CT-derived fat density as a predictor of cause-specific mortality in patients undergoing TAVI: Findings from a large registry subanalysis

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is increasingly performed in older and frailer patients with severe aortic stenosis. Pre-procedural computed tomography (CT) scans at the third lumbar vertebra (CTL3) can estimate overall patient survival after TAVI [1, 2]. This subanalysis investigated whether CTL3 parameters can predict specific causes of death, potentially allowing for more tailored post-operative therapy.

METHODS

Patients undergoing TAVI between 2010 and 2022 were included in the prospective TAVI Registry of a tertiary cardiac center. All patients with available preprocedural CT scans were included and provided informed consent. The study was approved by the Ethics Committee (EK 301/22) and registered (NCT05672160).

Automatic CT single-slice segmentation at the level of the third lumbar vertebra was performed using the UNET neural network called AutoMATiCA [3]. Through segmentation, we obtained eight new CTL3 parameters of muscle and fat tissue quality and quantity – four depicted the density of different tissue segments (in Hounsfield units [HU]), while the other four provided the area of these segments, indexed to the square of the height (cm^2/m^2). Specifically, the parameters were as follows: skeletal muscle density (SMD), intramuscular adipose tissue density (IMAT density), visceral adipose tissue density (VAT density), subcutaneous adipose tissue density (SAT density), skeletal muscle index (SMI), IMAT index, VAT index, SAT index.

A retrospective survival analysis of all-cause death and CTL3 parameters had already been performed, and we published the results of that study in 2024 [1]. In this new study, we performed a subanalysis of CTL3 parameters and specific causes of death. For the subanalysis, we divided the cohort into eight categories according to the cause of death (infection, cardiovascular, sudden death at home without an autopsy, tumor, respiratory failure, trauma, unknown circumstances of death, renal failure) (details in Supplementary material, *Table S1*).

Statistical analysis

Statistical analyses were performed using the R programming language. The multivariable Cox proportional hazards model (adjusted for age, sex, and the presence of comorbidities, including hypertension, diabetes mellitus,

A

CTL3 Parameter	Infection	Cardiovascular	Sudden death	Cancer	Respiratory failure	Traumatic	Unknown	Renal
SMI	0.977	0.987	0.969	0.996	0.975	0.931	0.983	NA
IMAT index	1.057*	1.034	1.036	0.929	1.046	0.954	1.045	NA
VAT index	1.003	0.997	0.993	0.994	0.999	0.995	0.998	NA
SAT index	1.004	0.998	0.990	0.985*	0.991	0.985	1.002	NA
SMD	0.993	1.011	1.021	1.012	0.994	1.039	0.999	NA
IMAT density	0.984	0.970	1.011	1.058*	0.974	0.914	0.978	NA
VAT density	1.006	1.034*	1.027	1.043*	1.013	0.991	1.032	NA
SAT density	1.010	1.023*	1.028	1.035*	1.017	1.000	1.022	NA
Colour scale describing RR	HR_{min}			HR = 1			HR_{max}	
	0.914	0.954	0.977	1	1.01	1.034	1.045	1.058

B

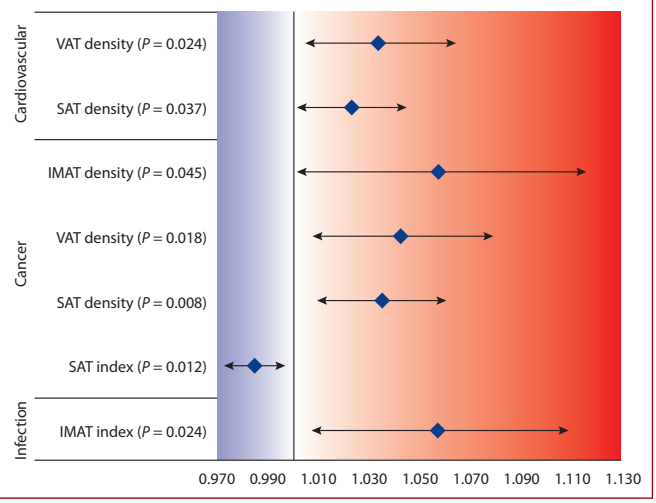

Figure 1. A. Heatmap of hazard ratios: CTL3 parameters and cause-specific mortality after transcatheter aortic valve implantation (TAVI). **B.** Forest plot of CTL3 parameters associated with mortality risk in TAVI patients. **A.** Heatmap showing the hazard ratios (HR) of different CTL3 parameters for different causes of death in patients after TAVI. Each cell represents the HR for a specific CTL3 parameter (rows) associated with a specific cause of death (columns). Parameters include SMI (skeletal muscle index), intramuscular adipose tissue (IMAT) index, visceral adipose tissue (VAT) index, subcutaneous adipose tissue (SAT) index, skeletal muscle density, IMAT density, VAT density, and SAT density. Statistically significant values are marked with an asterisk (*). A color scale is used to illustrate the HR, with blue indicating a lower risk and red indicating a higher risk. **B.** Forest plot showing statistically significant CTL3 parameters associated with specific causes of mortality in TAVI patients. The hazard ratio of each parameter is shown together with the 95% confidence interval. The plot highlights significant associations for cardiovascular, cancer, and infection-related deaths. The parameters and their *P*-values include VAT density ($P = 0.024$), SAT density ($P = 0.037$) for cardiovascular mortality, IMAT density ($P = 0.045$), VAT density ($P = 0.018$) and SAT density ($P = 0.008$) for cancer mortality as well as SAT index ($P = 0.012$) and IMAT index ($P = 0.024$) for infection-related mortality

history of myocardial infarction, and respiratory disease) was used to assess the association of both continuous and categorical variables with cause-specific mortality in eight categories. The hazard ratio (HR) with a 95% confidence interval (CI) was increased for each 1 HU and 1 cm^2/m^2 for density and area index, respectively. The model could not be used for renal failure due to the very small number of deaths due to that cause The outcome monitored was overall survival. A *P*-value <0.05 was considered statistically significant for all analyses.

RESULTS AND DISCUSSION

The study included 866 patients (median age 79.7 years; 49.5% men). Detailed cohort characteristics are presented in the Supplementary material, *Tables S2* and *S3*.

There were 100 (22.1%) patients who died because of infection, 87 (19.2%) because of cardiovascular causes, 50 (11.0%) because of sudden death, 55 (12.1%) because of cancer, 61 (13.5%) because of respiratory failure, 12 (2.6) because of trauma, 78 (17.2) because of unknown cause, 10 (2.2) because of renal failure.

Specific CT parameters were associated with mortality risk in three cause-specific categories: cardiovascular, cancer, and infection. VAT and SAT densities were associated with cardiovascular mortality; IMAT density, VAT density, SAT density, and SAT index with cancer mortality; and IMAT index with infection-related mortality. Figure 1 presents these results, with Figure 1A displaying all hazard ratios as a heatmap, and Figure 1B showing the hazard ratios (HR) with $P < 0.05$ from the multivariable model as a forest plot with 95% CI.

Infection-related mortality risk increased by 5.7% for each 1 cm^2/m^2 increase in IMAT index (HR, 1.057; 95% CI, 1.007–1.109; $P = 0.024$). Cardiovascular mortality risk increased by 3.4% for each 1 HU increase in VAT density (HR, 1.034; 95% CI, 1.004–1.065; $P = 0.024$) and by 2.3% for each 1 HU increase in SAT density (HR, 1.023; 95% CI, 1.001–1.045; $P = 0.037$). Cancer-related mortality risk decreased by 1.5% for each 1 cm^2/m^2 increase in the SAT index (HR, 0.985; 95% CI, 0.973–0.997; $P = 0.012$) and increased by 5.8% for each 1 HU increase in IMAT density (HR, 1.058; 95% CI, 1.001–1.117; $P = 0.045$), by 4.3% for each 1 HU increase in VAT density (HR, 1.043; 95% CI, 1.007–1.080; $P = 0.018$), and by 3.5% for each 1 HU increase in SAT density (HR, 1.035; 95% CI, 1.009–1.061; $P = 0.008$). For a discussion of the clinical significance of these findings and their context within our broader research, see Supplementary material, *Table S4*.

The results highlight the importance of examining CTL3 parameters' relationship with overall survival and specific causes of death. While sarcopenia traditionally assesses muscle amount and strength, our study found SMD and SMI parameters non-significant, challenging this model.

On the other hand, our study reproduces the relationship between CT-derived fat density and mortality in patients undergoing TAVI, as it has been well-defined in different patient cohorts — cancer [4], cirrhosis [5] or COVID-19 infection [6] and fat tissue density, as measured by CT, correlate very well with actual histological findings [7].

The pathophysiology for the increase of both SAT and VAT density and even the IMAT density is well understood [8]. To illustrate the problem briefly — fat tissue density is a hallmark of metabolic health and is tightly connected to insulin sensitivity. In patients with insulin resistance (IR), the free fatty acid levels in the blood are elevated, leading to ectopic and pathological fat accumulation, mainly in the liver, pancreas, and muscle, further worsening the insulin sensitivity due to intracellular lipotoxicity leading to mitochondrial dysfunction. Intramuscular fat tissue density is, therefore, a good marker of the severity of insulin resistance. Moreover, in these insulin-resistant patients, adipocytes in both subcutaneous and visceral fat are primarily storing additional triglyceride molecules in the process of cellular hypertrophy. If this continues long enough, adipocytes start to experience ischemia, leading to cell death, which further results in chronic inflammation and fibrosis in the adipose tissue, thus increasing density on the CT image. It is, therefore, safe to conclude that SAT, VAT, and IMAT density are all indicators of the degree of metabolic dysfunction.

Insulin resistance, a central determinant of metabolic disease, has become extremely prevalent during the last few decades, affecting at least 31% of the US population. IR significantly increases cardiovascular [9], as well as infection [10] and cancer [11] related mortality. It is clear that, compared to figures in the general population, the prevalence of IR in our TAVI cohort was much higher since 43.3% of patients had already been diagnosed with type 2 diabetes, which is the "end-stage" of the IR spectrum.

Our findings complement recent advances in improving TAVI outcomes, as reviewed by Pardo Sanz and Zamorano Gómez [12]. CT-derived fat density parameters offer additional tools for risk stratification, potentially guiding post-TAVI management strategies. While our study has limitations, including its single-center design and the potential for unmeasured confounding factors (detailed in Supplementary material, *Table S5*), it provides valuable insights into the relationship between CT-derived fat parameters and cause-specific mortality in TAVI patients.

To conclude, subcutaneous, visceral, and intramuscular fat densities are proxies for the degree of IR and metabolic dysfunction, thus they correlated well with cardiovascular, infection, and cancer-related mortality in our cohort. In light of these findings, it is worthwhile to think about how to improve the metabolic status of patients after TAVI in the future and thereby increase their overall survival.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

Conflict of interest: None declared.

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