ORIGINAL ARTICLE

Relationship Between ^{18}F-fluorodeoxyglucose Uptake on Positron Emission Tomography and Aortic Calcification

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Received: May 24, 2022/Revised manuscript received: July 12, 2022/Accepted: July 26, 2022

Abstract

***Introduction*: Although ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been widely utilized to assess the extent of inflammation, the association between the extent and severity of atherosclerosis and ^{18}F-FDG uptake on PET remains unexamined. The current study aimed to investigate whether aortic calcium (AC) scores were associated with increased aortic uptake of ^{18}F-FDG on PET.**

***Methods*: A total of 167 consecutive patients with suspected lung cancer but unproven malignancy who underwent non-contrast-enhanced computed tomography (CT) and ^{18}F-FDG PET/CT were enrolled. The average standardized uptake values in the ascending aorta were used to calculate the target-to-background ratio (Mean TBR). The total (thoracic and abdominal) AC scores were measured on non-contrast-enhanced chest and abdominal CT using the Agatston method, and were categorized into three groups (0, 1–399, and ≥400). The relationship between total AC scores and ^{18}F-FDG uptake in the ascending aorta was assessed using multivariate linear regression analysis.**

***Results*: In total, 68.26% were male, and a mean age was 67.10 ± 14.70 years. Mean TBR values increased progressively with total AC score 0, 1–399, and ≥400 (1.01 ± 0.07, 1.08 ± 0.09, and 1.11 ± 0.11, respectively; $p < 0.00001$). Multivariate linear regression analysis revealed that increased total AC scores of 1–399 ($\beta = 0.06$, 95% CI: 0.01–0.11, $p = 0.02$) and ≥400 ($\beta = 0.11$, 95% CI: 0.06–0.16, $p < 0.001$) were significantly associated with higher Mean TBR.**

***Conclusions*: The current study demonstrated that total AC scores were associated with Mean TBR. Patients with a greater extent and severity of aortic calcifications may possess increased atherosclerotic inflammatory activity as measured by ^{18}F-FDG PET/CT.**

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography, Atherosclerosis, Coronary calcium score, Thoracic calcium

Ann Nucl Cardiol 2022; 8 (1): 57–66

Atherosclerosis, a chronic disease of the arterial wall, remains one of the leading causes of mortality worldwide. Estimates show that coronary heart disease will become the largest cause of disability and death globally in the future. Various studies are currently being conducted to provide clear evidence regarding the importance of processes such as lipoprotein oxidation, inflammation, and immunity in human atherosclerosis. Inflammation has been long known as a risk factor for developing atherosclerosis, with recent studies highlighting it as a target marker for the treatment of atherosclerosis apart from cholesterol control (1, 2) given the approximately 15%–20% additional risk reduction (3, 4).

Coronary artery and aortic calcification have been surrogate markers of atherosclerosis, the severities of which have been associated with the risk of cardiovascular disease (5–7). However, recent evidence has emerged suggesting that calcification occurs during the late stage of atherosclerosis and may not capture the early stages of the disease. Therefore, no

doi: 10.17996/anc.22-00160

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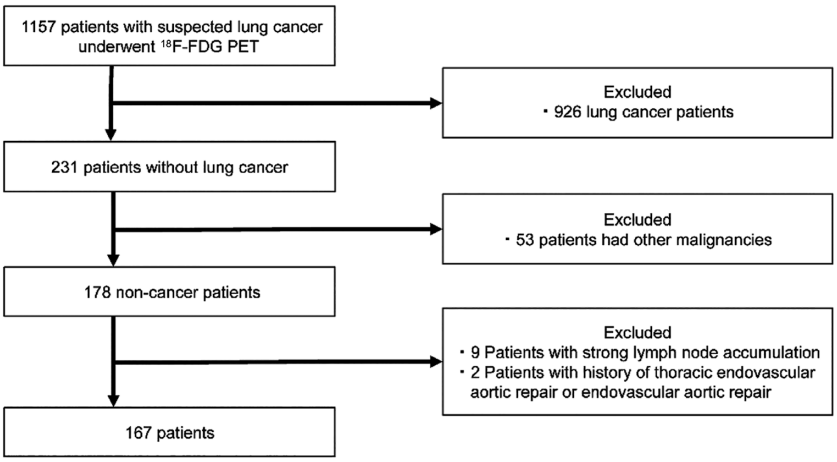

Figure 1 Flow chart of patient inclusion and exclusion criteria in the study.
^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography

definite conclusions have been established regarding the association between calcification and inflammatory activity.

The current study aimed to investigate whether the calcium score of arteries measured via thoracoabdominal plain computed tomography (CT) was associated with arterial accumulation of ^{18}F-fluorodeoxyglucose (FDG) on positron emission tomography (PET) /CT among patients without cancer.

Materials and methods

Study population

Between February 2015 and September 2017, 1157 patients with suspected lung cancer underwent non-contrast-enhanced chest and abdominal CT and ^{18}F-FDG PET examination within 6 months at our institute (Toho University Omori Medical Center, Tokyo, Japan). Among such patients, the following were sequentially excluded: patients with diagnosed lung cancer (n=926), any other malignancies (n=53), strong lymph node accumulation (n=9), and a history of thoracic or abdominal endovascular aortic repair (n=2). Ultimately, the current study enrolled 167 patients (Figure 1), the medical records of whom were then retrospectively reviewed. Our study protocol was approved by the ethics committee of Toho University Omori Medical Center (Ethics approval number: M21188 18020). An opt-out form was uploaded on the website of Toho University Omori Medical Center to inform patients regarding the option to exclude their information from this study.

Scanning and imaging protocol for non-contrast-enhanced chest and abdominal CT

Non-contrast-enhanced chest and abdominal CT was performed using four CT scanners (SOMATOM Definition Flash CT scanner, SIEMENS; SOMATOM Definition AS+ CT scanner, SIEMENS; SOMATOM Definition Edge CT scanner, Siemens Medical Solutions Forcheim, Germany; and Light Speed VCT VISION, General Electric Healthcare, Milwaukee, Wisconsin, USA). Patients were scanned without electrocardiographic gating. The slice thickness was 5 mm, while the rotation speed was 0.5 s/rot. The volume of the computed tomography dose index (CTDIvol) and the dose-length-product were 5–7 mGy and 180–290 mGy. cm, respectively.

Scanning and imaging protocol for ^{18}F-FDG PET/CT

All patients underwent ^{18}F-FDG PET/CT on a BIOGRAPH mCT Flow 20 PET/CT scanner (SIEMENS). Before scanning, participants were required to fast for at least 5 h and maintain a glucose level of 150 mg/mL or lower. Patients were instructed to avoid intense exercise the day before the exam. ^{18}F-FDG was administered at approximately 209 MBq. Patients were instructed to void before starting imaging. Approximately 60 min after ^{18}F-FDG administration, imaging in 3D-mode was initiated. Patients were imaged in the supine position, and CT scanning (100 mAs, 120 kV) was conducted before PET imaging. The slice thickness was 3 mm. The CT-based attenuation correction technique was used on PET data. A model-based scatter correction for PET was performed and then reoriented in axial, sagittal, and coronal slices.

Imaging analysis of non-contrast-enhanced chest and abdominal CT

Image analysis of aortic calcium (AC) scores was performed on a dedicated workstation (IntelliSpace Portal, PHILIPS, Amsterdam, Nederland). Ascending AC, descending AC, abdominal AC and coronary artery calcium (CAC) scores were measured using the Agatston method (8). AC scoring was performed using methods described by Agatston et al. on both scan types. Total (thoracic and abdominal) AC scores were determined by adding the AC scores for each slice.

Imaging analysis of ^{18}F-FDG PET/CT

An automated program (SYNAPSE VINSENT V5.3; FUJI FILM Co. Ltd., Tokyo, Japan) was used to measure standardized uptake values (SUV). This software can display CT and PET images on top of each other, as well as surrounding blood vessels, and measure SUV. As a measure of arterial inflammation arterial ^{18}F-FDG uptake in the ascending aorta was measured by drawing a region of interest (ROI) around the artery on every slice of the overlaid PET and CT images (Figure 2A). The ROI was drawn to include the arterial wall and lumen. Mean ^{18}F-FDG uptake on PET/CT using the SUV (SUV_{mean}) was measured at the ascending aorta in every three slices (9 mm) and as blood-pool SUV at the superior vena cava (SVC) in one slice at the level of the pulmonary artery bifurcation (SVC-SUV_{mean}) (Figure 2B). SUV values were measured from the ascending aortic root to branch of the brachiocephalic artery and the average value was calculated, and the degree of inflammation was defined. In this study, SUV_{mean} and SUV_{max} defined ^{18}F-FDG uptake, or inflammation. The average SUV_{mean} value (Mean SUV) in the ascending aorta was used to calculate the target-to-background ratio (Mean TBR) [Mean SUV/(SVC−SUV_{mean})]. Similarly, max ^{18}F-FDG uptake on PET/CT using the SUV (SUV_{max}) was measured at the ascending aorta in every three slices (9 mm) and as blood-pool SUV at the superior vena cava (SVC) in one slice at the level of the pulmonary artery bifurcation (SVC−SUV_{max}). The average SUV_{max} value (Max SUV) in the ascending aorta was used to calculate the target-to-background ratio (Max TBR) [Max SUV/(SVC−SUV_{max})].

Comparison of SUV values measured over the entire ascending aorta and limited areas thereof

This study calculated 1,176 slices of the entire aorta from 10 randomly selected patients in order to compare the SUV_{mean} at the entire aorta to that measured at the ascending and descending aorta in every three slices. Strong correlation among SUV_{mean} values was also observed (correlation coefficient 0.99, 95% confidence interval 0.96–0.99, $p<0.001$). Considering the high concordance, our analyses therefore included the SUV values at the ascending aorta in every three slices.

Statistical analysis

Continuous variables were expressed as mean ± SD, whereas categorical variables were expressed as frequencies or percentages. Total AC score, ascending AC score, and coronary artery calcium (CAC) score were categorized into three groups (0, 1–399, and ≥400), which is the standard threshold for risk prediction using CAC score and AC score (5, 6). The Mann–Whitney U test was performed to determine whether the total AC score was associated with clinical risk factors. SUV and TBR values were compared between total AC score, ascending AC score, and CAC score and groups using one-way analysis of variance or the Kruskal–Wallis test. Linear regression was used to evaluate the correlation between ^{18}F-FDG uptake and each calcium score. Mean TBR values were compared between the total AC score, ascending AC score, or CAC score groups stratified according to C-reactive protein (CRP) and low-density lipoprotein cholesterol. Multivariate linear regression analysis was used to assess whether the total AC score, ascending AC score, or CAC scores was associated with ^{18}F-FDG uptake on PET in the ascending aorta after adjusting for age, gender, body mass index (BMI), history of coronary artery disease (CAD), diabetes mellitus (DM), dyslipidemia (DL), hypertension (HT), and CRP value. All analyses were conducted using STATA (Version 11, Stata Corp LP, College Station, Texas, USA), with a p value of <0.05 indicating statistical significance.

Results

The baseline characteristics of the study population are listed in Table 1. Accordingly, the included patients, 68.26% of whom were male, had a mean age of 67.10 ± 14.70 years and a mean BMI of 21.90 ± 3.70 kg/m^2. Clinical CAD risk factors, such as HT, DL, and DM, were present in 28.74%, 11.98%, and 11.98% of the patients, respectively. Approximately half of patients were smokers, while 17.37% were current smokers. Compared to patients with a total AC score of 0, those with the total AC score of 1–399 and ≥400 were older and had greater rates of HT and history of CAD. Regarding the laboratory data, CRP and blood glucose levels were significantly increased in patients with a higher total AC score (<0.001 for all), whereas no significant differences in other laboratory data were noted between the three groups. ^{18}F-FDG PET/CT data from 167 patients showed that Mean TBR, Max TBR, Mean SUV, and Max SUV were 1.08 ± 0.10, 1.10 ± 0.10, 1.69 ± 0.33, and 2.34 ± 0.47, respectively. Table 2 compares the Mean and Max TBR and Mean and Mean SUV values between the total AC score groups, ascending AC score groups, and CAC score groups. Compared to those with a total AC score of 0, those with a total AC score of 1–399 and ≥400 had progressively greater Mean TBR values. However, such a relationship was not observed between patients with CAC score of 1–399, and ascending AC score of 0, 1–399, and ≥400. CAC scores ≥400 was significantly associated with higher Mean TBR compared to CAC score=0.

Table 3 compares the Mean TBR values between the AC score groups stratified according to low-density lipoprotein cholesterol (LDL-C) and CRP levels. Accordingly, those with a total AC score of 1–399 had higher Mean TBR values compared to those with a total AC score of 0, with those

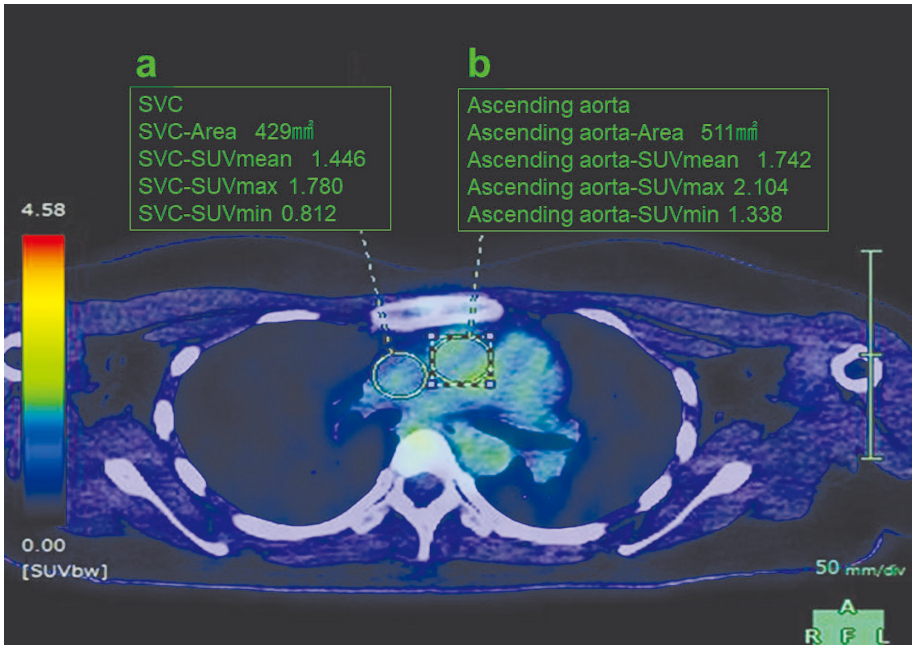

Figure 2A　Example of image measuring standardized uptake values (SUV) on PET/CT image.
The circular region of interest is drawn around blood vessel wall on the image and SUV was measured. SUV (SUVmax, SUVmean) was measured at aorta (a) and as blood-pool SUV at superior vena cava (b) in one slice at the level of the pulmonary artery bifurcation. The SUV was divided by the blood-pool SUV, yielding a target-to-background ratio (TBR).
CT: computed tomography, PET: positron emission tomography, SVC: superior vena cava, SUV: standardized uptake values

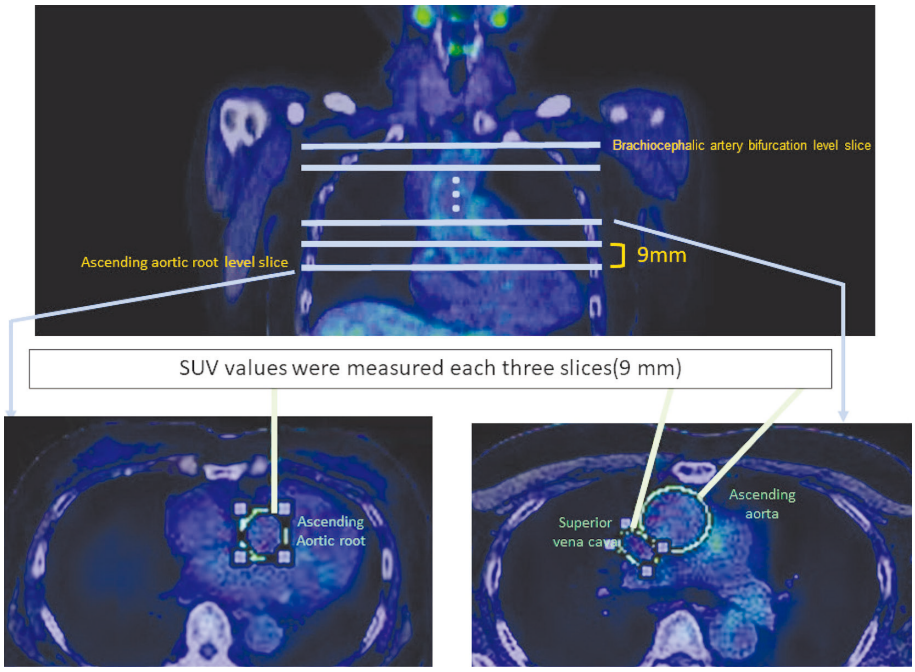

Figure 2B　Example of site where SUV values were measured.
SUV values measurements were taken every three slices (9 mm) from the ascending aortic root to branch of the brachiocephalic artery and the average value was calculated, and the degree of inflammation was defined. SUV at the superior vena cava in one slice at the level of the pulmonary artery bifurcation was measured as blood-pool. The arrows are examples of slices that measures SUV.
SUV: standardized uptake values

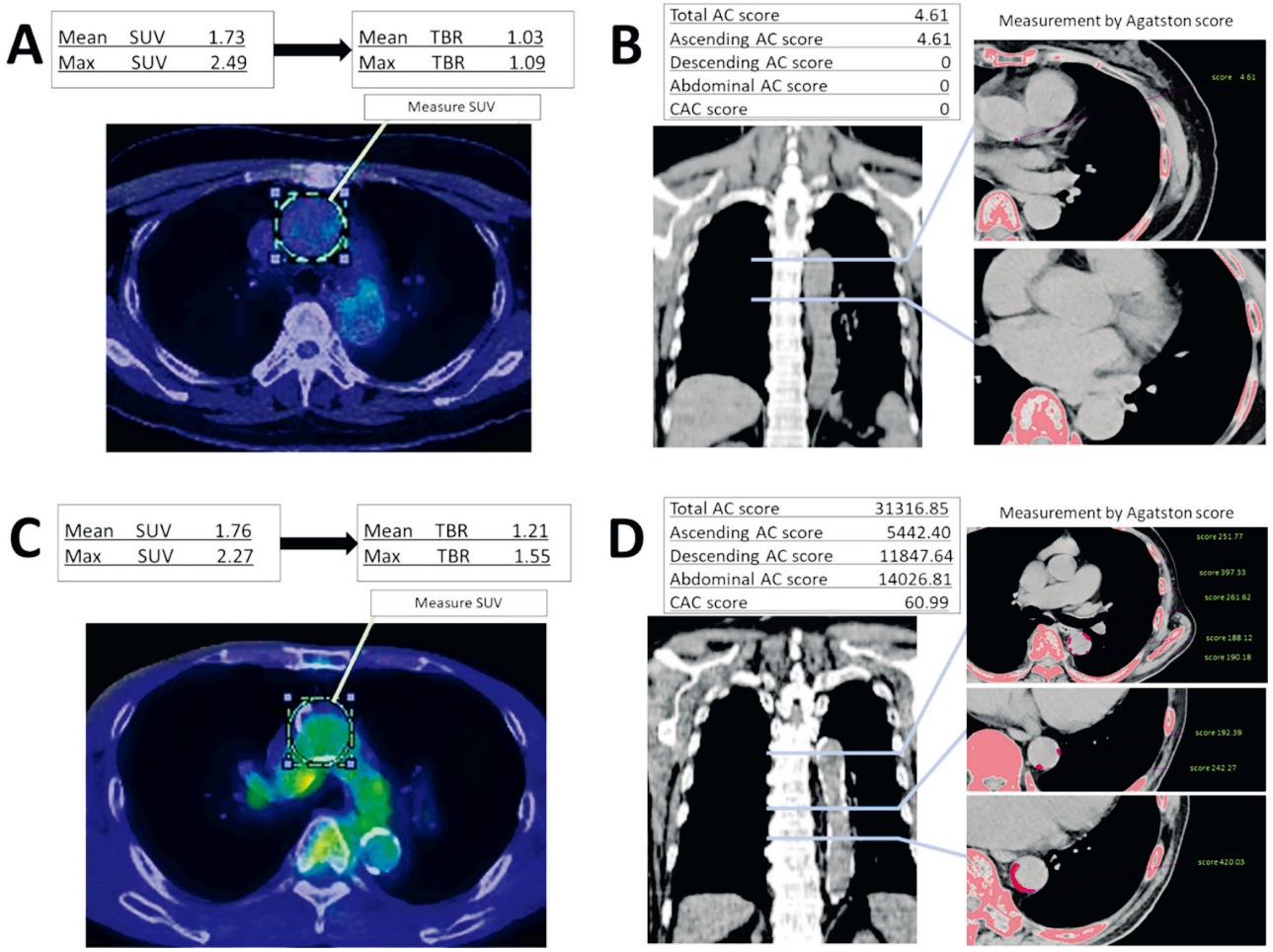

Figure 3 Image of visualization of [18]F-FDG uptake analysis in PET/CT and aortic calcification score with Agatston score in non-contrast CT.

Figure 3 is images of two examples that support the relationship association between vascular calcifications and inflammation. Patient 1 is a 70-year-old man who has the low [18]F-FDG uptake uptake with 1.03 and 1.09 for Mean TBR, and Max TBR (A), and a minimal total AC score, with 4.61 (B). In contrast, patient 2 is a 64-year-old woman with the high [18]F-FDG uptake PET uptake with 1.21, and 1.55 for Mean TBR, and Max TBR (C). She has the extensive calcification in the thoracic and abdominal aorta, with 31316.85 of the total AC score (D)."

[18]F-FDG: [18]F-fluorodeoxyglucose, AC: aortic calcium, CAC: coronary artery calcium, CT: computed tomography, PET: positron emission tomography, SUV: standard uptake values, TBR: target-to-background ratio

having a total AC score of ≥400 showing even greater Mean TBR values, regardless of CRP values (<0. 5 or ≥0. 5). Regarding the lower LDL-C values with <120, Mean TBR gradually increased with total AC 1–399 and ≥400 compared to total AC score=0, and higher Mean TBR was likely to be increased in total AC 1–399 and ≥400 compared to total AC score=0 when stratified by LDL-C ≥120. In terms of ascending AC score and CAC, significant increase in Mean TBR was not shown across the CAC and ascending AC groups regardless of CRP and LDL-C levels (Table 3).

Regarding the correlation between [18]F-FDG uptake and the calcium scores, no correlation was observed between [18]F-FDG uptake and the total AC score, ascending AC score, or CAC (Supplemental Figure 1).

The relationship between Mean TBR and total AC, ascending AC, or CAC score is presented in Table 4. After adjusting for age, sex, BMI, CAD, DM, DL, HT, and CRP value, multivariate linear regression analysis revealed that increased total AC scores (1–399 and ≥400) were significantly associated with higher Mean TBR compared to total AC score =0. In contrast, after adjusting for age, sex, BMI, CAD, DM, DL, HT, and CRP value, multivariate linear regression analysis revealed that ascending AC scores of 1–399, and ≥400 were not significantly associated with Mean TBR. In terms of CAC score, only CAC scores ≥400 was significantly associated with higher Mean TBR compared to CAC score =0.

Discussion

The current study demonstrated that the extent and severity of aortic calcifications was associated with increased [18]F-FDG uptake on PET. Although our results showed that CAC scores ≥400 was significantly associated with higher Mean TBR

Table 1 Baseline characteristics of the study population

	Total	Total AC score			P value
		0	1–399	≥400	
Number of patients	167	30	36	101	
Clinical demographics					
Age (years, mean ± SD)	67.10 ± 14.70	51.23 ± 16.74	60.28 ± 14.66*	74.22 ± 7.44*,**	<0.001
Male gender (n, %)	114 (68.26)	20 (66.67)	23 (63.89)	71 (70.30)	<0.001
Height (m)	1.62 ± 0.10	1.66 ± 0.09	1.63 ± 0.11	1.61 ± 0.09*	0.03
Body weight (kg)	57.80 ± 12.60	63.16 ± 17.28	56.94 ± 15.26	55.97 ± 10.74*	0.16
BMI (kg/m^2, mean ± SD)	21.90 ± 3.70	22.64 ± 4.73	21.96 ± 3.21	21.55 ± 3.50	0.36
Hypertension (n, %)	48 (28.74)	4 (13.33)	4 (11.11)	40 (39.60)*,**	<0.001
Dyslipidemia (n, %)	20 (11.98)	3 (10.00)	1 (2.78)	16 (15.84)**	0.11
Diabetes mellitus (n, %)	20 (11.98)	2 (6.67)	2 (5.56)	16 (15.84)	0.16
History of coronary artery disease (n, %)	14 (8.38)	0 (0.0)	1 (2.78)	13 (12.87)*	0.03
Current smoker (n, %)	29 (17.37)	6 (20.00)	9 (25.00)	14 (13.86)	0.29
Past smoker (n, %)	81(48.50)	12 (40.00)	16 (44.44)	53 (52.48)	0.42
Never smoker (n, %)	57 (34.13)	13 (43.33)	12 (33.33)	35 (34.65)	0.64
Laboratory data					
CRP (mg/dL, mean ± SD)	1.68 ± 0.60	0.32 ± 0.51	0.36 ± 0.59	0.76 ± 2.10	<0.001
BUN (mg/dL, mean ± SD)	15.67 ± 6.50	14.07 ± 4.56	13.94 ± 4.00	16.74 ± 7.48**	0.11
Creatinine (mg/dL, mean ± SD)	0.88 ± 0.61	0.79 ± 0.24	0.76 ± 0.18	0.95 ± 0.75	0.22
Blood glucose level (mg/dL, mean ± SD)	117.91 ± 36.89	104.00 ± 13.92	107.69 ± 25.80	125.58 ± 42.53*,**	<0.001
Hemoglobin A1c (%, mean ± SD)	5.93 ± 0.76	5.88 ± 0.90	5.74 ± 0.55	6.00 ± 0.77	0.28
Total cholesterol (mg/dL, mean ± SD)	191.61 ± 39.93	185.92 ± 32.01	202.63 ± 38.17	189.76 ± 41.99	0.22
Triglyceride (mg/dL, mean ± SD)	120.47 ± 81.73	110.69 ± 76.78	123.94 ± 91.57	121.99 ± 80.21	0.80
HDL-C (mg/dL, mean ± SD)	59.97 ± 19.08	54.83 ± 18.39	63.08 ± 20.58	60.53 ± 18.74	0.29
LDL-C (mg/dL, mean ± SD)	113.13 ± 33.20	111.46 ± 23.30	124.31 ± 30.09	110.19 ± 35.94**	0.10
LDH (U/L, mean ± SD)	216.27 ± 59.10	222.97 ± 69.30	213.46 ± 39.12	215.26 ± 61.73	0.83
CEA (ng/mL, mean ± SD)	5.97 ± 26.00	2.30 ± 2.23	2.64 ± 2.38	7.331 ± 32.83	<0.001
KL-6 (U/mL, mean ± SD)	424.90 ± 708.50	325.64 ± 292.95	311.54 ± 184.55	486.99 ± 868.46	0.18
NSE (ng/mL, mean ± SD)	11.56 ± 5.40	10.26 ± 2.76	12.67 ± 6.54	11.60 ± 5.48	0.17
ProGRP (pg/mL, mean ± SD)	47.79 ± 22.50	39.84 ± 16.25	48.11 ± 24.46	50.07 ± 23.21*	0.01

*P<0.05 compared to Total AC score= 0 ; **P<0.05 compared to Total AC score=1–399
AC: aortic calcium, BMI: body mass index, CRP: C-reactive protein, BUN: blood urea nitrogen, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, LDH: lactate dehydrogenase, CEA: carcinoembryonic antigen, KL-6: sialylated carbohydrate antigen, NSE: neuron-specific enolase, ProGRP: pro-gastrin-releasing peptide

compared to CAC score =0, no association between CAC scores=1–399 group and ^{18}F-FDG uptake. Our results also showed no association between the ascending AC scores and ^{18}F-FDG uptake. Regardless of CRP and LDL-C levels, those with higher total AC scores exhibited increased ^{18}F-FDG uptake on PET. In theory, vascular calcification and vascular metabolic activity rarely overlap, suggesting that these findings represent different stages of atheroma evolution (9). While macro-calcifications are thought to occur at the later stages of the atherosclerosis process, global calcifications have been suggested to reflect overall atherosclerosis, including noncalcified and calcified atherosclerosis. Therefore, atherosclerosis in the coronary artery or aorta (i.e., CAC or AC scores) have been associated with higher cardiovascular events or mortality (6, 10, 11). Numerous studies have evaluated ^{18}F-FDG uptake on PET in vascular inflammation (12, 13) and atherosclerotic lesions in patients with cancer, and autoimmune disease, as well as those taking anti-inflammatory drugs (9, 14, 15). Moreover, limited studies have reported an association between vascular calcifications and inflammation (16, 17). However, there is still an ongoing debate regarding the association between calcification, plaque vulnerability, and inflammatory activity in plaque. Our group recently reported that details related to calcified plaque (i.e., calcified density) measured by non-contrast-enhanced CT in the coronary artery were associated with optical coherence tomography (OCT)-

Table 2 Comparison of calcium scores for each artery with TBR and SUV

Total AC score (N=167)				
	0 (N=30)	1–399 (N=36)	≥400 (N=101)	P value
Mean TBR	1.01 ± 0.07	1.08 ± 0.09	1.11 ± 0.11	<0.001
Max TBR	1.07 ± 0.09	1.10 ± 0.10	1.11 ± 0.09	0.13
Mean SUV	1.73 ± 0.21	1.67 ± 0.35	1.69 ± 0.35	0.56
Max SUV	2.39 ± 0.35	2.30 ± 0.49	2.34 ± 0.50	0.74
Ascending AC score（N=167）				
	0 (N=90)	1–399 (N=45)	≥400 (N=32)	P value
Mean TBR	1.07 ± 0.10	1.11 ± 0.11	1.09 ± 0.10	0.16
Max TBR	1.10 ± 0.10	1.11 ± 0.08	1.10 ± 0.10	0.62
Mean SUV	1.70 ± 0.32	1.68 ± 0.30	1.69 ± 0.39	0.95
Max SUV	2.34 ± 0.46	2.33 ± 0.43	2.35 ± 0.59	0.98
CAC score（N=167）				
	0 (N=101)	1–399 (N=45)	≥400 (N=21)	P value
Mean TBR	1.08 ± 0.11	1.08 ± 0.09	1.07 ± 0.11	0.79
Max TBR	1.11 ± 0.10	1.10 ± 0.08	1.08 ± 0.11	0.53
Mean SUV	1.68 ± 0.35	1.70 ± 0.33	1.73 ± 0.26	0.77
Max SUV	2.31 ± 0.49	2.36 ± 0.44	2.43 ± 0.49	0.51

TBR: target-to-background ratio, SUV: standardized uptake values, AC: aortic calcium, CAC: coronary artery calcium

derived calcified size but not with OCT-derived plaque vulnerability (18). The aforementioned study emphasized that CT-derived calcium density in local macro-calcifications may not always indicate local plaque vulnerability, although the association between calcifications and plaque activity had not been assessed. Similarly, a study of 183 patients showed that those with increased local coronary ^{18}F-Fluoride uptake in at least one coronary artery were likely to have higher overall CAC scores (19). However, local coronary ^{18}F-Fluoride uptake was not associated with overall CAC progression. Our findings expanded these results by showing that Mean TBR of the aorta reflected the overall extent and severity of atherosclerosis (i.e., total AC scores in the current study). The Mean TBR value of 1.08 ± 0.10 in the aorta obtained herein was relatively low compared to that presents in previous studies, which ranged from 1.13 to 1.97 in the carotid and other vascular arteries (16, 20, 21). This may have been due to the lower presence of traditional risk factors for CAD, such as HT, DL, and DM, among our patients. However, no prior study had compared the association between calcification and ^{18}F-FDG uptake on PET in the aorta among low-risk patients. Despite such a lower risk of CAD, the current study observed a significant association between Mean TBR and total AC scores among patients with suspected but undiagnosed lung cancer. Additionally, the association between increased total AC scores and higher Mean TBR values was consistently observed regardless of CRP or LDL-C values. In the current study, no linear relationship between ^{18}F-FDG uptake and the calcium score was shown. We observed that increased TBR, not SUV, was associated with thoracic aortic calcifications. This is probably due to attenuated effects of SUV because SUV in the aorta included both aortic wall/calcification and blood activity in the aorta, therefore, it was necessary to normalize ^{18}F-FDG uptake to the blood activity or TBR, to correct for factors that may affect SUV in order to investigate a pure effect of aortic inflammation to thoracic calcifications. In a prior study, TBR, not SUV, was also used to identify plaque inflammation in carotid artery (20). Our findings suggest that ^{18}F-FDG PET can be an indicator of imperceptible vasculitis and that the association between ^{18}F-FDG uptake on PET and the extent and severity of calcified plaque in the aorta may be consistent regardless of coronary vascular risk, potentially suggesting that ^{18}F-FDG PET can be utilized for the early detection of atherosclerotic activity. Additionally, we found that Mean TBR, not Max TBR is associated with the extent and severity of total aortic calcification. It has been thought that Mean TBR is of use for monitoring the inflammatory status of the systemic aorta due to treatment, while Max TBR can be more capturing the inflammatory condition of the local aorta due to drugs (22).

Table 3 The comparison of Mean TBR values between the each AC score groups stratified according to C-reactive protein and low-density lipoprotein cholesterol

		Total AC score			
		0	1–399	≥400	P value
CRP (mg/dl)	0–0.5	1.01 ± 0.08	1.08 ± 0.07	1.10 ± 0.11	<0.001
	≥0.5	1.02 ± 0.03	1.03 ± 0.13	1.13 ± 0.11	0.02
LDL-C (mg/dl)	<120	1.02 ± 0.70	1.08 ± 0.08	1.10 ± 0.11	0.08
	≥120	1.02 ± 0.04	1.05 ± 0.10	1.11 ± 0.11	0.01
		Ascending AC score			
		0	1–399	≥400	P value
CRP (mg/dl)	0–0.5	1.08 ± 0.10	1.09 ± 0.10	1.06 ± 0.11	0.7
	≥0.5	1.03 ± 0.08	1.16 ± 0.12	1.12 ± 0.09	0.41
LDL-C (mg/dl)	<120	1.06 ± 0.10	1.10 ± 0.13	1.09 ± 0.11	0.32
	≥120	1.08 ± 0.09	1.11 ± 0.12	1.03 ± 0.09	0.29
		CAC score			
		0	1–399	≥400	P value
CRP (mg/dl)	0–0.5	1.09 ± 0.10	1.07 ± 0.08	1.05 ± 0.11	0.35
	≥0.5	1.08 ± 0.14	1.13 ± 0.02	1.12 ± 0.09	0.4
LDL-C (mg/dl)	<120	1.08 ± 0.11	1.10 ± 0.10	1.07 ± 0.11	0.58
	≥120	1.09 ± 0.10	1.06 ± 0.09	1.06 ± 0.06	0.57

TBR: target-to-background ratio, AC: aortic calcium, CRP: C-reactive protein, CAC: coronary artery calcium, LDL-C: low-density lipoprotein cholesterol

Our study is consistent with this study, indicating that the mean value, rather than the maximum value, may better reflect the overall aortic condition of atherosclerotic disease. This concept is also recently reported by Dzaye et al., demonstrating that mean CAC density potentially captures early atherosclerotic status more than peak CAC density (23). Investigating methods for assessing arterial calcification in combination with ^{18}F-FDG uptake on PET/CT may provide additional insights into atherosclerosis and facilitate new clinical applications. Moreover, studies investigating the prognostic utility of combined evaluation will be required.

Some limitations of the current study are worth noting. First, this study was a single-center, retrospective study with a relatively small sample size. Second, as noted earlier, our study population comprised patients who underwent ^{18}F-FDG PET/CT due to suspicion of malignant disease. Therefore, the association between ^{18}F-FDG PET and aortic calcifications in patients at higher CAD risk still remains unknown. Third, SUV values were determined according to the total body mass, whereas the distribution volume of ^{18}F-FDG uptake mainly corresponds to the lean body mass. The difference in SUV values reported according to total body mass or lean body mass may be very important in obese 29 subjects (BMI≥25), and this could impact the relationships between SUV values and AC scores. While the software corrected the factors of body mass index to SUV, BMI may affect our findings. However, the results have not changed regardless of obese (BMI≥25) or non-obese patients (data not shown). Fourth, given the retrospective nature of our study, we did not perform ECG-gated non-contrast coronary CT in conjunction to compare the CAC scores with ^{18}F-FDG uptake on PET. In this regard, such data was not available in the current study, although the great correlation of CAC scores between cardiac and non-cardiac CTs ($r=0.93$, $p<0.001$) (24), or the high interscan variability of CAC ($r=0.94$) (25) were previously reported. Fifth, although several cytokines, such as IL-6, have been associated with ^{18}F-FDG uptake on PET, such variables had not been assessed herein. Sixth, we listed results used the SUV values measured at only the ascending aorta, which may affect our findings in the current study. However, the strong correlations of the SUV values between the ascending aorta and whole aorta were observed, and this can be probably because the inflammation in the ascending aorta is more associated with pulse pressure amplification compared to other aortic sites (26). Lastly, this study focused on the relationship between systemic inflammation and overall calcification; the relationship between local inflammation and local severity of calcification is still unknown.

Conclusion

The current study demonstrated that among patients without cancer who underwent ^{18}F-FDG PET, the total AC scores were associated with Mean TBR. Patients with greater extent and severity of aortic calcifications may exhibit increased

Table 4 Multivariate linear regression models for the identification of the relationship between Mean TBR and total AC score, CAC score, or ascending AC score

	β (95% CI)	P value
Total AC score		
0	1 (REF)	
1–399	0.06 (0.01–0.11)	0.02
≥400	0.11 (0.06–0.16)	<0.001
Ascending AC score		
0	1 (REF)	
1–399	0.02 (−0.02–0.06)	0.3
≥400	0.01(−0.05-0.04)	0.7
CAC score		
0	1 (REF)	
1–399	−0.03 (−0.07 – −0.01)	0.17
≥400	−0.06 (−0.12 – −0.0008)	0.04

AC: aortic calcium, CAC: coronary artery calcium, TBR: target-to-background ratio

atherosclerotic inflammatory activity as measured by ^{18}F-FDG PET regardless of CAD risks.

Acknowledgments

The authors thank Dr. Ryo Okubo, Dr. Takayuki Yabe, Dr. Ryota Noike, and Dr. Kazuma Kishi, for helping with this study and Mr. Fuyuki Washizuka, Mr. Tadashi Kokubo, and Mr. Nobutomo Ishii for educating us regarding the scanning and imaging protocol as the radiological technologist.

Sources of funding

None.

Conflicts of interest

None.

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