Coronary computed tomography angiography as a screening tool for moderate-high risk asymptomatic type 2 diabetes mellitus patients

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Research Article

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Abstract

Background

There are few data on the clinical significance of coronary computed tomography angiography (CCTA) in asymptomatic type 2 diabetes mellitus (T2DM) patients. We performed a retrospective study to evaluate coronary heart disease screening in asymptomatic patients with T2DM using CCTA and coronary heart disease risk stratification prediction.

Methods

Data from 141 type 2 diabetes mellitus patients (58 ± 8 years, 57% males) without known symptoms suggestive of coronary heart disease who underwent CCTA were retrospectively analyzed. The patients were classified into three subgroups based on United Kingdom prospective diabetes study (UKPDS) coronary heart disease risk stratification prediction. Ninety-three patients without diabetes mellitus and coronary heart disease who underwent CCTA successively were chosen as the control group. The segment involvement score (SIS), segment stenosis score (SSS), stenosis coefficient (SC) and severe proximal plaque (SPP) positive ratio based on CCTA data were evaluated and compared among the groups.

Results

Compared with the patients in the control group, patients in the moderate-high risk DM groups had higher scores on the SIS, SSS and SC and a higher SPP positive ratio (all p values < 0.001), and no difference was observed between the low-risk group and the control group (p = 0.147, p = 0.116, p = 0.132, p = 0.663, respectively). Compared with patients in the control group, the patients in the moderate-high risk DM groups had increased odds of SIS > 3 (OR = 7.838, p < 0.001; OR = 5.325, p < 0.001, respectively), SSS > 5 (OR = 6.750, p < 0.001; OR = 6.027, p < 0.001, respectively) and obstructive stenosis (OR = 7.900, p < 0.001; OR = 6.320, p < 0.001, respectively).

Conclusions

The moderate-high coronary heart disease risk patients had increased odds of obstructive coronary artery stenosis, and the distribution of coronary artery stenosis was more extensive and more severe in that group compared to the patients without diabetes mellitus and coronary heart disease. Coronary heart disease can be effectively screened in moderate-high risk asymptomatic type 2 diabetes mellitus patients using CCTA.

Background

Diabetes will be a significant problem in the future, from 537 million patients affected worldwide in 2021 to 783 million people projected by 2045, representing an approximately 46% growth (1). Many studies in the literature have shown a clear correlation between type 2 diabetes mellitus (T2DM) and the risk of coronary heart disease (CHD) (2–5). Patients with T2DM are at a higher risk for developing CHD, even if they lack any pertinent symptoms (6).

Currently, coronary computed tomography angiography (CCTA) is widely used to evaluate the degree of coronary artery stenosis and the characteristics of atherosclerotic plaque (7–10). Although invasive coronary angiography (ICA) is still the gold standard for the diagnosis of coronary artery disease, CCTA is increasingly becoming a viable noninvasive alternative. In addition to providing a faster and possibly more cost-effective way to assess the patients at a moderate CHD fatal risk, CCTA also avoids the risks associated with invasive surgery. As a more advanced technology, CCTA now has enough temporal and spatial resolution to evaluate the coronary artery tree and even the distal lumen and has allowed for the accurate assessment of the stenosis severity and atherosclerotic plaque composition (11). Compared with ICA, CCTA has good sensitivity, specificity and negative predictive value in the detection of CHD, but the positive predictive value of CCTA is lower than that of ICA (12). There are few data on the clinical significance of CCTA in asymptomatic type 2 diabetes mellitus patients (13, 14).

This study was performed to investigate a method of CHD screening in asymptomatic T2DM patients using CCTA and CHD fatal risk stratification prediction. We compared the CCTA scores among different risk groups and the control group to clarify the role of CCTA in asymptomatic T2DM patient screening.

Methods

Patients

A total of 149 continuously T2DM patients at the Affiliated Hospital of Jining Medical University without known symptoms suggestive of CHD who underwent CCTA from July 2019 to December 2019 were enrolled in the study. All T2DM patients had at least one other cardiovascular risk factor such as hypertension, dyslipidemia, smoking, lack of exercise, and family history of myocardial infarction in first-degree relatives.

T2DM was confirmed according to the criteria of the American Diabetes Association (15): Glycated hemoglobin (HbA1c) levels ≥6.5%, fasting blood glucose levels ≥7.0 mmol/l and/or a postchallenge blood glucose level ≥11.1 mmol/l (2 hours after a 75 g oral glucose load) or the current use of hypoglycemic treatment. The symptom asymptomatic status of the patients was evaluated using the Rose questionnaire for angina. Patients without CHD were defined as asymptomatic.

The exclusion criteria were as follows: type 1 diabetes; known or suspected CHD; abnormal resting electrocardiographic results; history of prior myocardial infarction, history of coronary artery bypass grafting or stenting; and incomplete clinical data.

Ninety-three other continuous non-T2DM non-CHD patients at the Affiliated Hospital of Jining Medical University who underwent CCTA in December 2019 were chosen as the control group.

CHD fatal risk stratification prediction

The CHD fatal risk stratification of T2DM patients was forecasted by the United Kingdom Prospective Diabetes Study (UKPDS) risk engine 2.0 (http://www.dtu.ox.ac.uk/riskengine/). The UKPDS is a group of clinical trials, epidemiological analyses and health-modeling studies with an influence that can be assessed across a broad range of health domains. The UKPDS made the risk of age, hyperglycemia, elevated blood pressure, adverse blood lipids and smoking contributions more clear. Equations were developed, combined and incorporated into the UKPDS risk engine. The UKPDS risk engine provides risk estimates in individuals with T2DM not known to have heart disease (16, 17).

A structured interview was performed to record the demographic and clinical data. The following characteristics were used to calculate the patients' CHD fatal risk: age, duration of diabetes, sex, ethnicity, atrial fibrillation, smoking history, HbA1c, systolic blood pressure, total cholesterol and high-density lipoprotein (HDL) cholesterol. A positive smoking history was defined as current smoking or cessation of smoking within three months.

Multidetector CT Scan Protocol and image reconstruction

CCTA was performed using a dual source CT scanner (SOMATOM Definition Flash dual-source; Siemens Medical Solutions, Erlangen, Germany) following standard guidelines (18).

During the CCTA acquisition, 50-80 ml iodinated contrast (Ultravist 370, Bayer Schering, Berlin, Germany) was injected based on the individual's weight, followed by a 30 ml saline flush, the injection rate was 5-7 ml/s. A retrospective ECG-gated spiral scan was performed covering the region immediately beneath the aortic arch to the apex of the left ventricle during an inspiratory breath hold of 10-20 s. The scan parameters were as follows: gantry rotation for 330-420 ms, spiral imaging with retrospective ECG gating and automatic dose modulation, 750-850 mA, 100 kV or 120 kV and 0.75 mm slice thickness, 128×0.6 mm collimation. A multisegment algorithm was used to reconstruct overlapping images, typically at 75% of the cardiac cycle in central diastole. If motion artifacts were present, additional reconstructions were made at different points of the R-R interval, as needed. All reconstructed datasets were sent to a dedicated workstation (syngo.via VA 20B, Siemens Healthcare) for postprocessing and three dimensional reconstruction.

Coronary stenosis analysis

The coronary arteries were divided into 18 segments following the Society of Cardiovascular Computed Tomography guidelines (19). Each segment was examined for coronary plaques. The structures of >1 mm^2 and adjacent to or within the coronary artery lumen that could be clearly separated from the vessel lumen were scored as a coronary plaque (20). Each coronary segment was scored individually for the

presence of plaque, and any stenosis was visually quantified. Coronary stenosis was assessed by the following clinical coronary plaque scores: the segment stenosis score (SSS); segment involvement score (SIS); stenosis coefficient (SC); and severe proximal plaque (SPP) (21).

The SIS reflected the plaque distribution and was calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis within each segment (scores from 0 to 18). The SSS was used as a measure of the overall coronary artery plaque burden. Each individual coronary segment was graded as having no to severe plaque (scores from 0 to 3) based on the extent of the obstruction of the coronary luminal diameter. Then, the extent scores of all 18 individual segments were summed to yield a total score. The SC was defined as the ratio of the SSS to SIS (the SC was defined as 0 when the SIS was 0), which reflected the degree of artery stenosis. The presence of any severe plaque in the left main or proximal portion of the left anterior descending, left circumflex and right coronary arteries was defined as SPP positive. A vessel stenosis greater than 70% was defined as a severe plaque. An obstructed coronary vessel was defined as a ≥50% reduction in the diameter of the lumen (21, 22).

The examination results were independently interpreted and summarized by two doctors with more than five years of CCTA diagnosis experience. If there was any difference, the final results were decided by the two doctors after consultation and discussion.

Statistical analysis

Continuous variables with a normal distribution are presented as the mean ± standard deviation; nonnormal variables are presented as the median (interquartile range). Categorical variables were expressed as frequencies. Continuous variables were compared by the Mann Whitney U test or Kruskal Wallis test. Differences in the categorical variables were assessed using the $\chi 2$ test. The association of T2DM and CCTA findings was analyzed by binary logistic regression. All statistical analyses were performed using SPSS 26.0 software (SPSS, Inc., Chicago, IL, USA), and $p<0.05$ was considered statistically significant.

Results

Of the 149 T2DM patients who underwent CCTA, 8 (no HbA1c or HDL cholesterol results) were excluded and 141 patients (80 males, 57%) were evaluated in the current study. A flow diagram of the study is shown in Fig. 1.

In all the T2DM patients the median course of disease was 9 (4, 15) years, and 42 (30%) were current smokers. All patients were of Asian-Indian ethnicity and had no atrial fibrillation history. All 93 non-DM and non-CHD patients (48 males, 52%) were included in the control group, and 28 (30%) were current smokers. There were no significant between-group differences with respect to sex or current smoking ratio ($p = 0.441$, $p = 0.958$, respectively). Further patient demographics and characteristics are presented in Table 1.

Table 1
Clinical and biochemical characteristics of the study population.

Characteristics	Control group	DM group	p value ($p < 0.05$)
N	93	141	-
†Male gender	48 (52%)	80 (57%)	$\chi^2 = 0.594$ $p = 0.441^a$
‡Age (years)	65 ± 13	58 ± 8	$U = 4168.500$ $p < 0.001^{b*}$
†Current smoker	28 (30%)	42 (30%)	$\chi^2 = 0.003$ $p = 0.958^a$
‡Duration of diabetes (years)	-	9 (4, 15)	-
‡SBP (mmHg)	137 ± 21	136 ± 18	$U = 6589.500$ $p = 0.948^b$
§Triglycerides (mmol/l)	1.0 (0.8, 1.5)	1.5 (1.0, 2.1)	$U = 8350.000$ $p < 0.001^{b*}$
‡Total cholesterol (mmol/l)	4.5 ± 1.0	4.5 ± 1.0	$U = 6607.500$ $p = 0.920^b$
‡HDL cholesterol (mmol/l)	1.3 ± 0.5	1.2 ± 0.3	$U = 4995.000$ $p = 0.002^{b*}$
§FBG (mmol/l)	5.3 (4.8, 5.8)	7.1 (5.7, 8.9)	$U = 10718.500$ $p < 0.001^{b*}$
§HbA1c (%)	-	8.7 (7.4, 10.3)	-

†Data are expressed as n (%); ‡ Data are expressed as mean ± standard deviation; §Data are expressed as the median (interquartile range); [a]p value by χ^2 test; [b]p value by Mann Whitney U test; * $p < 0.05$; DM, diabetes mellitus; SBP, systolic blood pressure; HDL, high-density lipoprotein; FBG, fasting blood glucose.

The patients in the DM group had significantly higher CCTA stenosis scores (SPP, SIS, SSS and SC) than those in the control group (all p values < 0.001); see Table 2 for details.

Table 2
Coronary stenosis scores of the study population.

Coronary stenosis scores	Control group	DM group	p value (p < 0.05)
N	93	141	-
†SPP positive	0 (0%)	20 (14%)	$\chi2 = 14.424$ p < 0.001[a*]
‡SIS	2.0 (0.0, 3.0)	4.0 (2.0, 7.0)	U = 9492.000 p < 0.001[b*]
‡SSS	2.0 (0.0, 4.0)	5.0 (2.0, 9.0)	U = 9637.000 p < 0.001[b*]
‡SC	1.0 (0.0, 1.0)	1.0 (1.0, 1.5)	U = 9409.000 p < 0.001[b*]

†Data are expressed as n (%); ‡ Data are expressed as median (interquartile range); [a] p value by $\chi2$ test; [b] p value by Mann Whitney U test; * p < 0.05; DM, diabetes mellitus; SPP, severe proximal plaque; SIS, segment involvement score; SSS, segment stenosis score; SC, stenosis coefficient.

According to the CHD fatal risk in ten years predicted by the UKPDS risk engine, the DM group was divided into three subgroups: the low-risk group (fatal risk < 7.5%), moderate-risk group (fatal risk 7.5–15%) and high-risk group (fatal risk > 15%).

No significant differences were observed with respect to male sex or current smoking ratio in multiple groups (p = 0.184, p = 0.202, respectively). Further patient demographics and characteristics are presented in Table 3.

The SIS in the moderate-risk group [5.0 (3.0, 7.0)] and high-risk group [4.0 (2.5, 7.0)] were significantly higher than those in the control group [2.0 (0.0, 3.0)] (p < 0.001, p < 0.001, respectively), and no difference was observed between the low-risk group [3.0 (1.3, 4.0)] and the control group (p = 0.147). No difference was observed among the DM subgroups (see Tables 4 and 5 for details). This suggests a wider distribution of coronary artery stenosis in asymptomatic T2DM patients of moderate-high risk than in non-DM non-CHD patients. The difference in the SIS among the groups is shown in Fig. 2A.

The SSS in the moderate-risk group [5 (3, 10)] and the high-risk group [5 (3, 13)] were significantly higher than that in the control group [2.0 (0.0, 4.0)] (p < 0.001, p < 0.001, respectively), and no difference was observed between the low-risk group [3.5 (1.3, 5.0)] and the control group (p = 0.116). No difference was observed among DM subgroups (see Tables 4 and 5 for details). The overall burden of coronary plaque was more severe in the moderate-high risk asymptomatic T2DM patients than in the non-DM non-CHD patients. The difference in the SSS among the groups is shown in Fig. 2B.

The SC in the moderate-risk group [1.2 (1.0, 1.6)] and high-risk group [1.3 (1.0, 1.7)] was significantly higher than that in the control group [1.0 (0.0, 1.0)] (p < 0.001, p < 0.001, respectively), and no difference was observed between the low-risk group [1.0 (1.0, 1.3)] and the control group (p = 0.132). No difference

was observed among the DM subgroups (see Tables 4 and 5 for details). This suggests more severe coronary artery stenosis in the moderate-high risk asymptomatic T2DM patients than in the non-DM and non-CHD patients. The difference in the SC among the groups is shown in Fig. 2C.

The positive SPP ratios in the moderate-isk group (17%) and high-risk group (21%) were significantly higher than that in the control group (0%) ($p < 0.001$, $p < 0.001$, respectively), and no difference was observed between the low-risk group (3%) and the control group ($p = 0.663$). No difference was observed between the moderate and high-risk groups (see Tables 4 and 5 for details). Severe proximal coronary artery stenosis was observed in the moderate-high risk asymptomatic T2DM patients compared with the non-DM non-CHD patients, which suggests the poor prognosis of CHD. The difference in the SC among the groups is shown in Fig. 3.

There was no difference in any of the four CCTA stenosis scores (SPP, SIS, SSS and SC) between the low-risk group and the control group ($p = 0.663$, $p = 0.147$, $p = 0.116$, $p = 0.132$, respectively).

Compared with the patients in the control group, the patients in the DM group had an increased risk of SIS > 3 [OR = 4.756 (2.650–8.534), $p < 0.001$], SSS > 5 [OR = 4.717 (2.359–9.431), $p < 0.001$] and obstructive stenosis [5.408 (2.803–10.435), $p < 0.001$]. The risk was even higher in the moderate-risk group [OR = 7.838 (3.575–17.182), $p < 0.001$; OR = 6.750 (2.946–15.468), $p < 0.001$; OR = 7.900 (3.523–17.717), $p < 0.001$, respectively] and the high-risk group [OR = 5.325 (2.559–11.082), $p < 0.001$; OR = 6.027 (2.677–13.567), $p < 0.001$; OR = 6.320 (2.887–13.835), $p < 0.001$, respectively]. The risk in the low-risk group was lower than that in the whole DM group; see Table 6 and Fig. 4 for details.

Discussion

In the UKPDS risk engine, age, duration of diabetes, male sex, ethnicity, current smoking, glycated hemoglobin, systolic blood pressure, and ratio of total cholesterol to high-density lipoprotein cholesterol are associated with the development of sudden death or myocardial infarction (23) as a basis for risk stratification.

In this study, we found that all four CCTA stenosis scores (SIS, SSS, SC, SPP) in T2DM patients were significantly higher than those in non-DM non-CHD patients, which seems useful for CHD screening. However, no difference was observed between the low-risk T2DM patients and non-DM non-CHD patients when we divided the T2DM patients into three subgroups according to the CHD fatal risk, which was predicted by UKPDS risk engine. There was a significant difference between the moderate-high risk T2DM patients and non-DM non-CHD patients as before. The moderate-high risk T2DM patients had a higher risk of coronary artery stenosis than the patients without DM and CHD, which was shown in the higher odds ratio of SIS > 3, SSS > 5 and obstructive stenosis.

Compared with people without DM, the prevalence of CHD in T2DM patients is higher (24). According to the results of CCTA, the prevalence and severity of CHD in T2DM patients is higher than in those without

DM (25). However, there are few data on the clinical significance of CCTA in asymptomatic type 2 diabetes mellitus patients.

In previous studies, it wss observed that approximately 64–91.4% of asymptomatic T2DM patients had atherosclerosis, and 26–33.3% of patients had severe CHD (26–29). Consistent with previous studies, atherosclerotic plaques were found in 128 (90%) T2DM patients in this study, and 69 (49%) patients had ≥ 50% luminal diameter stenosis. This suggests that CHD in asymptomatic T2DM patients is a problem that cannot be ignored. Twenty (14%) patients with T2DM developed severe proximal stenosis of multiple coronary arteries, which indicates a poor prognosis (21). In the high-risk group, the proportion was as high as 21%, indicating that the increased severity of CHD is associated with an increased fatal risk in T2DM patients (25, 30).

Currently, it is thought that T2DM patients are not always at the highest CHD risk state, nor do all T2DM patients have the same high CHD risk (31). According to an asymptomatic diabetic study that evaluated the detection of ischemia, the heart risk of patients with moderate and severe ischemia is six times higher than that of patients with normal or small perfusion defects (32). These findings suggest that we should try to identify high-risk patients, especially asymptomatic T2DM patients.

Significant differences were observed in all four CCTA stenosis scores between the control group and the moderate-high risk group. No difference was observed in any of the four CCTA stenosis scores between the control group and low-risk group. Approximately 28% of T2DM patients received little benefit from CCTA examination but had to bear unnecessary risks (i.e., X-ray radiation, iodine contrast agent allergy and kidney injury). Using CCTA in the CHD screening of low-risk asymptomatic T2DM patients should not be recommended, which also supports the conclusion of previous studies (13, 14).

Compared with non-DM non-CHD patients, moderate-high risk T2DM patients have a higher risk of coronary artery stenosis, and the CCTA stenosis scores are significantly higher, which means more severe stenosis and worse prognosis. This finding demonstrates the screening role of CCTA in moderate-high risk asymptomatic T2DM patients using risk stratification prediction, especially in high-risk patients.

3. Study limitations.

This study is a single center retrospective study, subjects only represent a relatively single group, and there may be potential bias in the selection and test ability. The incidence and prognosis of CHD may be influenced by geographical factors, climate and the eating habits of subjects. The choice of patients without DM and CHD as the control group may not fully reflect the status of the whole healthy population.

This study did not systematically correlate the CCTA results with the ICA reference standards for intracoronary plaque assessment. Although the consistency effect of plaque postprocessing software has been verified in other studies (33, 34), the scores of plaque may still be different in different automatic postprocessing software programs. Therefore, the same postprocessing software should be

used in a series of studies. Likewise, the measurement of plaque stenosis may also be influenced by technology, e.g., by hardening-induced artifacts around severe calcified plaques and the attenuation level of vascular contrast enhancement (35).

Additionally, there is a potential difference between the risk stratification predicted by the UKPDS risk engine and the actual risk in asymptomatic T2DM patients. Therefore, these results might be applicable to very specific populations, and prospective studies on larger populations will be necessary to validate our findings.

Conclusions

The impact of DM on cardiovascular disease is well known. The incidence rate of CHD is higher in DM patients, and the prognosis is even worse. In asymptomatic T2DM patients, the diagnosis of CHD is usually missed or delayed, which in turn enhances the risk for cardiovascular events.

Through the UKPDS risk engine software, the moderate-high risk groups of asymptomatic T2DM patients may be screened out according to the risk stratification prediction of CHD. Using CCTA may effectively screen for coronary stenosis in corresponding patients.

It was observed in this study that coronary stenosis in moderate-high risk asymptomatic T2DM patients is more extensive and more serious than in non-DM non-CHD populations, and will result in more cardiovascular events. In these populations, early CCTA examination is necessary, which means early diagnosis of CHD and early treatment to ultimately reduce the incidence of cardiovascular events and improve prognosis.

List Of Abbreviations

CCTA	Coronary computed tomography angiography
CHD	Coronary heart disease
CI	Confidence interval
HDL	High-density lipoprotein
ICA	Invasive coronary angiography
OR	Odds ratio
OS	Obstructive stenosis
SC	Stenosis coefficient
SIS	Segment involvement score
SPP	Severe proximal plaque
SSS	Segment stenosis score
T2DM	Type 2 diabetes mellitus

Declarations

Ethics approval and consent to participate: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The study was approved by the Review Board of the Affiliated Hospital of Jining Medical University, and general research authorization was obtained, allowing for retrospective reviews. Informed consent was waived by the Review Board.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors have no conflicts of interest to declare.

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Author Contributions: QL, JQ and HZ designed the study. QL analyzed the data and wrote the manuscript. JQ participated in the study design, analyzed the data and edited and reviewed the manuscript. HZ supervised the overall study and contributed to the study design, editing and review of the manuscript. SS was responsible for collecting, sorting and statistical data. All authors have read and approved the final manuscript.

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Tables

Tables 3 to 6 are available in the Supplementary Files section.

Figures

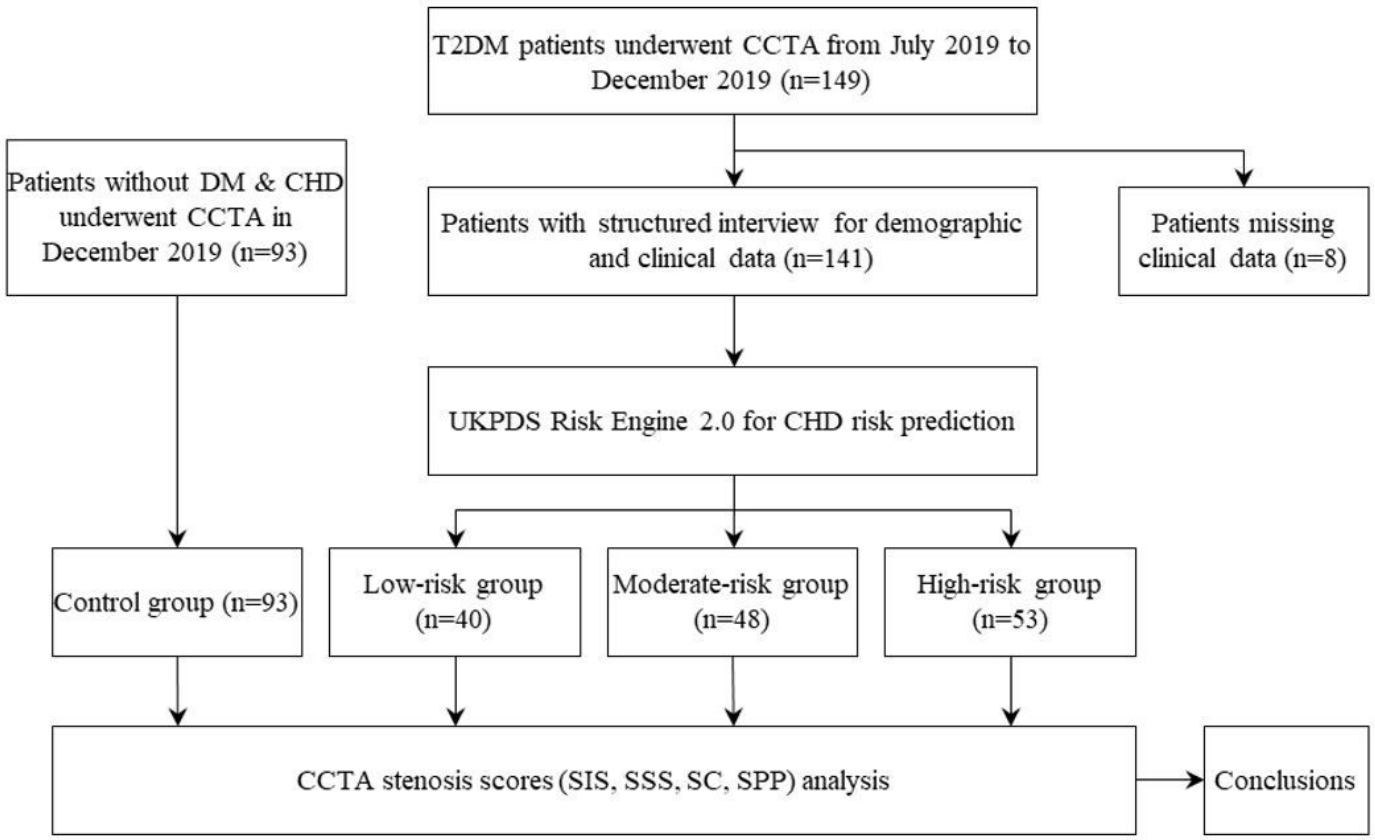

Figure 1

A flow diagram of the study.

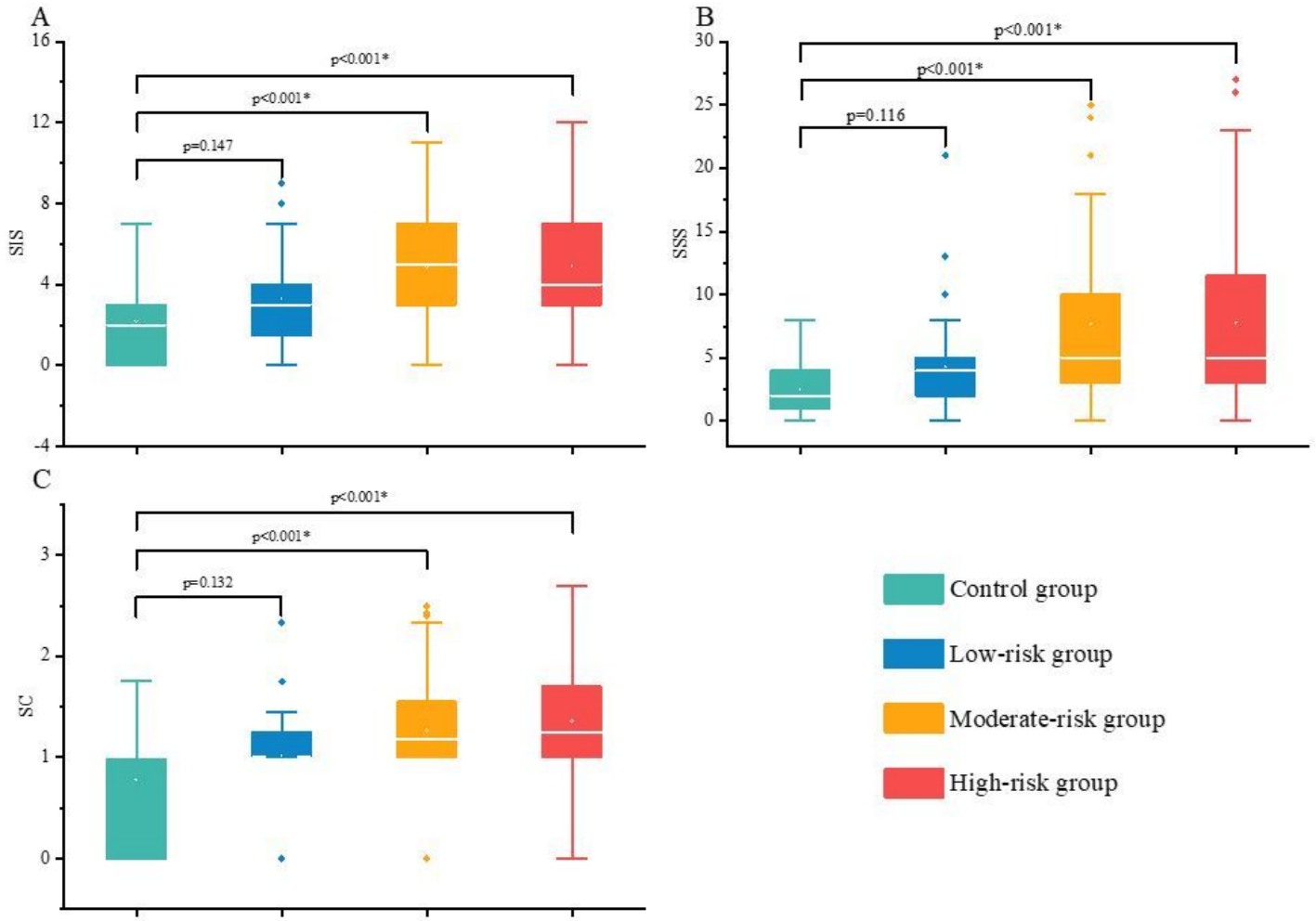

Figure 2

The difference in the CCTA stenosis scores among the control group and DM subgroups. SIS (A), SSS (B), SC (C).

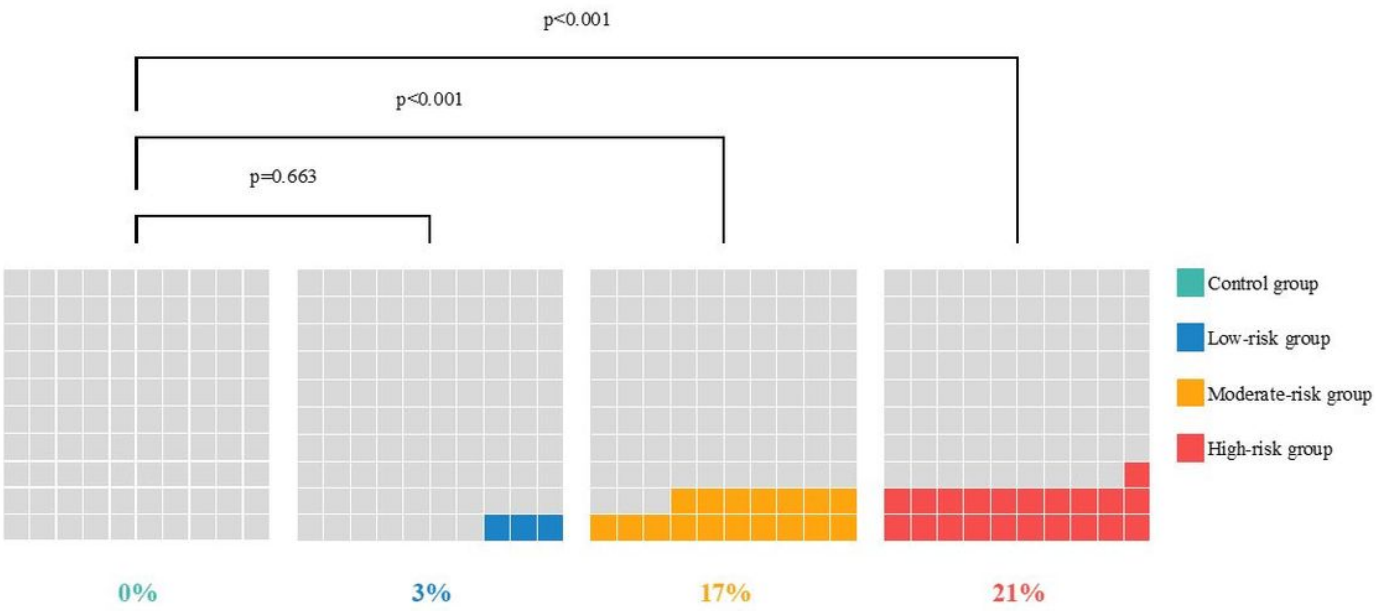

Figure 3

The SPP-positive ratio of the contorl group and DM subgroups.

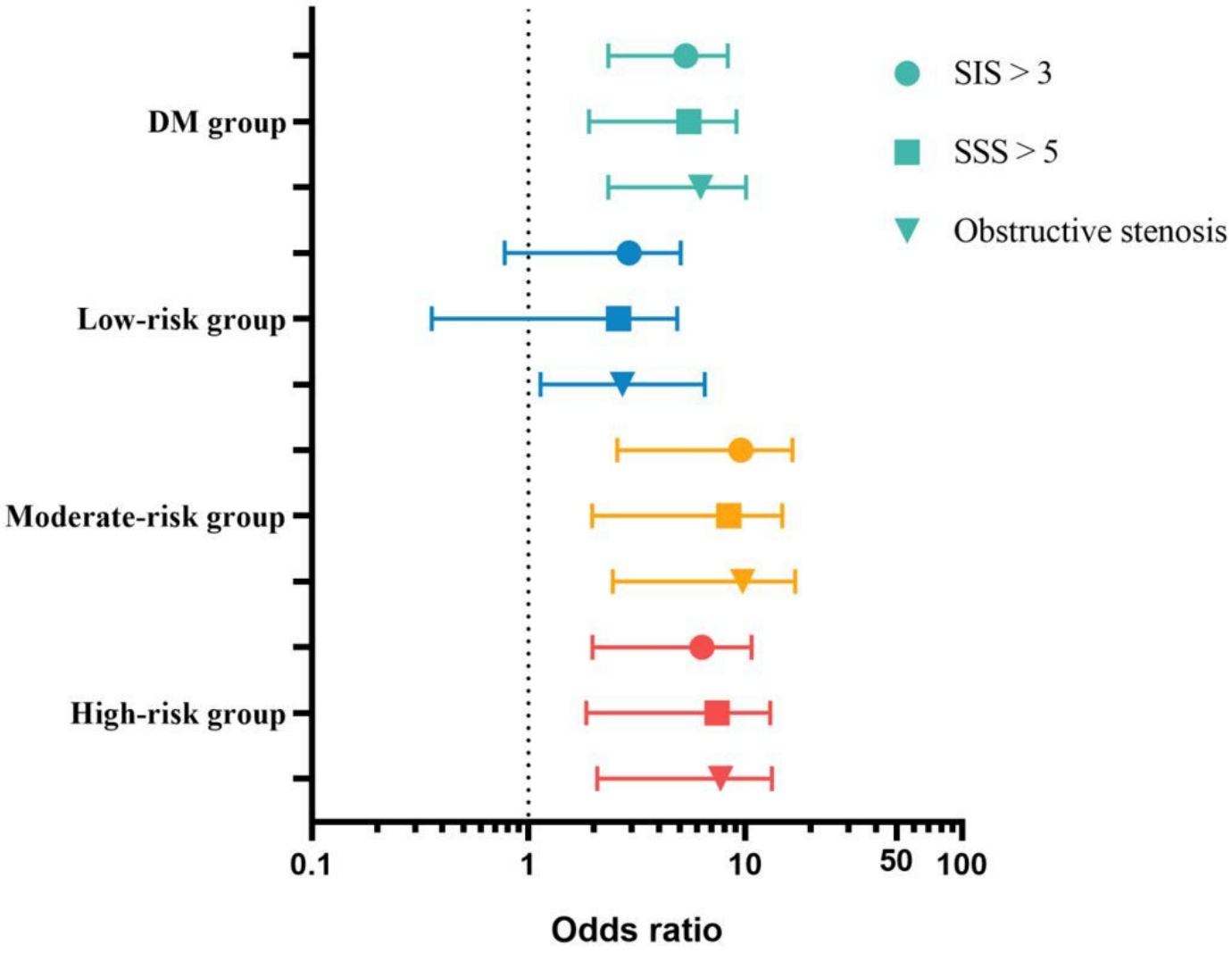

Figure 4

The SIS>3, SSS>5 and obstructive stenosis odds ratio (95% CI) of the DM group and subgroups. The control group was used as the reference group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table3.xlsx
- Table4.xlsx
- Table5.xlsx
- Table6.xlsx