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Evaluation of aortic arch calcification to predict prognosis after transcatheter aortic valve replacement

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Few centers routinely report aortic arch calcification (AAC) due to the lack of an easy and effective evaluation method. The association between AAC and the clinical prognosis of patients who undergo transcatheter aortic valve replacement (TAVR) is unclear. We aimed to develop a rapid method to evaluate AAC in patients who underwent TAVR and to further assess their prognosis. We enrolled 464 consecutive patients with aortic stenosis who underwent TAVR. Patients with severe (11.2%), moderate (18.5%), mild (58.2%), and no (12.1%) AAC had an estimated 3-year all-cause mortality incidence of 39.6%, 20.8%, 13.4%, and 6.7% (log rank $p < 0.001$), respectively. Patients with severe AAC had a significantly higher incidence of both cardiovascular (log rank $p = 0.002$) and non-cardiovascular mortality (log rank $p = 0.009$), whereas patients with moderate AAC had a higher incidence of only non-cardiovascular mortality ($p = 0.003$) compared with patients with no/mild AAC. Moderate/severe AAC was an independent predictor of 3-year all-cause mortality in univariate (hazard ratio [HR]: 2.39, 95% confidence interval [CI]: 1.41–4.03; $p = 0.001$) and multivariate COX regression analyses (HR: 1.78, 95%CI: 1.04–3.06; $p = 0.037$). Our rapid semi-quantitative method to evaluate AAC is highly reproducible and can be used to assess AAC in patients who undergo TAVR.

Keywords Aortic arch calcification, Transcatheter aortic valve replacement, Pre-operative evaluation, Clinical outcomes

Abbreviations

ACC	aortic arch calcification
TAVR	transcatheter aortic valve replacement
MDCT	multidetector computed tomography
AS	severe aortic stenosis
CT	computed tomography
IQR	interquartile ranges
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality

The number of transcatheter aortic valve replacements (TAVR) has rapidly increased during the last decade[1,2]. Randomized controlled studies have provided favorable evidence for TAVR; therefore, it is recommended as the first-line therapy for severe aortic stenosis (AS) in older patients[3]. However, patients with extensively calcified aortic arch are generally excluded from randomized controlled trials because of embolism and vascular complications associated with the passing of delivery system through the heavily calcified aortic arch[4,5]. In fact, aortic arch calcification (AAC) can provide lots of information. It can reflect arterial stiffness, the magnitude of calcified change in the whole aorta, and even the frailty of the patients[6–8]. A large prospective population-

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based study demonstrated that a more severe AAC was associated with a higher risk of all-cause mortality and cardiovascular mortality in middle-aged and elderly persons[7]. Besides, AAC was found in over 60% of patients who underwent TAVR[9]. Therefore, AAC should be carefully evaluated in TAVR candidates.

Computed tomography (CT) is an essential examination to assess the anatomy of patients before TAVR and is routinely performed in most centers. Theoretically, AAC is easily evaluated; however, few centers routinely report AAC in their CT analysis because of the lack of an easy and reliable method. Accordingly, a limited number of studies focus on AAC. The association between AAC and the clinical prognosis of patients who undergo TAVR is also unclear. Recording AAC information and images is very important since these are necessary for further machine learning or deep learning study, which can provide valuable insights in prediction in cardiovascular contexts[10,11]. Therefore, we envisaged this study to propose a simple and rapid method to assess AAC and to assess the impact of AAC on the prognosis after TAVR.

Materials and methods

Study population

Consecutive severe AS patients who underwent TAVR between March 2016 and December 2020 were included in this study. The majority of patients were enrolled from the TORCH registry (Transcatheter Aortic Valve Replacement Single Center Registry in Chinese Population, NCT02803294); this is a prospective, ongoing, real-world registry, launched in June 2016. Patients who had a history of aortic valve replacement or did not have analyzable pre-operative multidetector CT (MDCT) images were excluded.

TAVR procedure and follow up

All TAVR procedures were decided by our multidisciplinary heart team. Self-expanding valves from VenusA (Venus Medtech, China), VitaFlow (Microport, China), TaurusOne (Peijia Medical, China), J-valve (Jiecheng, China) series were used in the majority of patients. The remaining patients were implanted with balloon-expandable (SAPIEN 3/XT, Edwards Lifesciences, California, USA) or mechanically-expandable (Lotus valve, Boston Scientific, Massachusetts, USA) valves. Patients with bicuspid aortic valve underwent TAVR using Hangzhou Solution strategy[12,13]. The detailed procedure has been previously described[12–16]. Our professional team subsequently followed up with patients at 30 days, 1 year, and yearly thereafter through face-to-face or telephonic consultation. We collected data during the 3-year follow-up to reduce the influence of limited sample size in the fourth/fifth-year follow-up (many patients did not reach the fourth or fifth follow-up window). The clinical events were defined according to the Valve Academic Research Consortium-2 consensus document[17].

MDCT and its analyses

Contrast-enhanced MDCT was routinely performed on the second-generation dual-energy CT (SOMATOM Definition Flash, Siemens Medical Solutions, Germany) following our scan protocol. The anatomy of patients was assessed using 3mensio software (3mensio Medical Imaging BV, Bilthoven, The Netherlands). Aortic root anatomy was evaluated in a double-oblique reconstruction image using the best systolic phase. The severity of valve calcification was classified into no, mild, moderate, and severe, as previously described[18]. Maximal intensity projection image was used to assess AAC (Fig. 1). The aortic arch was defined as the segment between the ascending and descending aorta (between the innominate artery and the aortic isthmus)[19], and AAC was visible as high-density portions in this region. Notably, the calcification in the innominate, left common carotid, and left subclavian arteries was distinguished and was not included in the AAC.

According to our protocol, the optimized image for aortic arch length visualization was used to assess the calcification involving the ratio of the aortic arch length. Then, an image that visually overlapped the vascular lumen of the aortic arch was assessed to identify the calcification involving the ratio of the vessel circumference. In this way, AAC was graded as no (free of calcification), mild (calcification involving $\leq$ 1/3rd of aortic arch length or circumference), moderate (calcification involving $>$ 1/3rd of aortic arch length and circumference, but not both $>$ 2/3rd of aortic arch length and circumference), and severe calcification (calcification involving $>$ 2/3rd of aortic arch length and circumference). The typical images are shown in Fig. 1.

The analyses of AAC were performed by two authors (D.Z and H.Y.D) experienced in TAVR pre-operative CT imaging analyses. First, the two observers assessed the AAC in 20 patients together. Thereafter, CT images of 40 randomly selected consecutive patients were separately evaluated to measure interobserver variations. The two observers reassessed these cases independently at an interval of $>$ 3 months to measure intraobserver variations in AAC analyses. The reproducibility of this method was confirmed, and the remaining images are evaluated independently. The two experts who analyzed the MDCT images were blinded to the procedural data and clinical outcomes.

Statistical analyses

Quantitative variables were expressed as means with standard deviation or median with interquartile ranges (IQR) according to the distribution as determined by Shapiro–Wilk test. Student's t-test or Mann–Whitney U test was performed for continuous variables. All categorical data were presented as frequencies with percentages and were compared using a chi-square test or Fisher's exact test, as appropriate. Cohen's kappa coefficient was calculated to determine interobserver and intraobserver variations in the measurements of AAC grade. A kappa value of 0.81–1, 0.61–0.80, 0.41–0.60, 0.21–0.40, 0.01–0.20, and $<$ 0 indicated almost perfect, substantial, fair, slight, and no agreements, respectively[20,21]. The cumulative all-cause mortality and cardiovascular/non-cardiovascular mortality rates were determined using the Kaplan–Meier survival analysis and were compared using the log-rank test. COX regression analyses were performed to evaluate the correlation of baseline characteristics and estimated 3-year all-cause mortality. Univariate COX regression analyses were performed

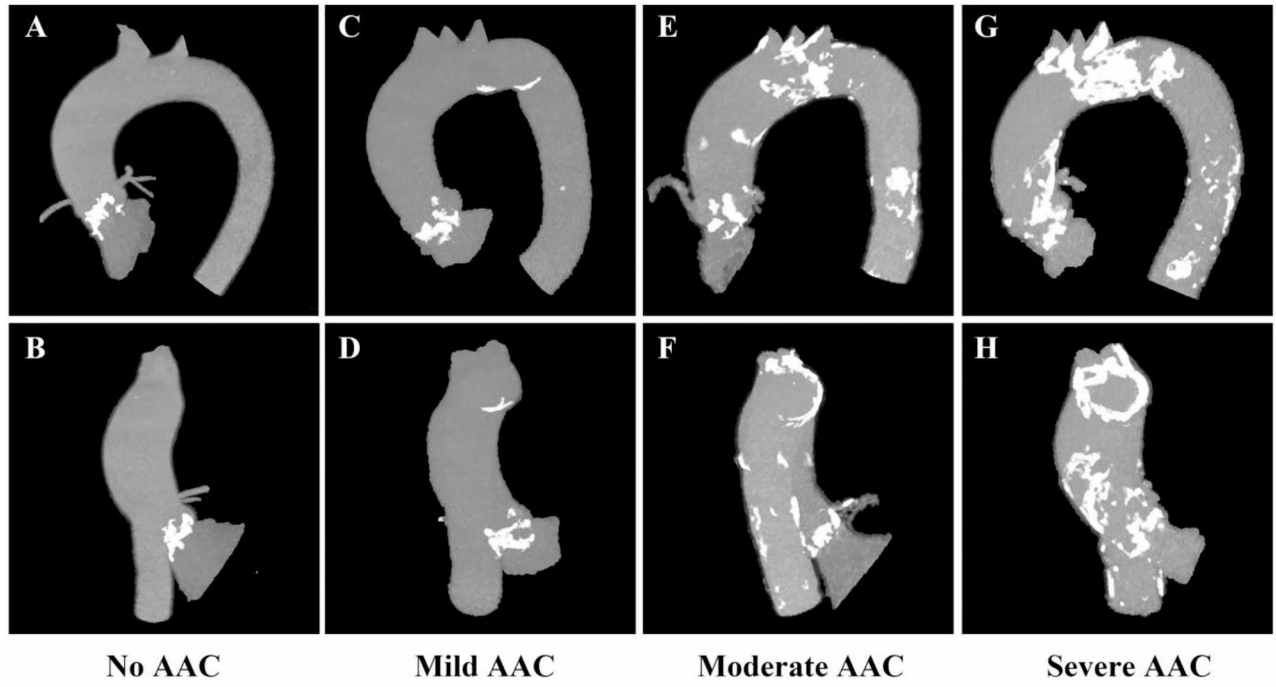


Fig. 1. Representative images showing different degrees of AAC. Maximal intensity projection image was used to assess AAC. (**A**, **C**, **E**, **G**) Optimized images for aortic arch visualization. These images were used to assess the calcification involving the ratio of the aortic arch length. (**B**, **D**, **F**, **H**) Images that visually overlapped the vascular lumen of the aortic arch were assessed to identify the calcification involving the ratio of the vessel circumference; (**A**, **B**) no AAC; (**C**, **D**) mild AAC: calcification involving ≤ 1/3rd of aortic arch length or circumference; (**E**, **F**) moderate AAC: calcification involving > 1/3rd of aortic arch length and circumference, but not both > 2/3rd of aortic arch length and circumference; (**G**, **H**) severe AAC: calcification involving > 2/3rd of aortic arch length and circumference. Notably, the calcification in the innominate, left common carotid, and left subclavian arteries was not included as AAC. AAC = aortic arch calcification.

for all baseline variables; variables with p-values < 0.05 in univariate COX regression analysis were entered in multivariate COX regression models using a forward likelihood-ratio method. A two-tailed p-value < 0.05 was considered to be statistically significant. All data analyses were performed using SPSS software version 20.0 (IBM, New York, USA).

Results

A total of 464 consecutive patients with AS who underwent TAVR were enrolled in our study, and 12.1%, 58.2%, 18.5%, and 11.2% of patients had no, mild, moderate, and severe AAC, respectively. Furthermore, we compared 138 (29.7%) patients with moderate or severe AAC and 326 (70.3%) patients with no or mild AAC. The baseline characteristics of the patients are shown in Table 1. Individuals in the moderate/severe AAC group were older (80.0 years [IQR: 73.8 to 84.0 years] vs.75.0 years [IQR: 70.0 to 79.0 years]; $p < 0.001$) and had higher Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scores (7.7 [IQR:4.4 to 10.5] vs.4.8 [IQR:3.2 to 8.3]; $p < 0.001$) than those in no/mild AAC group. Higher prevalence of hypertension (69.6% vs. 48.8%; $p < 0.001$), chronic kidney disease (18.1% vs. 7.4%; $p = 0.001$), and history of stroke (8.7% vs. 3.4%; $p = 0.016$) were found in moderate/severe AAC group. The proportion of sex and smokers was not significantly different between the two groups. Further, the proportion of patients with hyperlipidemia, diabetes, chronic obstructive pulmonary diseases, prior myocardial infarction, prior percutaneous coronary intervention, or prior pacemaker implantation was not significantly different between the two groups.

The echocardiography and CT data are displayed in Table 2. The left ventricular ejection fraction, maximum velocity, mean gradient, and aortic valve area were comparable between the two groups. Approximately 18.1% and 15.1% of patients had low-gradient AS (severe AS with mean gradient lower than 40 mm Hg) in the moderate/severe AAC and no/mild AAC groups ($p = 0.457$), respectively. MDCT data revealed that patients with moderate/severe AAC had a smaller sinotubular junction, smaller ascending aorta diameter, and lower left main coronary height. The proportion of patients with moderate/severe aortic valve calcification was similar between the moderate/severe AAC and no/mild AAC groups (76.1% vs. 81.0%, $p = 0.232$).

The reproducibility of the proposed method was determined by repeated assessment of randomly selected consecutive 40 AAC cases independently; the kappa value for interobserver variability was 0.807. The kappa values for intraobserver variation were 0.962 (D.Z) and 0.922 (H.Y.D). Kappa values can be interpreted as: ≤ 0 (no agreement), 0.01–0.20 (none to slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and

	Moderate/severe AAC (*n* = 138)	No/mild AAC (*n* = 326)	*P* value
Age, years	80.0 (73.8, 84.0)	75.0 (70.0, 79.0)	< **0.001**
Male	81 (58.7)	181 (55.5)	0.528
BMI, kg/m^2	23.3 ± 3.8	22.7 ± 3.5	0.068
BSA, m^2	1.64 ± 0.18	1.61 ± 0.16	0.059
STS, %	7.7 (4.4, 10.5)	4.8 (3.2, 8.3)	< **0.001**
Smoker	21 (15.2)	62 (19.0)	0.329
Hyperlipidemia	14(10.1)	41(12.6)	0.459
Hypertension	96 (69.6)	159 (48.8)	< **0.001**
Diabetes	32 (23.2)	74 (22.7)	0.909
COPD	38 (27.5)	76 (23.3)	0.334
NYHA III/IV	119 (86.2)	266 (81.6)	0.224
eGFR, ml/min/1.73 m^2	47.9 (35.8, 65.1)	56.8 (43.6, 72.0)	< **0.001**
CKD grade 4/5	25 (18.1)	24 (7.4)	**0.001**
Prior myocardial infarction	3 (2.2)	5 (1.5)	0.628
Prior PCI	23 (16.7)	34 (10.4)	0.061
Prior stroke	12 (8.7)	11 (3.4)	**0.016**
Prior pacemaker implantation	5 (3.6)	7 (2.1)	0.551

Table 1. Baseline characteristics. Data was presented as n (%) or mean ± SD or median (interquartile range, IQR). p Values in bold are statistically significant. AAC = aortic arch calcification; BMI = body mass index; BSA = body surface area; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary diseases; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

	Moderate/severe AAC (*n* = 138)	No/mild AAC (*n* = 326)	*P* value
Echocardiography			
LVEF, %	59.6 (50.7, 66.6)	58.8 (45.7, 64.5)	0.161
Max velocity, m/s	4.8 (4.3, 5.3)	4.7 (4.2, 5.3)	0.644
Mean gradient, mmHg	53 (42, 67)	51(42, 64)	0.828
Low gradient AS	25(18.1)	50(15.3)	0.457
Aortic valve area, cm^2	0.6 (0.5, 0.7)	0.6 (0.5, 0.8)	0.950
Morderate/severe aortic regurgitation	57 (41.3)	130 (39.9)	0.775
Morderate/severe mitral regurgitation	42 (30.4)	73 (22.4)	0.067
Morderate/severe tricuspid regurgitation	20 (14.5)	47 (14.4)	0.983
Computed tomography			
Perimeter derived diameter, mm	24.0 (22.4, 25.9)	24.3(22.8, 26.2)	0.134
Sinotubular junctional diameter, mm	29.03 ± 3.84	30.52 ± 4.48	**0.001**
Ascending aorta diameter at 4 cm, mm	36.00 ± 4.29	37.94 ± 4.58	< **0.001**
LM height, mm	13.4 (11.8,15.8)	14.4 (12.0, 16.7)	**0.027**
RCA height, mm	16.1 (14.3,17.7)	16.4 (14.4, 18.7)	0.211
Moderate/severe aortic valve calcification	105 (76.1)	264 (81.0)	0.232

Table 2. Baseline echocardiographic and computed tomography characteristics. Data was presented as n (%) or mean ± SD or median (interquartile range, IQR). p Values in bold are statistically significant. Low gradient AS was defined as severe AS with mean gradient lower than 40 mmHg. AAC = aortic arch calcification; AS = Aortic stenosis; LM = left main artery; LVEF = left ventricular ejection fraction; RCA = right coronary artery.

0.81–1.00 (almost perfect agreement). Therefore, we achieved almost perfect interobserver and intraobserver agreements.

The procedural characteristics and 30-day clinical outcomes are mentioned in Table 3. Self-expandable valves were the most commonly used prosthesis in moderate/severe AAC (83.3%) and no/mild AAC (88.3%) groups. The transfemoral approach was the most frequently adopted access approach in the two groups (92.0% vs. 95.7%; $p = 0.109$). The proportion of patients who underwent balloon predilatation was similar between the two groups (97.8% vs. 97.2%, $p = 0.965$), while the proportion of those who underwent post-dilation was higher in the no/

	Moderate/severe AAC ($n=138$)	None/mild AAC ($n=326$)	*P* value
Procedural characteristics			
Transfemoral access	127 (92.0)	312 (95.7)	0.109
Device type			**0.014**
Self-expanding	115 (83.3)	288 (88.3)	
Balloon-expandable	20 (14.5)	22(6.7)	
Mechanically-expandable	3 (2.2)	16 (4.9)	
Pre-dilatation	135 (97.8)	317 (97.2)	0.965
Post-dilatation	66 (47.8)	195 (59.8)	**0.017**
30-day clinical outcomes			
Mortality	5(3.6)	5(1.5)	0.286
Cardiovascular	4(2.9)	5(1.5)	0.544
Non-cardiovascular	1(0.7)	0(0)	0.297
Myocardial infarction	1(0.7)	2(0.6)	1.000
Stroke	1(0.7)	7(2.1)	0.493
Disabling	1(0.7)	4(1.2)	1.000
Non-disabling	0(0)	3(0.9)	0.558
Bleeding[a]	7(5.1)	15(4.6)	0.827
Permanent pacemaker implantation	19(13.8)	29(8.9)	0.115

Table 3. Procedural characteristics and in-hospital outcomes. Values are presented as number (%). P values in bold are statistically significant. [a] Bleeding represented life-threatening bleeding. AAC = aortic arch calcification.

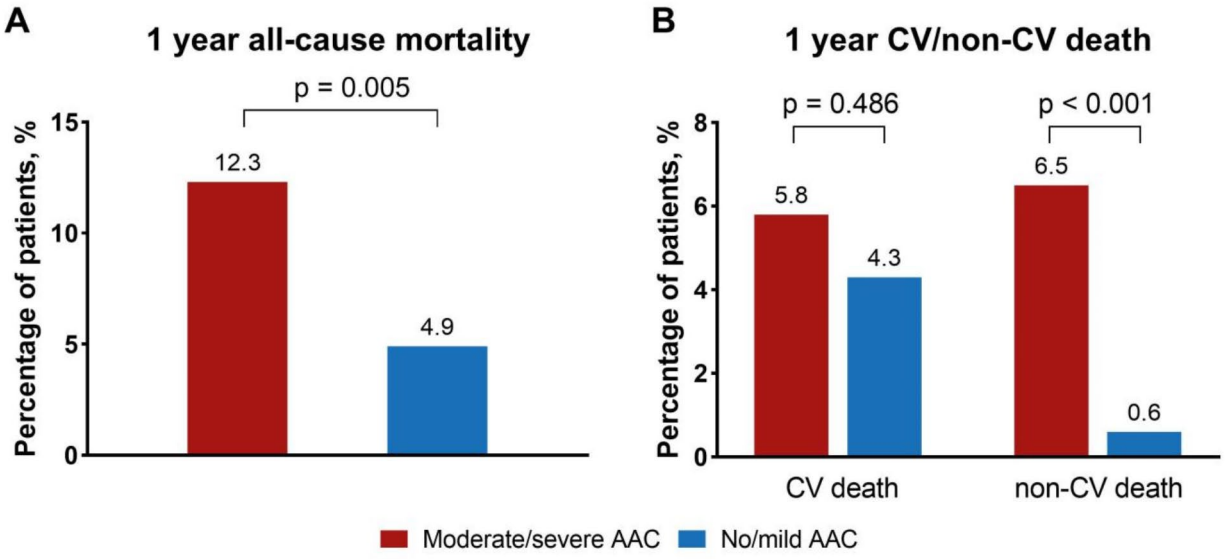
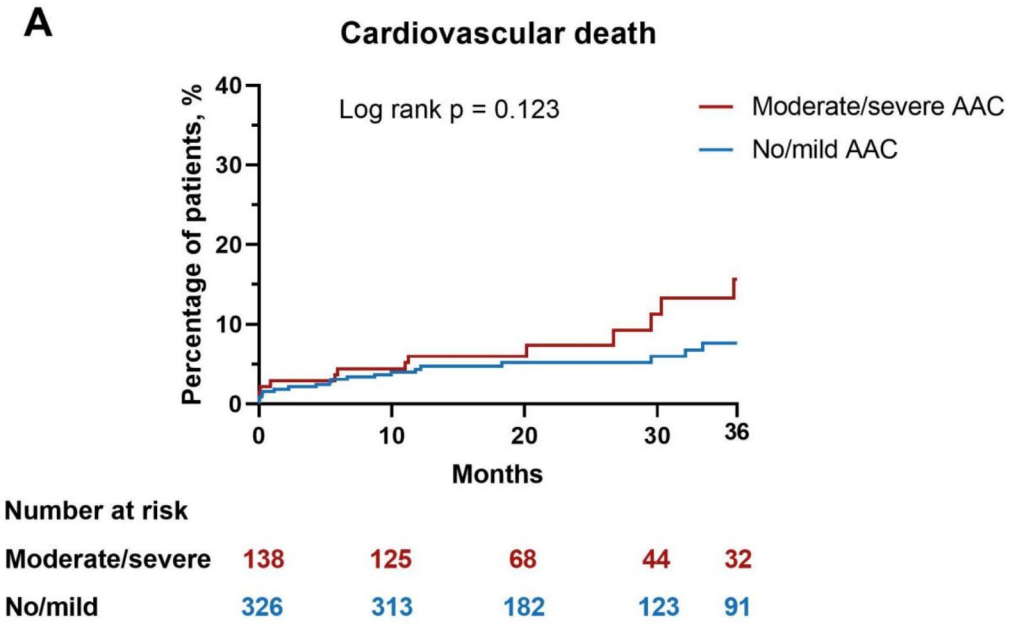


Fig. 2. 1-year all-cause mortality, and cardiovascular and non-cardiovascular mortalities. Comparison of 1-year all-cause mortality (**A**) and cardiovascular and non-cardiovascular mortalities (**B**) in patients with moderate/severe AAC and no/mild AAC. AAC = aortic arch calcification.

mild AAC group (47.8% vs. 59.8%; $p=0.017$). All-cause mortality during 30 days of follow-up after TAVR was numerically more frequent in the moderate/severe AAC group than in the no/mild AAC group (3.6% vs. 1.5%); however, the difference was not statistically significant ($p=0.284$). Moreover, the rates of myocardial infarction, stroke, bleeding, and permanent pacemaker implantation did not significantly differ between the two groups. Individuals with moderate or severe AAC had a statistically higher incidence of all-cause death than those with no or mild AAC (12.3% vs. 4.9%; $p=0.005$) at 1-year follow-up; non-cardiovascular deaths were the major contributory factors (6.5% vs. 0.6%; $p<0.001$; Fig. 2).

The median follow-up time was 25.1 months (IQR: 12.4–36.0). The time-to-event analysis determined that the patients with severe, moderate, mild, and no AAC had an estimated 3-year all-cause mortality of 39.6%, 20.8%,

13.4%, and 6.7% (log-rank $p < 0.001$, Figure S1). Figures 3 and 4 show that the patients with moderate/severe AAC had significantly higher 3-year all-cause mortality (27.7% vs. 12.3%, log-rank $p = 0.001$) and non-cardiovascular mortality (14.3% vs. 5.0%, log-rank $p = 0.001$) than those with no/mild AAC. Nonetheless, cardiovascular mortality was not significantly different between the two groups (15.6% vs. 7.7%, log-rank $p = 0.123$). Further, we evaluated patients with moderate or severe AAC separately and observed that patients with severe AAC had



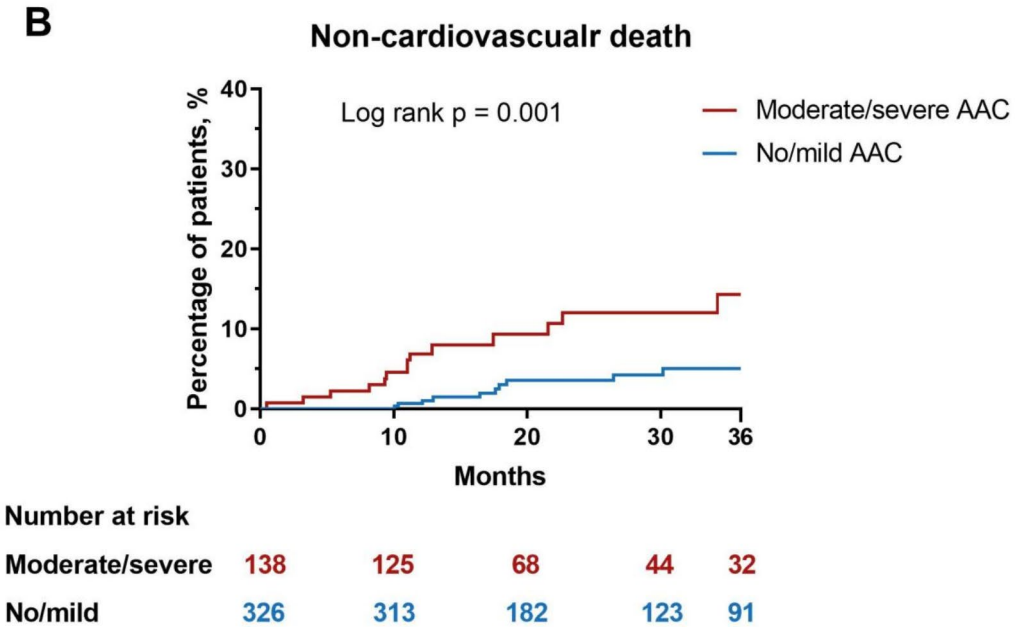


Fig. 3. Kaplan–Meier curves of 3-year cardiovascular/non-cardiovascular death. Comparison of 3-year cardiovascular (**A**) and non-cardiovascular (**B**) mortalities in patients with moderate/severe AAC and no/mild AAC. AAC = aortic arch calcification.

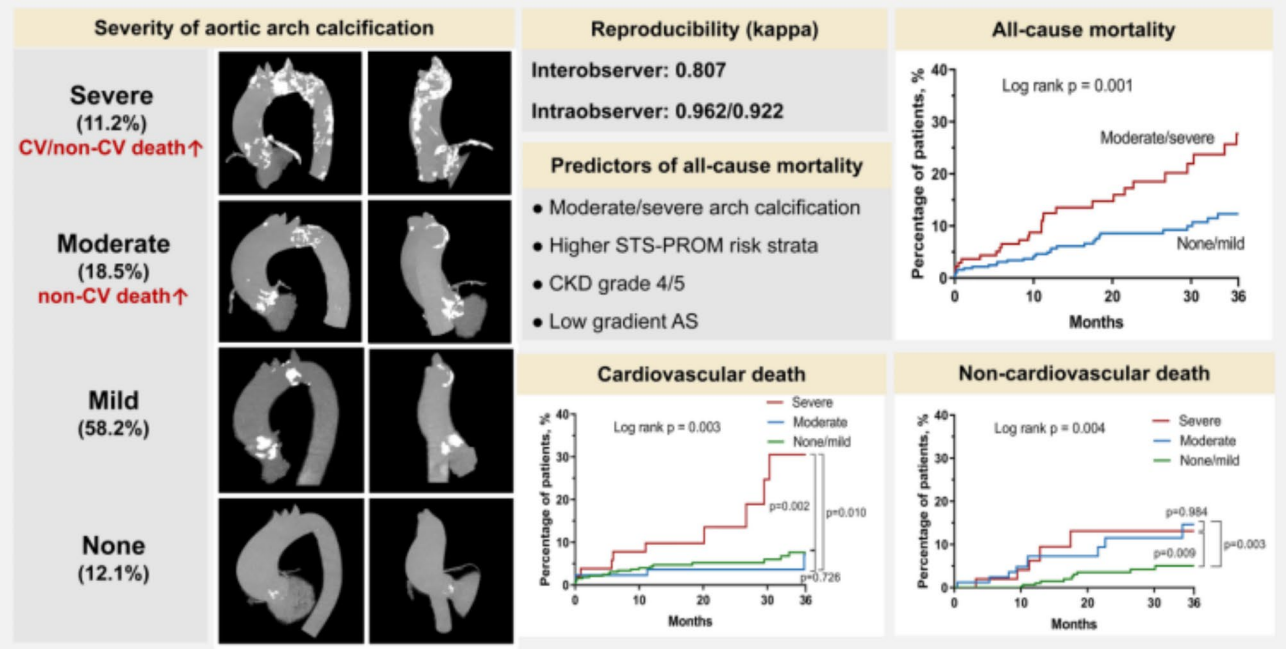


Fig. 4. This rapid semi-quantitative method assesses AAC in maximal intensity projection images with good reproducibility. Among patients with AS who underwent TAVR, a considerable number of patients had a moderate (18.5%) or severe AAC (11.2%), which was associated with an increased incidence of 3-year all-cause mortality (moderate/severe AAC) and cardiovascular (severe AAC) or non-cardiovascular mortality (moderate or severe AAC). Multivariate Cox regression analysis showed that moderate/severe AAC was an independent predictor of 3-year all-cause mortality. AAC = aortic arch calcification; AS = aortic stenosis; CV = cardiovascular; CKD = chronic kidney disease; TAVR = transcatheter aortic valve replacement.

significantly higher incidences of cardiovascular and non-cardiovascular mortality compared with patients with no/mild AAC (cardiovascular: 31.5% vs. 7.7%, log-rank $p = 0.002$; non-cardiovascular: 13.1% vs. 5.0%, log-rank $p = 0.009$). In addition, patients with severe AAC had a higher rate of estimated 3-year cardiovascular mortality than those with moderate AAC (31.5% vs. 7.2%, log-rank $p = 0.010$). Patients with moderate AAC had a higher incidence of non-cardiovascular mortality but had a similar incidence of cardiovascular mortality compared to patients with no/mild AAC (cardiovascular: 7.2% vs. 7.7%, log-rank $p = 0.726$; non-cardiovascular: 14.7% vs. 5.0%, log-rank $p = 0.003$).

Table 4 shows that moderate/severe AAC was a risk factor for 3-year all-cause mortality in univariate (hazard ratio [HR]: 2.39, 95% confidence interval [CI]: 1.41–4.03; $p = 0.001$) and multivariate COX regression analyses (HR: 1.78, 95% CI: 1.04–3.06; $p = 0.037$). Higher STS-PROM strata ($p = 0.011$), stage 4 or 5 chronic kidney disease ($p = 0.027$), and low gradient AS ($p = 0.018$) were suggested as independent predictors in multivariate regression analyses. Furthermore, in another COX regression analyses model in which AAC was classified according to the grade of arch calcification, a more severe AAC grade was also an independent predictor of all-cause mortality (univariate: $p < 0.001$; multivariate: $p = 0.025$) and the above-mentioned independent predictors were still valid (Table S1).

Discussion

The main findings of our studies are as follows: (1) we have proposed a rapid and reproducible method to assess AAC; (2) among patients who underwent TAVR in our centers, 87.9% patients had AAC; of these, 18.5% and 11.2% had moderate and severe AAC, respectively; (3) patients with moderate/severe AAC had a higher incidence of 1-year all-cause mortality and non-cardiovascular mortality; (4) moderate/severe AAC was an independent predictor of 3-year all-cause mortality; (5) compared with no/mild AAC, severe AAC was associated with a higher incidence of 3-year cardiovascular and non-cardiovascular mortalities, whereas moderate AAC was associated with a higher incidence of non-cardiovascular mortality.

The assessment of aortic arch calcification is important for the operator since many manipulations during the procedure involve the aortic arch. The current main limiting factor in evaluating AAC is the lack of an easy, effective, and repeatable method. Although calcium volume score can provide a quantitative assessment of calcification, calculating the aortic arch calcium volume score is complicated. The analysts need to decide centerline from the aortic root to descending aorta, make a reconstruction, place a region of interest to measure average Hounsfield units, and manually adjust the best cut-off of Hounsfield units to optimize calcification detection. Few centers routinely do this analysis since clinicians usually focus more on the anatomy of the aortic root and access. In addition, simply reporting arch calcium volume score misses information regarding calcification distribution. AAC can be evaluated using another semiquantitative assessment method. Sagittal and

	Univariate analysis		Multivariate analysis	
	p Value	HR (95%CI)	p Value	HR (95%CI)
Moderate/severe AAC	0.001	2.39(1.41–4.03)	0.037	1.78(1.04–3.06)
Age, per 5 years	< 0.001	1.53(1.23–1.91)	-	-
STS-PROM risk strata (versus low risk)[a]	< 0.001	-	0.011	-
Intermediate risk	0.021	3.59(1.21–10.69)	0.032	3.32(1.11–9.90)
High risk	< 0.001	7.51(2.67–21.15)	0.003	5.01(1.72–14.62)
Prior pacemaker	0.006	4.24(1.52–11.81)	-	-
CKD grade 4/5	< 0.001	3.47(1.92–6.27)	0.027	2.03(1.08–3.80)
Bicuspid aortic stenosis	0.005	0.45(0.26–0.78)	-	-
Low gradient AS	0.003	2.39(1.34–4.28)	0.018	2.04(1.13–3.68)
Moderate/severe MR	0.045	1.75(1.01–3.03)	-	-

Table 4. COX regression analysis of all-cause mortality. The variables with a p value < 0.05 in univariate analysis were showed. These variables were entered in multivariate cox regression analysis using a forward Likelihood Ratio method. No multicollinearity existed among the variables in multivariate regression model. [a] Patients were stratified by STS score: low risk (< 4%), intermediate risk (4–8%), and high risk (≥ 8%). Low gradient AS was defined as severe AS with mean gradient lower than 40 mmHg. AAC = aortic arch calcification; STS = Society of Thoracic Surgeon; STS-PROM = STS predicted risk of mortality; CKD = chronic kidney disease; AS = aortic stenosis; MR = mitral regurgitation.

reconstructed axial CT images are analyzed slice-by-slice, and the severity of arch calcification is determined by estimating the degree of calcification involving the vessel length and circumference[22]. This method is also relatively complicated and may have potentially large intraobserver and interobserver differences due to the slice-by-slice analyses. Therefore, we designed this study to provide a rapid and useful method to assess AAC.

Using our method, the AAC can be easily assessed during the analysis of access anatomy. During routinely analyzing aortic valve root structure before TAVR, it takes only 20 s to 1 min to finish the analyses and grading of AAC. Besides, adding typical imaging to the report of the anatomy of the patient is easy. The clinicians can also visualize the information of the AAC in patients just by reading the report. Severe AAC and porcelain aorta can be quickly identified, and then the operators can decide whether the patient should receive a transapical-TAVR rather than transfemoral-TAVR[23]. In addition, the application of cerebral protection devices has increased rapidly in recent years[24,25]. Some cerebral protection devices are placed in the aortic arch and information on the anatomy of the aortic arch is required. The routine use of this rapid assessment method can also provide information for evaluating the availability of cerebral protection devices.

In addition to providing important information for making clinical decision, using this approach to grade AAC and record images can also provide important data and information for conducting further research using machine learning techniques. Currently, more and more studies use machine learning techniques to enhance diagnostic accuracy and prediction by optimizing feature extraction and model performance. Related work in areas such as structural health monitoring and advanced imaging analysis has demonstrated the potential of these techniques[11,26,27]. Besides, novel algorithms have been proposed to enhance training performance and have been proven their predictive power in recent years[28,29]. However, the lack of an easy evaluate method of AAC results in this information being ignored in most center, restricting application of machine learning techniques to assess the predictive value of AAC in TAVR patients. Therefore, this method might help to conduct further machine learning studies.

Currently, the knowledge of AAC in old patients with severe AS is scarce. In our study, a considerable number of patients (29.7%) had moderate or severe AAC, suggesting that the occurrence of AAC should be critically considered. Intimal injury caused by hypertension and calcium and phosphorus metabolism disorder caused by renal insufficiency can lead to AAC. Thus, patients with moderate or severe AAC were older and had a higher proportion of hypertension and renal insufficiency, which were consistent with those of previous studies conducted in other populations[6,8,30]. Moreover, previous studies have indicated that prevalent stroke was associated with AAC[30,31]. Similarly, in our study, a history of stroke was more common in patients with moderate or severe AAC.

In a population-based cohort study including 2,408 participants from the Rotterdam study, AAC was found to be the strongest indicator of cardiovascular and non-cardiovascular mortalities among major vessel beds[7]. However, to the best of our knowledge, our study is the first one to illustrate the relationship between AAC and mid-to-long term clinical outcomes in patients who underwent TAVR. We also found that the patients with moderate or severe AAC had a higher incidence of estimated 3-year all-cause and non-cardiovascular mortalities, whereas patients with severe AAC had a higher incidence of 3-year all-cause, cardiovascular, and non-cardiovascular mortalities. Therefore, it is plausible that a better management of comorbidity after TAVR is needed in patients with moderate/severe AAC, especially in patients with severe AAC. For example, over 50% of patients can have an increased blood pressure after TAVR[32–34], and management of hypertension in such patients may help delay further progression of aortic arch atherosclerosis and calcification.

We also found that higher STS-PROM risk strata, chronic kidney disease stage 4 or 5, and low gradient AS were independent predictors of the 3-year all-cause mortality. STS score includes several clinical characteristics

(such as age, comorbidity, and medication) and is widely used in clinical practice. Low-gradient AS was associated with worse left heart function. All these three factors were classic strong risk factors for worse clinical outcomes. Although patients with moderate/severe AAC had higher STS scores and a higher proportion of chronic kidney disease stage 4 or 5 than those with no/mild AAC, moderate/severe AAC was still an independent predictor in multivariate COX regression analysis.

Limitation

Our study has some limitations. First, this method cannot identify low-density atherosclerosis. However, this rapid method can be combined with other assessment methods. Therefore, if obvious low-density atherosclerosis plaque or ulcers are present, we recommend that the analysts should further evaluate low-density atherosclerosis plaque or ulcers in the aortic arch in addition to the routine use of our method. Second, this method is only focused on assessing AAC. Nevertheless, the AAC can reflect the total burden of vascular calcification given its central location in the arterial system[7,8]. Third, since patients who had a history of aortic valve replacement or did not have analyzable MDCT images were excluded, patient selection biases may exist in this study. Fourth, although almost perfect agreement was achieved in our reproducibility test, there still existed some observer variability (especially interobserver variations). The variability were mainly found in analyzing AAC images with boundary values (such as 1/3rd and 2/3rd). Therefore, we suggest that clinicians should be trained using typical cases to reduce interobserver variability in clinical practice. Besides, some baseline characteristics differed between patients with moderate/severe and no/mild AAC (such as age, STS score, and renal function). Although moderate/severe AAC was an independent predictor of 3-year all-cause mortality in multivariate regression analysis, a well-designed study matching baseline characteristics well between different groups is needed to further verify our results. Finally, the sample size was relatively small and the follow-up was not long enough. Future large-scale studies with longer follow-ups are needed to validate our findings.

Conclusions

We developed a semi-quantitative method for evaluating patients undergoing TAVR and classified AAC into no, mild, moderate, and severe. The method had good reproducibility and can be routinely used to rapidly assess AAC in clinical practice. We found that approximately 30% of patients undergoing TAVR had a moderate/severe AAC, which was associated with a higher incidence of 1-year and 3-year all-cause mortalities. In addition, patients with moderate or severe AAC had an increased incidence of 3-year non-cardiovascular mortality, whereas only patients with severe AAC had a higher risk of 3-year cardiovascular mortality.

Data availability

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author with permission of Second Affiliated Hospital of Zhejiang University, Hangzhou, China.

Received: 13 September 2024; Accepted: 16 December 2024
Published online: 21 February 2025

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Acknowledgements

This work obtained funding support from the Second Affiliated Hospital Zhejiang University School of Medicine. Thanks to Hangzhou Qianjiang special expert, for the help and support.

Author contributions

Conceptualization, D.Z., JQ.F. and XB.L.; methodology, D.Z., HY.D. and YC.G.; formal analysis and investigation, D.Z., HY.D., WJ.S., R.R.Z. and J.C.; data curation, A.Y., A.A. and YX.H.; writing—original draft preparation, D.Z., HY.D., WJ.S. and RR.Z; writing—review and editing, XB.L. and QF.Z.; visualization, D.Z., SS.Y; supervision, Q.L. and YX.W.; project Administration, XB.L. and JA.W. All authors have read and agreed to the published version of the manuscript.

Funding

This research was funded by State Key Laboratory of Transvascular Implantation Devices; The National Key R&D Program of China (2019YFA0110400 for JW); The National Natural Science Foundation of China (No. 81870292 for JW, No. 81570233, 81770252 for XBL, No. 82200552 for JQF); National Science Fund for Distinguished Young Scholars of China (No.82425007 for XBL); Zhejiang Province Science and Technology Department Key R&D Program (No.2024C03024, 2021C03097, 2018C03084 for JW, No.2022C03063 for XBL); Zhejiang Province Science and Technology Innovation Leading Talents Project (No.2023R5236 for XBL); Zhejiang Research Center of Cardiovascular Diagnosis and Treatment Technology (JBZX-202001 for JW); Natural Science Foundation of Zhejiang Province of China (LQ21H020005 for YCG).

Declarations

Competing interests

The authors declare no competing interests.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhejiang University, Hangzhou, China.

Informed consent

All patients provided written informed consent for the TAVR procedures and the use of anonymous data for research.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-83536-8.

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