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The impact of computed tomography-derived aortic atheroma volume on prognosis after transcatheter aortic valve replacement

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ABSTRACT

Background: The impact of the extent of aortic atheroma on patients' prognosis after transcatheter aortic valve replacement (TAVR) has not been completely evaluated. This study aimed to evaluate the prognostic value of the aortic atheroma volume (AAV) derived from computed tomography, and the effect of its differences among the segments of the aorta, in patients undergoing TAVR.

Methods: In total, 143 patients with symptomatic severe aortic stenosis who underwent pre-procedural computed tomography before TAVR procedure indication were evaluated. AAV was calculated by measuring the aortic lumen and vessel volume using every 1-mm axial image and was further divided into thoracic (TAAV) and abdominal segments (AbAAV).

Results: During a median follow-up of 651 days, 24 all-cause and 14 cardiac deaths occurred. In the Kaplan-Meier analysis, the high AAV group had significantly higher all-cause and cardiac mortalities than the low AAV group ($p = 0.016$ and 0.023, respectively). Regarding segmental AAV, all-cause and cardiac mortalities did not have significant differences between the high and low TAAV groups. Moreover, all-cause and cardiac mortalities were significantly higher in the high AbAAV group than in the low AbAAV group ($p = 0.0043$ and 0.023, respectively). The multivariable analysis showed that only AbAAV was an independent predictor for all-cause mortality (hazard ratio: 1.06, $p = 0.046$).

Conclusion: AAV was significantly associated with the mortality after TAVR. The current study suggests the pre-procedural assessment of AAV is valuable in predicting prognosis after TAVR. However, further investigation with a larger sample size is needed to validate our findings.

List of abbreviations

AAV	aortic atheroma volume
AbAAV	aortic atheroma volume of the abdominal aorta
ACV	aortic calcification volume
AS	aortic stenosis
BNP	B-type natriuretic peptide
CT	computed tomography
eGFR	estimated glomerular filtration rate
ICC	intra-class correlation coefficient
IQR	interquartile range
LVEF	left ventricular ejection fraction
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TAAV	aortic atheroma volume of the thoracic aorta
TAVR	transcatheter aortic valve replacement

1. Introduction

Transcatheter aortic valve replacement (TAVR) is a widely accepted treatment for patients with severe aortic stenosis (AS), particularly for the elderly population or those with multiple comorbidities [1–5]. Although technical advancements in TAVR enhance procedural success

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and mitigate peri-procedural complications, some patients who undergo TAVR have a subtle improvement in symptoms and eventually die in the early phase after TAVR [6,7]. This implies that it is necessary to identify patients who truly benefit from this procedure in terms of preventing futile interventions.

Risk prediction models are important to optimize the indication for interventional procedures. The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, one of the most well-established tools for risk assessment in patients requiring cardiac surgery, is also commonly utilized for risk stratification in patients who plan to undergo TAVR. However, some studies have demonstrated that this risk score is not suitable for patients undergoing TAVR [8,9]. Furthermore, it was designed to predict short-term prognosis only and not mid-term or long-term prognosis. Therefore, a more robust risk stratification model for TAVR that uses other parameters is needed.

Extended aortic atheroma detected on pre-TAVR computed tomography (CT) is widely recognized as a periprocedural risk factor for systemic embolization, which has recently received increased attention. Recently, several studies indicated that the aortic atheroma volume (AAV) derived from CT contributes to periprocedural adverse events such as acute kidney injury and cerebral infarction [10,11]. The extent of aortic calcified atheroma has also been reported as an integrative predictor of long-term cardiac and all-cause mortalities after TAVR [12,13]. Furthermore, the prognostic impact of aortic calcification volume (ACV) has been reported to differ according to the segment of the aorta [12]. Meanwhile, the impact of aortic atherosclerotic plaques, including non-calcified atheroma, on prognosis after TAVR has not been completely evaluated. Thus, this study aimed to evaluate the prognostic impact of the AAV derived from CT and assess the differences in its prognostic impact among the segments of the aorta, in patients undergoing TAVR.

2. Methods

2.1. Study design and patient population

This retrospective, single-center, observational study enrolled consecutive patients with symptomatic severe AS who underwent TAVR between October 2015 and December 2019 at Kobe University Hospital. The exclusion criteria were as follows: inadequate CT image quality owing to artifacts; history of coronary artery bypass graft; or history of pacemaker implantation (as aorto-coronary anastomotic markers and metal-related artifacts due to pacemakers hamper accurate calculation of the AAV). All patients underwent pre-procedural CT to assess TAVR indication. The designated multidisciplinary heart team discussed all cases according to the current guideline, and a consensus was achieved regarding the therapeutic strategy in each case. TAVR was performed in a hybrid operating room with patients under general anesthesia or conscious sedation using balloon-expandable or self-expandable transcatheter aortic valves.

The study protocol adhered to the tenets of the 1975 Declaration of Helsinki. Because of the retrospective nature of this study, we obtained informed consent in the form of opt-out on the Internet. The study was approved by the institutional ethical committee of Kobe University Graduate school of Medicine.

2.2. CT image acquisition

All image acquisitions were performed using a commercially available third-generation dual-source CT scanner (SOMATOM Force, Siemens Healthcare, Forchheim, Germany). Following the test injection of 12 mL of a contrast agent (Iohexol 240, 240 mgI/mL; GE Healthcare Pharma Japan, Tokyo, Japan) to assess the contrast agent transit time, non-electrocardiogram-gated CT covering the whole thoracic and abdominal aorta was performed with a 40–100-mL contrast agent injection using the following parameters: collimation, 192 × 0.6 mm; scan pitch factor, 3.0; tube voltage, 70 kV; tube current, automated exposure control; and gantry rotation time, 250 ms. The image reconstruction algorithm included kernel (Bv36) and ADMIRE (3). Images for measuring AAVs were reconstructed with a 1-mm slice thickness.

2.3. Measurement of AAV and ACV

AAV and ACV were measured on a commercially available workstation (Ziostation2 version 2.4.2.3, Ziosoft Inc., Tokyo, Japan). The detailed procedure of AAV measurement is illustrated in Fig. 1. The aortic vessel wall and lumen boundaries were manually traced at every 1-mm axial slice throughout the entire aorta, from the sinotubular junction to the iliac bifurcation. The window level and width were adjusted to clearly differentiate the lumen from the vessel wall and minimize calcification artifacts. Subsequently, the software automatically quantified the lumen and vessel volume of the entire aorta based on two-dimensional data. The AAV was measured as the difference between the vessel and lumen volume. Using three-dimensional segmental tools, AAV was divided into the following two segments: (1) the thoracic aorta (TAAV) and (2) abdominal aorta (AbAAV). Then, ACV was quantified using the volume rendering method, as described previously [14].

2.4. Echocardiographic assessment

Commercially available echocardiography systems were used in this study. The left ventricular ejection fraction (LVEF) was measured using the modified Simpson method. The peak aortic jet velocity was measured using continuous wave Doppler mode. The aortic valve mean gradient was determined by tracing the velocity time integral of the transaortic valvar flow, which was measured using the continuous wave Doppler mode. The aortic valvar orifice area was calculated using the continuity equation.

2.5. Study endpoints

The primary endpoint of this study was defined as all-cause mortality. The secondary endpoint was defined as cardiac mortality, including sudden death, cardiac rupture, infectious endocarditis, and death owing to heart failure [15]. Clinical events were assessed by reviewing patients' electronic medical records and reports from family members and conducting telephone interviews.

2.6. Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range, IQR), as appropriate, and were compared using the Student *t*-test or Mann-Whitney *U* test. The normality of data distribution of all continuous variables was assessed using the Shapiro-Wilk test. Categorical variables were expressed as count and percentage and compared using the chi-square or Fisher exact tests. Twenty randomly chosen participants were used to evaluated intra-observer and inter-observer reliabilities of AAV measurements using the intra-class correlation coefficient (ICC), in addition to Bland-Altman analysis. Survival after TAVR was established using Kaplan-Meier curves, and event rates were compared using the log-rank test. Univariable Cox regression analysis was performed to identify variables associated with all-cause mortality. Following Bonferroni's correction, *p*-values < 0.0025 were considered statistically significant in a univariable analysis. The variables with variance inflation factor < 10 and p-values < 0.10 in the univariable analysis were included in a multivariable Cox regression analysis with the forward-backward stepwise selection method. All statistical analyses were performed using commercially available software (JMP 14.2.0; SAS Institute, Cary, NC, USA). *P*-values < 0.05 were considered statistically significant.

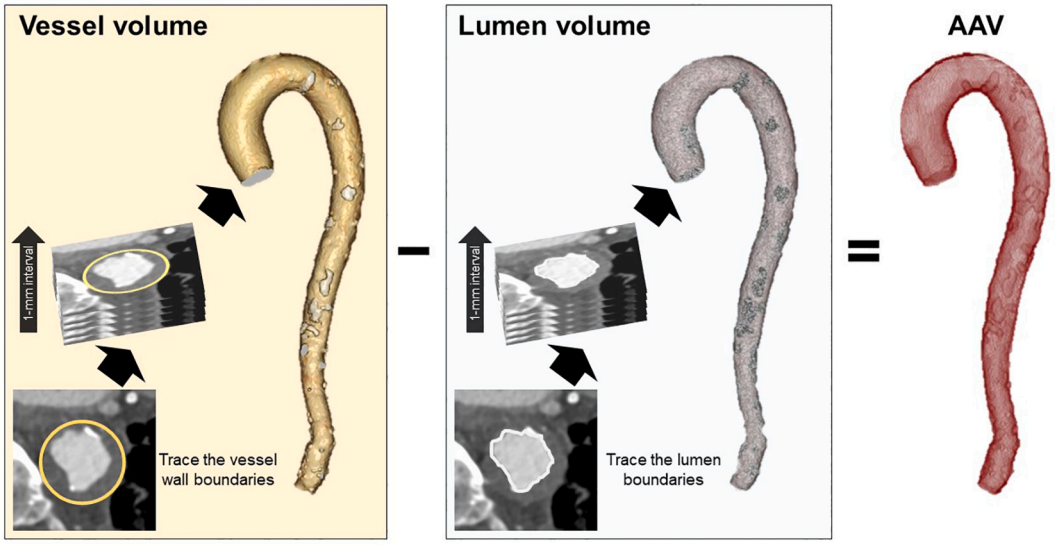

Fig. 1. Measurements of AAV using enhanced CT.
The aortic vessel wall and lumen boundaries were manually traced at every 1-mm axial 2-dimensional image for the entire aorta, from the sinotubular junction to the iliac bifurcation. Vessel and lumen volume were automatically computed via summation of the 2-dimensional vessel and lumen area. Finally, the AAV was calculated as the difference between the vessel and lumen volume.
AAV, aortic atheroma volume; CT, computed tomography.

3. Results

3.1. Study population

In total, 151 patients with severe AS underwent pre-TAVR planning CT during the study period. We excluded 8 patients because of poor image quality ($n = 2$), pacemaker implantation ($n = 4$), and coronary artery bypass graft (n = 2). Finally, 143 patients were analyzed in this study. The patient characteristics are shown in Table 1. Patients' mean age was 85.4 ± 4.1 years, and 73% of patients were female. The median STS-PROM score was 6.4% (IQR: 4.6–9.2%), and the median logistic EuroSCORE was 12.1% (IQR: 8.9–18.5%). The median B-type natriuretic peptide (BNP) level was 285 pg/mL (IQR: 102–519 pg/mL).

3.2. The distribution of AAV

AAV ranged from 28.5 mL to 174.7 mL, and the median AAV was 63.6 mL (IQR: 51.2–78.2 mL). Intra-observer and inter-observer reliabilities were substantial (ICC = 0.913 and 0.7904, respectively) (Supplementary Fig. 1). The median TAAV and median AbAAV values were 46.2 mL (IQR: 37.4–57.5 mL) and 16.8 mL (IQR: 13.0–24.3 mL), respectively (Table 1).

3.3. Comparison of patient data between the low and high AAV groups

Patients were divided into low and high AAV groups based on the median AAV (Table 1). The median AAV values were 51.2 mL (IQR: 43.8–57.6 mL) and 78.2 mL (IQR 71.0–89.4 mL) in the low and high AAV groups, respectively ($p < 0.0001$). Male sex, body surface area, and ankle brachial pressure index were significantly higher in the high AAV group than in the low AAV group. Age, STS-PROM score, and logistic EuroSCORE were not significantly different between the groups. Regarding medical history, the high AAV group had a higher rate of dyslipidemia than the low AAV group. These two groups had no significant differences in echocardiographic measurements related to AS severity, including the transaortic valve mean pressure gradient and aortic valve area. ACV was significantly higher in the high AAV group than in the low AAV group.

3.4. Clinical impact of AAV on prognosis

During a median follow-up of 651 days (IQR: 252–936 days) after TAVR, 24 (16.8%) all-cause deaths and 14 (9.8%) cardiac deaths occurred. In terms of periprocedural complications within 30 days after TAVR, 2 (1.4%) cardiac deaths and 2 (1.4%) cerebral infarctions occurred. In the Kaplan-Meier analysis, the high AAV group had significantly higher all-cause and cardiac mortalities than the low AAV group ($p = 0.016$ and 0.023, respectively) (Fig. 2). Regarding segmental AAV, when patients were divided into the low and high groups based on the median TAAV and median AbAAV, as well as the AAV, all-cause and cardiac mortalities did not have significant differences between the high and low TAAV groups. Moreover, all-cause and cardiac mortalities were significantly higher in the high AbAAV group than in the low AbAAV group ($p = 0.0043$ and 0.023, respectively) (Fig. 2).

In the univariable analysis with the Cox hazard model, AbAAV was significantly associated with all-cause mortality ($p = 0.0023$) (Table 2). Higher logistic EuroSCORE, increased BNP level, lower LVEF, and higher ACV were related to higher all-cause mortality, although the data did not reach statistical significance. The multivariable Cox regression analysis revealed that only AbAAV was an independent predictor for all-cause mortality (hazard ratio: 1.06, 95% confidence interval: 1.001–1.11, $p = 0.046$).

3.5. Demographic factors related to the burden of abdominal AAV

Scattergrams indicating the relationship between AbAAV and variables are shown in Supplementary Fig. 2. AbAAV was significantly negatively correlated with the estimated glomerular filtration rate and ankle brachial pressure index ($r = -0.19$, $p = 0.027$ and $r = -0.24$, $p = 0.0057$, respectively). There were no significant correlations between AbAAV and body mass index, mean blood pressure, glycated hemoglobin level, and BNP level.

4. Discussion

The present study demonstrates that higher AAV and AbAAV were significantly associated with increased all-cause and cardiac mortalities in time-to-event analysis; furthermore, AbAAV was an independent

Table 1
Patient characteristics.

	All patients	Low AAV group	High AAV group	p-Value
	(n = 143)	(n = 71)	(n = 72)	
Age, years	85.4 ± 4.1	85.2 ± 0.5	85.6 ± 0.5	0.47
Female sex, n (%)	105 (73)	62 (87)	43 (60)	**<0.0001**
Body surface area, m^2	1.42 ± 0.16	1.39 ± 0.02	1.46 ± 0.02	**0.0075**
Mean blood pressure, mmHg	87 ± 17	84 ± 2	90 ± 2	0.12
Systolic blood pressure, mmHg	132 ± 23	130 ± 3	135 ± 3	0.14
STS-PROM score, %	6.4 (4.6–9.2)	6.3 (4.6–8.8)	6.7 (4.6–9.4)	0.72
Logistic EuroSCORE, %	12.1 (8.9–18.5)	12.3 (9.5–18.1)	12.0 (8.6–19.7)	0.27
Hypertension, n (%)	99 (69)	52 (73)	47 (65)	0.3
Diabetes mellitus, n (%)	36 (25)	22 (31)	14 (19)	0.11
Dyslipidemia, n (%)	61 (43)	24 (34)	37 (51)	**0.033**
Chronic kidney disease, n (%)	70 (49)	31 (44)	39 (54)	0.21
Atrial fibrillation, n (%)	31 (22)	14 (20)	17 (24)	0.57
Cerebral infarction, n (%)	18 (13)	7 (10)	11 (15)	0.33
Coronary artery disease, n (%)	40 (28)	19 (27)	21 (29)	0.75
Ankle brachial pressure index	0.97 ± 0.17	1.02 ± 0.02	0.93 ± 0.02	**0.0032**
Blood test results				
Creatinine, mg/dL	1.1 ± 0.7	1.0 ± 0.1	1.2 ± 0.1	0.07
eGFR, mL/min/1.73 m^2	49.2 ± 19.5	52.2 ± 2.3	46.2 ± 2.3	0.07
HbA1c, %	6.0 ± 0.7	6.1 ± 0.1	5.8 ± 0.1	**0.018**
LDL-C, mg/dL	101 ± 31	103 ± 4	99 ± 4	0.40
TG, mg/dL	111 ± 53	116 ± 6	106 ± 6	0.26
BNP, pg/mL	285 (102–519)	232 (97–416)	303 (131–598)	0.75
Echocardiographic measurements				
LVEF, %	61.9 ± 12.7	61.9 ± 1.5	61.9 ± 1.5	0.99
Peak aortic jet velocity, cm/s	427 ± 109	451.5 ± 7.6	444.6 ± 7.5	0.52
Mean aortic valve gradient, mmHg	50.7 ± 3.2	52.3 ± 1.6	49.2 ± 1.5	0.16
Aortic valve area, cm^2	0.6 ± 0.2	0.6 ± 0.02	0.7 ± 0.02	0.086
CT measurements				
AAV, mL	63.6 (51.2–78.2)	51.2 (43.8–57.6)	78.2 (71.0–89.4)	**<0.0001**
TAAV, mL	46.2 (37.4–57.5)	37.4 (31.2–41.5)	57.2 (50.7–65.3)	**<0.0001**
AbAAV, mL	16.8 (13.0–24.3)	13.0 (10.2–15.8)	24.2 (19.4–27.2)	**<0.0001**
ACV, mL	13.9 (8.9–22.9)	8.9 (5.4–11.7)	22.9 (17.9–31.2)	**<0.0001**

Values are expressed as mean ± standard deviation, n (%), or median (interquartile range). P-values <0.05 are shown in **bold**.
AAV, aortic atheroma volume; AbAAV, aortic atheroma volume of the abdominal aorta; ACV, aortic calcification volume; BNP, B-type natriuretic peptide; CT, computed tomography; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; STS-PROM, Society of Thoracic Predicted Risk of Mortality; TAAV, aortic atheroma volume of the thoracic aorta; TG, triglyceride.

predictor for all-cause mortality after TAVR. These findings suggest that the pre-procedural assessment of AAV could be an important risk stratification for mortality after TAVR. To the best of our knowledge, the current study is the first to demonstrate the significant relationship between aortic atheroma burden and long-term mortality in patients undergoing TAVR.

Several clinical studies revealed that aortic atheroma burden is associated with long-term mortality after cardiovascular surgery. Kurra et al. demonstrated that the extent of thoracic aortic atheroma burden was independently associated with increased long-term mortality in a semi-quantitative CT assessment of 862 patients following cardiothoracic surgery [16]. Butler et al. showed a significant relationship between the grade of aortic atheroma determined using transesophageal and epiaortic ultrasound data and long-term mortality in a retrospective cohort of over 20,000 cardiac surgery patients [17]. These findings are supportive of the current study's results. Indeed, this potential causal relationship between the aortic atheroma burden and long-term mortality seems to be intuitive. However, among these studies, the explicit mechanism by which aortic atheroma confers an increased risk of mortality has not been elucidated.

In the clinical settings, aortic atheroma has been considered a potential cause of systemic embolization [18,19], which can be induced mainly by mechanical contact owing to catheter or surgical interventions. There are two types of embolization derived from aortic atheromas: thromboembolism and atheroembolism. Thromboembolism tends to become lodged in medium or large arteries, resulting in symptomatic diseases such as stroke and acute ischemia of the intestines [18,20,21]. Iatrogenic embolization immediately after TAVR should be considered a cause of thromboembolism. However, in the current study, only two recognized thromboembolic events occurred during the periprocedural period. Therefore, this mechanism cannot explain the mechanistic link between AAV and the long-term all-cause mortality in the present study. Moreover, atheroembolism occurs when atherosclerotic plaque is disrupted and fragments of cholesterol crystal thrombus become lodged in the peripheral arteries. According to a previous study, this type of atheroembolism is an underdiagnosed multisystem disorder that may lead to ischemia of vital organs, resulting in chronic kidney disease, accelerated hypertension, myocardial infarction, stroke, and markedly increased cardiovascular and all-cause mortalities [22]. Another study indicated that prognosis in patients with atheroembolism is typically poor because of xenobiotic reaction, incomplete occlusion, and local inflammatory reaction owing to embolism, which may lead to progressive chronic multiorgan disorder [23]. The concept of “occult atheroembolism” might offer a potential explanation for the significant prognostic impact of AAV. As this concept was based on a hypothesis, further investigations are warranted to elaborate on it.

Notably, AbAAV – rather than TAAV – was significantly associated with mortality after TAVR. Several possible mechanisms that can explain this discrepancy are hinted at in the literature. Pathological studies revealed that aortic vulnerable atheroma, including intense yellow plaque, ruptured plaque, and thrombus, was observed more frequently in the abdominal aorta [24,25]. Zarins et al., in their pathological study that evaluated the relationship between plaque formation and aortic size in 30 male cadaver aortas, reported that plaques in the abdominal aorta usually have larger necrotic cores with frequent rupture or ulceration. These plaques are associated with increased inflammatory markers and elevated levels of homocysteine and prothrombin, which may contribute to increased mortality in patients with high AbAAV. A previous clinical study demonstrated that the abdominal aortic calcification burden measured on CT was significantly associated with all-cause mortality in 164 patients treated with TAVR, although its thoracic counterpart was not similarly associated with all-cause mortality [12]. The study suggested that calcifications frequently occurred from the intima of the abdominal aorta, which indicates the severity of systemic atherosclerotic disease, and was therefore associated with poor prognosis. Thus, the degree of abdominal aortic atheroma burden may be a hallmark of severe systemic atherosclerotic diseases, which is consistent with our findings that estimated glomerular filtration rate (eGFR) and ankle brachial pressure index were significantly correlated with the AbAAV.

Several recent studies have revealed the significant relationship between the AbAAV value and clinical adverse events in patients who underwent TAVR. Using preoperative CT images in 278 patients who underwent TAVR, Shishikura et al. demonstrated that the suprarenal

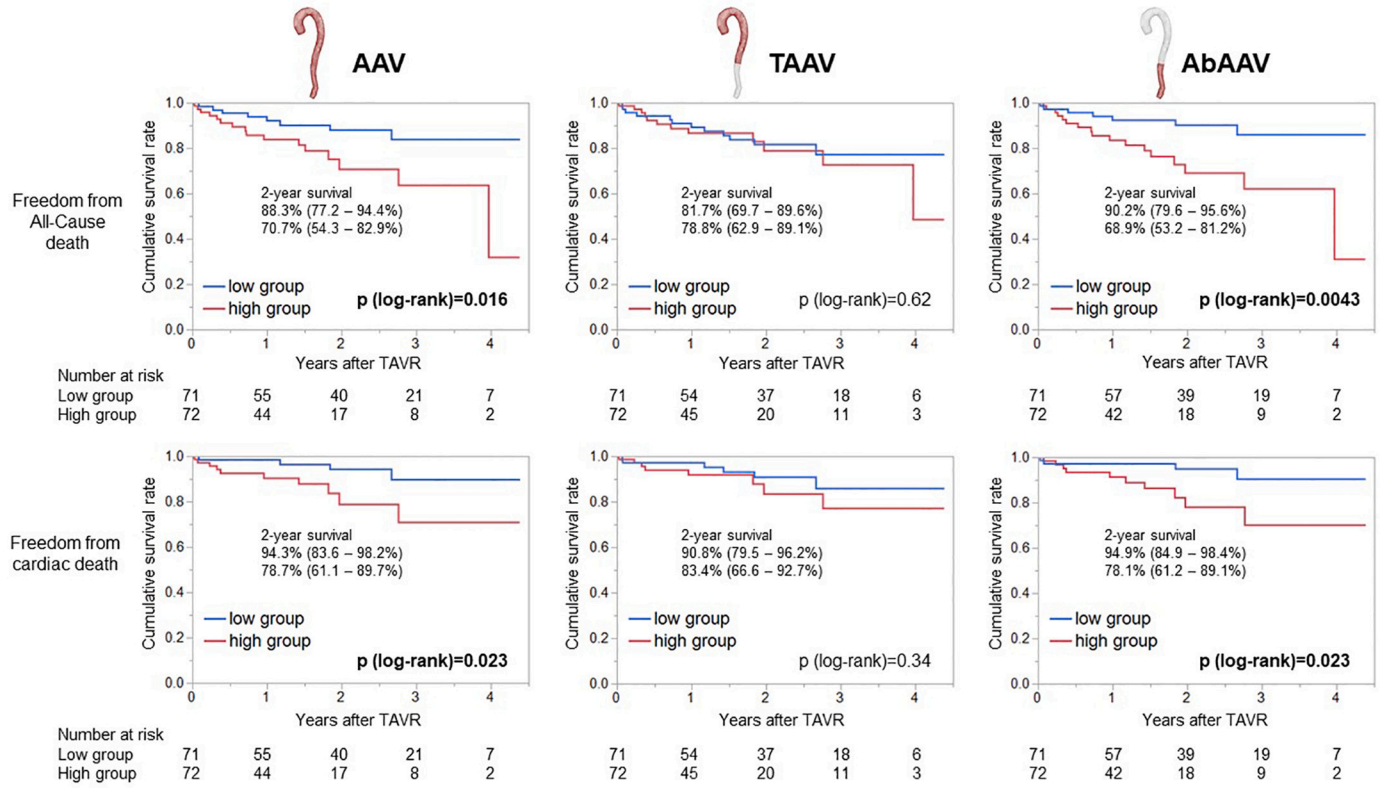

Fig. 2. Kaplan–Meier survival curves for all-cause mortality and cardiac mortality.
AAV, aortic atheroma volume; AbAAV, aortic atheroma volume of the abdominal aorta; TAAV, aortic atheroma volume of the thoracic aorta; TAVR, transcatheter aortic valve replacement.

Table 2
Results of univariable and multivariable Cox regression analyses for all-cause mortality.

	Univariable			Multivariable		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Age	1.06	0.96–1.19	0.27			
Female sex	0.56	0.24–1.28	0.17			
Body mass index	0.39	0.05–2.77	0.35			
Logistic EuroSCORE	1.03	0.998–1.05	0.065	1.009	0.97–1.04	0.60
STS-PROM score	1.04	0.98–1.09	0.17			
Ankle brachial pressure index	0.15	0.02–1.50	0.10			
Hypertension	1.17	0.76–3.87	0.19			
Dyslipidemia	1.23	0.55–2.75	0.61			
Diabetes mellitus	1.22	0.48–3.16	0.67			
Coronary artery disease	1.24	0.53–2.90	0.62			
Chronic kidney disease	1.32	0.60–2.95	0.49			
Cerebral infarction	1.11	0.63–1.95	0.71			
BNP	1.0004	0.99995–1.0007	0.079	1.0001	0.9995–1.0007	0.66
LVEF	0.97	0.95–1.001	0.058	0.98	0.94–1.03	0.44
Mean aortic valve gradient	1.01	0.98–1.04	0.69			
Aortic valve area	1.38	0.10–17.13	0.81			
AAV	1.01	0.99–1.03	0.14			
TAAV	1.01	0.98–1.03	0.62			
AbAAV	1.07	1.02–1.11	**0.0023**	1.06	1.001–1.11	**0.046**
ACV	1.03	0.996–1.06	0.092	1.01	0.98–1.05	0.53

P-values <0.05 are shown in **bold**.
AAV, aortic atheroma volume; AbAAV, aortic atheroma volume of the abdominal aorta; ACV, aortic calcification volume; BNP, B-type natriuretic peptide; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; STS-PROM, Society of Thoracic Predicted Risk of Mortality; TAAV, aortic atheroma volume of the thoracic aorta.

aortic atheroma burden in the abdominal aorta is associated with the occurrence, severity, and recovery of acute kidney injury after TAVR [10]. Although the serial alternation of renal function before and after TAVR was not evaluated, acute renal dysfunction could have attributed to poor prognosis in TAVR patients with a high AbAAV. Interestingly, eGFR at baseline in this study was lower in the high AbAAV group than in the low AbAAV group, although this did not reach statistical significance. These results are consistent with our results. Currently, preprocedural CT was utilized for only evaluating the indication for TAVR and devising the treatment strategy. Our study's findings suggests

that AAV may be a beneficial marker for predicting clinical adverse events, including all-cause death after TAVR.

The present study had some limitations that need to be addressed. First, the sample size was relatively small, and the follow-up period was short. To increase the clinical significance of our findings, a larger sample size and longer follow-up period are needed in a future study. Second, the current study was a single-center, retrospective, observational study, which could have the possibility of selection bias, although we enrolled patients consecutively. Third, AAV quantification using CT was affected by calcium blooming artifacts, potentially leading to AAV overestimation. Finally, the perioperative and postoperative managements depended on the discretion of each physician, which could have affected each patient's clinical course after TAVR.

In conclusion, AAV was significantly associated with mortality after TAVR. The current study may suggest that the pre-procedural assessment of AAV is valuable for predicting prognosis after TAVR and is helpful for preventing futile interventions. However, further studies with a larger sample size are necessary to elaborate on this possible relationship.

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Declaration of Competing Interest

None.

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