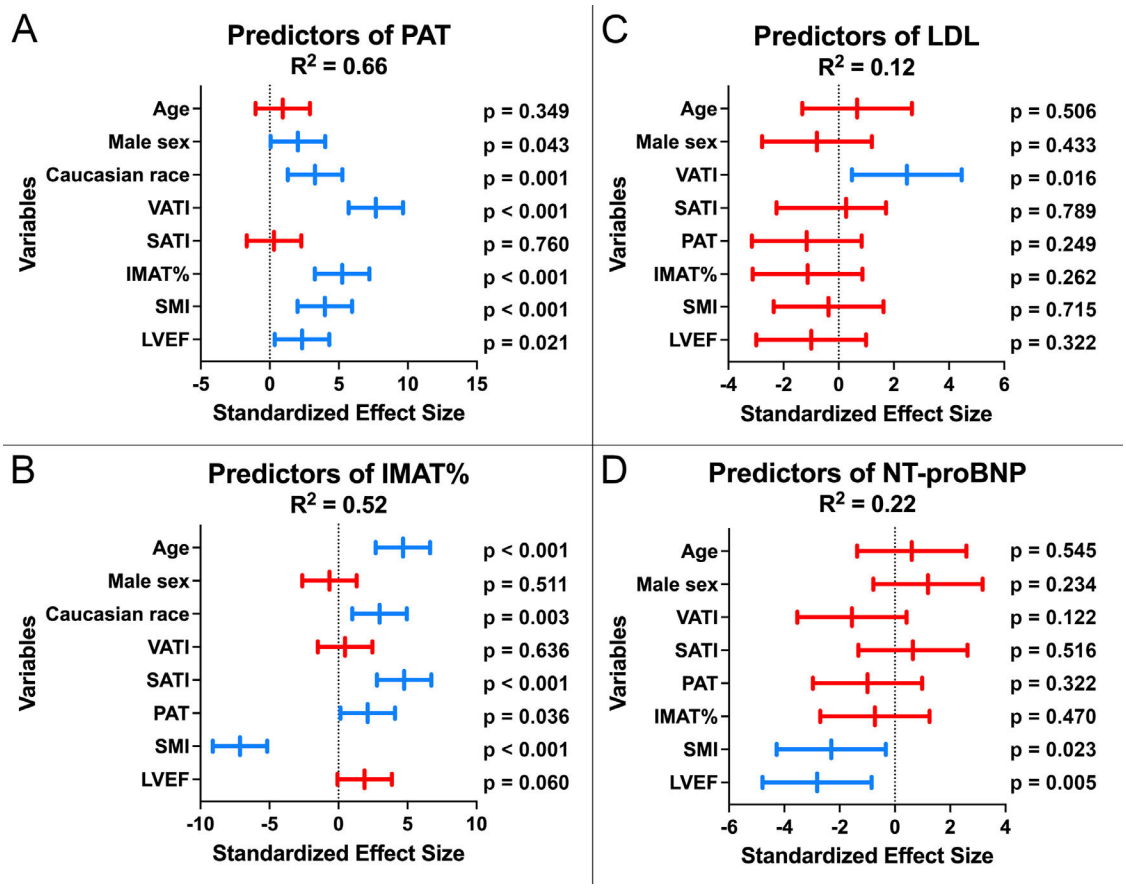

Figure 5.

Linear regression predictive models. Adjusted models showing significant associations with PAT (A), IMAT% (B), LDL-C (C), and NT-proBNP (D). IMAT% = intermuscular adipose tissue percentage; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; NT-proBNP = aminoterminal pro-B-type natriuretic peptide; PAT = paracardial adipose tissue area; SATI = subcutaneous adipose tissue index; SMI = skeletal muscle index; VATI = visceral adipose tissue index.

Table 1

Patient characteristics, measurement averages, outcomes, and cutoffs by sex

Parameters	Female (n=89)	Male (n=111)	P-value
Basic characteristics			
Age (years)	72 ± 15	70 ± 12	0.310
Height (cm)	160.0 ± 7.8	176.0 ± 7.2	**<0.001**
Weight (kg)	74.9 ± 19.9	86.7 ± 21.4	**<0.001**
Waist circumference (cm)	101.0 ± 16.3	106.0 ± 15.9	0.068
BSA (m^2)	1.81 ± 0.25	2.05 ± 0.26	**<0.001**
BMI (kg/m^2)	29.2 ± 7.5	27.9 ± 6.7	0.195
LVEF			**<0.001**
Preserved	57 (64.0%)	41 (36.9%)	
Mildly reduced	9 (10.1%)	14 (12.6%)	
Reduced	23 (25.8%)	56 (50.5%)	
NT-proBNP (pg/mL)	4716 (1881–10357)	5129 (1849–10046)	0.670
Hemoglobin A1c (%)	6.3 ± 1.3	6.4 ± 1.3	0.550
LDL-C (mg/dl)	70 (50–93)	69 (51–101)	0.984
Albumin (g/dL)	3.1 ± 0.6	3.3 ± 0.6	**0.036**
Body composition - averages			
TATI (cm^2/m^2)	142.0 (91.6–205.0)	121.0 (74.0–171.0)	0.061
VATI (cm^2/m^2)	37.7 (17.1–55.3)	49.1 (24.4–83.5)	**0.016**
SATI (cm^2/m^2)	92.5 (55.2–139.0)	62.8 (33.1–91.9)	**<0.001**
PAT (cm^2)	9.2 (4.4–15.8)	11.7 (5.4–23.6)	**0.037**
IMAT% (%)	18.0 (13.5–23.2)	14.1 (9.2–19.6)	**<0.001**
SMI (cm^2/m^2)	36.6 (29.6–43.4)	41.2 (33.9–48.7)	**0.001**
Outcomes			
Ninety-day readmission	55 (61.8%)	67 (60.4%)	0.836
All-cause mortality	39 (43.8%)	53 (47.7%)	0.580
Body composition - tertile cutoffs			
Highest TATI (cm^2/m^2)	180.0	160.0	-
Highest VATI (cm^2/m^2)	52.3	69.3	-

Parameters	Female (n=89)	Male (n=111)	P-value
Highest SATI (cm^2/m^2)	123.0	80.1	-
Highest PAT (cm^2)	13.1	19.1	-
Highest IMAT% (%)	21.1	16.2	-
Lowest SMI (cm^2/m^2)	31.5	36.9	-

BMI = body mass index; BSA = body surface area; IMAT% = intermuscular adipose tissue percentage; LVEF = left ventricular ejection fraction; PAT = paracardial adipose tissue area; SATI = subcutaneous adipose tissue index; SMI = skeletal muscle index; TATI = total adipose tissue index; VATI = visceral adipose tissue index.

Table 2

Patient characteristics, measurement averages, and outcomes by heart failure classification

Parameters	HFpEF (n=98)	HFrEF (n=79)	P-value
Basic characteristics			
Age (years)	71 ± 15	70 ± 12	0.485
Female sex	57 (58.2%)	23 (29.1%)	**<0.001**
Race			**0.008**
Caucasian	81 (82.7%)	52 (65.8%)	
Black	15 (15.3%)	21 (26.6%)	
Other	2 (2.0%)	6 (7.6%)	
Height (cm)	167.0 ± 10.6	172.0 ± 11.1	**0.003**
Weight (kg)	83.3 ± 22.9	78.8 ± 20.3	0.170
Waist circumference (cm)	105.8 ± 17.5	100.9 ± 14.4	0.064
BSA (m^2)	1.95 ± 0.30	1.93 ± 0.27	0.560
BMI (kg/m^2)	29.8 ± 7.4	26.8 ± 6.8	**0.005**
LVEF (%)	60 ± 7	27 ± 8	**<0.001**
NT-proBNP (pg/mL)	3367 (1234–7292)	6755 (3923–16056)	**0.002**
Hemoglobin A1c (%)	6.5 ± 1.5	6.2 ± 1.2	0.316
LDL-C (mg/dl)	61 (46–84)	73 (58–98)	0.196
Albumin (g/dL)	3.2 ± 0.6	3.3 ± 0.6	0.111
Body composition averages			
TATI (cm^2/m^2)	147.8 (86.1–220.0)	110.4 (73.9–157.0)	**0.002**
VATI (cm^2/m^2)	45.3 (18.7–77.6)	37.7 (21.4–62.7)	0.085
SATI (cm^2/m^2)	86.6 (52.4–130.0)	58.7 (32.3–91.9)	**0.001**
PAT (cm^2)	12.8 (6.9–23.0)	7.7 (3.4–13.4)	**0.014**
IMAT% (%)	18.4 (13.4–23.9)	13.6 (8.9–18.3)	**<0.001**
SMI (cm^2/m^2)	38.3 (30.7–44.2)	40.4 (32.7–46.7)	0.287
Outcomes			
Ninety-day readmission	58 (59.2%)	28 (35.4%)	**0.002**
All-cause mortality	62 (63.3%)	43 (54.4%)	0.234

BMI = body mass index; BSA = body surface area; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; IMAT% = intermuscular adipose tissue percentage; LVEF = left ventricular ejection fraction; PAT = paracardial adipose tissue area; SATI = subcutaneous adipose tissue index; SMI = skeletal muscle index; TATI = total adipose tissue index; VATI = visceral adipose tissue index.

Table 3

Comparison between different adipose tissue deposition profile groups

Parameters	Total sample (n=200)	Low VATI and SATI (n=111)	High VATI low SATI (n=22)	Low VATI high SATI (n=22)	High VATI and SATI (n=45)	P-value
Basic characteristics						
Age (years)	71 ± 14	71 ± 15	73 ± 11	64 ± 15	72 ± 10	0.121
Female sex	89 (44.5%)	48 (43.2%)	11 (50.0%)	11 (50.0%)	19 (42.2%)	0.872
Race						
Caucasian	151 (75.5%)	81 (73.0%)	20 (90.9%)	13 (59.1%)	37 (82.2%)	
Black	40 (20.0%)	25 (22.5%)	1 (4.5%)	7 (31.8%)	7 (15.6%)	
Other	9 (4.5%)	5 (4.5%)	1 (4.5%)	2 (9.1%)	1 (2.2%)	0.062
Height (cm)	169.2 ± 10.9	170.0 ± 10.3	169.0 ± 11.1	165.0 ± 14.6	170.0 ± 10.2	0.574
Weight (kg)	81.5 ± 21.5	70.7 ± 15.0	81.7 ± 16.0	87.5 ± 17.5	104.9 ± 19.6	**<0.001**
Waist circumference (cm)	104.0 ± 16.2	94.7 ± 11.7	107.6 ± 8.7	109.8 ± 10.1	123.5 ± 11.0	**<0.001**
BSA (m^2)	1.94 ± 0.28	1.82 ± 0.22	1.95 ± 0.24	2.00 ± 0.26	2.22 ± 0.24	**<0.001**
BMI (kg/m^2)	28.5 ± 7.1	24.5 ± 4.5	28.5 ± 4.4	32.1 ± 5.6	36.5 ± 6.2	**<0.001**
LVEF						
Preserved	98 (49.0%)	49 (44.1%)	7 (31.8%)	11 (50.0%)	31 (68.9%)	
Mildly reduced	23 (11.5%)	11 (9.9%)	7 (31.8%)	0 (0%)	5 (11.1%)	
Reduced	79 (39.5%)	51 (45.9%)	8 (36.4%)	11 (50.0%)	9 (20.0%)	**0.016**
Body composition averages						
TATI (cm^2/m^2)	134.0 (78.8–189.0)	85.7 (50.8–112.0)	152.0 (141.0–169.0)	183.0 (163.0–214.0)	244.0 (205.0–279.0)	**<0.001**
VATI (cm^2/m^2)	43.1 (20.5–71.2)	23.4 (11.3–37.7)	81.0 (61.5–90.7)	43.8 (34.1–54.2)	95.8 (76.2–121.0)	**<0.001**
SATI (cm^2/m^2)	75.5 (39.6–112.0)	47.0 (29.4–68.6)	73.8 (49.1–94.0)	137.0 (98.8–151.0)	130.0 (99.8–152.0)	**<0.001**
PAT (cm^2)	10.4 (5.0–19.3)	7.2 (3.1–11.1)	17.6 (12.5–26.5)	13.3 (6.0–22.6)	24.2 (16.0–34.7)	**<0.001**
IMAT% (%)	15.3 (11.1–21.1)	14.9 (9.3–20.5)	12.9 (10.5–15.5)	16.1 (13.4–20.6)	19.3 (13.9–23.8)	**0.012**
SMI (cm^2/m^2)	39.6 (31.2–46.0)	35.5 (29.1–42.0)	42.3 (37.1–48.0)	41.6 (33.4–47.0)	43.9 (37.9–54.1)	**<0.001**
Laboratory data						
NT-proBNP (pg/mL)	5016 (1859–10183)	6755 (3367–14603)	3720 (2064–7349)	4540 (1197–10755)	3065 (1363–6524)	**0.023**
Hemoglobin A1c (%)	6.4 ± 1.3	6.2 ± 1.2	6.2 ± 0.9	6.3 ± 1.1	6.8 ± 1.8	0.565
LDL-C (mg/dl)	70 (50–99)	62 (50–83)	86 (62–106)	48 (41–74)	101 (74–135)	**0.015**

Parameters	Total sample (n=200)	Low VATI and SATI (n=111)	High VATI low SATI (n=22)	Low VATI high SATI (n=22)	High VATI and SATI (n=45)	P-value
Albumin (g/dL)	3.4 ± 0.6	3.1 ± 0.6	3.3 ± 0.6	3.1 ± 0.6	3.4 ± 0.6	0.124
Comorbidities						
Hypertension	173 (86.5%)	93 (83.8%)	21 (95.5%)	17 (77.3%)	42 (93.3%)	0.132
Hyperlipidemia	147 (73.5%)	75 (67.6%)	20 (90.9%)	14 (63.6%)	38 (84.4%)	**0.026**
Diabetes	100 (50.0%)	53 (47.7%)	13 (59.1%)	8 (36.4%)	26 (57.8%)	0.298
Chronic kidney disease	85 (42.7%)	45 (40.9%)	10 (45.5%)	5 (22.7%)	25 (55.6%)	0.077
Coronary artery disease	93 (46.5%)	43 (38.7%)	15 (68.2%)	13 (59.1%)	22 (48.9%)	**0.039**
Prior myocardial infarction	64 (32.0%)	38 (34.2%)	11 (50.0%)	6 (27.3%)	9 (20.0%)	0.081
Prior CABG or PCI	43 (21.5%)	20 (18.0%)	10 (45.5%)	5 (22.7%)	8 (17.8%)	**0.034**
Peripheral vascular disease	61 (30.5%)	35 (31.5%)	6 (27.3%)	6 (27.3%)	14 (31.1%)	0.964
Prior stroke or TIA	64 (32.0%)	39 (35.1%)	7 (31.8%)	8 (36.4%)	10 (22.2%)	0.445
Atrial fibrillation	95 (47.5%)	54 (48.6%)	10 (45.5%)	7 (31.8%)	24 (53.3%)	0.411
Chronic obstructive pulmonary disease	83 (41.5%)	52 (46.8%)	9 (40.9%)	9 (40.9%)	26 (57.8%)	0.445
Cirrhosis	16 (8.0%)	8 (7.2%)	1 (4.5%)	3 (13.6%)	4 (8.9%)	0.703
Cancer	81 (40.5%)	49 (44.1%)	11 (50.0%)	8 (36.4%)	23 (51.1%)	0.665
Smoking						0.201
Active	39 (20.5%)	26 (24.5%)	2 (9.5%)	6 (28.6%)	5 (11.9%)	
Prior	92 (48.4%)	51 (48.1%)	9 (42.9%)	7 (33.3%)	25 (59.5%)	
Never	59 (31.1%)	29 (27.4%)	10 (47.6%)	8 (38.1%)	12 (28.6%)	
Medications						
Statin	108 (54.0%)	59 (53.2%)	12 (54.5%)	11 (50.0%)	26 (57.8%)	0.933
ACEi or ARB	86 (43.0%)	49 (44.1%)	11 (50.0%)	8 (36.4%)	18 (40.0%)	0.787
Beta-blocker	118 (59.0%)	67 (60.4%)	14 (63.6%)	10 (45.5%)	27 (60.0%)	0.579
Outcomes						
Need for ICU	83 (41.5%)	49 (44.1%)	7 (31.8%)	10 (45.5%)	17 (37.8%)	0.667
Hospital LOS (days)	7 (4–15)	7 (4–15)	8 (4–14)	15 (4–20)	7 (4–11)	0.491
Discharged to a facility	52 (28.6%)	30 (30.3%)	3 (15.0%)	9 (42.9%)	10 (23.8%)	0.211
In-hospital mortality	13 (6.5%)	8 (7.2%)	2 (9.1%)	1 (4.5%)	2 (4.4%)	0.853
Ninety-day readmission	60 (30.0%)	33 (29.7%)	5 (22.7%)	6 (27.3%)	16 (35.6%)	0.730
One-year mortality	78 (39.0%)	53 (47.7%)	5 (22.7%)	4 (18.2%)	16 (35.6%)	**0.017**

Parameters	Total sample (n=200)	Low VATI and SATI (n=111)	High VATI low SATI (n=22)	Low VATI high SATI (n=22)	High VATI and SATI (n=45)	P-value
All-cause mortality	122 (61.0%)	79 (71.2%)	11 (50.0%)	8 (36.4%)	24 (53.3%)	**0.005**

High VATI or SATI refers to the highest tertile, whereas low VATI or SATI refers to the middle and lowest tertiles.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft; ICU = intensive care unit; IMAT% = intermuscular adipose tissue percentage; LOS = length of stay; LVEF = left ventricular ejection fraction; PAT = paracardial adipose tissue area; PCI = percutaneous coronary intervention; SATI = subcutaneous adipose tissue index; SMI = skeletal muscle index; TATI = total adipose tissue index; TIA = transient ischemic attack; VATI = visceral adipose tissue index.

Table 4

Univariable and multivariable Cox regression models comparing different adiposity profiles to the control group

	Univariable analysis			Multivariable analysis		
Variables	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Adipose type categories						
Low VATI and SATI	reference	reference	reference	reference	reference	reference
High VATI low SATI	0.55	0.29–1.03	**0.061**	0.71	0.36–1.38	0.309
Low VATI high SATI	0.35	0.17–0.73	**0.005**	0.39	0.18–0.82	**0.013**
High VATI and SATI	0.62	0.39–0.98	**0.040**	0.73	0.45–1.18	0.195
Covariates included in the adjustment						
Low SMI tertile (cm^2/m^2)	2.00	1.39–2.88	**<0.001**	1.49	1.00–2.22	**0.049**
Albumin (g/dL)	0.56	0.41–0.76	**<0.001**	0.54	0.39–0.75	**<0.001**
High PAT tertile (cm^2)	0.86	0.59–1.26	0.448	-	-	-
High IMAT% tertile (%)	1.70	1.18–2.45	**0.004**	1.19	0.80–1.77	0.388
Age (years)	1.02	1.00–1.03	**0.009**	1.01	1.00–1.03	0.132
Caucasian race	1.47	0.95–2.28	**0.086**	1.28	0.80–2.04	0.308
Male sex	0.96	0.67–1.38	0.838	-	-	-
Peripheral arterial disease	1.65	1.15–2.38	**0.007**	1.35	0.91–2.00	0.133
Chronic obstructive pulmonary disease	1.71	1.20–2.44	**0.003**	1.71	1.17–2.49	**0.005**

IMAT% = intermuscular adipose tissue percentage; PAT = paracardial adipose tissue area; SATI = subcutaneous adipose tissue index; SMI = skeletal muscle index; VATI = visceral adipose tissue index.