## Title

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## Authors

Foldyna, Borek
Troschel, Fabian M
Addison, Daniel
et al.

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# Computed tomography-based fat and muscle characteristics are associated with mortality after transcatheter aortic valve replacement

**Borek Foldyna**[a,b,*,1], **Fabian M Troschel**[c,1], **Daniel Addison**[a], **Florian J. Fintelmann**[c], **Sammy Elmariah**[d], **Deborah Furman**[d], **Parastou Eslami**[a], **Brian Ghoshhajra**[a], **Michael T. Lu**[a], **Venkatesh L. Murthy**[e,1], **Udo Hoffmann**[a,1], and **Ravi Shah**[a,1]

[a] Cardiac MR PET CT Program, Massachusetts General Hospital, Harvard Medical School, Boston, USA

[b]Department of Diagnostic and Interventional Radiology, University of Leipzig, Heart Center, Leipzig, Germany

[c]Department of Radiology, Division of Thoracic Imaging and Intervention, Massachusetts General Hospital, Harvard Medical School, Boston, USA

[d]Department of Medicine, Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, USA

[e]Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, USA

## Abstract

**Background:** Computed tomography (CT)-based fat and muscle measures are associated with outcome in large populations. We tested if muscle and fat characteristics are associated with long-term outcomes after TAVR.

**Methods:** We included 403 clinical CTs performed prior to TAVR at our center between 2008 and 2016, measuring area ($cm^2$) and density (Hounsfield units, HU) of both psoas muscles (PM), subcutaneous adipose (SAT), and visceral adipose tissue (VAT). Area measures were indexed to height, log-transformed and both area and density were standardized for analysis. We assessed the association of each measure with all-cause mortality (adjusted for age, sex, body mass index (BMI), and the Society of Thoracic Surgeons (STS) risk score.

[*]Corresponding author. Cardiac MR PET CT Program, Massachusetts General Hospital, Harvard Medical School, 165 Cambridge Street, Suite 400, Boston, MA 02114, USA. bfoldyna@mgh.harvard.edu (B. Foldyna).

[1]Authors Foldyna and Troschel contributed equally to this study. Drs. Shah, Murthy, and Hoffmann supervised the study jointly, and are joint senior authors. https://doi.org/10.1016/jjcct.2018.03.007

Conflict of interest/financial disclosure

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcct.2018.03.007.

**Results:** Of the 403 individuals (83 ± 8 years; 52% female), 167 (41.4%) died during a median follow-up of 458 days (interquartile range IQR 297–840). Fat measures were feasible and rapid. Fat area was available in 242 (60%) patients with an adequate field of view. Individuals with the lowest PM area, SAT area or VAT area exhibited the highest hazard of mortality. In addition, greater SAT density was associated with a higher mortality hazard (adjusted HR per standard deviation increase in density= 1.35, 95%CI 1.10–1.67, P = 0.005).

**Conclusion:** Rapid CT-based tissue characterization is feasible in patients referred for TAVR. Decreased PM area and increased SAT density are associated with long-term mortality after TAVR, even after accounting for age, sex, BMI, and STS score. Further studies are necessary to interrogate sex-specific relationships between CT tissue metrics and mortality and whether CT measures are incremental to well-established frailty metrics.

### Keywords

Computed tomography; Transcatheter aortic valve replacement; Psoas muscle; Adipose issue; Body composition

## 1. Introduction

In patients at high surgical risk with severe aortic stenosis, transcatheter aortic valve replacement (TAVR) has demonstrated survival benefit relative to medical therapy.[1,2] With increased experience in TAVR performance and perioperative care, there is growing enthusiasm to extend indications for TAVR to lower risk patients,[3,4] prompting efforts to gauge and optimize risk effectively. To assess perioperative risk in TAVR, physicians have adopted the Society of Thoracic Surgeons (STS) 30-day mortality risk score,[5] designed to assess risk prior to cardiac surgery. In addition, clinical frailty measures[6–10] used in the elderly are predictive of mortality after TAVR.[6,11,12] While these questionnaire and examination metrics (e.g. 5-minute walking time, grip strength) define accessible, functional and clinical parameters for risk stratification, identification of specific imaging-based pathophenotypes of frailty may provide further biological insights into why certain patients fare worse after TAVR.

Recently, computed tomography (CT)-based measures of visceral adiposity and abdominal muscle composition have been adopted as markers of frailty in the pre-operative setting (e.g. general surgery and TAVR).[13–17] Since CT scans of chest, abdomen and pelvis are routinely performed in TAVR patients for pre-operative planning, these images can be used to obtain these non-cardiovascular tissue characteristics. While data from large cohorts have defined a role for regional fat and muscle characteristics in outcomes,[18–20] most studies of regional tissue composition in TAVR patients have been limited to small sample size or short-term (≤1 year) post-operative follow-up. Furthermore, associations of CT-derived skeletal muscle area and post-TAVR outcomes have been mixed.[14,21,22] In order to clarify the implications of body composition metrics on outcomes post-TAVR, we investigated the association between regional fat and muscle measures and long-term mortality after TAVR.

## 2. Methods

### 2.1. Study population

This is a retrospective cohort study of all patients who underwent TAVR at the Massachusetts General Hospital between 6/2008–7/2016 and had received a CT scan as part of routine clinical pre-procedural evaluation (see CONSORT diagram; Fig. 1). We excluded individuals with unavailable, corrupted, or incomplete CT datasets or beam hardening artifacts due to implanted orthopedic hardware or oral contrast agents. We extracted standard clinical-demographic characteristics from the electronic medical record, including the STS 30-day mortality risk score (as reported in the medical record).[5] Our primary endpoint was all-cause mortality, which was determined by review of hospital records at our institution and search of online obituaries. Follow-up started at the day of TAVR procedure and ended at death or censoring (loss to follow-up). This study was approved by our local Institutional Review Board.

### 2.2. Image acquisition

All scans were performed on 64+ slice CT scanners (SOMATOM Definition Flash, Siemens, Forchheim, Germany or Discovery CT750 HD, GE Healthcare, Waukesha, WI) using a standard pre-TAVR protocol. Detailed description is provided in Supplemental Text 1.

### 2.3. Image analysis

Non-contrast CT images were analyzed with dedicated post-processing software (3D Slicer, v.4.7.0, http://www.slicer.org)[23] using a single axial image at the level of mid fourth lumbar vertebra (L4), (Fig. 2). We measured area ($cm^2$) as well as mean attenuation (Hounsfield units, HU) of psoas muscle (PM), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT). We manually segmented PM (right and left side separately), SAT, and VAT (Fig. 2). The Overall PM area was calculated by adding right and left PM areas, as previously described.[14,16,21] For the PM segmentation, we used additional density thresholds ( — 45 to +130 HU) to detect lean muscle and to exclude intramuscular as well as capsular fat. SAT was defined as fat between skin and the underlying muscular layer and VAT was defined as fat within the peritoneal cavity, demarcated by manually tracing the inner border of the transversus abdominis muscle.[18,20,24] The SAT and VAT were segmented using fat specific thresholds ( — 195 to — 45 HU)[18,25] (Fig. 2). Inter-observer (BF, DA) reliability analysis was performed in 20 randomly chosen patients, revealing a high inter-reader agreement (intraclass correlation coefficients: 0.937–0.999; $P < 0.001$; Supplemental Table 1, Supplemental Fig. 1).

### 2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (inter-quartile range, IQR), as appropriate. Categorical variables were expressed as frequencies and percentages. We used a Wilcoxon rank-sum (continuous) and Fisher's exact test (categorical variables) to compare covariates stratified by vital status.

CT-based area measures were divided by patient height (in meters) to index the measure to body size. We log-transformed area indices (SAT, VAT, and PM area), BMI and STS score

for further analysis. Next, area, density, age, and BMI were mean-centered and standardized (to variance 1) in males and females separately for regression analyses to allow ease of interpretation (effect estimates for CT indices reported per standard deviation change). Standardization of metrics in males and females separately limited biases introduced due to necessarily higher PM areas and fat areas in men versus women. The male- and female-specific standardized CT metrics were then pooled for downstream analysis.

We estimated partial Spearman correlations (adjusted for age) for the association among CT metrics and clinical indices. To test whether the association between area or density metrics with mortality was linear, we first constructed Kaplan-Meier survival curves for mortality stratified by quartiles of each CT metric. We examined the raw- and Bonferroni-adjusted log-rank P-values for comparison across quartiles of each CT metric (Kaplan-Meier curves shown in Supplemental Fig. 2). In general, we concluded evidence of non-linearity in the associations of outcome with CT area metrics, with the lowest quartile of each CT metric having a distinct prognosis relative to other quartiles ($2^{nd}$–$4^{th}$). Therefore, for subsequent Cox analysis we treated each area metric as binary (with one class as "$1^{st}$ quartile" and the other class as a pooled "$2^{nd}$, $3^{rd}$, $4^{th}$ quartile"). We did not observe as much non-linearity for the density metrics, and as such, they were considered as continuous variables in regression.

Subsequent sex-stratified and pooled Cox regressions for all-cause mortality, adjusted for age, sex, BMI, and STS score were estimated. Proportional hazards assumption was tested using the supremum test. We found that STS score violated proportionality in several models, and as such, we stratified the STS score around 10% (with one class as ≥10% and one class as < 10%) and used the STRATA command in PHREG (in SAS) to address non-proportionality. We stratified in this manner for STS across all models for consistency (regardless of lack of proportionality). In addition to the sex-specific models (e.g., models in males and females separately), in an exploratory analysis, we tested whether the associations between CT metrics and outcome were different by sex by including a multiplicative interaction term between sex and each CT metric in Cox regression (sex*CT metric). All analyses were performed in SAS 9.3 (Cary, NC), or Stata 14.0 (StataCorp LP, College Station, TX).

## 3. Results

### 3.1 Study population stratified by vital status

Our analytic cohort consisted of 403 patients (age 82.5 ± 8.0 years; 52% female; Fig. 1, Table 1). As expected, we observed significant differences between males and females in imaging indices of fat and muscle (Supplemental Table 2), which was addressed by sex-specific mean-centering and standardization for subsequent regression analyses (see Statistical Methods). SAT/VAT density and PM area were measured in all 403 patients. However, we could not measure SAT or VAT area in 161 individuals (39.7%) due to an inadequate field-of-view (FOV). As expected, individuals in whom SAT and VAT could not be measured were more obese and had a lower STS risk score, but a comparable PM area (Supplemental Table 3).

During a median follow-up of 458 days (IQR 297–840 days), 167 (41.4%) patients died. The median time interval between CT exam and TAVR was 57 days (IQR 29–99 days). When stratified by vital status, individuals who died had greater mean STS risk score and lower BMI (Table 1). In addition, individuals who died had a significantly lower PM and SAT area and a higher SAT and VAT density.

### 3.2 Relationship of obesity to CT measures

We observed significant relationships among the CT parameters quantified in this study (Supplemental Table 4). Most associations between PM area and density and other CT indices or BMI were modest (Spearman correlation coefficients of magnitude 0.2–0.3), while SAT and VAT area and density were significantly interrelated (Spearman correlation coefficients magnitude 0.5–0.8), and associated with BMI.

### 3.3. CT-based muscle and fat metrics and long-term mortality after TAVR

We observed that the lowest quartile of PM area (HR = 1.9, 95% confidence interval (CI) 1.35–2.68, P = 0.0003), SAT area (HR = 1.99, 95%CI 1.19–3.33, P = 0.009), and VAT area (HR = 1.73, 95%CI 1.12–2.67, P = 0.01) measured before TAVR were associated with long-term mortality after TAVR (Table 2, Fig. 3). A higher SAT density was associated with greater mortality (HR = 1.35, 95%CI 1.10–1.67, P = 0.005), depicted by upper quartile versus rest in Fig. 3 for display. While exploratory testing of interaction with sex did not suggest effect modification by sex, stratified models did suggest a statistically significant effect only in men (HR = 1.64, 95%CI 1.23–2.19, P = 0.0008). Similarly, while the VAT density was not associated with outcome in the pooled cohort, a greater VAT density was associated with outcome in men (HR = 1.57, 95%CI 1.22–2.04, P = 0.0006) but not in women (HR = 0.8, 95%CI 0.61–1.04, P = 0.09), with a significant interaction (P = 0.008).

Among the 11% of the overall cohort in the highest quartile of SAT density and the lowest quartile of PM area (both related to adverse prognosis) there was a significant unadjusted hazard of all-cause mortality (HR = 1.78, 95% CI 1.18–2.67, P = 0.006; which diminished after full adjustment (HR = 1.57, 95% CI 0.99–2.50, P = 0.057).

## 4. Discussion

The principal finding of our study is that selected CT-based metrics of fat and muscle (decreased PM, SAT, VAT area; increased SAT density) were associated with higher long-term mortality after TAVR over a median follow-up 458 days, which persisted after adjustment for age, sex, BMI, and a clinical risk predictor (STS score). Individuals at the extremes of muscle and fat area were at higher risk of death after TAVR. Importantly, PM area and density were only modestly associated with each other and with other markers of regional (SAT, VAT) fat quantity or density or overall BMI. On the other hand, VAT and SAT parameters were more closely interrelated, even though SAT and VAT density only required a small region of interest for estimation (as opposed to the entire FOV for assessment of VAT or SAT area). Given the impact of rehabilitative, nutritional, and obesity-directed interventions on muscle mass in the elderly,[9,10] our findings that regional measures of

muscle and fat characteristics may be related to mortality call for additional validation and therapeutic efforts to target regional fat and muscle quality to improve post-TAVR outcomes.

Our study is supportive of prior literature in the field[14,16]. In one of the largest studies to date assessing CT metrics in TAVR patients, Mok et al. reported an association between sarcopenia (based on abdominal muscle quantification by CT) and outcomes in 460 patients referred for TAVR,[15] consistent with our findings. Of note, these investigators required patients to have complete VAT, SAT, and PM measures, thereby excluding patients with an insufficient FOV to encompass all three. As shown in our study, exclusion of these study participants introduces a selection bias, particularly with SAT and VAT. Given the increasing prevalence of sarcopenic obesity in the elderly, exclusion of these primarily more obese individuals may limit generalizability. Our study extends current data in the TAVR literature by reporting a large, single-center experience using a standardized imaging protocol to characterize muscle and regional fat depots with long-term follow-up. In addition, all measurements in our study were (1) reproducible across different interpreters, (2) technically facile (generally less than 5 min of postprocessing time), (3) performed on publically available software at no additional cost without any additional imaging beyond what was obtained for clinical pre-TAVR evaluation at our center, highlighting the feasibility of this approach.

The association of lower regional fat and muscle with increased mortality is in keeping with the notion that these depots may reflect reserve. However, the observed associations between fat radiodensity and outcomes are more complex. In large studies of community-dwelling individuals who are younger than the participants of this study, a lower fat density has been associated with metabolic syndrome.[18,19] In a seminal study by Murphy and colleagues in older Americans and European adults (Health ABC and AGES-Reykjavik studies), a higher abdominal fat density was associated with increased all-cause mortality,[20] similar to our findings. Of note, these investigators did not observe an association between inflammatory markers and measures of fat density. While it is possible that the observed difference in association between fat density and outcomes across these different studies may be a phenomenon of aging, it is also possible that tissue properties that contribute to fat radiodensity (e.g., increased fibrosis) may also be relevant in TAVR patients.[26]

There are several important next steps that derive from our results. First, an important ancillary question in this study is whether these CT-based measures meet the standard of a contemporary biomarker of mortality in TAVR patients by providing incremental prognostic information (e.g., discrimination, reclassification) beyond known frailty metrics (e.g., 5-m walk time, grip strength) prognostic in TAVR.[6,12,27] Assessment of incremental value will require large, multi-center studies with careful prospective, comprehensive phenotyping of modern frailty indices (e.g., Fried index) alongside CT imaging to provide a definitive answer. Second, the role of interventions that combat obesity and sarcopenia (e.g., fitness training post-TAVR convalescence) is relevant, and the use of CT-based imaging markers that directly quantitate tissue phenotypes may be important alongside clinical metrics (frailty, exercise capacity, survival) to understand mechanisms of benefit for these interventions. Finally, larger studies that integrate imaging, clinical outcome, and frailty may further our understanding of sex-based differences in TAVR outcome and why they occur—a

critical next step in improving global care post-TAVR. Nevertheless, the results of our study should be viewed in the context of its retrospective design. As such, we could not exclude a potential impact of unmeasured confounders. Similar to prior work,[19] almost 40% of our population failed SAT and VAT quantification due to body size (FOV exceeded); however, PM area and fat densities were not impacted by this limitation. Furthermore, we found that fat densities were closely associated with fat quantity, suggesting that density may be able to "stand-in" for total fat quantity in future models as a more rapidly assessed metric. Also, we did not differentiate cause-specific mortality or perform competing risk models in this work, and further validation across multiple cohorts is necessary.

In conclusion, decreased fat and muscle areas and increased SAT density were associated with greater long-term mortality after TAVR, independent of age, sex, BMI, and clinical risk. Further efforts to assess differences across sex and frailty metrics will be important to target interventions aimed at improving skeletal muscle and adipose tissue health post-TAVR.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
|---|---|
| **BMI** | body mass index |
| **CT** | computed tomography |
| **FOV** | field of view |
| **HU** | Hounsfield units |
| **IQR** | Inter-quartile range |
| **PM** | psoas muscle |
| **SAT** | subcutaneous adipose tissue |
| **STS** | Society of Thoracic Surgeons |
| **TAVR** | transcatheter aortic valve replacement |
| **VAT** | visceral adipose tissue |

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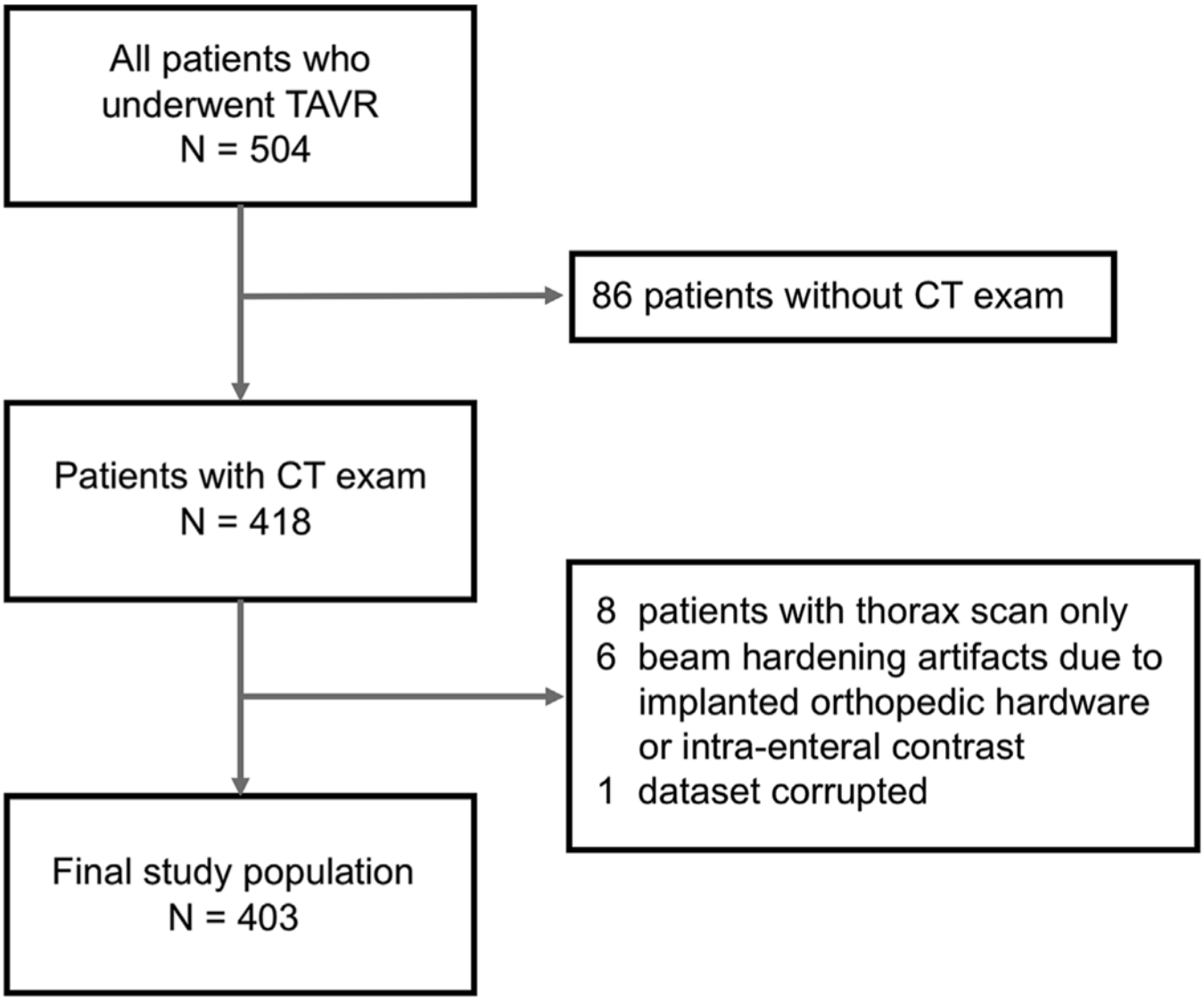


**Fig. 1.**

Consort diagram with inclusion and exclusion criteria.

*CT* = computed tomography, *TAVR* = transcatheter aortic valve replacement.

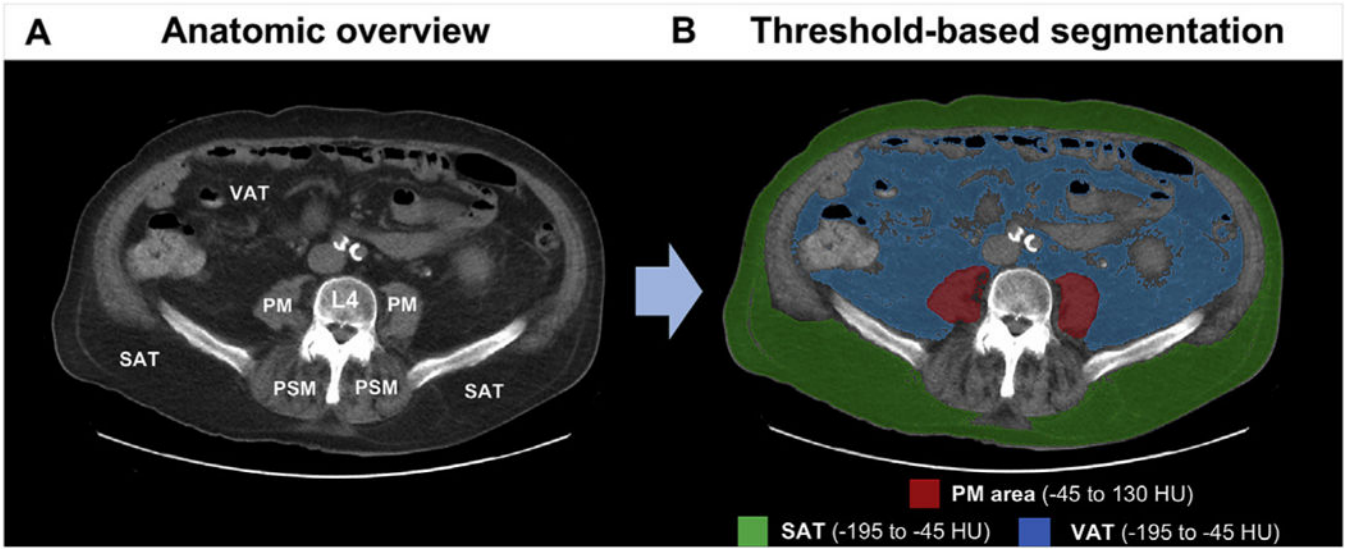


**Fig. 2.**

CT measures.

Axial CT slice (10 mm) at the level of the mid fourth lumbar vertebral body (L4). A: Anatomic overview and B: threshold-based segmentation of tissue of interest. *PSM* = paraspinal muscles; *PM* = psoas muscle; *SAT* = subcutaneous adipose tissue; *VAT* = visceral adipose tissue.

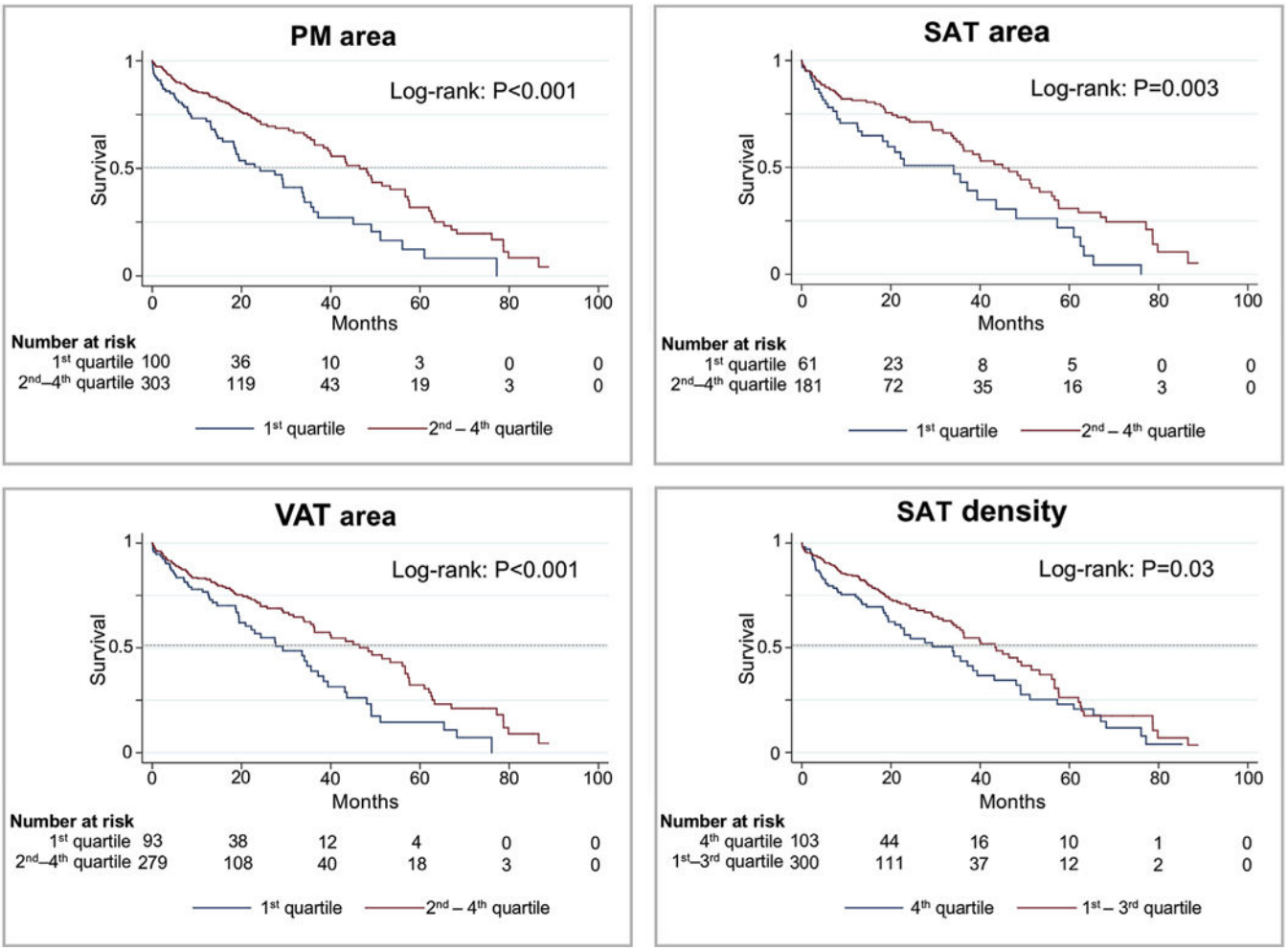


**Fig. 3.**

Kaplan-Meier estimates for PM, SAT, and VAT area as well as SAT density by the highest risk quartile vs. rest.

Lowest quartile of PM, SAT, ad VAT area and the highest quartile of SAT density were associated with higher mortality. *PM* = psoas muscle, *SAT* = subcutaneous adipose tissue, *VAT* = visceral adipose tissue.

**Table 1**

Baseline clinical and CT characteristics (N = 403).

| Clinical characteristics | All patients (N = 403/100%)* | Dead (N = 167/41.4%) | Alive (N = 236/58.6%) | P |
|---|---|---|---|---|
| Age – yrs. | 82.5 ± 8.0 | 83.4 ± 7.7 | 81.8 ± 8.1 | 0.061 |
| Females – No. | 210 (52.1) | 85 (50.9) | 125 (53.0) | 0.683 |
| Height – m | 1.6 ± 0.1 | 1.6 ± 0.1 | 1.6 ± 0.1 | 0.880 |
| Weight – kg | 75.2 ± 20.4 | 71.9 ± 18.0 | 77.5 ± 21.7 | 0.024 |
| BMI – kg/m$^2$ | 27.7 ± 6.9 | 26.5 ± 5.9 | 28.6 ± 7.4 | 0.005 |
| PVD – No. | 146 (36.2) | 79 (47.3) | 67 (28.4) | < 0.001 |
| HTN – No. | 366 (90.8) | 146 (87.4) | 229 (93.2) | 0.048 |
| Hx of stroke – No. | 42 (10.4) | 25 (15.0) | 17 (7.2) | 0.012 |
| Hx of CABG – No. | 99 (24.6) | 46 (27.5) | 53 (22.5) | 0.243 |
| Hx of MI – No. | 69 (17.1) | 35 (21.0) | 34 (14.4) | 0.086 |
| Hx of PCI – No. | 131 (32.5) | 62 (37.1) | 69 (29.2) | 0.096 |
| Hx of diabetes – No. | 140 (34.7) | 56 (33.5) | 84 (35.6) | 0.669 |
| Hx of smoking – No. | 14 (3.5) | 5 (3.0) | 9 (3.8) | 0.659 |
| STS Score – % | 8.5 ± 5.2 | 10.5 ± 5.7 | 7.1 ± 4.3 | < 0.001 |
| 5 m walk time* – s | 8.5 ± 4.2 | 9.8 ± 5.2 | 8.0 ± 3.6 | 0.001 |
| Grip strength* – kg | 18.6 ± 7.5 | 22.6 ± 9.4 | 18.0 ± 7.2 | 0.180 |
| **CT measures** | | | | |
| PM area – cm$^2$/m (N = 403) | 12.4 ± 3.3 | 12.0 ± 3.3 | 12.7 ± 3.2 | 0.047 |
| PM density – HU(N = 403) | 27.4 ± 9.6 | 28.4 ± 9.8 | 26.7 ± 9.4 | 0.075 |
| SAT area – cm$^2$/m (N = 242) | 125.4 ± 73.8 | 115.1 ± 73.6 | 134.2 ± 73.6 | 0.014 |
| SAT density – HU (N = 403) | – 96.3 ± 11.9 | – 92.6 ± 10.6 | – 99.0 ± 12.0 | <0.001 |
| VAT area – cm$^2$/m (N = 242) | 108.3 ± 65.4 | 100.8 ± 69.4 | 113.7 ± 61.9 | 0.020 |
| VAT density – HU (N = 403) | – 90.5 ± 8.8 | – 88.6 ± 9.2 | – 91.9 ± 8.2 | <0.001 |

Values expressed as mean ± SD or N (%). *BMI* = body mass index; *CABG* = coronary artery bypass graft; *CT* = computed tomography; *HTN* = hypertension; *HU* = Hounsfield units; *MI* = myocardial infarct; *PCI* = percutaneous coronary intervention; *PM* = psoas muscle; *PVD* = peripheral vascular. disease; *STS* = Society of Thoracic Surgeons; *SAT* = subcutaneous adipose tissue; *VAT* = visceral adipose tissue.

*clinical frailty measures available in subgroups: 5 m walk time N = 252 (62.5%); grip strength N = 42 (10.4%).

**Table 2**

Survival analysis for all-cause mortality as a function of CT measures of metabolic frailty.

| CT measures | N* | Adjusted model | | | Males | | | Females | | | P interaction by sex |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **AREA** | | | | | | | | | | | |
| Reference is 2nd –4th quartile | | **HR** | **95% CI** | **P** | **HR** | **95% CI** | **P** | **HR** | **95% CI** | **P** | |
| PM area | 403 | 1.90 | 1.35–2.68 | < 0.001 | 2.29 | 1.36–3.87 | 0.002 | 1.66 | 1.03–2.68 | 0.04 | 0.58 |
| SAT area | 242 | 1.99 | 1.19–3.33 | 0.009 | 2.60 | 1.22–5.50 | 0.01 | 1.42 | 0.69–2.91 | 0.34 | 0.73 |
| VAT area | 372 | 1.73 | 1.12–2.67 | 0.01 | 1.97 | 1.06–3.64 | 0.03 | 1.59 | 0.86–2.94 | 0.14 | 0.65† |
| **DENSITY** | | | | | | | | | | | |
| Per SD increase (less negative) | | **HR** | **95% CI** | **P** | **HR** | **95% CI** | **P** | **HR** | **95% CI** | **P** | |
| PM density | 403 | 0.87 | 0.73.–1.03 | 0.10 | 0.74 | 0.57–0.95 | 0.02 | 1.00 | 0.78–1.28 | 0.98 | 0.08 |
| SAT density | 403 | 1.35 | 1.10–1.67 | < 0.001 | 1.64 | 1.23–2.19 | < 0.001 | 1.08 | 0.79–1.49 | 0.63 | 0.22 |
| VAT density | 403 | 1.12 | 0.93–1.35 | 0.22 | 1.57 | 1.22–2.04 | < 0.001 | 0.80 | 0.61–1.04 | 0.09 | < 0.001 |

Each hazard ratio (HR) represents the hazard of all-cause mortality adjusted for age, sex, BMI, and STS score. *BMI* = body mass index; *CI* = confidence interval; *PM* = psoas muscle; *SAT* = subcutaneous adipose tissue; *STS* = Society of Thoracic Surgeons; *VAT* = visceral adipose tissue.

*in adjusted model regression;

†VAT area*sex interaction violated proportionality, and as such, this P value is for the interaction time in a multivariable model that includes both the interaction and a time-dependent covariate between the interaction and log-survival time.