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Prognostic value of coronary artery calcium score in patients with stable angina pectoris after percutaneous coronary intervention

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Abstract

Objectives   To evaluate the prognostic value of the coronary artery calcium (CAC) score in patients with stable angina pectoris (SAP) who underwent percutaneous coronary intervention (PCI). **Methods**   A total of 334 consecutive patients with SAP who underwent first PCI following multi-slice computer tomography (MSCT) were enrolled from our institution between January 2007 and June 2012. The CAC score was calculated according to the standard Agatston calcium scoring algorithm. Complex PCI was defined as use of high pressure balloon, kissing balloon and/or rotablator. Procedure-related complications included dissection, occlusion, perforation, no/slow flow and emergency coronary artery bypass grafting. Main adverse cardiac events (MACE) were defined as a combined end point of death, non-fatal myocardial infarction, target lesion revascularization and rehospitalization for cardiac ischemic events. **Results**   Patients with a CAC score > 300 (n = 145) had significantly higher PCI complexity (13.1% $vs.$ 5.8%, P = 0.017) and rate of procedure-related complications (17.2% $vs.$ 7.4%, P = 0.005) than patients with a CAC score ≤ 300 (n = 189). After a median follow-up of 22.5 months (4–72 months), patients with a CAC score ≤ 300 differ greatly than those patients with CAC score > 300 in cumulative non-events survival rates (88.9 $vs.$ 79.0%, Log rank 4.577, P = 0.032). After adjusted for other factors, the risk of MACE was significantly higher [hazard ratio (HR): 4.3, 95% confidence interval (95% CI): 2.4–8.2, P = 0.038] in patients with a CAC score > 300 compared to patients with a lower CAC score. **Conclusions**   The CAC score is an independent predictor for MACE in SAP patients who underwent PCI and indicates complexity of PCI and procedure-related complications.

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Keywords: Angina, Coronary angiography; Multi-slice computed tomography; Heart catheterization; Vascular calcification

1   Introduction

Artery calcification, as part of the development of atherosclerosis, occurs almost exclusively in atherosclerotic arteries, and is absent in the normal arterial wall.[1] The amount of calcium in the coronary arteries can be quantified as a coronary artery calcium (CAC) score measured by coronary multi-slice computed tomography (MSCT). It has been demonstrated that the CAC score is correlated well with histological plaque analyses.[2] Recent studies have showed

the CAC score is also an independent predictor for coronary events and all-cause mortality in asymptomatic individuals.[3,4] In symptomatic coronary artery disease, percutaneous coronary intervention (PCI) nowadays has become the standard of care with suitable anatomy, and it is increasingly used in the treatment of complex lesions.[5] Lesion localization, severe calcifications, and vessel tortuosity may challenge the skills of the operator and increase the risk of procedural complications, such as coronary artery dissection and perforation.[6] Stähli, *et al.*[7] reported that, in 66 coronary lesions, preprocedural assessment by CAC score indicates complexity of PCI. However, it is unclear whether the CAC score could predict the prognosis in patients with symptomatic coronary artery disease undergoing PCI.

In the present study, we investigated whether the CAC score predicted the complexity of PCI in patients with stable angina pectoris (SAP). We also evaluated the predictive

value of CAC score on major adverse cardiovascular events (MACE) in SAP patients undergoing PCI.

2 Methods

2.1 Study population

A total of 334 consecutive SAP patients (age 65.7 ± 9.1 years, male 61.9%) undergoing a first PCI were recruited to the study from January 2007 to June 2012 at Peking University Third Hospital. All patients were evaluated with MSCT and CAC scores were calculated before PCI. The time interval from MSCT examination to PCI was less than 6 months. SAP was defined according to guidelines of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA). Patients with acute coronary syndrome, old myocardial infarction, history of PCI or coronary artery bypass grafting (CABG), arrhythmia, renal insufficiency (glomerular filtration rate < 30 mL/min) and known allergy to iodine contrast material were excluded. The study was approved by the Ethics Committee of Peking University Third Hospital. All subjects signed their informed consent.

2.2 Laboratory measurements

Blood samples were obtained on the second day of hospitalization after fasting for 8 h or overnight for analysis of clinical chemistry. Fasting serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (sCr) and high sensitivity C-reactive protein (hs-CRP) were analyzed by colorimetric enzymatic assays with use of an auto-analyzer (HITACHI-7170).

2.3 MSCT and CAC score

All MSCT examinations were performed using a 64-row scanner (General Electric, South San Francisco, California) with a protocol for prospective triggering (SnapShot Pulse, GE Healthcare). Scanning parameters for the unenhanced calcium scoring scan were: 100 kV tube voltage, tube current was adjusted according to the body mass index (BMI), 0.28 s rotation time, and 2.5 mm slice thickness. CAC measurements were performed by two experienced readers separately blinded to the patient information with CaScoring software and then used the average as score. CAC was defined as a plaque of at least 3 contiguous pixels (area of 1.02 mm^2) with a density of > 130 Hounsfield units (HU). The lesion score was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield unit within this area, as described by Agatston, *et al.*[8] Total CAC score was determined by summing individual lesion

scores from each of the four main coronary arteries [left main coronary (LM), left anterior descending coronary (LAD), left circumflex coronary (LCX), and right coronary arteries (RCA)]. Previous studies had established an Agatston score of larger than 300 as a strong predictor of incident coronary heart disease and provided predictive information.[4,9] Therefore, in this study, all subjects were divided into two groups according to CAC score: lower CAC score group (CAC score ≤ 300) and higher CAC score group (CAC score > 300).[4,9]

2.4 Coronary angiography and PCI

Selective coronary arteriography and PCI were performed via radial artery or femoral artery by five chief physicians in our catheterization lab randomized and they have a similar experience. Coronary artery stenosis was defined by quantitative coronary angiography, and complete revascularization was defined as all lesions with more than 75% diameter stenosis in ≥ 2 mm coronary artery having been subjected to PCI. Any remaining of stenosis ≥ 75% was defined as incomplete revascularization. Successful PCI was defined as residual stenosis ≤ 20%.[10] Coronary angiograms were analyzed by two cardiologists who were blinded to the clinical data and CAC score.

The complexity of PCI including the use of post-dilation balloon, kissing balloon and/or rotablator was retrospectively assessed. Complications were recorded according to the AHA/ACC Guidelines for PCI.[10] Dissection, occlusion, perforation and slow flow were summarized as procedure-related complications.[6]

2.5 Follow-up and patients' outcome

All participants were followed up clinically. MACE, including death, non-fatal myocardial infarction, target lesion revascularization and rehospitalization for cardiac ischemic events, were recorded by standard case report form. The primary endpoint was defined as death from all cause, or non-fatal myocardial infarction. The second endpoint was defined as target lesion revascularization (PCI or CABG) and rehospitalization for cardiac ischemic events (typical ischemic chest pain or positive result of stress test or determinate by coronary angiography). The event-free survival time was the time from the PCI procedure to the occurrence of the first post-procedure cardiac event. Follow-up data were obtained by the same physician who was blinded to the angiographic data or CAC score.

2.6 Statistical analysis

Data analyses were performed using the SPSS 20.0 software package (SPSS Inc., Chicago, Illinois, USA). We pre-

sented the measurements as mean ± SD for continuous variables and frequencies and percentages for categorical variables. Univariate and multivariable logistic regression analyses were used to determine the predictive impacts of the CAC score on PCI complications. Group comparisons of continuous variables were made using *t*-test and ANOVA. Pearson's Correlation coefficients were calculated to evaluate the linear relation between continuous variables. Time-to-event analyses were performed using Kaplan-Meier survival curves and Cox regression analysis. Significance was assumed at *P* value < 0.05.

3   Results

3.1   Clinical characteristics of the study participants

Baseline characteristics of 334 patients with SAP in the study group were presented in Table 1. There were no significant differences between the two groups with respect to the gender, blood pressure (BP), heart rates, BMI, hs-CRP, creatinine, TC, LDL-C, HDL-C and hypertension, hyperlipidemia history. Compared with lower CAC score Group, the higher CAC score group was significant older (69.2 ± 8.5 *vs*. 61.9 ± 10.1 years, *P* < 0.001) and contained a higher number of diabetes mellitus (DM) patients (37.5% *vs* 26.1%, *P* = 0.025) and multi-vessel coronary disease patients (59.3% *vs*. 32.1%, *P* < 0.001). The average CAC scores in the CAC score ≤ 300 and CAC score > 300 were 91.7 and 988.5 with the range 0–298 and 302–4796, respectively, for each category.

3.2   Association between CAC score and clinical characteristics

The CAC score was positively correlated with age (*r* = 0.342, *P* < 0.001), systolic blood pressure (*r* = 0.199, *P* = 0.02). The CAC score in DM patients and non-DM patients was 343 (interquartile range: 95–946) and 197 (interquartile range: 58–687), respectively (Figure 1A). In patients having one, two or three vessel lesions, the CAC score was 77 (in-

terquartile range: 0–259), 194 (interquartile range: 68–632) and 475 (interquartile range: 120-1026), respectively, with ANOVA analysis (Figure 1B).

Table 1.   Characteristics of study population.

Characteristics	CAC score ≤ 300 (*n* = 189)	CAC score > 300 (*n* = 145)	*P* value
Age, yrs	61.9 ±10.1	69.2 ±8.5	< 0.0001
Male, %	64.7	66.9	0.395
Hypertension, %	72.1	74.2	0.395
Diabetes mellitus, %	26.1	37.5	0.025
Hyperlipidemia, %	52.4	48.4	0.289
Current smoker, %	34.5	30.2	0.256
Family history of premature CAD, %	19.0	18.8	0.538
Systolic blood pressure, mmHg	126.3 ±10.4	129.5 ±13.9	0.127
Diastolic blood pressure, mmHg	74.6 ±9.2	74.3 ±7.2	0.798
Body mass index, kg/m^2	26.3 ±3.8	25.5 ±2.8	0.279
Hs-CRP, mg/L	4.7 ±8.4	3.6 ±4.4	0.613
Creatinine, µmol/L	86.5 ±16.8	86.6 ±17.5	0.955
Total cholesterol, mmol/L	4.38 ±1.03	4.37 ±1.02	0.915
HDL-C, mmol/L	1.02 ±0.27	1.02 ±0.27	0.839
LDL-C, mmol/L	2.59 ±0.82	2.58 ±0.81	0.953
Multi-vessel coronary disease, %	66.3	87.6	0.000
Complete revascularization, %	91.6	90.3	0.401
Coronary artery calcium score	91.7 (0–298)	988.5 (302–4796)	0.000
Event-free survival time	12 (5.5–27.5)	15 (6–29)	0.564

Continuous variables expressed as mean ± SD, coronary artery calcium score was expressed as mean (range), event-free survival time was expressed as median (interquartile range). Compared with CAC score ≤ 300, cohorts with a CAC score > 300 were older and included more diabetes mellitus patients and multi-vessel coronary disease patients. CAC: coronary artery calcium; CAD: coronary artery disease; HDL-C: high-density lipoprotein cholesterol; Hs-CRP: high sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol.
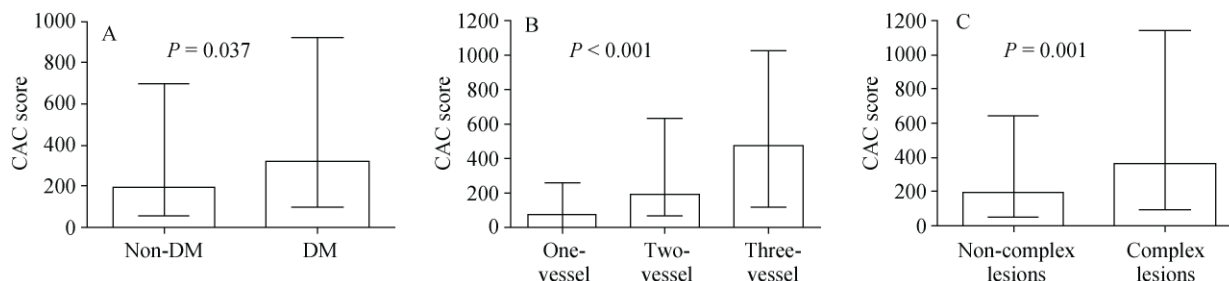

Figure 1.   CAC score is depicted as bars (bar height represents median, error bars represent interquartile range). (A): The CAC score in DM patients; (B): multi-vessel lesions; (C) complex lesions are significant higher. CAC: coronary artery calcium; DM: diabetes mellitus. *T*-test was used in two groups and ANOVA was used in three groups.

3.3 Association between CAC score and complex PCI

Complex PCI as specifically defined above was reported in 90 (26.9%) patients. Two (0.6%) and 21 (6.3%) of them received either rotablator or kissing balloon simultaneously. Attempted PCI failed in 11 interventions (3.3%). Successfully completed revascularization was performed in 305 (91%) patients. Compared with the lower CAC score group, the higher CAC score group had a significantly higher rate of PCI complexity (33.1% *vs.* 22.1%, *P* = 0.017). The CAC score was also significantly higher in complex lesions as compared with the non-complex lesions [365 (interquartile range: 98–1145) *vs.* 194 (51–647); *P* = 0.001] (Figure 1C).

There were 32 procedure-related complications in 32 patients (22 dissections, 2 acute target artery occlusions, 4 occlusions of side branch, 1 perforation, and 3 slow flow). No emergency CABG or no-flow occurred. These procedural complications were successfully managed without any adverse consequences for the patients. The univariate logistic regression analysis showed the risk of occurrences of intra-procedure complications increased 5.35 fold in the patients of the higher CAC score group compared with those of the lower CAC score group [odds ratios (OR): 5.35, *P* = 0.020]. Adjusted for age, DM history and multi-vessel coronary disease, the CAC score was also an independent risk factor of intra-procedure complications (OR: 4.56, *P* = 0.033) (Table 2).

3.4 Association between CAC score and MACE

Out of 334 patients, three patients had dropped from the study. After a median 22.5 months (range, 4–72 months) of follow-up, 74 MACE occurred in 51 (15.4%) patients, including 2 (0.6%) deaths, 4 (1.2%) non-fatal myocardial infarctions, 26 (7.8%) target lesion revascularizations and 42 (12.7%) rehospitalizations for cardiac ischemic events. Figure 2 provides the distribution of CAC of patients with and without MACE. The average CAC scores in patients with and without MACEs were 452.4 and 648.4 with the range 0–2868 and 0–4796 for each category (Figure 2). Kaplan-Meier survival analysis showed significantly different cumulative event-free survival rates between patients with CAC score ≤ 300 and CAC score > 300 (88.9 *vs.* 79%, Log rank: 4.577, *P* = 0.032) (Figure 3). Cox regression analysis showed that adjusted age, gender, family history, history of hypertension, hyperlipidemia, DM and smoking, systolic/diastolic blood pressure, multi-vessel coronary disease, complete revascularization, PCI complexity, procedure-related complications, the risk of MACE was significantly higher [hazard ratio (HR): 4.3, 95% confidence interval (CI):

2.4–8.2, *P* = 0.038] in patients with a CAC score > 300 compared to patients with a lower CAC score (Figure 4, Table 3).

Table 2. Logistic regression models for procedural complications.

	HR (95% CI)	*P* value
Age	1.00 (0.96–1.05)	0.960
Diabetes mellitus history	1.46 (0.63–3.37)	0.377
Multi-vessel coronary disease	2.28 (0.96–5.45)	0.063
CAC subcategories	4.56 (2.14–7.51)	0.033

CAC was divided into two subcategories of CAC ≤ 300 and CAC score > 300. CAC: coronary artery calcium; CI: confidence interval; HR: hazard ratio.
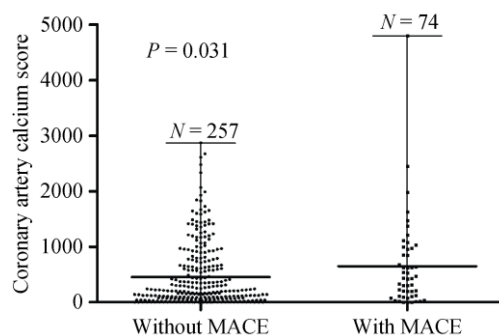

Figure 2. CAC score is depicted as scatter dot plot (median line represent mean, error bars represent range). CAC were 452.4 and 648.4 with the range 0–2868 and 0–4796 for the patient without and with MACE. CAC: coronary artery calcium; MACE: main adverse cardiac events.
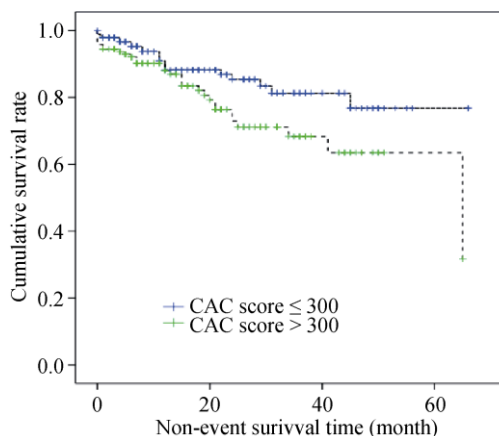

Figure 3. Kaplan-Meier survival analysis showed significantly different cumulative event-free survival rates between stable angina pectoris patients with CAC score ≤ 300 and CAC score > 300 (88.9% *vs.* 79.0%, Log rank: 4.577; *P* = 0.032). CAC: coronary artery calcium; PCI: percutaneous coronary intervention.
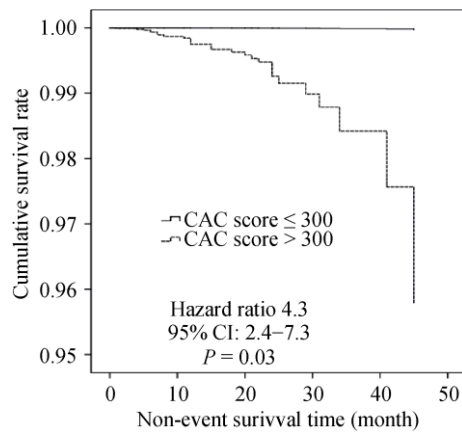
Figure 4. **Cox regression analysis showed that adjusted age, gender, family history, history of hypertension, hyperlipidemia, diabetes mellitus and smoking, systolic/diastolic blood pressure, multi-vessel coronary disease, complete revascularization, PCI complexity, and procedure-related complications, the risk of MACE was significantly higher (HR: 4.3, 95% CI: 2.4–8.2; P = 0.038) in patients with a CAC score > 300 compared to patients with a lower CAC score.** CAC: coronary artery calcium; CI: confidence interval; HR: hazard ratio; MACE: main adverse cardiac events; PCI: percutaneous coronary intervention.

Table 3. **Cox regression models for main adverse cardiac events.**

	HR (95%CI)	*P* value
Age	0.98 (0.93–1.04)	0.514
Gender	0.86 (0.33–2.27)	0.768
Family history	1.27 (0.43–3.74)	0.662
Hypertension	1.00 (0.34–3.00)	0.995
Hyperlipidemia	1.01 (0.46–2.24)	0.976
Diabetes mellitus	0.56 (0.24–1.29)	0.170
Smoking	0.96 (0.38–2.43)	0.930
Systolic blood pressure	–	0.847
Diastolic blood pressure	–	0.909
Multi-vessel coronary disease	–	0.051
Complete revascularization	1.03 (0.33–3.18)	0.976
Procedure complexity	1.11 (0.43–2.91)	0.962
Procedure-related complications	1.64 (0.68–3.92)	0.271
CAC subcategories	4.28 (2.4–8.2)	0.038

CAC was divided into two subcategories of CAC ≤ 300 and CAC score > 300. CAC: coronary artery calcium; CI: confidence interval; HR: hazard ratio.

4 Discussion

Atherosclerosis is a complex pathological process, characterized by lipoprotein deposition, inflammatory response,

ensuing apoptosis and necrosis, and in healing stages, by calcification and fibrosis. Rumberger, *et al*.[2] showed that calcium was histologically identified only when plaque area measured at least 5–10 mm^2 per 3-mm segment, and calcium assessments significantly under represented total plaque area. Development of multi-slice spiral CT has elevated non-invasive diagnosis of coronary heart disease to a new level. Particularly, in diagnosing calcification of coronary arteries, CT has incomparable accuracy and allows quantification; and the CAC score calculated using the automatic analysis software is favorably correlated, quantitatively, to the area of atherosclerotic plaques.[8] CAC scores have been reported to increase with age,[11] advanced atherosclerotic plaques and stenotic lumens,[12] which were consistent with our study. We also found that the CAC score was positively correlated with systolic blood pressure and elevated in DM patients, which was known to be intimately associated with the atherosclerosis, even in a pre-atheroma stage.

Studies indicate that the CAC score not only has high sensitivity to diagnosis of coronary heart disease,[12,13] but also correlates to prognosis of all patients with chest pain or without symptoms accepting coronary CT.[14] However, whether the CAC score correlates to prognosis of patients with established coronary heart disease (especially those receiving PCI) is still not clear. In this study, follow-up of SAP patients treated with PCI showed that the cumulative event-free survival of patients with a CAC score > 300 was 79%, significantly lower than that of patients with CAC score ≤ 300, and the combined risk of death, non-fatal myocardial infarction, target lesion revascularization and rehospitalization for cardiac ischemic events increased by 4.57 times. Detrano, *et al*.[4] performed follow-up of 6,722 non-cardiovascular disease patients undergoing coronary CT for 3.9 years on average and found that the risk of myocardial infarction and death due to coronary heart disease was 9.67 times higher in patients with CAC score > 30 than in patients with CAC score = 0, irrespective of their race. Budoff, *et al*.[15] performed follow-up of 25,253 asymptomatic patients for 6.8 years on average and found that the risk of cardiac events was 12.5 times higher in patients with a CAC score > 1000 than in patients with CAC score = 0. Laudon, *et al*.[16] followed patients visiting in emergency due to chest pain and found no cardiac events within 5 years in patients with CAC score = 0. Our study findings indicate that, the higher CAC score implies a poorer clinical prognosis in patients with stable coronary heart disease, not only in these asymptomatic patients but also the patients visiting due to chest pain. We also found that, following correction for risk factors, including age, gender, history of hypertension, hyperlipidemia, DM and smoking, family history,

systolic/diastolic blood pressure, multi-vessel coronary disease, complete revascularization, PCI complexity, procedure-related complications, the risk of MACE was still 4.3 times higher in patients with CAC score > 300 than in patients with CAC score ≤ 300. These findings indicate the CAC score is an independent predictor for the combined endpoint of primary heart events in PCI-treated SAP patients. Mosseri, *et al*.[17] also found that a higher proportion of patients with obvious plaque calcification presented with non-ST segment elevation myocardial infarction after PCI treatment. This may be one of the reasons for the increased risk of MACE after PCI in stable coronary heart disease patients with an increased CAC score. More and deeper mechanisms await further study.

Pathological studies indicate that coronary artery calcification and scleratheroma are two independent but mutually correlated pathological processes, which are not completely parallel in distribution and degree in vessel walls of coronary arteries. Plaque calcification and arterial medial calcification are the two primary forms of vessel calcification.[18] Calcified plaques are usually more stable than non-calcified plaques, but vessel calcification may lead to vascular remodeling, thereby affecting the luminal area and restricting coronary blood flows. Calcified plaques usually occur where cellular necrosis, inflammation and cholesterol deposition are also present.[17] Patients with chronic stable coronary heart disease usually present with more extensive calcified plaques in coronary arteries than patients with acute coronary syndrome.[19] It has been found in clinical studies that, PCI treatment of calcified plaques usually poses great operation difficulty, low successful ratio and the tendency to form coronary artery dissection and may require more auxiliary tools, such as rotablator, cutting balloons.[20] In this single center study, we found that, compared with the patients with a CAC score ≤ 300, the rate of PCI complexity was higher (13.1% *vs*. 5.8%, *P* = 0.017) and the risk of occurrences of intra-procedural complications increased more significantly in the patients with CAC score > 300 (17.2% *vs*. 7.4%, *P* = 0.005). These correlations suggest that the degree of coronary calcification is of vital importance in the prognosis of patients with stable coronary heart disease.

This study is limited by a single-center study with a relatively small number of enrolled patients. Prospective multi-center studies with larger numbers of patient cohorts are needed to assess the impact of CAC score on short- and long-term patient outcomes after PCI. Furthermore, some patients in this study were followed for several months; longer follow-up would support more advanced information.

In conclusion, we found the CAC score indicates complexity of PCI and predicts procedure-related complications. CAC score is an independent predictor for MACE in SAP patients who underwent PCI. Thus, we suggest that in patients with a higher CAC score, coronary angiography for planning subsequent PCI strategy should be undertaken more seriously and these patients should be more tightly followed up.

Acknowledgements

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