



## Computed Tomographic Quantification of Thoracic Aortic Wall Calcification as a Predictor of Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Grafting

Se Jin Oh<sup>1</sup>, Kwang Nam Jin<sup>2</sup>, Jae-Sung Choi<sup>1\*</sup>, Hyeon Jong Moon<sup>1</sup>, Yong Won Seong<sup>1</sup>, and Jeong Sang Lee<sup>1</sup>

<sup>1</sup>Department of Thoracic and Cardiovascular Surgery, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

<sup>2</sup>Department of Radiology, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

**\*Corresponding author:** Jae-Sung Choi, MD, Ph.D, Department of Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine, SMG-SNU Boramae Medical Center, 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 156-707, Korea, Tel: 82 028702293, Fax: 82 02 8703866, E-mail: [turejsreal@hanmail.net](mailto:turejsreal@hanmail.net)

### Abstract

**Background:** We evaluated computed tomographic (CT) measurement of thoracic aortic wall calcification as a predictor of the postoperative clinical outcomes in patients who underwent coronary artery bypass grafting (CABG).

**Methods:** Between 2009 and 2013, a total of 100 patients with isolated CABG underwent chest CT or total aorta CT angiography preoperatively. Using dedicated calcium measuring software, we measured thoracic aortic calcification score (TACS) on CT images. A high TACS was defined as a TACS above the 75<sup>th</sup> or greater percentile. Postoperative clinical outcome variables were analyzed.

**Results:** The mean TACS was  $3892.4 \pm 5580.0$ , and the median and 75<sup>th</sup> percentile values of TACS were 1965.0 and 5408.8, respectively. The number of patients with a high TACS was 25, and postoperative outcome variables were detected in 43 patients. Multivariate analysis showed that preoperative use of intra-aortic balloon pump ( $p = 0.048$ ), peripheral arteriopathy ( $p = 0.047$ ) and a TACS above the 75<sup>th</sup> percentile ( $p = 0.011$ ) were independent risk factors of postoperative mortality and cardiovascular complications.

**Conclusions:** Severe thoracic aortic wall calcification significantly correlated with poor clinical outcome. Therefore, CT quantification of thoracic aortic wall calcification may be a useful option for predicting early postoperative prognosis in patients undergoing isolated CABG.

### Keywords

Coronary artery bypass surgery, Computed tomography, Vascular disease, Calcification

### Introduction

Thoracic aortic wall calcification is associated with coronary and valvular calcification, and has been recognized as an independent predictor of increased prevalence of cardiovascular events [1,2]. Moreover, there have been several reports that have demonstrated a

significant correlation between severe thoracic aortic wall calcification and cardiovascular risk factors in a large population-based cohort [3-6]. The aim of this study was to evaluate thoracic aortic wall calcification quantified by preoperative computed tomography as a predictor of clinical outcomes in patients who underwent coronary artery bypass grafting (CABG).

### Material and Methods

The study protocol was reviewed by the Institutional Review Board of our hospital and approved as a minimal risk retrospective study that did not require patient consent.

### Patients

This study included a total of 100 patients (mean age,  $66.2 \pm 8.9$  years; M:F = 61:39) who underwent isolated CABG and preoperative CT work-up between March 2009 and June 2013. We retrospectively reviewed the medical records and preoperative chest CT angiography or total aorta CT angiography. Baseline demographic data and risk factors are shown in table 1. Hypertension, Dyslipidemia, and diabetes were acknowledged when the patients were taking corresponding medicine or had been medically diagnosed elsewhere. We defined preoperative chronic kidney disease (CKD) as CKD stage  $> 3$  (estimated glomerular filtration rate using the Modification of Diet in the Renal Disease equation  $< 60 \text{ mL/min/1.73 m}^2$ ).

Using the dedicated calcium measuring software, we measured thoracic aortic calcification score (TACS) on CT images (detection range, above the left main coronary artery to the bottom of both ventricles). A high TACS was defined as a TACS above the 75<sup>th</sup> or greater percentile.

### Surgical procedure

We performed either off-pump CABG or conventional CABG as surgical revascularization strategies in the study periods. Conventional CABG was mainly performed for complete revascularization and

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reasonable clinical outcomes during the 3 years of learning period, but we changed our operative strategy from conventional CABG to off-pump CABG to avoid the ascending aorta manipulation and the use of cardiopulmonary bypass after 2012 according to the improved technical skill.

**Table 1:** Baseline demographic data and risk factors.

Variables	Total (N = 100)
Mean age, years	66.2 ± 8.9
Male gender	61
Current smoker	52
Diabetes mellitus	50
Hypertension	73
Dyslipidemia	41
Arteriopathy	22
Chronic kidney disease	15
History of cerebrovascular accident	18
Body mass index, kg/m <sup>2</sup>	24.2 ± 2.9
Body surface area	1.7 ± 0.2
LV EF on echocardiography, %	55.8 ± 14.9
Preoperative use of IABP	9
Left main coronary disease	26
Logistic EuroSCORE (%)	5.8 ± 5.7

LVEF: Left Ventricular Ejection Fraction

IABP: Intraaortic Balloon Pump

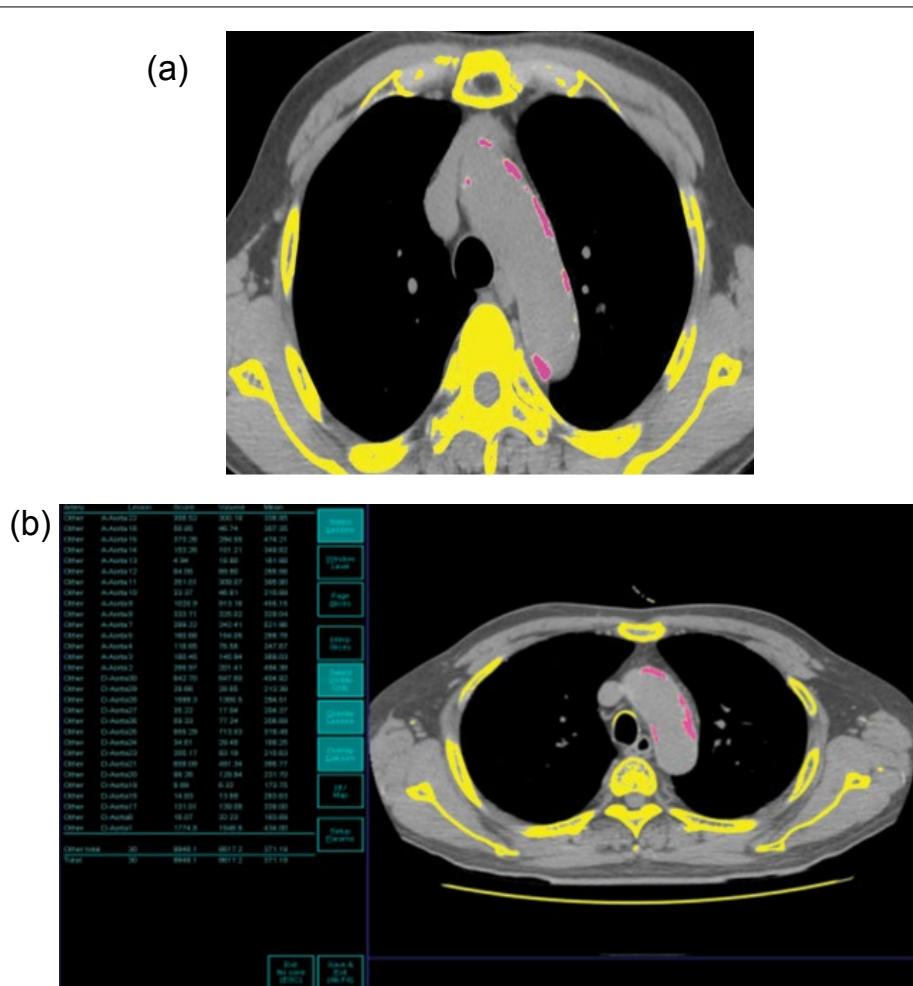
EuroSCORE: European system for cardiac operative risk evaluation.

**Off-pump CABG:** All operations were performed through a median sternotomy incision under normothermia and intraoperative monitoring methods, including Swan-Ganz catheterization and transesophageal echocardiography, were routinely used. Our off-pump revascularization strategies were the use of a composite graft based on the left internal thoracic artery (ITA) and the avoidance of aortic manipulation in most patients. Immediately after the side-arm conduit (right ITA, radial artery (RA), and saphenous vein (SV)) was harvested, it was anastomosed to the side of the left ITA to construct a Y-composite graft. After the Y-composite graft was constructed, in almost all the patients the left anterior descending coronary artery territory was revascularized first by using the left ITA, and the left circumflex coronary artery territory was then revascularized, followed by the right coronary artery territory. A sequential anastomotic technique was used for complete revascularization when more than 2 coronary arterial anastomoses were needed. Patients were given an initial dose of heparin (1.5 mg/kg) and periodic supplemental doses to maintain an activated clotting time of > 300 seconds.

**On-pump CABG:** The conventional cardiopulmonary bypass using the ascending aorta and right atrium was performed under moderate systemic hypothermia. Transesophageal echocardiography was used to evaluate postoperative cardiac function and the presence of significant atheroma on the ascending aorta. The aorta was cross-clamped, and myocardial protection was achieved with intermittent antegrade, or combined antegrade and retrograde infusion of histidine-tryptophan-ketoglutarate solution (HTK-Custodiol; Koehler Chemi, Alsbach-Haenlein, Germany).

### Postoperative clinical events

We defined postoperative clinical events as at least one occurrence



among 8 clinical outcome variables; major adverse cardiac and cerebral events (MACCE) (death, perioperative myocardial infarction (PMI), stroke, and repeated revascularization), acute kidney injury (AKI), low cardiac output requiring intra-aortic balloon pump (IABP) and/or extracorporeal membrane oxygenation (ECMO), pulmonary complication, and atrial fibrillation. Operative mortality was defined as any death within 30 days, including deaths after hospital discharge. Postoperative AKI was defined as an increase of 50% in serum creatinine level from the preoperative value or a need for renal replacement therapy regardless of serum creatinine level. PMI was defined as the combination of new ST changes or Q waves, echocardiographic demonstration of new regional wall motion abnormality, and elevation of troponin level. Pulmonary complications included postoperative pneumonia or > 48 hours of prolonged ventilator support.

### Thoracoabdominal CT angiography scan protocol

CT scan was performed on a 16-channel, multi-detector CT (MDCT) (Light-Speed, GE Healthcare) or a 64-channel MDCT (Brilliance; Philips Medical Systems, Cleveland, Ohio). Scans were obtained with or without contrast media enhancement. Images were acquired in the crano-caudal direction. CT scan with contrast enhancement was performed from the carotid bulb level to the inguinal area. For contrast-enhanced CT images, 120 to 140 mL of iopamidol (Iopamiro 300; Bracco, Milan, Italy) was administered intravenously at a rate of 3.0 mL/s. Helical scan data were acquired using  $16 \times 1.5$ -mm, or  $64 \times 0.625$ -mm collimation, with a rotation speed of 0.5 or 0.42 seconds, a pitch of 1.11 to 1.25, and 120 kilovolt (peak). Effective milliampere-seconds ranged between 120 and 187, using the automatic tube current modulation technique. Transverse datasets were reconstructed with 1.2 mm thickness at 1.2 mm increments. Resultant images were transferred to a commercially available workstation (Aquarius, TeraRecon, San Mateo, Calif) for image analysis.

### Quantification of thoracic aortic calcification score (TACS) on CT images

An experienced cardiothoracic radiologist evaluated non-contrast axial CT images by using a commercially available workstation (Aquarius; TeraRecon, San Mateo, Calif). An aortic wall calcification was quantified by using the calcium scoring software system, based on a threshold of 130 Hounsfield units (HU) [7]. Automatic quantification of aortic wall calcification was initiated with the radiologist's designation for calcification on each axial CT image (Figure 1). The overall score of calcification was recorded in the workstation. We measured wall calcifications in the ascending and descending thoracic aorta from the aortic root (above the left main coronary artery) to the level of the diaphragmatic crura (the bottom of both ventricles). Calcifications in the carotid or subclavian arteries were not included. And we did not measure wall calcification in abdominal aorta due to difficult and inaccurate differentiation between the aortic wall calcification and adjacent vertebrae on the measurement software.

### Statistical analysis

Statistical analysis was performed with commercially available statistical software, SPSS version 20.0 (SPSS, Chicago, Illinois). Continuous variables are expressed as the mean  $\pm$  standard deviation, median and ranges, or proportions. Comparisons between the 2 groups were made using the chi-square test and Fisher's exact test for categorical variables and the Student *t* test for continuous variables. Simple and multiple linear regression analysis were used. For multiple regression analysis, variables with a *P* value of less than 0.1 in simple linear regression analysis were selected. The body surface area (BSA) was used for analysis as a covariate to avoid the variation in scores according to patient height. The percentiles of TACS score were used to determine the relative standing of an individual in our population. The 75<sup>th</sup> percentile was the third quartile. All statistical tests were 2-tailed, and a *P* value of less than 0.05 was considered statistically significant.

**Table 2:** Comparison of risk factors between the high and low TACS groups.

Variables	TACS $\geq$ the 75 <sup>th</sup> percentile (n = 25)	TACS $\leq$ the 75 <sup>th</sup> percentile (n = 75)	P value
Age, years	71.1 $\pm$ 6.8	64.5 $\pm$ 9.0	0.001
Smoker	12 (48.0)	40 (53.3)	0.653
Body mass index, kg/m <sup>2</sup>	24.3 $\pm$ 2.7	24.2 $\pm$ 3.1	0.905
Body surface area	1.7 $\pm$ 0.2	1.7 $\pm$ 0.1	0.588
Diabetes mellitus	16 (64.0)	34 (45.3)	0.165
Hypertension	23 (92.0)	50 (66.7)	0.018
Dyslipidemia	9 (36.0)	32 (42.7)	0.642
Arteriopathy	7 (28.0)	15 (20.0)	0.413
Chronic kidney disease	4 (16.0)	11 (14.7)	1.000
History of CHVA	8 (32.0)	10 (13.3)	0.067
Preoperative use of IABP	2 (8.0)	7 (9.3)	1.000
LVEF, %	52.5 $\pm$ 17.7	56.9 $\pm$ 13.8	0.201
Left main coronary disease	7 (28.0)	19 (25.3)	0.797
OPCAB	16 (64.0)	48 (64.0)	1.000
Logistic EuroSCORE (%)	8.3 $\pm$ 6.2	5.0 $\pm$ 5.4	0.013

TACS: Thoracic Aortic wall Calcium Score

CVA: CerebroVascular Accident

IABP: Intra-Aortic Balloon Pump

LVEF: Left Ventricular Ejection Fraction

OPCAB: Off Pump Coronary Artery Bypass Grafting

Euroscore: European system for cardiac operative risk evaluation.

## Results

### Patient and operative characteristics

Preoperative BMI and left ventricular ejection fraction (EF) on echocardiography were 24.2 kg/m<sup>2</sup> and 55.8%, respectively. Twenty-six patients had left main coronary artery disease on preoperative coronary angiography. Of all the 100 patients, 38 underwent off-pump CABG and 9 needed preoperative use of IABP. The number of distal anastomoses and different grafts used per patient were  $2.9 \pm 0.9$  and  $2.1 \pm 0.4$ , respectively. In off-pump CABG group, left ITA was used for revascularization in all patients except one in whom the right ITA was used for revascularization of the left anterior descending coronary artery due to proximal left ITA stenosis. Other conduits used included SV (60.5%, 23/38), right ITA (31.6%, 12/38), and RA (21.1%, 8/38). In on-pump CABG group, left ITA was used in 96.8% (60/62), SV in 67.7% (42/62), RA in 20.9% (13/62), and right ITA in 14.5% (9/62). Mean cardiopulmonary bypass time in on-pump CABG group was  $170.2 \pm 62.3$  min.

### Analysis of TACS

The mean TACS was  $3892.4 \pm 5580.0$ , and the median and 75<sup>th</sup> percentiles of TACS were 1965.0 and 5408.8, respectively. The number of patients with a high TACS was 25. There was no significant difference in risk factors between the high and low TACS groups except age (*p* = 0.001) and hypertension (*p* = 0.018). Most of patients in the high TACS group had a hypertension. Moreover, high TACS group showed higher logistic EuroSCORE (*p* = 0.013) (Table 2).

### Postoperative clinical outcomes: MACCE and other morbidities

The MACCE were detected in 14 patients. Among them, two operative mortalities occurred resulting from sudden cardiac arrest with PMI and intractable ventricular fibrillation after surgery. Moreover, there were 3 strokes and 7 PMIs. Repeated revascularization including bypass graft revision or percutaneous coronary intervention was needed in 4 patients. Postoperative clinical events were detected in 43 patients. Most of the complications were atrial fibrillation (*n* = 31) and pulmonary complications (*n* = 8). Seven patients showed

**Table 3:** Predictors of postoperative clinical outcomes (univariate).

Variables	P value	Odd Ratio	95% CI
Age	0.010	1.065	1.015 -1.117
Male	0.783	1.120	0.501 -2.504
Current smoker	0.564	1.261	0.574 -2.770
Body mass index, kg/m <sup>2</sup>	0.061	0.871	0.754 -1.006
Body surface area	0.272	0.238	0.018 -3.074
Hypertension	0.055	2.437	0.981 -6.051
Diabetes mellitus	0.548	0.786	0.358 -1.726
Dyslipidemia	0.912	1.046	0.471 -2.325
Arteriopathy	0.016	3.500	1.263 -9.698
Chronic kidney disease	0.557	1.398	0.457 -4.272
History of CVA	0.778	0.864	0.311 -2.397
Preoperative use of IABP	0.052	8.178	0.982 -68.038
LVEF	0.220	0.983	0.957 -1.010
Left main coronary disease	0.417	0.690	0.281 -1.692
High TACS	0.087	2.302	0.886 -5.980

CVA: CerebroVascular Accident

IABP: Intra-Aortic Balloon Pump

LVEF: Left Ventricular Ejection Fraction

TACS: Thoracic Aortic wall Calcium Score.

**Table 4:** Predictors of postoperative clinical outcomes (multivariate).

Variables	P value	Odd Ratio	95% CI
Age	0.097	1.061	0.989 -1.138
Male	0.366	2.005	0.444 -9.064
Hypertension	0.569	1.409	0.432 -4.596
Diabetes mellitus	0.394	0.637	0.226 -1.796
Preoperative use of IABP	0.011	19.547	1.988 -192.147
Arteriopathy	0.047	3.600	1.017 -12.739
Left main coronary disease	0.069	0.340	0.106 -1.089
High TACS	0.048	3.319	1.012 -10.882

IABP: Intra-Aortic Balloon Pump

TACS: Thoracic Aortic wall Calcium Score.

postoperative low cardiac output requiring intra-aortic balloon pump (IABP) and/or extracorporeal membrane oxygenation (ECMO). AKI developed in 6 patients.

### Predictors of postoperative clinical events

Univariate analysis showed that age, preoperative use of IABP, peripheral arteriopathy, and a high TACS were significant predictors of clinical events (Table 3). Multivariate analysis revealed that the preoperative use of IABP (odds ratio, 3.6,  $p = 0.048$ ), peripheral arteriopathy (odds ratio, 3.6,  $p = 0.047$ ) and a high TACS (odds ratio, 3.3,  $p = 0.011$ ) were independent risk factors for clinical events, meaning postoperative mortality and cardiovascular complications (Table 4).

### Discussion

Thoracic aortic wall calcification reflecting the atherosclerotic process on arterial wall has been shown to be a risk factor for atherosclerosis and to increase the risk of cardiovascular and cerebrovascular events [3-6,8]. Moreover, descending thoracic aortic calcification (DTAC) has been found to be a strong predictor of coronary artery calcification in the multi-ethnic study of atherosclerosis (MESA) [1]. A previous study of stable angina pectoris patients has demonstrated that there is a significant correlation between thoracic aortic calcification and the presence of coronary artery calcification as expressed by coronary calcium score, and aortic valve and mitral annulus calcifications [2]. In that study, during 4, 5 to 6 years of follow-up, patients with thoracic aortic calcification had a higher incidence of cardiovascular events in a multivariable analysis,

and the severity of calcification was higher in patients with any event than in those without. Therefore, thoracic aortic calcification along with coronary artery and valvular calcifications was associated with an increased risk of death and cardiovascular disease in symptomatic patients [2]. In addition, thoracic aorta calcification has been recognized as an independent predictor of an increased prevalence of cardiovascular events, including hypertension and myocardial infarction [2,9]. In a large population-based cohort of the MESA, a significant correlation between severe thoracic aortic wall calcification and increased coronary heart disease events was founded in women independent of coronary artery calcium [10].

Although numerous studies have demonstrated the predictive value of thoracic aorta calcification in several imaging techniques for future cardiovascular disease in the non-cardiac surgery population, there have been few studies evaluating the relationship between thoracic aorta calcification as measured by CT and clinical outcomes in cardiac surgery patients. Therefore, in the present study, we first evaluated thoracic aortic wall calcification quantified on CT scans as a predictor of clinical outcomes in patients undergoing CABG.

As an advance in diagnostic imaging techniques, unrequested information on coronary and aortic calcification collected from routine diagnostic chest CT can predict future cardiovascular events in a clinical care population with fatal and non-fatal cardiovascular disease [11]. Moreover, a recent increase in preoperative chest CT or CT angiography investigations in patients undergoing elective cardiac surgery has led to an increase in unexpected information not related to the clinical indication. Especially in coronary artery disease patients requiring CABG, preoperative CT work-ups provide numerous abnormal findings of clinical relevance, including the aorta and peripheral vascular wall calcification/stenosis, pulmonary and mediastinal diseases, and skeletal osteoporosis. Therefore, we have routinely performed preoperative chest CT or total aorta CT angiography in CABG patients, and have examined whether subclinical thoracic aortic wall calcification and aortic wall calcium is associated with postoperative clinical outcomes. We used 16-channel, multi-detector CT (MDCT) or 64-channel MDCT, and the scans were obtained with or without contrast media enhancement. It has been reported that inter-scan reproducibility of measurement of coronary calcium using images from MDCT is excellent, irrespective of slice thickness and type of calcium parameter [12,13]. Therefore, it can be acceptable to measure calcium score using two different channel MDCT scanners.

Previous studies showed the variable distribution of TACS. One study demonstrated that a total of 69% of subjects had Agatston TACS of 0; 5% 1 to 9; 12% 10 to 99; 8% 100 to 399; and 7%  $\geq 400$  in a total of 2,303 asymptomatic adults (mean age 55.7 years, 38% female) with CT scans [14]. In another study, overall 2,538/4,025 (63.1%) participants revealed thoracic aortic wall calcification (median Agatston-score: 17.5, lower quartile 0, upper quartile 124.7) in a general unselected population [15]. In our study, we included specific population with old age and known coronary artery disease. To our knowledge, there is no reference for the threshold of the high TACS for the population. Therefore, we arbitrarily defined the threshold of high TACS for our study population by the use of the percentiles of the TACS distribution as the study by Kalsch *et al.* [15].

There have been several studies indicating aortic calcification increases arterial stiffness [16-19]. Roos *et al.* [16] have demonstrated that atherosclerosis in the descending thoracic aorta as measured by DTA thickening and calcium score on the CTA is associated with arterial stiffness as determined by carotid-femoral pulse wave velocity (PWV) in patients with diabetes mellitus. In multivariate analysis, they concluded that DTA calcium score is independently associated with arterial stiffness and that an increase in arterial stiffness by atherosclerosis is mediated and exacerbated by arterial calcification. Although arterial stiffness was not evaluated in the present study, it is thought that poor postoperative clinical outcomes in patients with severe aortic calcification may be associated with the progression of atherosclerosis and arterial stiffness. Diastolic myocardial dysfunction

caused by chronic aortic stiffness can be worsened by variable factors associated with cardiac surgery, including cardiopulmonary bypass with hypothermia, transient ischemia/reperfusion injury during procedures, and heart manipulation/volume overload. It may aggravate the systolic and diastolic dysfunction and frequently induce arrhythmia after surgery. In our study, a high TACS was an independent risk factor for postoperative cardiovascular complications.

There are limitations to the current study that must be recognized. First, this study was not performed in a prospective manner and the number of patients enrolled was relatively small. However, a selective enrollment of 100 patients who underwent isolated CABG, and consistent CT protocols with quantification of TACS may compensate for that limitation. Second, the distribution of TACS showed wide range. Because we included subjects retrospectively, we did not make specific inclusion criteria. Third, we did not evaluate independent value of TACS or its additional value for traditional risk prediction methods. Having low statistical power, this work was preliminary report trying to reveal the usefulness of a new tool, thoracic aortic wall calcification, for the prediction of postoperative clinical outcomes. Further study will be necessary to reveal the clinical impact of the TACS.

## Conclusions

In conclusion, severe thoracic aortic wall calcification was strongly associated with poor clinical results. Therefore, thoracic aortic wall calcification quantified on preoperative CT scans may be a useful predictor of early postoperative outcomes in patients undergoing isolated CABG.

## Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship or publication of this article.

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