Clinica Chimica Acta 499 (2019) 128–133

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Biomarkers and their relative contributions to identifying coronary artery stenosis based on coronary computed tomography angiography in asymptomatic adults

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ARTICLE INFO

Keywords:
Coronary artery stenosis
Coronary computed tomography angiography
γ-glutamyl transferase
Brachial-ankle pulse wave velocity

ABSTRACT

Background: Coronary computed tomography angiography (CCTA) has emerged as an important, non-invasive imaging modality for the assessment of coronary vascular disease. However, CCTA as a screening tool still has issues with radiation exposure and cost in asymptomatic adults. In this study, we investigated the relationship between cardio-metabolic biomarkers and coronary artery stenosis on CCTA in asymptomatic, apparently healthy adults.

Methods: Data for this cross-sectional study were obtained from 306 subjects who underwent a comprehensive medical check-up including CCTA. A 128-slice CT device was used to detect earlier stages of coronary stenosis, which was defined as > 25% luminal reduction in the most severe stenosis in the calcified segments of the coronary arteries.

Results: On multivariate analysis, after adjustment for age, only γ-glutamyl transferase (GGT) was significantly and independently associated with CCTA stenosis (OR 1.006, 95% CI 1.001–1.011, $P = .026$). In a subgroup analysis of 103 subjects with brachial-ankle pulse wave velocity (baPWV) data, baPWV was significantly associated with CCTA stenosis (OR 1.005; 95% CI 1.003–1.008, $P < .001$).

Conclusions: GGT and baPWV were associated independently with the presence of CCTA stenosis in apparently healthy adults. Further research is needed to re-confirm on these findings.

1. Introduction

Coronary vascular disease (CVD) is one of the leading global causes of death [1,2]. Conventional coronary angiography has been considered to be the gold standard method for diagnosing CVD. However, coronary angiography is unlikely to be accepted as a screening tool for early detection of coronary atherosclerosis in asymptomatic adults because of its invasiveness [3]. Recently, coronary computed tomography angiography (CCTA) has emerged as an important, non-invasive imaging modality for the assessment of CVD [4]. Several studies with adequate follow-up periods and sample size have proved the prognostic value of CCTA for adverse cardiac events [5,6]. Thus, UK National Institute for Health and Care Excellences (NICE) guidance recommends cardiac CT as the first-line test for the evaluation in patients with angina symptoms or those who are asymptomatic with suggested EKG changes for ischemia [7]. When implementing CCTA as a screening tool among apparently healthy people, we need to take into consideration that there are still issues with radiation exposure and cost. Therefore, before using CCTA among apparently healthy people, other simple, safe, less expensive, and validated tests, such as biomarkers, are required.

Diabetes, dyslipidemia, metabolic syndrome, and obesity are well-known risk factors for CVD [8,9]. Clinically, biomarkers such as uric acid, γ-glutamyl transferase (GGT), homeostasis model assessment insulin resistance index (HOMA-IR), and brachial-ankle pulse wave velocity (baPWV) are all easily and safely measured, and alterations in these biomarkers have been associated with increased risk of coronary heart disease (CHD) events [10–12].

2. Methods

2.1. Subjects

This cross-sectional study was conducted by a chart review of records in the Center for Health Promotion, Pusan National University

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https://doi.org/10.1016/j.cca.2019.09.007
Received 13 July 2019; Received in revised form 4 September 2019; Accepted 9 September 2019
Available online 11 September 2019
0009-8981/

Yangsan Hospital. Initially, data were collected from 306 subjects who underwent a comprehensive medical check-up, including CCTA, between February 2009 and February 2010 in Koreans at least 30 y of age. One subject diagnosed with gastric cancer and liver cirrhosis, 2 subjects with suspected laboratory errors, 3 subjects without abdominal ultrasonography, and 100 subjects who did not respond to the questionnaire including smoking, alcohol drinking, and taking medicines were excluded. Finally, a total of 200 subjects were included in this analysis. As this study used pre-existing, de-identified data, it was exempt from institutional review board approval (IRB No.05–2015-129).

2.2. Coronary computed tomography angiography (CCTA)

In the study, a 128-slice CT device (Definition AS+, Siemens Medical Solutions) was used. Before the imaging, all subjects were reminded to fast for at least 8 h. Subjects with a heart rate over 70 beats per minute were given a single 20 mg dose of propranolol. Seventy ml of iopromide (Ultravist 370) was administered via the antecubital vein at a rate of 5 ml/s. Subsequently, iopromide mixed with saline in a 4:1 ratio was administered. In the present study, coronary stenosis was defined as > 25% luminal reduction in the most severe stenosis in the calcified segments of the coronary arteries for earlier stages of CVD.

2.3. Demographics

Data on medication history, alcohol intake, smoking status, and physical activity were obtained by a simple self-report questionnaire. History of treatment for hypertension, dyslipidemia, and diabetes mellitus was collected. Subjects were divided into 2 groups according to alcohol consumption: non-drinker or drinker. Smoking status was classified as non-smoker, including former smoker, or current smoker. Effective physical activity was determined as 3 or more times per week.

2.4. Anthropometrics

Waist circumference (WC) measurement was made at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest according to World Health Organization protocol [13]. Body mass index was measured by bioelectric impedance analysis (BIA, Inbody 720, Biospace Co., Ltd.). Abdominal visceral fat area (VFA) also was estimated using three multifrequency BIA measurements for each individual [14]. The device scans at X-scan uses 1, 5, 50, 250, 500 kHz, and 1 MHz frequencies to analyze intracellular and extracellular fluid values and water content. Sagittal abdominal diameter (SAD) was measured using a SECA 207 baby measuring rod with large calipers (Seca Ltd.). The subject was asked to undress from the waist up and lie on the examination table. The caliper's upper arm was placed under the subject's back, at the high point of the iliac crest. The subject was asked to relax and breathe gently. The other arm of the caliper was lowered gently onto the subject's stomach without compression. The measurement was performed after normal expiration and was taken to the nearest tenth of a centimeter [15].

2.5. Biochemical tests

Blood samples were obtained from the antecubital vein after overnight fasting. Aspartate aminotransferase, alanine aminotransferase, GGT, total cholesterol, and uric acid were measured by the enzymatic colorimetric method (TBA-200FR, Toshiba). Low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein-cholesterol were measured using the direct method (TBA-200FR, Toshiba). Triglyceride levels were measured using lipase, glycerol kinase, glycerol-3-phosphate oxidase, and peroxidase with glycerol blanking. Fasting glucose levels were determined using the glucose oxidase method (LX20, Beckman Coulter), and insulin was measured by a solid-phase 125I radioimmunoassay (Coat-A-Count®, Diagnostic Products Corp.) Cystatin C and homocysteine were measured with a turbidimetric immunoassay (TBA-200FR NEO, Toshiba) and the enzymatic spectrophotometric method (BHI Co., Ltd.), respectively, using Modular Analytics E170 (Roche Diagnostics). Plasma free fatty acids levels were measured by enzymatic methods using NEFAZYME-S (Eiken Chemical). HOMA-IR and quantitative insulin sensitivity check index (QUICKI) were calculated using the following formula [15]:

$$\text{HOMA} - \text{IR} = [\text{fasting insulin (uIU/ml) x fasting glucose (mg/dl)}]/(22.5 \times 18.182)$$

$$\text{QUICKI} = 1/[\log(\text{fasting insulin (uIU/ml)}) + \log(\text{fasting glucose (mg/dl)}))$$

2.6. Components of metabolic syndrome

Metabolic syndrome (MetS) was defined using the harmonizing definition proposed in 2009 by the American Heart Association/International Diabetes Federation [16]. Each component of the Mets is as follows: (1) central obesity; waist circumference (WC) of ≥ 90 cm for men and ≥ 85 cm for women in Koreans [13], (2) hyperglycemia; fasting plasma glucose (FPG) ≥ 100 mg/dl or the use of antidiabetes medication, (3) high blood pressure (BP); systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or the use of antihypertensive medication, (4) hypertriglyceridemia; fasting plasma triglyceride ≥ 150 mg/dl or the use of triglyceride-lowering medication, and (5) reduced high-density lipoprotein cholesterol; fasting level < 50 mg/dl (female) and 40 mg/dl (male) or drug therapy for raising HDL.

2.7. Liver ultrasound

Liver ultrasonography (iU22, Philips Healthcare) was performed by experienced radiologists at Pusan National University Yangsan Hospital. The diagnosis of fatty liver was classified into five groups as mild, mild to moderate, moderate, moderate to severe, or severe based on standard criteria, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, and bright vessel walls [17].

2.8. Atherosclerosis

Ankle-brachial index (ABI) and baPWV were measured using an oscillometric sphygmomanometer (VP-1000 plus; Omron Colin) by a trained technician in accordance with the manufacturer's recommendations [18].

2.9. Statistical analysis

Data were presented as the mean ± standard deviation, median (range), or frequency (percent). Normality of continuous variables was assessed by the Shapiro-Wilk test. Comparison between groups was done with two-sample *t*-test or Mann-Whitney *U* test and χ^2 test or Fisher's exact test for continuous and categorical variables, respectively. Correlations between parameters were calculated with Spearman's correlation coefficients as appropriate. Multivariate logistic regression analysis was performed to assess the impact of coronary artery stenosis on CCTA. ROC curves were used for comparison of the diagnostic value for CCTA stenosis between the cardio-metabolic biomarkers and to find the optimal cut-off values of each biomarkers. Also, sensitivity, specificity and Youden index [19] using the cut-off points were calculated through ROC curve analysis. *P* values < .05 were considered significant. All analyses were performed using SPSS ver. 21) and MedCalc ver. 9.6.4.0.

Table 1
Demographic and anthropometric characteristics in the groups with and without coronary computed tomography angiography stenosis.

	Total			baPWV subgroup		
	No stenosis (*n* = 151)	Stenosis (*n* = 49)	P value	No stenosis (*n* = 80)	Stenosis (*n* = 23)	P value
Age (y)	50 ± 8	56 ± 9	< 0.001	50 ± 8	57 ± 9	< 0.001
Male, *n* (%)	107 (70.9)	39 (79.6)	NS	60 (75.0)	18 (78.3)	NS
Smoker, *n* (%)	50 (33.1)	13 (26.5)	NS	34 (42.5)	5 (21.7)	NS
Drinker, *n* (%)	101 (66.9)	33 (67.3)	NS	53 (66.3)	15 (65.2)	NS
Medication						
DM, *n* (%)	8 (5.3)	5 (10.2)	NS*	5 (6.3)	3 (13.0)	NS*
Hypertension, *n* (%)	31 (20.5)	15 (30.6)	NS	15 (18.8)	6 (26.1)	NS*
Dyslipidemia, *n* (%)	3 (2.0)	7 (14.3)	0.002*	2 (2.5)	3 (13.0)	NS*
Fatty liver, *n* (%)	55 (36.4)	26 (53.1)	0.039	32 (40.0)	14 (60.9)	NS
Anthropometric marker						
BMI (kg/m^2)	24.2 (17.5–35.4)	24.5 (20.3–38.4)	NS	24.3 (17.5–35.4)	23.7 (22.3–29.2)	NS
SAD (cm)	19.0 (14.0–27.5)	20.5 (16.0–29.0)	0.004	19.5 (15.0–27.5)	20.0 (17.5–29.0)	NS
WC (cm)	87.0 (67.5–110.0)	90.0 (76.0–123.0)	0.001	88.5 (69.0–110.0)	91.0 (77.0–105.0)	0.186
Visceral fat area (cm^2)	123.6 (21.6–238.8)	147.7 (63.4–307.4)	< 0.001	131.8 (28.4–238.8)	139.2 (85.9–217.6)	0.092

DM, diabetes mellitus; BMI, body mass index; SAD, sagittal abdominal diameter; WC, waist circumference.
Data are expressed as the mean ± SDs, median (range), or frequency (percent). *P* values were determined using the two-sample *t*-test, Mann-Whitney *U* test, χ^2, or Fisher's exact test*.

3. Results

Demographic and anthropometric characteristics were presented in Table 1. Subjects with CCTA stenosis were older (50 ± 8 vs. 56 ± 9 y; *P* < .001) and more likely to have or treat dyslipidemia (2.0 vs. 14.3%, *P* = .002). Predictors of central obesity such as SAD, WC, and VFA were higher in the CCTA stenosis group (*P* = .004, *P* = .001, and P < .001, respectively) although BMI was not significantly different between subjects with and without CCTA stenosis. MetS was observed at a higher rate in the CCTA stenosis group (*P* = .038, data not shown). Various parameters between the groups with and without CCTA stenosis are shown in Table 2. Glucose, GGT, and uric acid were higher in the CCTA stenosis group (*P* = .017, *P* = .004, and *P* = .039, respectively). In subgroup analysis, there was no difference between the groups with and without CCTA stenosis except age (Tables 1, 2).

Fig. 1 shows Spearman's correlation coefficient for coronary vascular and metabolic disease related biomarkers. Coronary artery stenosis detected with CCTA had a positive correlation with the other seven variables (*P* < .001 for age and VFA, and *P* < .05 for the others).

Univariate and multivariate analyses were performed to assess whether metabolic disease-related variables were independent prognostic factors of CCTA stenosis (Table 3). On univariate analysis, VFA, GGT, uric acid, and MetS with four or more diagnostic components were associated with CCTA stenosis (odds ratio [OR] for VFA 1.016, 95% confidence interval [CI] 1.007–1.025; OR for GGT 1.005, 95% CI

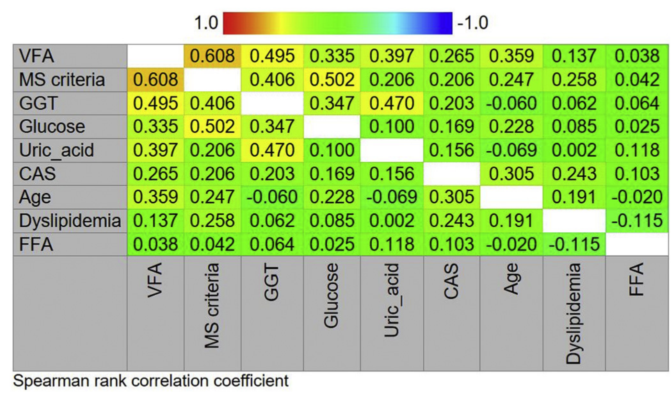

Fig. 1. Correlogram of Spearman rank correlation coefficients for coronary vascular and metabolic disease related traits. VFA, visceral fat area; MS, metabolic syndrome; GGT, γ-glutamyl transferase; FL, fatty liver; CAS, coronary artery stenosis. CAS had a positive correlation with the other variables (*P* < .001 for age and VFA, and *P* < .05 for the others).

Table 2
Various parameters of the groups with and without coronary computed tomography angiography stenosis.

	Total			baPWV subgroup		
	No stenosis (n = 151)	Stenosis (n = 49)	P- value	No stenosis (n = 80)	Stenosis (n = 23)	P- value
Glucose (mg/dl)	92.0 (61.0–272.0)	97.0 (74.0–215.0)	NS	90.5 (61.0–263. 0)	100.0 (78–175)	NS
Insulin (uU/ml)	4.9 (0.5–51.2)	5.1 (1.4–18.7)	NS	4.8 (0.9–51.2)	5.6 (1.7–11.0)	NS
HOMA-IR	1.1 (0.1–22.3)	1.1 (0.3–9.8)	NS	1.0 (0.1–22.3)	1.5 (0.5–3.2)	NS
QUICKI	0.4 (0.3–0.6)	0.4 (0.3–0.5)	NS	0.4 (0.3–0.6)	0.4 (0.3–0.4)	NS
GGT (IU/l)	35.0 (10.0–340.0)	50.0 (12.0–747.0)	0.004	38.5 (11.0–340.0)	43.0 (12.0–551.0)	NS
Uric acid (mg/dl)	5.7 ± 1.5	6.2 ± 1.3	0.039	5.8 ± 1.5	6.2 ± 1.2	NS
Cystatin C (mg/l)	0.8 (0.5–1.3)	0.8 (0.5–1.2)	NS	0.8 (0.5–1.2)	0.8 (0.5–1.2)	NS
Total cholesterol (mg/dl)	214.0 (142.0–368.0)	213.0 (152.0–329.0)	NS	214.5 (142.0–368.0)	238.0 (152.0–329.0)	NS
Triglyceride (mg/dl)	112.0 (31.0–679.0)	146.0 (39.0–569.0)	NS	116.0 (38.0–679.0)	115.0 (39.0–569.0)	NS
HDLC (mg/dl)	50.0 (29.0–105.0)	49.0 (33.0–82.0)	NS	48.0 (29.0–105.0)	47.0 (37.0–82.0)	NS
LDLC (mg/dl)	135.3 ± 33.8	140.7 ± 34.5	NS	138.2 ± 34.6	146.3 ± 37.7	NS
Homocysteine (umol/l)	11.9 (5.7–25.4)	12.2 (5.9–23.3)	NS	12.3 (5.8–25.4)	12.2. (7.9–23.3)	NS
Free fatty acid (uEq/l)	598.0 (149.0–1732.0)	679.0 (268.0–1070.0)	NS	605.5 (149.0–1555.0)	742.0 (268.0–1070.0)	NS

HOMA-IR, Homeostasis model assessment insulin resistance index; QUICKI, quantitative insulin sensitivity check index. Data are expressed as the mean ± SDs or median (range). P values were determined using the two-sample *t*-test or Mann-Whitney U test.

Table 3

Univariate and multivariate logistic regression[a] for the presence of coronary artery stenosis on coronary computed tomography angiography.

	Total				baPWV subgroup			
	Univariable		Multivariable		Univariable		Multivariable	
	Odds	95% CI	Odds	95% CI	Odds	95% CI	Odds	95% CI
Dyslipidemia (1, 0)	–	–	4.677	0.948–23.077	5.850	0.915–37.407	–	–
VFA (cm^2)	1.016*	1.007–1.025	–	–	1.010	0.998–1.023	–	–
Glucose (mg/dl)	1.006	0.996–1.016	–	–	1.004	0.990–1.018	–	–
GGT (IU/l)	1.005*	1.001–1.009	1.006*	1.001–1.011	1.004	1.000–1.009	–	–
Uric acid (mg/dl)	1.262*	1.009–1.578	1.259	0.970–1.634	1.235	0.890–1.713	–	–
MetS components ≥4 (1, 0)	4.567*	1.765–11.820	–	–	4.167*	1.089–15.946	–	–
baPWV (cm/s)					1.005*	1.003–1.008	1.005*	1.003–1.008

CI, confidence interval; VFA, visceral fat area; MetS, metabolic syndrome; baPWV, brachial-ankle pulse wave velocity.

[a] Adjusted for age. Backward conditional multivariable logistic regression model (probability for stepwise: entry: 0.05 removal: 0.20).

* $P < .05$.

1.001–1.009; OR for uric acid, 1.262, 95% CI 1.009–1.578; and OR for MetS with four or more diagnostic components 4.567, 95% CI 1.765–11.820, $P < .05$ for all). On multivariate analysis, after adjustment for age, only GGT was significantly and independently associated with CCTA stenosis (OR 1.006, 95% CI 1.001–1.011, $P = .026$). In subgroup analysis, there was no difference between the groups with and without CCTA stenosis except age (Table 3). On multivariate analysis of subgroup, after adjustment for age, only baPWV was significantly and independently associated with CCTA stenosis (OR 1.005, 95% CI 1.003–1.008, $P < .05$).

Receiver operating characteristic (ROC) analysis for the individual biomarkers is shown in Fig. 2. The diagnostic accuracy for CCTA stenosis, as quantified by the area under the curve (AUC), was similar among the three variables (AUC for GGT 0.636, 95% CI 0.550–0.722, $P = .004$; AUC for uric acid, 0.605, 95% CI 0.518–0.691, $P = .028$; and AUC for VFA 0.678, 95% CI 0.595–0.762, $P < .001$). The optimal GGT, uric acid and VFA cut-off for predicting CCTA stenosis was 129.8, 29.0, and 5.5, respectively (Table 4).

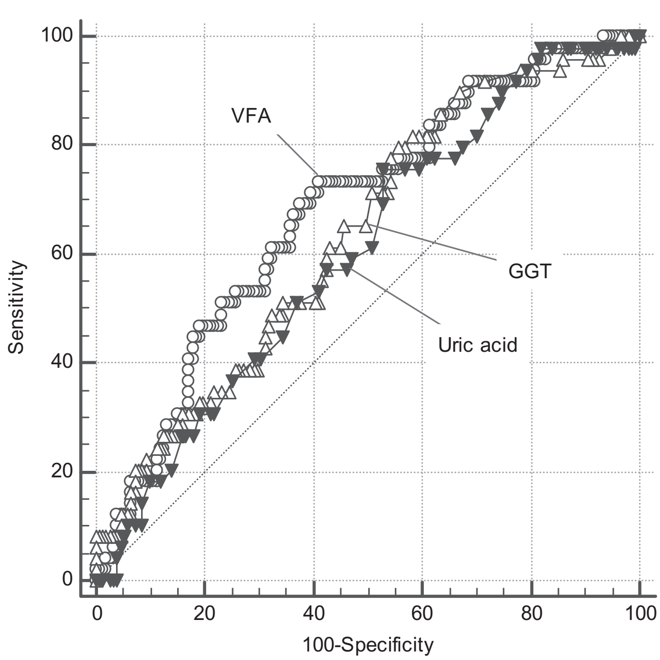

Fig. 2. Receiver-operating-characteristic curves for prediction of coronary artery stenosis on coronary computed tomography angiography. Areas under the curve were 0.636 (95% CI, 0.550–0.722; $P = .004$) for γ-glutamyl transferase (GGT), 0.605 (95% CI, 0.518–0.691; $P = .028$) for uric acid, and 0.678 (95% CI, 0.595–0.762; P < .001) for visceral fat area (VFA).

Additionally, we performed subgroup analysis of the 103 subjects with baPWV and ABI data. Among them, 23 subjects had CCTA stenosis. After adjustment for age, only baPWV was significantly and independently associated with CCTA stenosis (OR, 1.005; 95% CI, 1.003–1.008; P < .001; data not shown). The area under the ROC curve was 0.804 (95% CI, 0.714–0.895; P < .001) for baPWV. The comparison of ROC curves between baPWV and GGT was statistically significant ($P = .0034$, Fig. 3). The optimal baPWV cut-off for predicting CCTA stenosis was 1250.0 in subgroup (Table 4).

4. Discussion

We investigated the relationship between CCTA stenosis and various metabolic biomarkers and found that VFA, GGT, uric acid, and MetS with four or more diagnostic components were associated with the presence of CCTA stenosis in asymptomatic adults. After multivariate analysis, only GGT remained.

GGT is an independent predictor of the development of all-cause and CVD-related mortality in patients with or without CHD [20–22]. There are also a number of studies presenting the association of GGT with acute coronary syndrome or CVD. A meta-analysis reported that an increase of 1 U/l of natural logged GGT was related to a 20% increased risk of CHD [23]. One longitudinal 20-y study revealed that the adjusted relative risk comparing the highest GGT quartile to the lowest was 1.67 (95% CI 1.25–2.22) for CVD [24]. Our results are consistent with those of previous studies. In contrast, a recent study concluded that GGT activity tended to only marginally predict CHD. However, this study was conducted on a relatively small number of patients and over a short period of time [25].

According to prior pathology studies, as a protein catalyst in the degradation of glutathione, GGT contributes to LDL oxidation and inflammatory atheroma formation [26]. This might be one reason why GGT levels were associated with CCTA stenosis in asymptomatic individuals in the present study. This finding is in accordance with that of a recent study that included 237 patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and age and sex-matched controls. They reported that presence of significant stenosis on coronary angiography was independently associated with the GGT level (OR: 1.17), and a GGT activity > 26 U/l identified significant stenosis in patients with NSTE-ACS, with a sensitivity of 86% and a specificity of 89% [27]. On the other hand, the study was performed in asymptomatic adults, and as a result, a GGT level above 29 U/l identified significant stenosis, with a sensitivity of 79.6% and a specificity of 44.4% (Table 4).

It seems likely that association between serum uric acid concentration and presence of CAD remains controversial. Some studies found that high levels of serum uric acid were significantly associated with severity of CAD in patients with CAD [28] and that the serum uric

Table 4
Sensitivity, specificity and Youden index using sex-specific cut-off points for various parameters to predict coronary computed tomography angiography stenosis.

	Cur-off	Specificity (%)[a]	Sensitivity (%)[a]	Youden index	+LR	-LR
Total (N = 200)						
Visceral fat area (cm^2)	129.8	73.5 (58.9–85.1)	58.9 (50.7–66.9)	0.32	1.79	0.45
γ-glutamyl transferase (IU/l)	29.0	79.6 (65.7–89.8)	44.4 (36.3–52.7)	0.24	1.43	0.46
Uric acid (mg/dl)	5.5	75.5 (61.1–86.7)	47.0 (38.9–55.3)	0.23	1.43	0.52
Subgroup (n = 103)[b]						
baPWV	1250.0	100.0 (85.2–100.0)	47.5 (36.2–59.0)	0.48	1.90	0.00
Visceral fat area (cm^2)	135.3	69.6 (47.1–86.8)	55.0 (43.5–66.2)	0.25	1.55	0.55
γ-glutamyl transferase (IU/l)	102.0	30.4 (13.2–52.9)	85.0 (75.2–92.0)	0.15	2.03	0.82
Uric acid (mg/dl)	4.1	100.0 (85.2–100.0)	17.5 (9.9–27.6)	0.18	1.21	0.00

[a] Point estimates and 95% confidence intervals (in parentheses).
[b] had brachial-ankle pulse wave velocity (baPWV) data.

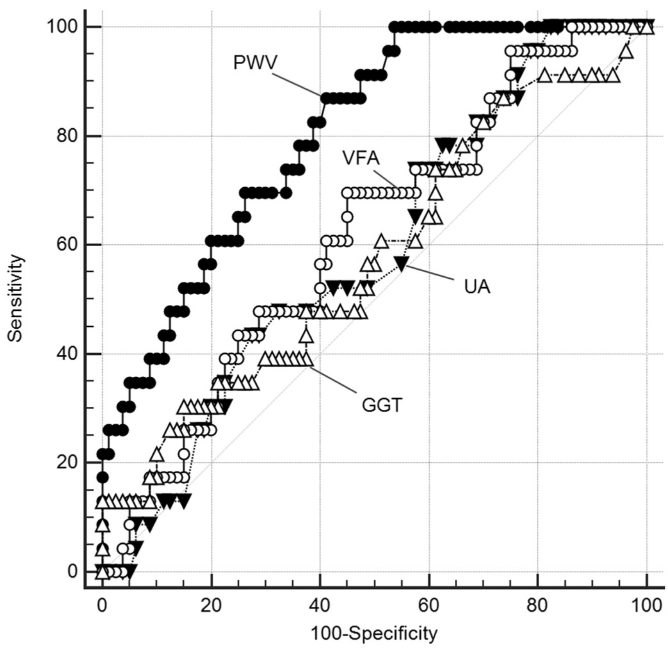

Fig. 3. Receiver-operating-characteristic (ROC) curves for prediction of coronary artery stenosis on coronary computed tomography angiography in the subgroup analysis. Area under the curve was 0.804 (95% CI, 0.714–0.895; P < .001) for brachial-ankle pulse wave velocity (baPWV). P = .0034 between baPWV and γ-glutamyl transferase (GGT) by pairwise comparison of ROC curves. UA, uric acid.

acid was directly linked to angiographic evidence of CAD in women [29]. On the other hand, one meta-analysis concluded that measurement of serum uric acid levels is unlikely to usefully enhance the prediction of CHD [30]. Another recent study demonstrated that serum uric acid levels were negatively associated with the presence of CHD in men [31]. In the present study, after multivariate logistic regression, the relationship between uric acid and CCTA stenosis was not statistically significant. This discrepancy between the previous studies could be explained in part by the fact that the subjects were predominantly men. Traditionally, obesity was considered a risk factor for coronary artery disease [32]. WC, SAD and fatty liver were all evaluated as included in Table 1, but as is well known, WC, SAD and fatty liver are all indexes that indirectly evaluate VFA. In this study, we measured VFA directly, so the multivariable analysis included only VFA. Previous studies reported that central obesity, especially the abdominal visceral adipose tissue, correlates with prevalence of CAD and mortality [33,34]. We also found the association between VFA and CCTA stenosis in the univariable regression, but this association was no longer significant after multivariable regression. MetS comprises the presence of three or more classic cardiovascular risk components [16]. A previous study concluded that the number of MetS risk components seems to be more informative than the MetS classification when determining risk of CHD in clinical practice [35]. We found a significant association between four or more MetS components and CCTA stenosis, however the relationship was not significant after adjustment for age.

baPWV is considered reflective of not only the progression of individual atherosclerosis but also the overall cardiovascular risk. A meta-analysis of 12 cohort studies concluded that baPWV predicts the risk of total cardiovascular events and all-cause mortality and showed that an increase in baPWV by 1 m/s corresponds with an increase in total cardiovascular events, cardiovascular mortality, and all-cause mortality of 12%, 13%, and 6%, respectively [36]. A recent study of an asymptomatic population reported that subjects with high baPWV had a significantly higher prevalence of composite coronary and carotid atherosclerosis on coronary computed tomography and carotid ultrasonography. However, multivariable logistic regression analyses failed to show baPWV as an independent risk predictor for composite coronary and carotid atherosclerotic changes [37]. Additionally, in our subgroup analysis of 103 subjects with baPWV and ABI data, we demonstrated that baPWV was independently associated with the presence of CCTA stenosis in the subgroup analysis, and this corresponds with previous studies [38]. In subgroup analysis, a baPWV level above 1250 cm/s identified significant stenosis in asymptomatic adults, with a sensitivity of 100.0% and a specificity of 47.5% (Table 4).

Subgroup analysis can give additional informative information if used properly [39]. As a result, there were significant differences in glucose, GGT or uric acid found in the total group between subjects with CAS and no-CAS disappeared in the baPWV subgroup (n = 103). Also, in the multivariable analysis of the baPWV subgroup, the predictive capacity of CAS found in the total group for GGT and uric acid disappeared. Only baPWV was predictive of CAS. Those results can be explained, partially, as follows: In the present study, we separately analyzed the subgroup of patients in whom the measurement of baPWV was available. The baPWV subgroup was not generated by stratified randomization among the entire group [40]. Therefore, the demographic, anthropometric and biochemical characteristics of the two groups (no stenosis vs. stenosis) in the baPWV subgroup (n = 103) differ in part from those of the two groups (no stenosis vs. stenosis) in the total (N = 200) (Tables 1, 2). It might, therefore, be necessary to reconfirm these findings with a larger data set.

Our study is limited by its retrospective, cross-sectional study design, which cannot determine causality. Further investigation with a cohort study is warranted. GGT activity is quantitatively related to alcohol consumption. Therefore, if the drinkers were classified as light, moderate and heavy drinkers, the statistical power of multivariate analysis would have been better, but unfortunately the alcohol consumption data was not collected in the present study. Another limitation is that the number of subjects with CCTA may not be sufficient to analyze the association with the degree of stenosis. However, we compared and analyzed various biomarkers, such as homocysteine, cystatin C, free fatty acid, HOMA-IR, QUICKI, and SAD.

In this study, we found that GGT and arterial stiffness as determined by baPWV were associated independently with the presence of CCTA stenosis in apparently healthy adults in a cross-sectional study. Our findings suggest that GGT and baPWV may be utilized as easily accessible screening tools for detecting the presence of CCTA stenosis in asymptomatic individuals, although longitudinal studies are needed in the future. The etiology of CCTA stenosis is thought to be a combination of genetic, metabolic, and environmental factors. Therefore, a more comprehensive approach is needed to identify and optimally manage CCTA stenosis.

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