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Evaluation of the clinical value of CCTA as the preferred screening method in patients with chronic coronary syndrome

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Abstract

Background The advantages and disadvantages of direct invasive coronary angiography (ICA) and coronary computed tomographic angiography (CCTA) + ICA were compared in patients with suspected chronic coronary syndrome (CCS) who presented with angina symptoms or who had nonangina chest pain with abnormal electrocardiogram results.

Methods A total of 1200 patients who met the inclusion criteria at TEDA International Cardiovascular Hospital from January 2021 to December 2022 were randomly divided into two groups at a 1:1 ratio: the CCTA + ICA strategy (CCTA group) and the direct ICA strategy (ICA group). The baseline data were collected. All patients in the CCTA group underwent CCTA examination first. If these results showed positive obstructive coronary artery disease (CAD), then typical angina with coronary artery stenosis ranging from 50 to 70% or vascular segments could not be analysed due to severe calcification, so ICA was further performed for definitive diagnosis, and the ICA results were taken as the final diagnosis. All patients in the ICA group underwent ICA examination directly. Demographic data, cardiovascular risk factors, biochemical criteria, chest pain classification, coronary vessel lesion severity and drug use were compared between the two groups. All patients were followed for 1 year after discharge to observe major adverse cardiovascular events (MACE). The differences in unnecessary ICA rates, 1-year MACE rates, allergic reactions to contrast agents and hospitalization costs between the two groups were analysed. On the basis of the baseline clinical data of patients included in this study, a risk prediction model for obstructive CAD was established by logistic regression.

Results (1) There were 592 patients in the CCTA group and 594 patients in the ICA group. The percentage of unnecessary ICA procedures was 7.5% in the CCTA group and 55.2% in the ICA group ($P < 0.001$), which was a decrease of 86.4%. (2) Eighteen patients in the CCTA group were readmitted for severe angina, 4 of whom underwent unplanned percutaneous coronary intervention (PCI). Eight patients in the ICA group were readmitted for severe angina, 2 of whom underwent unplanned PCI. There were no cardiac deaths, nonfatal myocardial infarctions or strokes in either group over the 1-year follow-up. There was no statistically significant difference in the rate of MACE-free survival between the two groups (97.0% vs. 98.7%, log-rank$\chi^2 = 1.996$, $P = 0.158$). (3) Allergic reactions to

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contrast agent were observed in 28 patients in the CCTA group and 16 in the ICA group ($P=0.190$). (4) The median hospitalization cost in the CCTA group was $1259.54, and that in the ICA group was $1399.41, which was a significant difference ($P<0.001$) and a decrease of 9.99%. (5) Based on the combination of the logistic regression forward selection method and backward elimination method, variables with $P<0.05$, including creatinine, age, physical activity-induced symptoms, hyperlipidaemia, diabetes and smoking history, were selected from the baseline data of patients to predict obstructive CAD. The above variables were used to establish a risk prediction model for obstructive CAD. The area under the ROC curve (AUC) of this model was 0.721, indicating good predictive ability.

Conclusion In patients with suspected CCS, including typical angina, atypical angina and nonangina chest pain with abnormal electrocardiogram results, the use of CCTA as a first-line diagnostic test can reduce the unnecessary incidence of ICA and hospitalization costs without increasing the incidence of MACE. A risk prediction model of obstructive CAD was established on the basis of the baseline data of the patients enrolled in this study, providing a clinical basis for the decision to use CCTA or ICA. Patients with a low probability of obstructive CAD can be given priority for CCTA, whereas patients with a high probability can be given priority for ICA.

Keywords Invasive coronary angiography, Coronary computed tomographic angiography, Chronic coronary syndrome, Obstructive coronary artery disease, Major adverse cardiovascular events, Unnecessary ICA rate

Background

Coronary heart disease (CHD) is a dynamic pathological process characterized by the accumulation of epicardial atherosclerotic plaques and changes in circulatory function. It is divided into two categories: acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) [1]. In clinical practice, the diagnostic and treatment processes of ACS are relatively fixed. According to the symptoms of chest pain, electrocardiogram (ECG) changes and elevated myocardial injury markers, the risk for ACS can be rapidly stratified, and the corresponding diagnosis and treatment process can be formulated [2, 3]. The diagnosis of CCS is more difficult because patients with CCS have more atypical symptoms (such as shortness of breath, persistent cough, indigestion and nausea, loss of appetite, unexplained fatigue, muscle weakness, dizziness and lightheadedness, fainting, jaw or tooth pain, and back pain) and a longer course of disease than CHD patients do. The 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of CCS recommend coronary computed tomographic angiography (CCTA) as a first-line test for patients with a low or intermediate clinical likelihood of CHD [1]. CCTA is a noninvasive imaging technology. It combines computed tomography and angiography techniques to obtain detailed images of the coronary arteries, helping doctors diagnose and evaluate coronary heart disease and other cardiovascular diseases. Additionally, the Cardiovascular CT Society 2021 expert consensus recommends CCTA as the first-line test to evaluate patients with or without prior CHD presenting with stable ischaemic symptoms [4]. However, in the current clinical setting, ICA is still used as the preferred examination for the early diagnosis of CCS patients because ICA is the gold standard for the diagnosis of CHD [5]. Invasive coronary angiography (ICA) is an invasive diagnostic test. It is primarily used to directly visualize the coronary arteries and determine if there are any blockages or narrowing that could lead to heart problems. It is a relatively direct and accurate method for diagnosing coronary artery diseases. It provides important information for doctors to formulate treatment plans, but it also has certain risks and complications because of its invasive nature. The advantage of ICA over CCTA is that percutaneous coronary intervention (PCI) can be performed at the same time as lesion detection. However, evidence from the United States [6] and Europe [7] suggests that ICA is overused; in more than half of the patients who underwent ICA, the coronary vessels were normal or had no more than 50% stenosis. Moreover, ICA can lead to rare but potentially life-threatening complications, such as malignant arrhythmia, thromboembolism, coronary perforation, no-reflow, anaphylactic shock, and retroperitoneal haematoma [8]. Therefore, ICA is an invasive, expensive, and possibly unnecessary procedure for these patients.

CCTA is the most accurate noninvasive test for diagnosing CHD [9]. Prospective, multicentre studies have demonstrated the diagnostic accuracy of CCTA in patients with suspected but undiagnosed CHD, with sensitivities ranging from 85 to 99% and specificities ranging from 64–92% [10–12]. The ISCHEMIA study [13] showed a high degree of agreement between CCTA and ICA in identifying patients with significant coronary stenosis without left main disease. The ICA confirmed that only 4.9% of the 1,593 patients without left main disease with at least a single-vessel disease identified by CCTA had no significant coronary stenosis. Given that the actual prevalence of CHD is lower than expected and that not all patients with ≥ 50% coronary artery stenosis require invasive treatment, two-thirds of those with 50-70% coronary artery stenosis have no significant functional significance [14]. Therefore, CCTA is a "safety

gatekeeper" for ICA, with the aim of selecting patients for ICA more accurately [15]. However, in patients with suspected CCS, there is still a lack of studies on the downstream efficacy, safety and cost of using CCTA as the first-line examination to decide whether the patient should undergo ICA. There have been few comparative studies in China, especially large-sample randomized controlled clinical studies. The aim of this study was to investigate whether CCTA can effectively reduce the use of ICA and reduce the cost of diagnosis and treatment in patients with suspected CCS without increasing the incidence of major adverse cardiovascular events (MACEs).

Methods

Sample size Estimation

For a clinical trial study comparing coronary CT and coronary angiography, factors such as the expected differences between the two groups need to be considered when the sample size is calculated. The calculation formula is

$$n = \frac{\left(\begin{array}{l} Z_{\alpha/2}\sqrt{2p\left(1-p\right)}+ \\ Z_{\beta}\sqrt{p_1\left(1-p_1\right)+p_2\left(1-p_2\right)} \end{array}\right)^2}{\left(p_1-p_2\right)^2}$$

where n is the required sample size for each group. Zα/2: When the two-sided α = 0.05, Zα/2 = 1.96. Zβ: Generally, Zβ is taken (with a power of 80%). p: The combined positive rate of the two groups. If the positive rate of coronary angiography is p1 = 50% and the positive rate of coronary CT is p2 = 40%, then p=(p1 + p2)/2=(0.5 + 0.4)/2 = 0.45. p1 and p2: the expected positive rates of the two groups. Substituting the values into the formula, we obtain:

$$\begin{aligned} n &= \frac{\left(\begin{array}{l} 1.96\sqrt{2\times 0.45\times(1-0.45)} \\ +1.28\sqrt{0.5\times(1-0.5)+0.4\times(1-0.4)} \end{array}\right)^2}{(0.5-0.4)^2} \\ &= \frac{\left(1.96\sqrt{0.495}+1.28\sqrt{0.25+0.24}\right)^2}{0.01} \\ &= \frac{(1.96\times 0.7036+1.28\times 0.7)^2}{0.01} \\ &= \frac{(1.3791+0.896)^2}{0.01} \\ &= \frac{(2.2751)^2}{0.01} \\ &= \frac{5.1767}{0.01} \\ &= 517.67 \approx 518 \end{aligned}$$

That is, the required sample size for each group is approximately 518 cases. Considering possible situations such as drop-outs, if the estimated drop-out rate is 10%, then the adjusted sample size for each group is n'=518/(1-0.1) ≈ 576 cases.

Research subjects

From January 2021 to December 2022, patients with suspected CCS who received medical care at TEDA International Cardiovascular Hospital, a specialized cardiovascular hospital located in Tianjin, were enrolled in three categories: typical angina pectoris, atypical angina pectoris, and nonangina chest pain with electrocardiogram changes. There are three characteristics of typical AP: (1) contractive discomfort in the anterior chest, neck, shoulder, jaw, or arm; (2) physical activity induced; and (3) symptoms that resolve after approximately 5 min of rest or the use of nitrates. Patients with atypical angina pectoris were defined as having two of these three features, and patients with nonangina chest pain were defined as having one or none [1]. Electrocardiographic changes indicate the presence of any one of the following: Q waves, left bundle-branch block, ST-segment abnormality, or T-wave abnormality. The following patients were excluded: A, previous history of CHD; B, ACS, including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina pectoris; C, typical angina patients with left ventricular ejection fraction < 50%; D, nonsinus rhythm (atrial fibrillation and frequent premature beats, etc.), which affects the accuracy of CTCA imaging; E, unable to hold breath for 5 s; F, refusal or inability to provide informed consent; G, aged less than 30 years; H, renal insufficiency, which results in contrast-induced nephropathy; I, known congenital heart disease; J, pregnant women. The baseline data of the patients were collected, including sex, age, history of hypertension, diabetes status, hyperlipidaemia status, smoking status, family history of CHD, creatinine, uric acid, creatine kinase–myocardial band (CK-MB), prothrombin time, international normalized ratio (INR), fibrinogen quantification, D-dimer, homocysteine, hypersensitive CRP, free fatty acid, left atrial anterior and posterior diameter, left ventricular diastolic end diameter and left ventricular ejection fraction (LVEF), and so on. The study was approved by the local ethics committee of TEDA International Cardiovascular Hospital ([2021]-0114-3). All experiments were performed in accordance with relevant guidelines and regulations, such as the Declaration of Helsinki. Informed consent was obtained from all participants or their family members before CCTA or ICA, and the patients signed the informed consent form and agreed to be published.

Methods

Grouping

The enrolled patients were randomly divided into two groups at a ratio of 1:1 by a randomized envelope with a block size of four: (1) CCTA + ICA strategy (CCTA group): CCTA was performed first; if CCTA results showed positive obstructive coronary artery disease (CAD), typical angina with coronary artery stenosis ranging from 50 to 70% or vascular segments could not be analysed due to severe calcification, ICA was further performed for definitive diagnosis. (2) In the ICA group (direct ICA strategy), ICA examination was performed directly. In both tests, obstructive CAD was defined as at least one 50% diameter stenosis in the left main coronary artery or at least one 70% diameter stenosis in other coronary arteries.

CCTA

Patients were scanned with a Siemens dual-source CT (Somatom Definition flash). First, continuous scanning from the root of the autonomic artery to the apex of the heart was performed with a collimation of 24 mm×1.2 mm, a pitch of 1.2 mm, and a slice thickness of 1.5 mm in one respiratory motion at a tube voltage of 120 kV. A high-pressure syringe was then used to inject iodine contrast agent and normal saline into the anterior elbow vein at a flow rate of approximately 5 ml/s. The test bolus technique was applied to calculate the delayed trigger scan time, and the area of interest was selected at the aortic root level to monitor CT values. The peak time plus 5 s was taken as the delayed trigger scan time. CCTA analysis was performed independently by readers who were unaware of the results of the clinical data, and discordant results were resolved by at least two readers. The degree of coronary stenosis was analysed via curved planar reconstruction (CPR) and maximum-intensity projection (MIP) of a Siemens image postprocessing workstation. All segments larger than 2 mm in diameter were classified into the following groups: no stenosis, 1–49% stenosis, 50–70% stenosis, and more than 70% stenosis.

ICA

ICA was performed on patients using standard techniques on a Philips FD20 single-channel X-ray tube fluoroscopy device. We used the standard Judkins method. The coronary arteries were examined in multiple positions; at least 2 positions were selected for each lesion, and 0.2 mg of nitroglycerine was applied to the target vessel if necessary. The luminal diameter stenosis rate, estimated by visual inspection, was equal to 1 – the minimum lumen diameter/mean diameter of the reference segment, multiplied by 100%. The results were determined by consensus among three senior cardiologists qualified for interventional treatment of CHD.

Indicators of observation

Baseline data (including sex, age, hypertension status, diabetes status, hyperlipidaemia status, smoking history, family history of CHD, chest pain classification, electrocardiogram results, etc.), degree of CAD, contrast agent allergy status, medication use and hospitalization costs were compared.

Primary and secondary clinical endpoints

The primary clinical endpoint of the study was nonessential ICA, which was defined as ICA performed in patients who were diagnosed as negative for obstructive CAD, which caused a greater economic burden and increased likelihood of secondary complications. The secondary endpoints were (1) MACEs [15], including cardiac death (any death that could not be explained by noncardiac causes), nonfatal myocardial infarction, stroke, readmission for severe angina symptoms, and unplanned revascularization (PCI or CABG was performed according to the patient's condition during the follow-up period); (2) hospitalization expenses; and (3) contrast-induced allergic conditions.

Therapeutic management

Revascularization was planned for patients with ≥ 50% diameter stenosis in the left main coronary artery or ≥ 70% diameter stenosis in other epicardial artery segments. Small collateral lesions with a diameter less than 2 mm that were controlled by drugs were treated conservatively with drugs. Regardless of the number of vessels processed at ICA, the number of stents implanted, and the need for a second completion of residual vascular disease treatment, a single PCI was performed.

Follow-up

Patients were followed up by telephone or in the outpatient clinic after discharge. The follow-up time points were 1 month (± 1 week), 3 months (± 1 week), 6 months (± 1 week) and 12 months (± 1 week) from the index date. MACEs that occurred during follow-up were recorded. The study procedure is shown Fig. 1.

Statistical analysis

SPSS 25.0 was used to process and analyse the research data. Normally distributed measurement data are expressed as the mean ± standard deviation ($\bar{x} \pm s$). Comparisons between groups were performed by the two-independent-sample t test. The normally distributed data are expressed as the median (interquartile range) [M (P25, P75)] and were compared between groups by the Mann–Whitney U test. Count data are expressed as

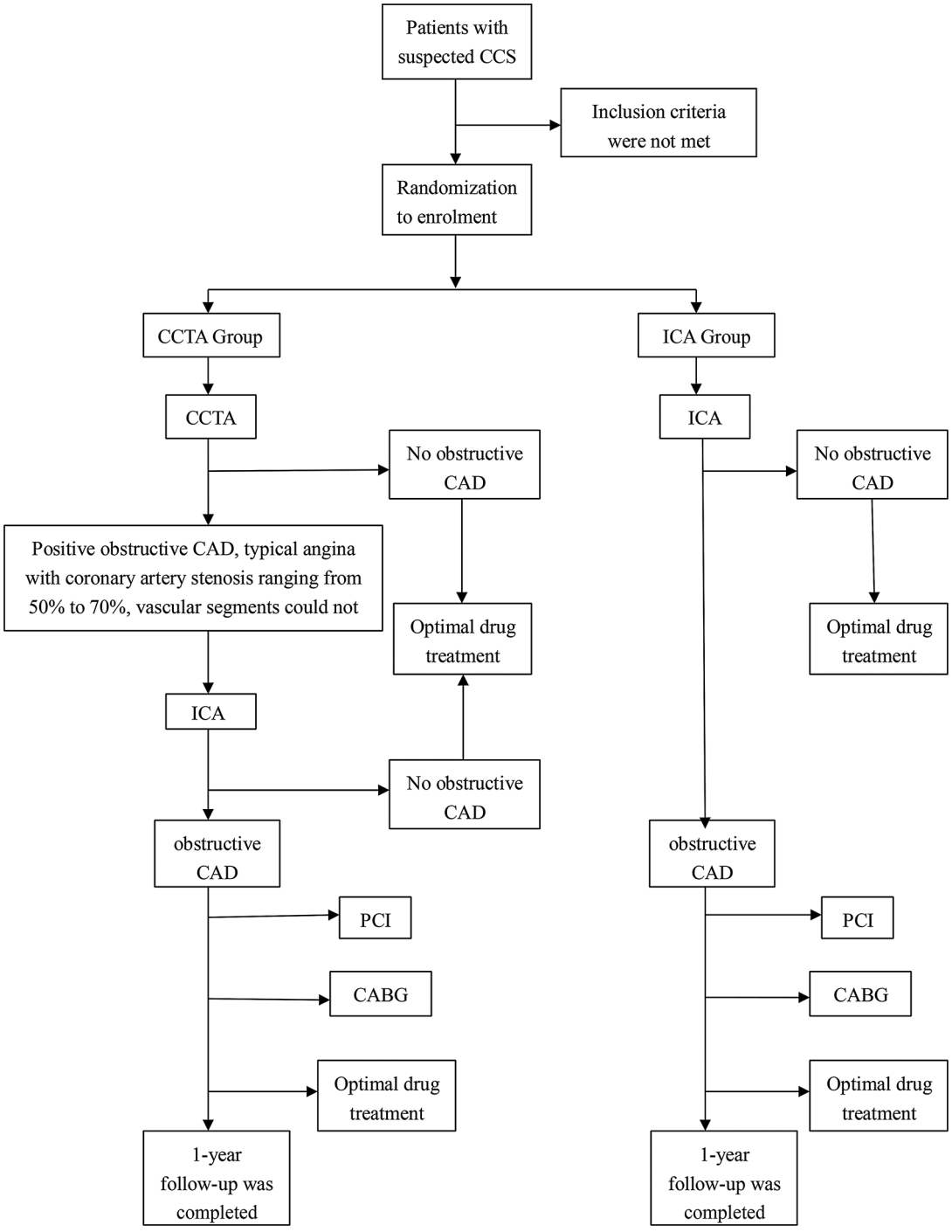

Fig. 1 Flow chart of the research

n or % and were compared between groups by the chi-square test (χ^2) or Fisher's exact test. The Kaplan–Meier method was used to draw the survival curves of the two groups of patients, and the log-rank χ2 test was used to compare the survival rates between the two groups. $P<0.05$ indicated a significant difference. The forward selection method and backward elimination method for logistic regression were combined. Variables with clinical significance and $P<0.05$ were selected as variables in the prediction model from the baseline data, and an obstructive CAD risk prediction model was established. After the model was established, the Stata command "nomogram" was used to establish the obstructive CAD risk prediction score, the score was assigned according to the risk ratio of the variable from the regression analysis, and the nomogram was drawn. The area under the receiver

operating characteristic (ROC) curve (AUC) was used to evaluate the predictive ability of the screened clinical indicators for obstructive CAD.

Results

Study population

A total of 1200 patients with suspected CCS who met the inclusion criteria were enrolled during the study period. The participants were randomly divided into groups of 600 at a 1:1 ratio. Eight patients in the CCTA group and six patients in the ICA group were lost to follow-up. The reasons for loss to follow-up included patients changing their contact number (5 cases), changing their place of residence (3 cases), and refusing to respond (6 cases).

Characteristics of patients

Data for 620 males and 566 females were analysed, and the average age was 62 ± 8.24 years. There were no statistically significant differences in sex, age, cardiovascular risk factors, severity of cardiovascular lesions, or medication between the two groups ($P \geq 0.05$) (Table 1). A total of 1186 patients were analysed; 56.8% of the patients had coronary artery stenosis ≥ 50%, and the percentage of patients with obstructive CAD was 45.2%. Among the three types of chest pain, atypical angina pectoris was the most common, accounting for 40.1%, followed by typical angina pectoris, accounting for 35.0%, and nonangina chest pain with ECG changes was the least common, accounting for 25.0%.

Primary clinical endpoints

In the CCTA group, ICA was performed in 292 of 592 patients to confirm the diagnosis of obstructive CAD, resulting in a 50.7% reduction in the use of ICA compared with the 100% rate (594/594) in the ICA group ($P < 0$ (Fig. 2). In the CCTA group, 270 out of 292 patients who underwent ICA were ultimately diagnosed with obstructive CAD, and the percentage of patients with a nonessential ICA was 7.5%. In the ICA group, 266 of the 594 patients who underwent ICA were ultimately diagnosed with obstructive CAD, and the percentage of patients who underwent surgery via the nonessential ICA was 55.2% ($P < 0$ (Fig. 3). In the CCTA group, 56 of 292 patients who underwent ICA did not undergo revascularization (including PCI and CABG), whereas in the ICA group, 380 of 594 patients who underwent ICA did not undergo revascularization (19.2% vs. 64.0%, $P < 0$ (Fig. 4).

Secondary clinical endpoints

There was no significant difference in the MACE rate between the two groups. In the CCTA group, 18 patients were readmitted due to severe angina pectoris, among whom 8 patients underwent CCTA only during the first hospitalization; no obvious vascular stenosis was found at ICA upon readmission, and optimized drug therapy was administered. Six patients underwent ICA and stent implantation during the first hospitalization; no in-stent stenosis or significant stenosis of other vessels was found after ICA was readmitted, and optimized drug therapy was given. Two patients who did not undergo stenting after ICA during the first hospitalization were readmitted with stenting. Two patients underwent stent implantation during the first hospitalization, and ICA showed no stenosis in the stent upon readmission, while other vascular lesions progressed, and stent implantation was performed. In the ICA group, 8 patients were readmitted due to severe angina pectoris, 2 of whom underwent stent implantation during the first hospitalization, and ICA showed no stenosis in the stent upon readmission, while other vascular lesions progressed, and stent implantation was performed. Six patients underwent ICA and stent implantation during the first hospitalization; no in-stent stenosis or significant stenosis of other vessels was found after ICA was readmitted, and optimized medical therapy was started. There were no cases of cardiac death, myocardial infarction, or stroke in the two groups during the 1-year follow-up, as shown in Table 2. Kaplan–Meier curves were drawn to compare the MACE-free survival rates between the two groups during follow-up, which were 97.0% in the CCTA group and 98.7% in the ICA group. The log-rank test revealed no significant difference (log-rank c^2=1.996, $P = 0.158$), as shown Fig. 5. Contrast allergies occurred in 28 patients in the CCTA group and 16 patients in the ICA group ($P > 0.190$) (Table 1). The median hospitalization costs were $1259.54 (¥9194.61) in the CCTA group and $1399.41 (¥10215.67) in the ICA group ($P < 0$ (Fig. 6).

Logistic regression analysis

The forward selection method and the backward elimination method were combined for logistic regression. The baseline data of the patients included sex, age, history of hypertension, diabetes status, hyperlipidaemia status, smoking status, family history of CHD, creatinine, uric acid, creatine kinase–myocardial band (CK-MB), prothrombin time, international normalized ratio (INR), fibrinogen quantification, D-dimer, homocysteine, hypersensitive CRP, free fatty acid content, left atrial anterior and posterior diameter, left ventricular diastolic end diameter and left ventricular ejection fraction (LVEF) status; the variables with $P < 0.05$ for predicting obstructive CAD were creatinine (OR = 1.027; 95% CI: 1.015–1.040; $P < 0.001$), age (OR = 1.030; 95% CI: 1.010–1.050; P=0.003), physical activity-induced symptoms (OR = 2.362; 95% CI: 1.010–1.050; $P = 0.003$), hyperlipidaemia (OR = 1.424; 95% CI: 1.128–1.714; $P = 0.015$), diabetes (OR = 1.793; 95% CI: 1.181–2.724; $P = 0.006$),

Table 1 Clinical data of the included patients

	CCTA group (*n*=592)	ICA group (*n*=594)	Z or χ^2	*P*
Demographic Data				
Male (%)	324 (54.73%)	296 (49.83%)	1.426	0.232
Age (y)	61 (55, 67)	63 (57, 67)	-1.342	0.180
Cardiovascular Risk Factors				
Hypertension (%)	340 (57.43%)	378 (63.64%)	2.389	0.122
Diabetes (%)	114 (19.26%)	154 (25.93%)	3.770	0.052
Hyperlipemia (%)	178 (30.07%)	212 (35.70%)	2.124	0.145
Smoking history (%)	268 (45.27%)	246 (41.41%)	0.969	0.325
CHD family history (%)	74 (12.50%)	82 (13.80%)	0.206	0.650
Laboratory Index				
Ccr (μmol/L)	71 (62, 81)	71 (59, 81)	-0.505	0.613
UA (μmol/L)	302 (251, 365)	296 (254, 352)	-0.415	0.678
CK-MB (U/L)	13 (11, 15)	13 (11, 15)	-0.285	0.776
PT (s)	12.90 (12.50, 13.30)	12.80 (12.50, 13.20)	-1.643	0.100
INR	0.97 (0.94, 1.01)	0.96 (0.93, 1.01)	-1.426	0.154
Fib (g/L)	3.12 (2.74, 3.57)	3.13 (2.76, 3.60)	-0.479	0.632
D-dimer(μg/ml)	0.26 (0.21, 0.37)	0.26 (0.21, 0.37)	-0.267	0.789
HCY (μmol/L)	12.50 (10.20, 14.90)	11.80 (9.50, 15.40)	-1.323	0.186
H-CRP (mg/L)	1.07 (0.51, 2.40)	1.20 (0.55, 3.07)	-1.614	0.107
Lipoprotein-a (nmol/L)	25.45 (13.45, 58.83)	24.10 (9.25, 57.40)	-1.698	0.090
TC (mmol/L)	4.31 (3.59, 5.12)	4.35 (3.72, 5.00)	-0.517	0.605
TG (mmol/L)	1.46 (1.06, 2.04)	1.53 (1.10, 2.25)	-0.832	0.406
LpA (g/L)	1.28 (1.11, 1.40)	1.26 (1.14, 1.45)	-0.694	0.487
LpB (g/L)	0.98 (0.78, 1.17)	0.97 (0.83, 1.17)	-0.276	0.783
HDL-c (mmol/L)	1.06 (0.90, 1.24)	1.03 (0.87, 1.22)	-0.638	0.524
LDL-c (mmol/L)	2.78 (2.15, 3.50)	2.83 (2.20, 3.43)	-0.020	0.984
FFA (mmol/L)	0.36 (0.25, 0.50)	0.39 (0.26, 0.52)	-1028	0.304
LAAP (mm)	35 (33, 38)	36 (33, 39)	-1.547	0.122
LVEDD (mm)	50 (48, 52)	49 (47, 52)	-1.098	0.272
LVEF (%)	62 (61, 65)	62 (60, 65)	-0.158	0.875
Classification of chest pain			0.419	0.811
Typical angina pectoris (%)	210 (35.47%)	204 (34.34%)		
Atypical angina pectoris (%)	230 (38.85%)	246 (41.41%)		
Nonangina chest pain with electrocardiogram changes (%)	152 (25.68%)	144 (24.24%)		
Degree of coronary artery disease				
Obstructive CAD (%)	270 (45.61%)	266 (44.78%)	0.041	0.840
Single vessel disease (%)	128 (21.62%)	114 (19.19%)	0.539	0.463
Double vessel disease (%)	72 (12.16%)	84 (14.14%)	0.508	0.476
Triple vessel disease (%)	70 (11.82%)	70 (11.78%)	<0.001	0.988
Left main disease (%)	22 (3.72%)	18 (3.03%)	0.214	0.644
Adverse reaction				
Allergy to contrast media (%)	28 (4.73%)	16 (2.69%)	1.720	0.190
Drug use				
Aspirin (%)	398 (67.23%)	410 (69.02%)	0.220	0.639
Clopidogrel (%)	224 (37.84%)	192 (32.32%)	1.980	0.159
Statins (%)	464 (78.38%)	452 (76.09%)	0.440	0.507
β-blocker (%)	336 (56.76%)	342 (57.58%)	0.041	0.840
ACEI/ARB (%)	198 (30.07%)	200 (33.67%)	0.886	0.347
Ticagrelor (%)	48 (8.11%)	74 (12.46%)	1.986	0.159
CCB (%)	186 (31.42%)	184 (30.98%)	0.014	0.907

The data are presented as n (%) or M (P25, P75)

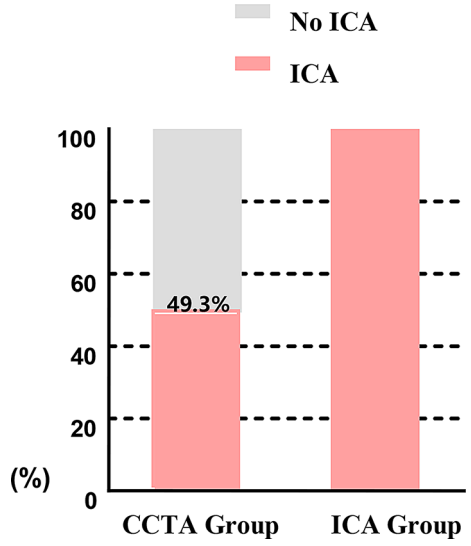

Fig. 2 Proportion of patients who underwent ICA surgery in the two groups

Table 2 MACE during follow-up

	CCTA group (*n*=592)	ICA group (*n*=594)	χ^2	*P*
MACE (%)	18 (3.04%)	8 (1.35%)	3.81	0.057
Cardiac death (%)	0 (0)	0 (0)	-	-
Myocardial infarction (%)	0 (0)	0 (0)	-	-
Stroke (%)	0 (0)	0 (0)	-	-
Readmission for severe angina (%)	18 (3.04%)	8 (1.35%)	3.81	0.057
Unplanned revascularization (%)	4 (0.68%)	2 (0.34%)	0.69	0.406

The data in the table are presented as examples (%)

and smoking history (OR = 1.785; 95% CI: 1.237–2.575; $P = 0.002$) (Table 3).

Establishment and validation of the obstructive CAD prediction model

From the baseline data of patients in this study, variables that had clinical significance and statistical significance ($P < 0.05$) were input as variables in the prediction model

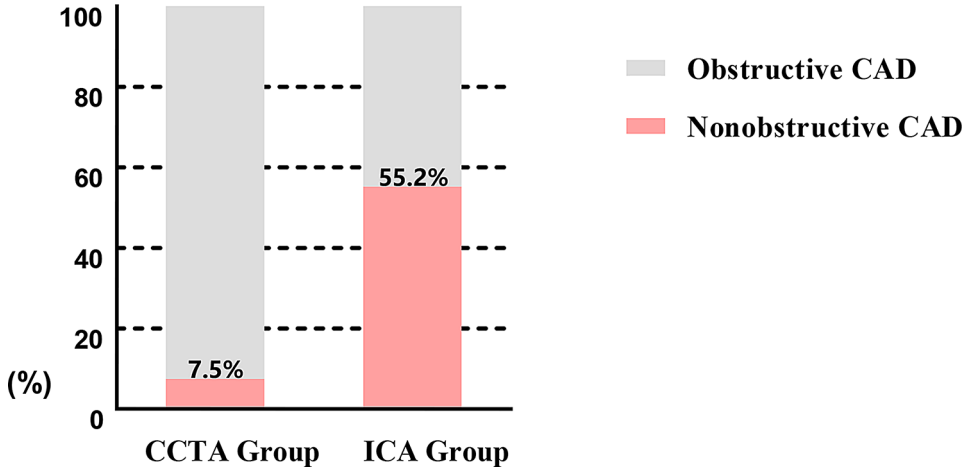

Fig. 3 Proportion of patients diagnosed with nonobstructive CAD after ICA in both groups

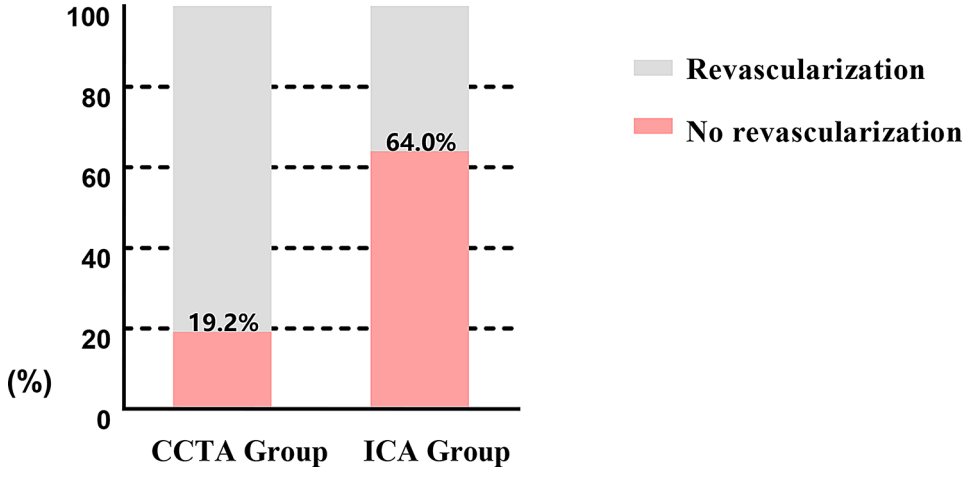

Fig. 4 Proportion of patients without revascularization after ICA in the two groups

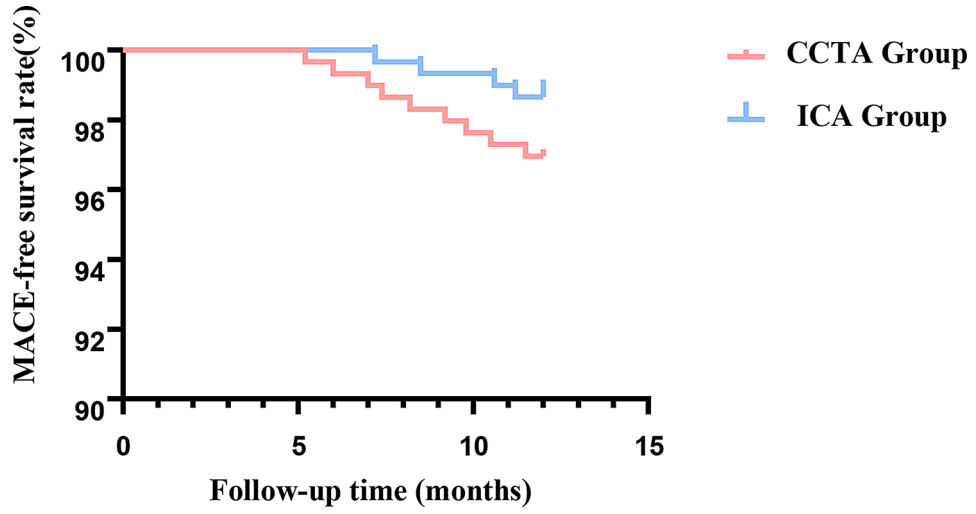

Fig. 5 Kaplan–Meier curves of the two groups

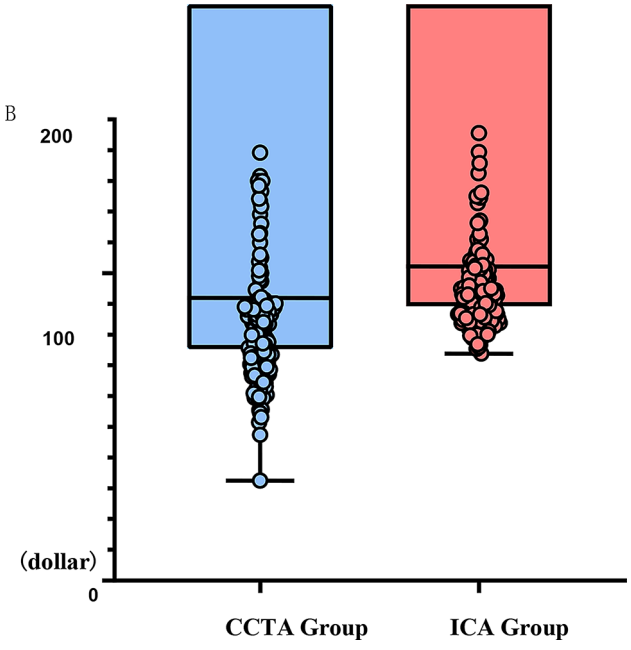

Fig. 6 Comparison of hospitalization costs between the two groups

Table 3 Variables screened by logistic regression to predict obstructive CAD

	OR value	95% CI	*P* value
Ccr	1.027	1.015—1.040	< 0.001
Age	1.030	1.010—1.050	0.003
Induced by physical activity	2.362	1.663—3.356	< 0.001
Hyperlipemia	1.424	1.128—1.714	0.015
Diabetes	1.793	1.181—2.724	0.006
Smoking history	1.785	1.237—2.575	0.002

to establish a risk prediction model for obstructive CAD. The risk prediction score of obstructive CAD was established according to the risk ratio of the variable in the regression analysis, and a line chart was drawn (Fig. 7). The ROC curve was used to evaluate the predictive ability of the selected clinical indicators for obstructive CAD, and the AUC was 0.721, indicating that the model had a strong ability to distinguish patients at high or low risk of obstructive CAD in the selected population of this shown (Fig. 8).

Discussion

In this study, the risks and benefits of noninvasive CCTA versus invasive ICA were compared, and patients with typical angina, atypical angina, and nonangina chest pain with electrocardiographic changes who were suspected of having CCS were randomly assigned to the CCTA group or ICA group. In the enrolled population, CCTA was shown to act as a "safety gatekeeper" for ICA, and using CCTA as a first-line test reduced nonessential ICA without increasing MACE. This study also confirmed that CCTA can reduce the cost of diagnostic evaluation in patients with stable chest pain. Moreover, the outpatient characteristics of CCTA can further shorten the diagnosis and treatment time of patients and reduce the waste of unnecessary medical resources. Patients are more willing to undergo noninvasive CCTA.

Comparison with other relevant studies

The PROMISE study [16] and SCOT-HEART study [17] show that CCTA, as a first-line examination for stable patients with suspected CHD, could detect a higher rate of obstructive CAD than other noninvasive diagnostic tests, including exercise ECG, nuclear stress tests and stress echocardiography, making the use of ICA more reasonable. The retrospective PLATFORM study [18] revealed that computed tomography-derived fractional flow reserve (CT-FFR) reduced the use of ICA by 61% and significantly reduced the proportion of patients with nonobstructive CAD on ICA. However, the present study

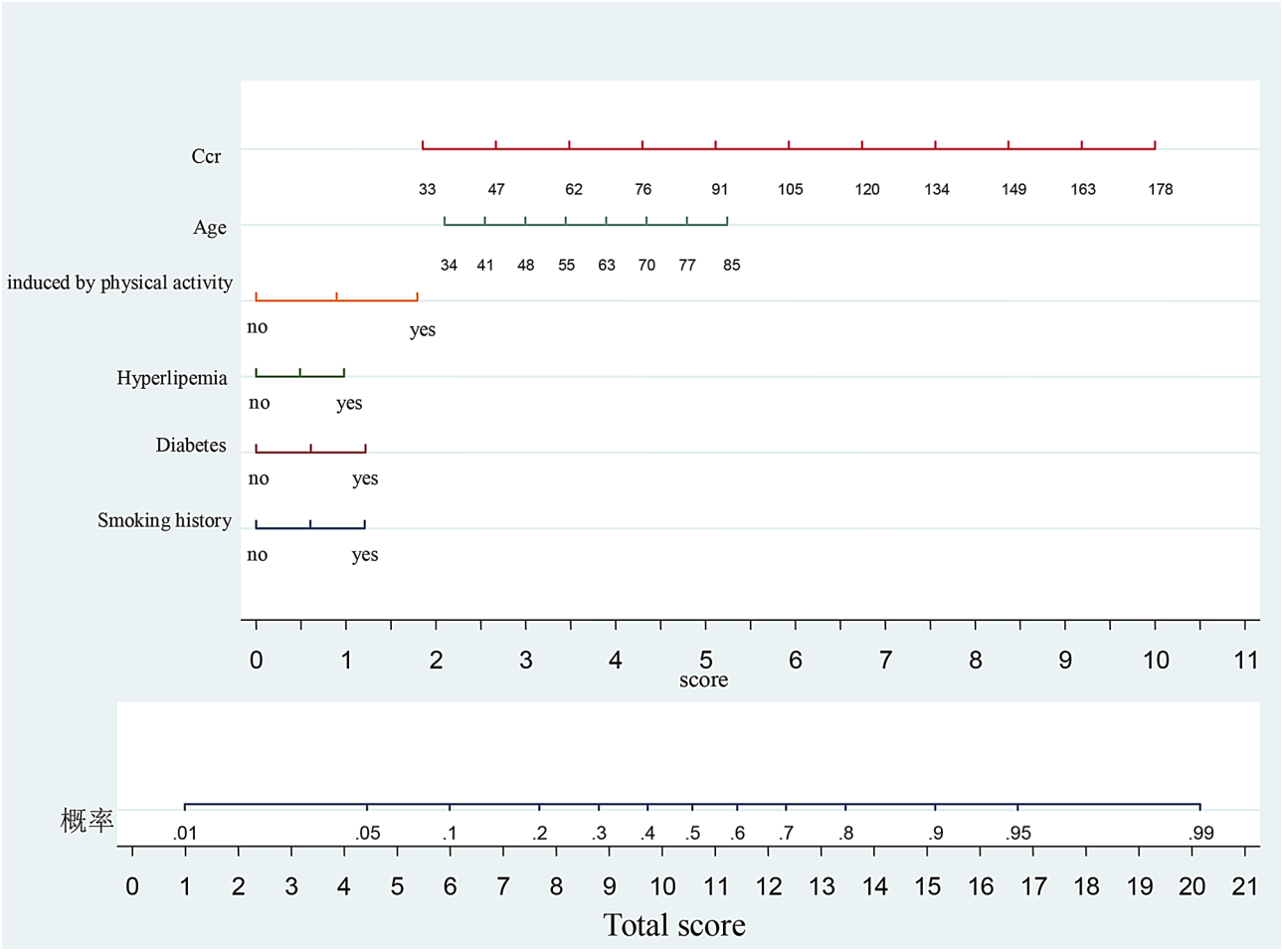

Fig. 7 Risk prediction score for obstructive CAD

did not assess the value of CCTA alone. A randomized single-centre study by Dewey et al. [19] reported that CCTA as a first-line test could significantly increase the rate of obstructive CAD caused by ICA, but the included population had atypical angina pectoris, with a prevalence of obstructive CAD of only 13%. In contrast, our study included patients with typical angina pectoris and nonangina chest pain with ECG changes, and the prevalence of obstructive CAD was 45.2%, expanding the scope of the application of CCTA as a "safety gatekeeper" for ICA to some extent. An early study by Dewey et al. [19] randomized 340 patients, 168 of whom were assigned to CCTA and 172 to ICA. The primary clinical endpoint of the study was complications within 48 h after CCTA or ICA, of which serious complications (including myocardial infarction, death, stroke, etc.) were uncommon (0.3%) and had similar rates in the two groups. However, complications such as haematoma at the puncture site and secondary bleeding at the puncture site were significantly less common in the CCTA group than in the ICA group. Our study compared the number of patients with contrast agent allergy in the CCTA group and the ICA group and revealed that there were more patients with contrast agent allergy in the CCTA group, but this difference was not significant. The reason may be that some patients in the CCTA group received two contrast agent injections in a short period, which may increase the likelihood of contrast agent allergy. In addition, Dewey et al. [19] completed a 3.3-year (median) follow-up of 329 patients in the CCTA and ICA groups and reported few MACE events: 7 of 167 patients in the CCTA group and 6 of 162 patients in the ICA group. This demonstrated that CCTA guidance alone was safe and did not increase long-term clinical events in patients who did not have ICA in the CCTA group, which was also confirmed in our study; however, the follow-up time in our study was shorter, at 1 year. The CONSERVE study [20] also demonstrated that first-line use of CCTA can reduce unnecessary ICA examination, but in the CONSERVE study, 33.2% of the patients had ≥ 50% stenosis in either coronary artery, compared with 56.8% in our study. These findings suggest that our study evaluated the efficacy of CCTA in a population with a relatively high risk of CHD. The CAT-CAD randomized single-centre study [21], which was

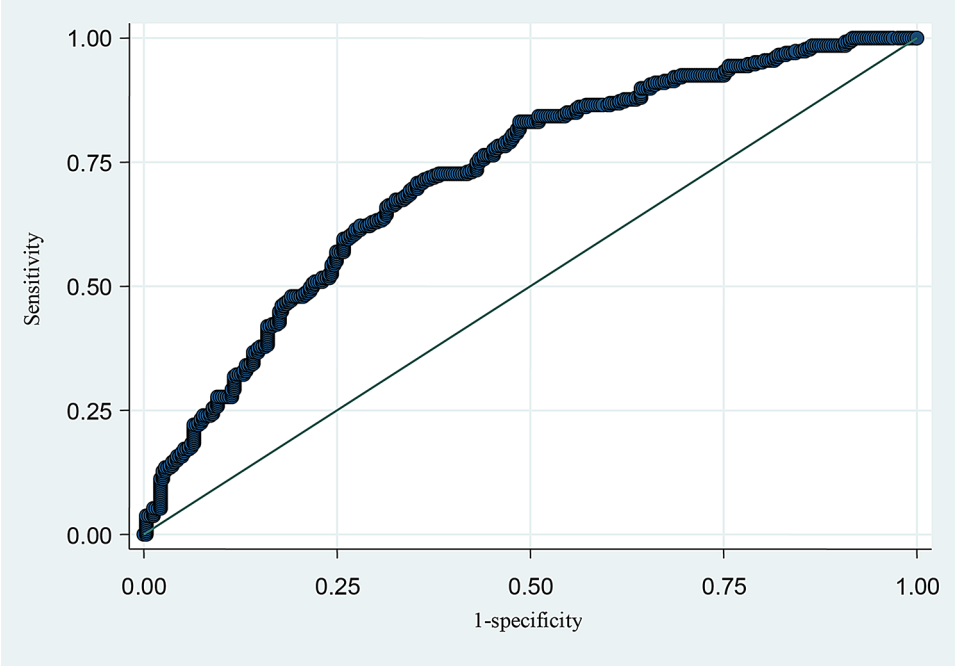

Fig. 8 ROC curve

based on the 2013 European Society of Cardiology (ESC) guidelines for the management of stable CAD, included patients with an ICA indication, including patients with typical angina with a left ventricular ejection fraction < 50%, patients with PTP between 50% and 80% with a positive or inconclusive functional test, and patients with PTP > 85%. PTP was assessed on the basis of criteria for age, sex, and angina symptoms. The CAT–CAD study [21] revealed that the use of CCTA as a first-line test reduced the number of patients with ICA by 64.4% and the number of nonrevascularized patients after ICA by 88.1% compared with those who underwent ICA. However, that study included only 120 patients in total and 45 patients with typical angina. The DISCHARGE trial [22] was a randomized controlled study comparing CCTA and ICA as initial tests in 3561 patients with stable chest pain and a moderate predictive probability of CHD. At 3.5 years of follow-up, there was no substantial difference in the incidence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke between the CCTA and ICA groups, and the incidence of MACE was very low, at 2.1% for CCTA and 3.0% for ICA. There was also no difference in the incidence of angina during follow-up. These results are similar to our conclusion. However, the proportion of patients enrolled in the DISCHARGE trial who had at least 50% stenosis in any coronary artery was 25.7%, compared with 56.8% in our study, and the patients enrolled in our study were at greater risk for obstructive CAD.

Analysis of CHD risk factors

Diabetes mellitus (DM) is a traditional risk factor for CHD. Fasting blood glucose is linearly and significantly associated with the risk of cardiovascular disease (CVD) at all concentrations. Even when it is below the DM threshold (7 mmol/L), an increase in blood glucose starting from a fasting blood glucose concentration of 5.6 mmol/L has a negative effect on the prognosis of CHD [23]. Data from the international prospective EpiDREAM cohort study revealed that the risk of CVD gradually increases among individuals with normal blood glucose, those with impaired fasting glucose or impaired glucose tolerance, and newly diagnosed DM patients. Every 1 mmol/L increase in fasting blood glucose is associated with a 17% increase in the risk of future cardiovascular events or death [24]. A systematic review of 4,549,481 patients with type 2 DM revealed that the overall prevalence of macrovascular complications was 32.2%, with CHD being the most common at 21.2% [25]. Different pathophysiological mechanisms underlie the relationship between DM and CVD. A large amount of epidemiological data support the pathophysiological role of hyperglycaemia in directly affecting endothelial function as well as the induction and progression of atherosclerosis [26]. However, other pathophysiological factors, such as hyperinsulinaemia and insulin resistance, are also involved. Hyperlipidaemia refers to the presence of abnormally high levels of lipids, such as cholesterol and triglycerides, in the blood. Elevated low-density lipoprotein cholesterol in the plasma tends to deposit on the arterial wall, which may lead to progressive hardening

of the arterial wall and the formation of atherosclerotic plaques, significantly affecting the supply of oxygenated blood to tissues and ultimately causing ischaemia. In addition, hyperlipidaemia promotes platelet activation through multiple mechanisms, putting patients at risk of thrombosis. Smoking is a major factor in the development of CHD and affects its progression rate. The nicotine and carbon monoxide contents in cigarettes have a destructive effect on arteries. High levels of accumulated nonesterified fatty acids in circulating blood can induce cell damage, trigger an inflammatory response, and lead to the formation of atherosclerotic plaques. The positive correlation between serum creatinine levels and the severity of coronary artery lesions has also been confirmed in previous studies. Ageing is the most important factor affecting cardiovascular health. The risk of CVD increases approximately 10-fold between the ages of 50 and 80. Ageing leads to increased oxidative stress and shortened telomere length, resulting in DNA damage, impaired cell division, and ageing of cardiovascular tissues [71]. These factors strongly affect the integrity of the vascular system and the cardiovascular repair mechanism, increasing the vulnerability of cardiovascular tissues to damage. The risk prediction model for obstructive CAD established on the basis of logistic regression in this study included diabetes, hyperlipidaemia, smoking history, creatinine level, age, and typical angina symptoms, which is consistent with previous studies. Hypertension is also a traditional risk factor for CHD. It is estimated that 54% of strokes and 47% of CHD worldwide are the result of hypertension. Hypertension exerts a pro-inflammatory effect in arteries through vasoactive peptides, leading to the recruitment of monocytes into the intima, which is a prerequisite for the occurrence of atherosclerosis. Although CVD is the leading cause of death in both men and women, it has been determined that men are more prone to CVD, whereas the onset of CVD in women is relatively delayed. The Framingham study investigated the incidence of CVD in the general population for more than 50 years. Compared with that in men, the occurrence of atherosclerosis-related CVD events in women is delayed by 10–20 years. This is due mainly to sex-based differences in hormones that regulate cardiovascular function. Previous studies have shown that endogenous oestrogen in women has different cardiovascular protective effects, such as protecting blood vessels from the formation of atherosclerotic lesions, reducing the level of low-density lipoprotein cholesterol, and increasing the concentration of high-density lipoprotein cholesterol in the plasma. However, in this study, there were no significant differences in hypertension or sex between patients with obstructive CAD and control patients, and these factors were not included as variables in the prediction model. This may be related to factors such as the small number of our selected subjects.

Limitations and prospects

This study was conducted at a single centre, and patients were not enrolled on consecutive working days, which could introduce some bias. Second, this study chose non-essential ICA rather than MACE as the primary endpoint because the MACE rate was very low in the study population. A much larger sample will be needed for future studies. In addition, the MACE follow-up in this study lasted for only 1 year, so longer follow-up is needed to test the results of this study. Third, owing to the small sample size, this study was unable to provide a robust assessment of the clinical complications associated with the two examinations. Fourth, patients with impaired renal function were excluded. One study showed that intravenous iodine contrast agents are less risky than arterial iodine injections are [23], which supports the better safety profile of CCTA. Fifth, the sample size was relatively small for establishing a predictive model for obstructive CAD.

Future studies can develop a risk score model for obstructive CAD with stronger predictive power on the basis of a larger sample size. Extending the follow-up time to evaluate the long-term prognosis of patients receiving CCTA and ICA treatments is recommended. Multicentre studies should be conducted to validate the research findings in different populations and medical settings. Additionally, the potential of artificial intelligence-driven tools to increase the diagnostic accuracy and efficiency of CCTA should be explored.

Conclusion

In patients with suspected CCS, including typical angina, atypical angina and nonangina chest pain with abnormal electrocardiogram results, the use of CCTA as a first-line diagnostic test can reduce the unnecessary incidence of ICA and hospitalization costs without increasing the incidence of MACE. A risk prediction model of obstructive CAD was established on the basis of the baseline data of the patients enrolled in this study, providing a clinical basis for the decision to use CCTA or ICA. Patients with a low probability of obstructive CAD can be given priority for CCTA, whereas patients with a high probability can be given priority for ICA. Our findings have wide-ranging implications for healthcare systems, especially in resource-scarce settings. Our findings can be used to optimize the diagnosis and treatment processes, enable more efficient utilization of medical insurance resources, avoid medical waste, and reduce healthcare expenditures.

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Author contributions
Clinical data collection and analysis were performed by HL and RJF. CTCA imaging data was collected and analyzed by WZ. The first draft of the manuscript was written by LXD, and all authors commented on previous versions of the manuscript. LXD and RJF also did the statistics work. RJ contributed to the study conception and design. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the local ethics committee of TEDA International Cardiovascular Hospital ([2021]-0114-3). All experiments were performed in accordance with relevant guidelines and regulations, such as the Declaration of Helsinki, and the patients signed the informed consent form and agreed to be published.

Consent for publication
All authors approve the publication of the final manuscript. Written informed consent was obtained from the patients for publication of this study.

Declaration of generative AI in scientific writing
The authors declare that they did not use AI or AI technologies in the writing process.

Competing interests
The authors declare no competing interests.

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