

Cardiac computed tomography improves prediction of long-term cardiovascular events: a retrospective cohort study of type 2 diabetic with higher cardiovascular risk

Zhijie Jian

the First Affiliated Hospital of Xi'an Jiaotong University

Zhe Liu

the First Affiliated Hospital of Xi'an Jiaotong university

Li Zhou

the First affiliated Hospital of Xi'an Jiaotong Universty

Ningning Ding

the First Affiliated Hospital of Xi'an Jiaotong University

Hui Zhang

the First Affiliated Hospital of Xi'an Jiaotong University

Peining Liu

the First Affiliated Hospital of Xi'an Jiaotong University

Bolin Li

the First Affiliated Hospital of Xi'an Jiaotong University

Yue Wu

the First Affiliated Hospital of Xi'an Jiaotong University

Ge Yan

the First Affiliated Hospital of Xi'an Jiaotong University

Yun Zhang

the First Affiliated Hospital of Xi'an Jiaotong University

Bolang Yu

the First Affiliated Hospital of Xi'an Jiaotong University

Jian Yang (✉ yj1118@mail.xjtu.edu.cn)

The First Affiliated Hospital of Xi'an Jiaotong University <https://orcid.org/0000-0003-4250-1391>

Research article

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Abstract

Background: The value of cardiac computed tomography (CT) for screening and risk stratification in patients with type 2 diabetes mellitus (DM) who are at a higher cardiovascular risk is unclear. Thus, this study aims to investigate the efficacy of cardiac CT in predicting long-term cardiovascular events (CVEVs) in this subset of patients.

Methods: Type 2 diabetic with a higher cardiovascular risk who underwent cardiac CT between 2012 and 2014 were included in this study. Cardiac CT was performed, and coronary artery calcium score, location and extent of lesion, stenosis severity, plaque composition, and epicardial adipose tissue (EAT) volume were assessed. The endpoints were a composite of CVEVs (cardiac death, non-fatal myocardial infarction, or coronary revascularization, non-fatal stroke, hospitalization for unstable angina, and hospitalization for congestive heart failure). Potential predictors of CVEVs were identified. Predictive models were created and compared.

Results: CVEVs occurred in 26.8% of the patients. Independent predictors of CVEVs included diabetes duration (odds ratio [OR]=10.003), mean creatinine level (OR=3.845), hypertension (OR=3.844), atheroma burden obstructive score (OR=14.060), segment stenosis score (OR=7.912), and EAT volume (OR=7.947). The model including cardiac CT data and clinical parameters improved the prediction of CVEVs, with an area under the receiver operating characteristic curve of 0.912 (95% confidence interval 0.829–0.963; $p < 0.05$) for the prediction of the study endpoints.

Conclusion: Cardiac CT showed a great value in risk stratification for patients with diabetes with higher cardiovascular risk. Cardiac CT data may help predict CVEVs and potentially improve outcomes.

Background

Coronary artery disease (CAD) is the leading cause of death and disability in patients with diabetes, and diabetes accelerates the process of atherosclerosis[1, 2]. However, a marked heterogeneity of risk among patients with diabetes exists[3, 4]. According to the 2019 European Society of Cardiology (ESC) guidelines[4], patients with D2M and established cardiovascular disease (CVD), other target-organ damage, or three or more major risk factors should be considered to be at a very high risk; those with DM duration ≥ 10 years without target-organ damage plus any other additional risk factor, to be at a high risk. High-risk patients are more likely to have left main or diffuse lesions and more severe calcification[5]. The guidelines emphasized differentiated treatment options for patients with different risk stratifications. Hence, the anatomical pattern and plaque characteristics of CAD in patients with DM may influence the prognosis and response to [intervention](#).

Coronary computed tomography angiography (CCTA) has been well validated as a non-invasive test that provides comprehensive information on coronary atherosclerosis, including location, severity, and characteristics of plaques[6]. Cardiac computed tomography (CT) could quantify epicardial adipose tissue (EAT) volume, which has been indicated as an inflammatory biomarker in D2M[7]. Whether cardiac

CT, which includes features of epicardial fat, is useful in the stratification of patients at a higher cardiovascular risk is unknown.

Thus, we sought to retrospectively analyze the risk factors for long-term cardiovascular events (CVEVs) in diabetic patients with higher cardiovascular risk (3–6 years' follow-up) and aimed to investigate the long-term prognostic value of cardiac CT in these patients.

Methods

Study population

In this study, 173 hospitalized patients with D2M and suspected CAD were consecutively recruited in the First Affiliated Hospital of Xi'an Jiaotong University between 2012 and 2014. The inclusion criteria included the following: (1) CCTA performed within 1 month before or after hospitalization; (2) patients under the very high risk and high risk categories according to the 2019 ESC guidelines[4]. Very high risk was defined as a history of established CVD, other target-organ damage (i.e., proteinuria, renal impairment [eGFR >30 mL/min/1.73 m²], left ventricular hypertrophy, or retinopathy), or three or more major risk factors [age, hypertension, dyslipidemia, smoking, obesity). High risk was defined as patients with D2M duration ≥10 years without target-organ damage plus any other additional risk factors; and (3) medical records with adequate baseline clinical status. The exclusion criteria were (1) active cancer or blood disease, immune disease, thyroid dysfunction; (2) previous valvular heart disease, congenital heart disease, myocardial infarction, cerebral infarction, heart failure, coronary stent, or bypass therapy; and (3) subjects with poor CCTA image quality, with insufficient clinical data, or failing to complete follow-up (Fig. 1). This retrospective study was approved by the local institutional review board.

Data collection

We obtained data on demographic characteristics, traditional CVD risk factors, diabetes characteristics, laboratory tests, and medical treatment on admission from electronic medical records.

Outcome data

CVEVs including non-fatal myocardial infarction (MI), non-fatal stroke, cardiac deaths, hospitalization for unstable angina, or hospitalization for congestive heart failure were defined as endpoints. Participants were followed up by telephone interviews and hospital records. In patients who experienced two CVEVs, the first event was chosen. When two CVEVs occurred simultaneously, the worse event was chosen (i.e., death over MI, MI over revascularization, and revascularization over hospital readmission). All those CVEVs and outcomes were performed by individuals blinded to the patients' CT data.

CT data acquisition

Cardiac CT was performed using a 128-section multidetector CT (Brilliance iCT; Philips, Medical Systems, Best, The Netherlands). First, the patients underwent non-enhanced prospective electrocardiography

(ECG)-gated sequential scan to measure the coronary artery calcium score. Thereafter, CCTA was performed using retrospective ECG-gated tube current modulation. A weight-dependent bolus of 70–90 ml iodine contrast agent (iohexol [350 mg iodine/ml]; GE Healthcare, Shanghai, China) was administered at a speed of 4 to 5.5 ml/s, which was followed by a 30-ml saline flush. Reconstructed images were at 75% and 45% of the RR interval.

CT Image interpretation

All the scans were retrospectively analyzed on an offline workstation (EBW 4.4, Philips Medical Systems, Best, The Netherlands). Total calcium burden in the coronary arteries was quantified using the scoring algorithm proposed by Agatston et al.[8], and predefined calcium score categories (0, 1–100, 101–400, and >400) were employed[9].

The coronary artery tree was divided into 16 segments according to the Society of Cardiovascular Computed Tomography guidelines[10]. The degree of stenosis was classified as significant if the patient had >50% diameter stenosis on the longitudinal images. We evaluated the plaque extent and stenosis rate by summing the number of epicardial vessels with significant stenosis (i.e., no plaque, no obstruction, 1-vessel disease, 2-vessel disease, 3-vessel disease). Atheroma burden obstructive score (ABOS), segment involvement score (SIS), and segment stenosis score (SSS) were measured. ABOS was defined as the number of plaques with >50% stenosis in the entire coronary artery tree. SIS was calculated as the total number of coronary artery segments that exhibited plaque, irrespective of the degree of luminal stenosis within each segment (minimum = 0; maximum = 16)[11]. SSS was used as a measure of the overall extent of the coronary atherosclerosis. To determine the SSS, each coronary segment was graded based on Coronary Artery Disease—Reporting and Data System (scores ranged from 0 to 5)[12]. The extent scores of all 16 segments were then summed to yield a total score ranging from 0 to 80.

Moreover, coronary plaques were classified as calcified (composed exclusively of a high-density material >130 HU), non-calcified (composed exclusively of a material with a density \leq 130 HU), and mixed (with components of both calcified and non-calcified plaques)[13]. Vulnerable plaques were confirmed by the following characteristics: positive remodeling, low-attenuation plaque, spotty calcification, and the napkin-ring sign[14].

EAT depot was defined as the fat tissue between the outer wall of the myocardium and the visceral layer of the pericardium[15]. Epicardial fat volume was assessed using a dedicated workstation (Advantage Workstation 4.6; GE Healthcare). The pericardium was manually traced from the right pulmonary artery to the diaphragm to determine a region of interest. Within the region of interest, fat was defined as pixels within a window of –190 to –30 HU. Overall, only pixels with Hounsfield units equivalent to fat within the pericardial sac were counted as EAT (Fig. 2). Reproducibility was excellent (for interobserver variability, intraclass correlation coefficient=0.889, $p<0.05$; for intraobserver variability, intraclass correlation coefficient=0.814, $p<0.05$).

Two experienced computed tomography readers who were blinded to the clinical characteristics and procedural outcomes and to each other's assessment measured the characteristics of CTA and EAT volume separately. In cases of discrepancy, consensus was reached by discussion.

Statistical analysis

Patient characteristics were expressed as mean±standard deviation for continuous data and counts and proportions for categorical data. Kolmogorov-Smirnov test was used to test the normal distribution of the continuous variables. Chi-square test, Student's *t*-test, and non-parametric equivalent tests were employed when appropriate. A comparative analysis of diabetes with and without CVEVs was performed to evaluate potential predictors. The independent predictors of CVEVs were identified by multivariate regression analysis.

The following prediction models were created through multivariate analysis (binary logistic regression with the method Enter) using event predictors: clinical model, which includes diabetes duration, mean creatinine level, and hypertension); CT model, which includes ABOS, SSS, and EAT volume; and a combined model, which is composed of parameters included in both the clinical and CT models. The regression coefficients obtained were used to calculate predicted risks according to prediction models.

SPSS Statistics for Windows v18.0 (SPSS Inc., Chicago, USA) and MedCalc Statistical Software version 13.0 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014) were used for data analysis. A two-tailed *p* value <0.05 indicated statistical significance.

Results

Study endpoints

A total of 82 patients were analyzed in this study. A median clinical follow-up of 56 months (range 41–76) was performed. During this period, 22 CVEVs (26.8%) were reported: one cardiac death (1.2%), four non-fatal MI (4.9%), two coronary revascularizations (2.4%), five non-fatal strokes (6.1%), and ten hospitalization for unstable angina (12.2%).

Patient characteristics

Mean age of the study population was 59±8.0 years, and 48 (58.5%) patients were men. Mean diabetes mellitus duration was 6.7±6.0 years, and mean HbA1c value was 7.5±1.4%. The demographic, clinical, and laboratory characteristics and therapeutic approach at baseline were compared between patients with and those without CVEVs (Table 1). Patients with CVEVs had a significantly longer diabetes duration and higher serum creatine levels than those without CVEVs. The patients with a CVEV were more likely to have hypertension and be treated with ACE inhibitor/ARB.

Table 1

Baseline characteristics Between Subjects With and Without a CVEV

Characteristic	Overall(n=82)	No CVEV(n=60)	CVEV(n=22)	P Value
Demographics				
Mean age (yrs)	59±8.0	58.8±7.7	62.3±8.1	.083
Male*	48(58.5)	34(56.7)	14(63.4)	.621
Mean BMI (kg/m ²)	24.6±2.7	24.8±2.6	24.2±3.1	.376
LV ejection fraction	67.5±6.1	68.0±5.4	66.0±7.6	.130
Hypertension*	31(37.8)	18(30)	13(59.1)	.016
Family history of CAD*	11(13.4)	7(11.7)	4(18.2)	.332
Current smoker*	30(36.6)	23(38.3)	7(31.8)	.392
Diabetic characteristics				
Duration of diabetes(yrs)	6.7±6.0	5.6±4.5	9.7±8.3	.004
Mean HbA1c level (%)	7.5±1.4	7.9±1.5	7.2±1.3	.058
Fasting blood glucose(mmol/L)	8.0±2.1	7.9±1.9	8.4±2.6	.498
Postprandial plasma glucose(mmol/L)	13.1±3.4	12.9±3.2	13.4±3.9	.572
Other laboratory findings				
Mean creatinine level (µmol/L)	59.6±14.5	57±13.4	66.1±15.7	.013
Total cholesterol (mmol/L)	4.1±1.0	4.0±1.1	4.1±0.75	.614
LDL cholesterol (mmol/L)	2.4±0.8	2.3±0.8	2.5±0.9	.683
HDL cholesterol (mmol/L)	1.0±0.2	1.1±0.4	0.9±0.2	.244
Triglycerides (mmol/L)	1.9±1.1	1.9±1.2	1.7±1.0	.473
Medical treatment				
Insulin therapy*	24(29.3)	16(26.7)	8(36.4)	.421
Oral hypoglycaemic agents*	71(86.6)	54(90.0)	17(77.3)	.136
Antiplatelets*	66(80.5)	46(76.7)	20(90.1)	.152
Statins*	67(81.7)	50(83.3)	17(77.3)	.532
ACE inhibitor/ARB*	21(25.6)	10(16.7)	11(50)	.002
Beta-blocker*	25(30.5)	20(33.3)	5(22.7)	.358
Percutaneous revascularisation *	2(2.4)	1(1.7)	1(4.5)	.457

Note.—Except where indicated, data are means ± standard deviations, *Data are numbers of patients, with percentages in parentheses. BMI = body mass index

Coronary computed tomography angiography findings

Patients with D2M with a CVEV had a higher EAT volume than those without a CVEV ($p = 0.007$). Obstructive CAD, which was defined as >50% luminal stenosis, and vulnerable plaque were found more frequently in those with a CVEV (obstructive, $p = 0.013$; vulnerable, $p = 0.029$). Compared to those without a CVEV, those with a CVEV had a significantly higher ABOS ($p = 0.016$) and SSS ($p = 0.049$). Results of the subgroup analysis are summarized in Table 2.

Table 2
Differences in Cardiac CT findings Between Subjects With and Without a CVEV

Finding	Overall (n=82)	No CVEV(n=60)	CVEV (n=22)	P Value
Total Agatston score *	101.6±290.9	72.2±261.9	181.8±352.9	.194
Calcium score categories				.072
0	44(53.6)	35(58.3)	10(45.5)	
0-100	21(25.6)	16(26.7)	4(18.2)	
101-400	11(13.4)	6(10)	5(22.7)	
>400	6(7.3)	3(5)	3(13.6)	
Presence of plaque	63(76.8)	44(73.3)	19(86.4)	.254
SIS*	2.4±2.3	2.1±2.1	3.0±2.8	.222
Plaque range				.369
1-vessel	22(26.8)	14(23.3)	8(36.4)	
2-vessel	25(30.5)	20(33.3)	5(22.7)	
3-vessel	16(19.5)	10(16.7)	6(27.3)	
Character of plaque				
Calcified plaque	38(46.3)	25(41.7)	13(59.1)	.213
Non-calcified	46(56.1)	33(55.0)	13(59.1)	.805
Mixed plaque	13(15.8)	7(11.7)	6(27.3)	.100
Stability of plaque				.029
Vulnerable plaque	8(9.8)	3(5.0)	5(22.7)	
Stable plaques	74(91.2)	57(95.0)	17(77.3)	
Stenosis Severity				.013
Obstructive plaques	25(30.5)	12(20)	13(59.1)	
Nonobstructive plaques	57(69.5)	48(80)	9(40.1)	
ABOS*	0.48±1.0	0.25±0.65	1.09±1.5	.016
SSS*	4.6±5.1	3.27±3.2	8.23±7.3	.049
EAT volume*	147.3±41.9	139.9±37.8	167.5±44.5	.007

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. * Data are means ± standard deviations. SIS—the segment involvement score, ABOS—the atheroma burden obstructive score, SSS—the segment stenosis score, EAT = Epicardial adipose tissue

Predictors of CVEVs by multivariate regression

All the predictors of CVEVs on univariate analysis were included in the multivariate regression analysis. Diabetes duration (odds ratio [OR] 10.003, 95% confidence interval [CI] 1.044–1.202; $p = 0.002$), mean creatinine level (OR 3.845, 95% CI 1.000–1.075; $p = 0.049$), hypertension (OR 3.844, 95% CI 1.000–10.056; $p = 0.020$), ABOS (OR 14.060, 95% CI 1.359–2.661; $p = 0.000$), SSS (OR 7.912, 95% CI 1.029–1.175; $p = 0.005$), and EAT volume (OR 7.947, 95% CI 1.006–1.034; $p = 0.005$) were independently associated with CVEVs (Table 3).

Table 3
Predictors of CVEVs by multivariate regression

Different prediction models were created based on clinical features and CT predictors of CVEVs. Receiver operating characteristic curve analysis for the isolated parameters and the different models is presented in Fig. 3 and Table 4.

Predictors	OR	95%CI	P
Duration of diabetes	10.003	1.044-1.202	0.002
Mean creatinine level	3.845	1.000-1.075	0.049
Hypertension	3.844	1.000-10.056	0.020
ABOS	14.060	1.359-2.661	0.000
SSS	7.912	1.029-1.175	0.005
EAT volume	7.947	1.006-1.034	0.005

The clinical parameters showed a good discriminatory power for identifying CVEVs. The CT model showed a higher area under the receiver operating characteristic curve (AUC), higher specificity, and lower sensitivity than the clinical model. The combined model showed the highest discriminatory power for identifying and excluding CVEVs and had the highest AUC among the three prediction models (AUC 0.912, 95% CI 0.829–

0.963). Moreover, the combined model showed a trend for a higher discriminatory power compared to the clinical model (difference between AUC 0.120, 95% CI 0.021–0.220; $p = 0.02$). However, the combined model did not perform significantly better than CT model (difference between AUC 0.074, 95% CI –0.103–0.157; $p = 0.09$) (Table 4).

Table 4
Receiver operating characteristic (ROC) curve evaluation for CVEV prediction

Prediction of CVEV	AUC	95% CI	Specificity	Sensitivity
Clinical_mode	0.792	0.688 to 0.874	60.0	90.1
CT_model	0.839	0.741 to 0.911	76.7	77.3
Combined_model	0.912	0.829 to 0.963	76.7	95.5
ROC comparisons-Combined model vs:	AUC (difference)	95% CI	P	-
Clinical_mode	0.120	0.021 to 0.220	0.02	-
CT_model	0.074	-0.103 to 0.157	0.09	-

Note.—Clinical model: composed by duration of diabete, mean creatinine level and hypertension; CT model: composed by ABOS, SSS and the EAT volume; Combined model: composed by parameters included in both Clinical and CT models.

Areas under ROC curves (AUC), 95% confidence intervals (CI) and the significance level (p) are presented. Results presented in this table are related to curves showed in Figure 3.

Discussion

The main findings of this study were as follows: (1) In patients with D2M and a higher cardiovascular risk, those with longer diabetes duration, combined with renal dysfunction and hypertension, are more likely to have subsequent CVEVs. (2) ABOS, SSS, and EAT volume by cardiac CT could predict cardiac events in type 2 diabetic with higher cardiovascular risk. (3) Cardiac CT showed an incremental prognostic utility over clinical risk factors for predicting CVEVs in these patients.

CVEVs remains the first causes of death in patients with D2M[16]. Our study suggest that a long course and the heavy burden of diabetes and complications may contribute to poor prognosis in patients with D2M, which is consistent to the results of some previous studies[17]. Thus, to prevent future cardiovascular events in patients with D2M, identifying patient subgroups with high-risk features and improving the prognosis through appropriate evidence-based treatment are crucial.

Based on the diagnostic accuracy of CCTA for CAD, CCTA has a long-term prognostic value for predicting CVEVs in patients with suspected CAD[18]. Despite the heterogeneity between study endpoints, study

population, and length of follow-up, previous systematic literature reviews and meta-analyses[19, 20] confirmed that the presence and extent of CAD on CCTA are strong, independent predictors of CVEVs in asymptomatic individuals with D2M. In our study, obstructive CAD in patients with D2M were associated with a poor prognosis, which is consistent with the findings of previous studies[21]. Moreover, ABOS, which represents the involvements of coronary obstructive stenosis, showed the highest OR (14.060) among all risk factors and was an independent predictor of CVEVs. In addition, the SSS, which represents the overall extent of coronary atherosclerosis, was higher in patients with CVEVs than those without. These results suggest that the overall atherosclerotic burden of coronary arteries has a greater long-term prognostic value than obstructive CAD in type 2 diabetic with higher cardiovascular risk.

Regarding plaque composition, Yong-Seop Kwon et al.[22] showed that mixed plaque types significantly contribute to the total plaque burden in patients with D2M compared to those without diabetes. The ROMICAT-II trial study[14] indicated that high-risk plaques on CCTA increases the likelihood of acute coronary syndrome(ACS), independent of significant CAD and clinical risk assessment. In our study, no significant difference in the composition of coronary plaque between those with and those without CVEVs was found. Nevertheless, the incidence of coronary vulnerable plaque was significantly higher in patients with diabetes with CVEVs than in those without. However, the presence of vulnerable plaques was not statistically significant in the multivariate logistic regression analysis. A possible explanation for this discrepancy could be the different investigated patient populations.

The Framingham Heart Study[23] demonstrated a strong association between EAT and coronary plaque burden as well as the presence of CAD, which could be explained by the strong association of EAT with cardiovascular risk factors, such as regional adiposity, inflammation, and oxidative stress[24]. The Heinz Nixdorf Recall Study[25] demonstrated that epicardial fat is associated with fatal and non-fatal coronary events in the general population, independent of traditional cardiovascular risk factors, and complements information from cardiac CT. Some studies found that patients with D2M have increased epicardial volume, which is an independent predictor of CAD[26]. Our study showed the EAT volume is an independent predictor of CVEVs. Moreover, the results implied that the myocardial dysfunction and atherosclerosis of the coronary arteries are due to changes in the endocrine function of the EAT and inflammatory conditions in patients with D2M.

Based on the aforementioned results, we added cardiac CT features to clinical parameters in CVEV prediction, which in turn improved the discriminatory power for type 2 diabetic with a higher cardiovascular risk who are at risk of CVEVs. Hence, cardiac CT features, including ABOS, SSS, and EAT volume, could predict CVEVs in those patients. These findings suggest that cardiac CT may be a potential tool in discriminating patients with D2M at a high cardiovascular risk, who may benefit from early and potentially more aggressive treatment with statins, antiplatelet agents, revascularization, and targeted treatment of systemic inflammation, as well as tight control of glucose levels.

This study has some limitations. This is an observational single-center study with a limited number of enrolled patients, and CCTA was performed at the discretion of the attending endocrinologist; thus,

selection bias was possible. Furthermore, the outcomes might be confounded by the efficacy of treatment decisions and the patients' attitude toward treatment, compliance, and self-management.

Conclusion

Cardiac CT could provide additive prognostic value for patients with D2M with a higher cardiovascular risk. These findings indicate the potential of integrating clinical risk factors and cardiac CT data in improving risk stratification, which may in turn help establish a more individualized therapy and could possibly lead to better outcomes. Nevertheless, larger outcome studies are warranted.

Abbreviations

ABOS: atheroma burden obstructive score; ACS: acute coronary syndrome; AUC: area under the receiver operating characteristic curve; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CI—confidence interval; CT: computed tomography; CVD: cardiovascular disease; CVEVs: cardiovascular events; DM: diabetes mellitus; D2M—type 2 diabetes mellitus; EAT: epicardial adipose tissue; ECG: electrocardiography; ESC: [European Society of Cardiology](#); MI: myocardial infarction; OR: odds ratio; SIS: segment involvement score; SSS: segment stenosis score

Declarations

Ethics approval and consent to participate

Approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiaotong University with a waiver of informed consent due to the retrospective nature of this investigation

Consent for publication

Not applicable

Competing interests

The authors have no competing interests.

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Authors' Contribution

ZJ,BY and JY participate in the study concept and design; ZJ,LZ and PL analyzed and interpreted the patient data; GY,HZ and YZ performed CT acquisition; BL and ND collected clinical data and performed

phone call follow-up for the cardiovascular events; ZJ,ZL performed statistically analysis and drafting of the manuscript; BY ,JY and YW revised manuscript. All authors have read and approved the manuscript.

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Author details

¹Department of Radiology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, P.R. China;²Department of Cardiovascular Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, P.R. China

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Figures

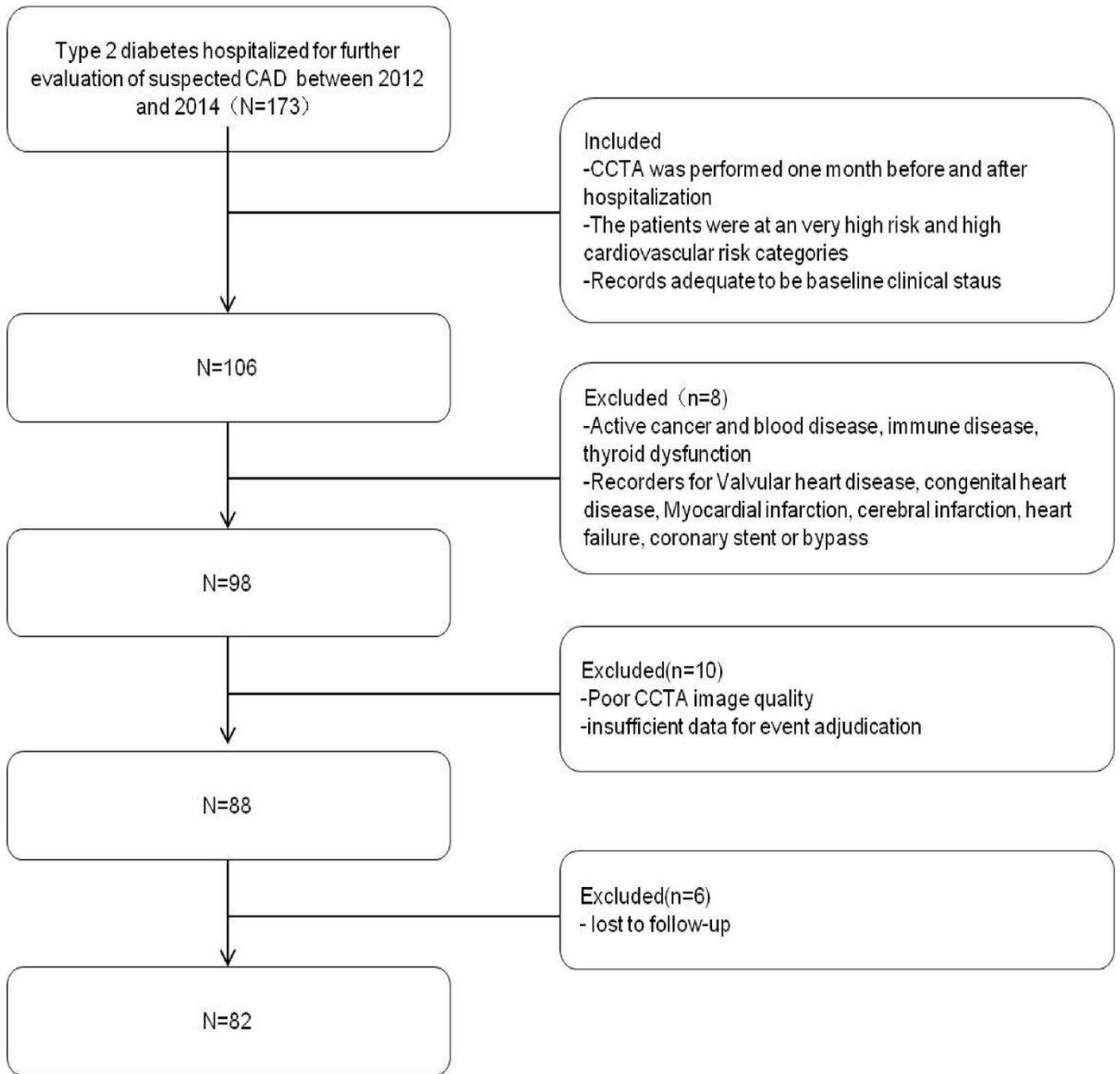


Figure 1

Flowchart of study design. CCTA indicates computed tomography coronary angiography



Figure 2

Epicardial adipose tissue (EAT) total volume measurement.

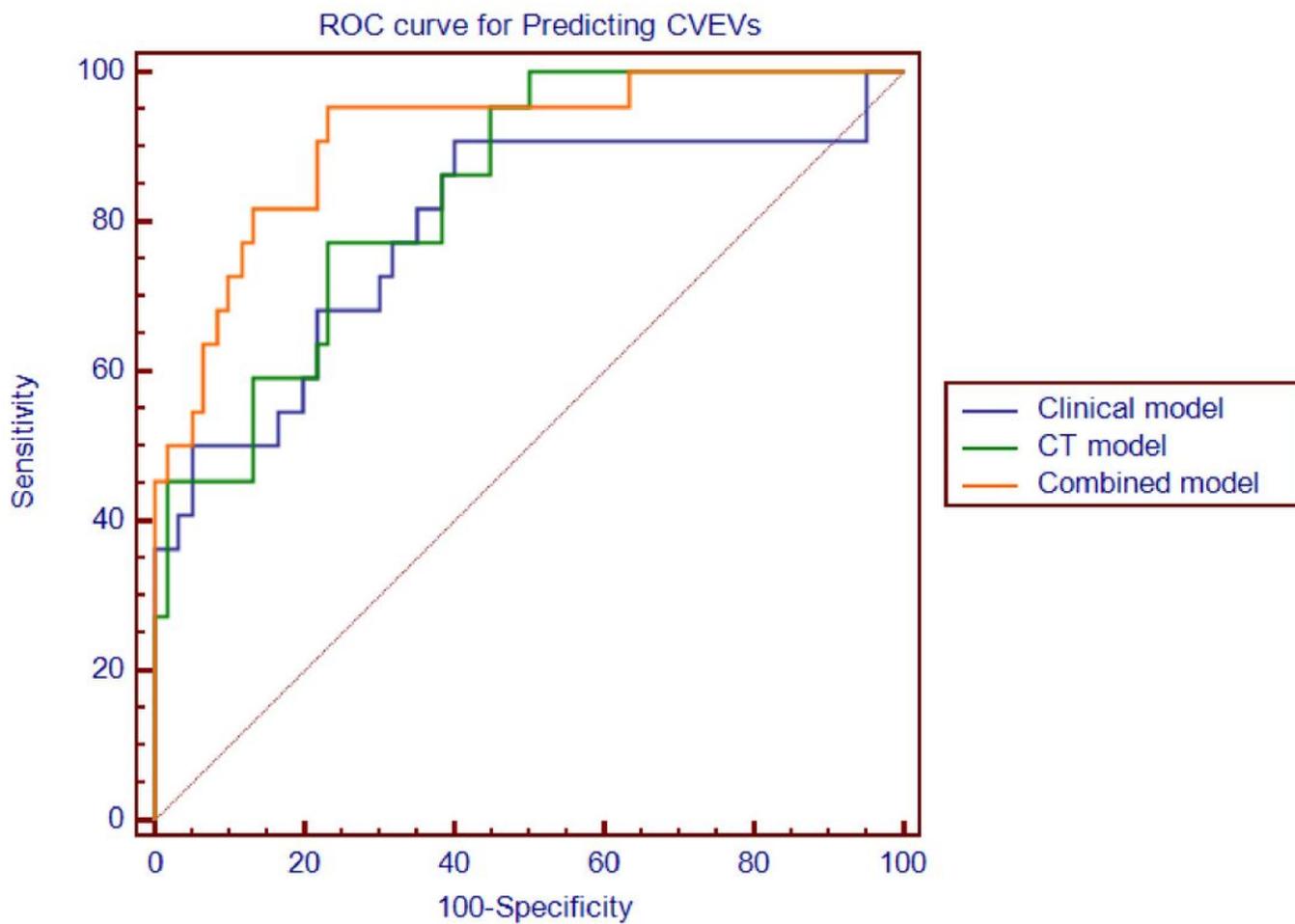


Figure 3

ROC curve of different parameters and models for identifying patients with CVEVs.