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Clinical characteristics and biomarkers of coronary microvascular dysfunction and obstructive coronary artery disease

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Abstract

Objective: The purpose of this study was to determine the clinical characteristics and biomarkers in patients with coronary microvascular dysfunction (CMVD) and to compare them with patients with obstructive coronary artery disease (OCAD).

Methods: We conducted a single-center, hospital-based, observational, descriptive, comparative, clinical study of 40 patients, including 20 patients with CMVD and 20 with OCAD. We assessed laboratory biomarkers (low-density lipoprotein [LDL], high-density lipoprotein [HDL], red blood cell distribution width [RDW], brain natriuretic protein [BNP], troponin I), and PET/CT coronary flow reserve was performed.

Results: The mean coronary flow reserve (CFR) in patients with CMVD was 1.96±0.55. Mean low-density lipoprotein cholesterol (LDL-C) levels were significantly higher in the CMVD subgroup (2.53±0.63 mmol/L) compared with the OCAD subgroup (1.76±0.97 mmol/L). Logistic regression analysis identified LDL-C as a predictor for the development of CMVD (odds ratio, 5.24).

Conclusion: It is difficult to differentiate between OCAD and CMVD based on the patient's medical history, clinical characteristics, and coronary angiography results. Further investigations may be needed to allow an accurate diagnosis. CFR measurements based on non-invasive

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positron emission tomography/computed tomography may aid the diagnosis of CMVD. We also identified LDL-C as a predictor for the development of CMVD.

Keywords
Coronary microvascular disease, obstructive coronary artery disease, low-density lipoprotein, hypertension, diabetes mellitus, coronary flow reserve

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Introduction

Coronary artery disease (CAD) is a clinical syndrome that is characterized by impedance or blockage of one or more coronary arteries. CAD may be associated with a high risk of angina, ischemic fraction, arrhythmia, heart failure, or sudden death, although some patients remain asymptomatic. The American Heart Association 2016 heart disease and stroke statistics update reported that 15.5 million people $\geq$20 years of age in the United States have coronary artery disease, and this prevalence increases with age.[1]

Ischemic heart disease is divided into obstructive coronary artery disease (OCAD), which develops from the erosion or rupture of atherosclerotic plaques, and non-obstructive CAD (NOCAD), resulting from impaired vasodilation of arterioles and leading to an inadequate increase in blood flow from rest to stress. OCAD is defined as epicardial coronary stenosis $\geq$50% by quantitative coronary angiography (CAG), with non-obstructive lesions that are additionally grouped as normal coronary vessels (0% lumen stenosis in all vessels) and mild coronary stenosis (1%–49% lumen stenosis in at least 1 vessel).[2] NOCAD is a common finding on diagnostic CAG, with rates of up to 50% to 60% in patients with stable angina and about 30% in certain populations with acute coronary syndrome. Symptomatic patients with NOCAD have often been reassured of the innocuous nature of the results, and frequently, no further preventive measures are taken.[3]

Coronary microvascular dysfunction (CMVD) is a specific type of NOCAD. However, epidemiological data on CMVD is limited, and its reported morbidity varies depending on the statistical methods used. CMVD is usually present in 50% to 65% of angina patients with NOCAD.[4] CMVD also tends to have a poor prognosis when it is not properly treated, and this is associated with higher rates of hospitalization and increased risks of adverse cardiovascular events.[4] In a study of 4,711 women with stable angina pectoris who were referred for CAG and 3,326 asymptomatic women, the hazard ratios for major adverse cardiovascular events (MACE) in women with angina and normal coronary arteries and diffuse non-obstructive stenosis were 1.52 and 1.85, respectively, compared with asymptomatic women. They also reported a higher prevalence of cardiovascular events in 540 symptomatic women without CAD compared with 1,000 asymptomatic age- and race-matched women.[5] Another study examined sex differences in outcomes after CAG in patients with angina and diffuse NOCAD, and found that women were three times more likely than men to experience a cardiac event within the first year.[6]

CMVD is common but it is likely to be ignored in patients with NOCAD in clinical practice, and it is therefore necessary to ensure the accurate detection and definitive treatment of CMVD. In this study, we aimed to differentiate between CMVD and OCAD using clinical data and to detect CMVD in angina-like patients to prevent MACE. Smoking, alcohol, hypertension, diabetes mellitus, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), red cell distribution width (RDW), and troponin I were identified as risk factors, while coronary flow reserve (CFR) was determined by cardiac positron emission tomography (PET)/computed tomography (CT), which is considered to be the gold standard for diagnosing CMVD.

Methods

Study population

We assessed 40 patients at the Department of Cardiology, Wuhan Union Hospital, China, including 20 patients with CMVD and 20 age- and sex-matched patients with OCAD. The inclusion criteria were as follows: patients with chest pain whose symptoms could not be relieved by treatment with nitrates; ST-T dynamic changes on electrocardiography (ST-segment depression in at least two adjacent leads $\geq$0.1 mV, symmetrical T wave deep inversion in at least two adjacent leads, or dynamic change during chest discomfort); coronary artery examination by CAG; age 18 to 75 years; and patients who were attending hospital for the first time and had not received any medications before their visit. The exclusion criteria were as follows: acute coronary syndrome; patients who had received coronary revascularization (stent implantation or coronary artery bypass graft); heart failure (elevated brain natriuretic peptide [BNP] levels); other myocardial diseases affecting ventricular wall motion or cardiac ejection function (stress cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, myocardial amyloidosis); severe arrhythmias (permanent atrial fibrillation, recurrent and poorly controlled ventricular arrhythmias); severe valvular heart disease; follow-up patients receiving medications including statins; allergic habitus; and patients or family members who refused to participate in the study.

Study design and objectives

This was a single-center, hospital-based, observational, cross-sectional, descriptive, comparative, clinical study using qualitative and quantitative data. The aim of this study was to determine the clinical characteristics and biomarkers in patients with CMVD and to compare them with patients with OCAD. Clinical characteristics included symptoms, smoking, alcohol, hypertension, and diabetes mellitus. Laboratory biomarkers included LDL-C, HDL-C, red blood cell distribution width (RDW), BNP, and troponin I.

Image acquisition

PET/CT scanning was used to measure CFR and to assess microvascular coronary perfusion. Images were obtained using a dedicated PET/CT scanner (Discovery VCT®, GE Medical Systems, Milwaukee, WI, USA) immediately after intravenous injection of 3.75 to 5.55 MBq/kg of ^{13}N-NH_3, rest, and ATP-stress, respectively. A low-dose CT scan was obtained for attenuation correction using the following parameters: tube voltage, 120 kV; 80 mAs; and slice collimation, 3.75 mm. PET data were constructed with the ordered subset expectation maximization algorithm. Both CT and PET data were evaluated using a

workstation (Xeleris®, GE Medical Systems, Waukesha, WI, USA).

The cut-off CFR value for CMVD in this study was 2.6, based on a previous study.[7]

Cardiac catheterization

All patients underwent CAG using the Seldinger technique, via right radial artery access. Selective CAG was performed with multiple projections. Images were obtained using a Siemens Artis Zee Floor (Siemens Medical Solutions, Munich, Germany), and were reviewed by two experienced cardiologists with no knowledge of the patient's clinical information. Any contradictory opinions were resolved by a third independent cardiologist. Even slight angiographic abnormalities were considered as evidence of coronary lesions. The number of diseased arteries was determined and arteries with $\geq$50% stenosis were classified as OCAD and those with <50% stenosis as CMVD.

Ethics statement

The clinical protocol and informed consent forms were approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology. All patients provided written informed consent. This clinical study was conducted according to the revised Declaration of Helsinki regarding the use of patient information in biomedical research. All authors agreed to publication of this manuscript.

Statistical analysis

All data are presented as the mean $\pm$ standard deviation for continuous variables and n (%) for categorical variables. Comparisons between groups were made using Student's *t*-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. A *P* value of <0.05 was considered to be statistically significant. Logistic regression analysis was performed to predict CMVD and OCAD. Statistical analysis was performed using SPSS version 20 (IBM Corp., Armonk, NY, USA).

Results

Diagnostic basis for differentiating between OCAD and CMVD in angina-like patients

Angina-like patients with abnormal electrocardiography results underwent CAG using the Seldinger technique to confirm if the coronary arteries were stenosed. This minimally invasive procedure can access and identify the exact location and severity of CAD. Epicardial coronary stenosis $\geq$50% was diagnosed as OCAD (Figure 1). Arteries with <50% stenosis were further examined by PET/CT to calculate the CFR, and CMVD was diagnosed if the CFR was <2.6 (Figure 2). We performed PET/CT to assess the coronary flow reserve between the two subgroups. The mean CFR was low in the CMVD patients (1.96$\pm$0.55) compared with the OCAD patients (2.50$\pm$0.79).

Clinical characteristics in CMVD and OCAD subgroups

The baseline characteristics of the CMVD and OCAD subgroups are shown in Table 1. There were no significant differences between the subgroups in terms of most parameters. However, hypertension and diabetes were significantly more common in the OCAD compared with the CMVD subgroup ($P<0.001$ and $P=0.001$, respectively). Regarding clinical symptoms, chest tightness was more common in the CMVD subgroup compared with the OCAD subgroup ($P=0.04$). Among the laboratory results, LDL-C levels were significantly lower in the OCAD subgroup compared with the CMVD subgroup ($P<0.001$),

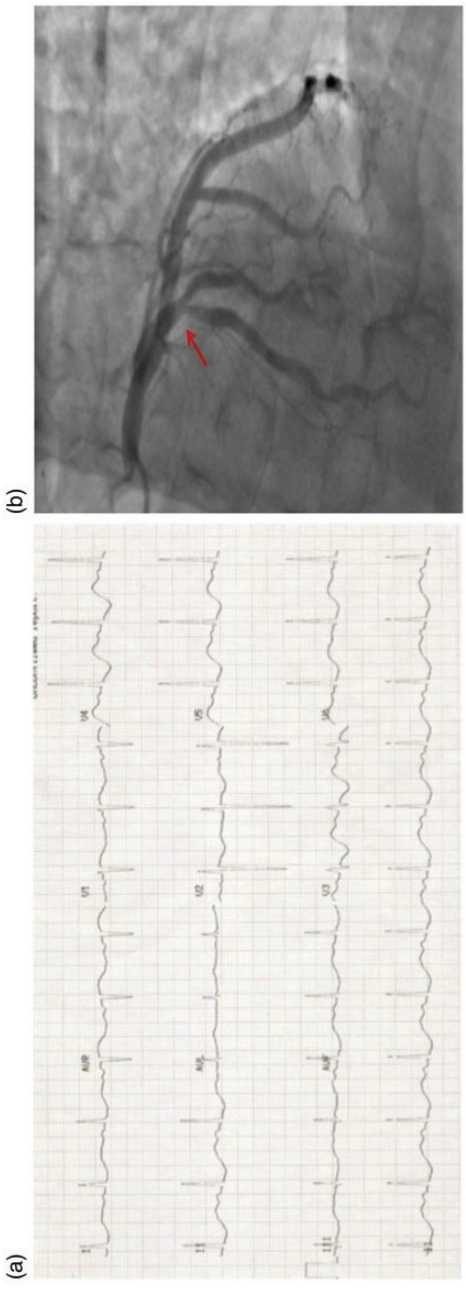

Figure 1. Electrocardiography and coronary angiography in a 54-year-old woman with chest pain. (a) Electrocardiography with ST-depression on leads II, III, aVF, and V1-6 and (b) Coronary angiography showing a 55% lesion in the left circumflex coronary artery (arrow).

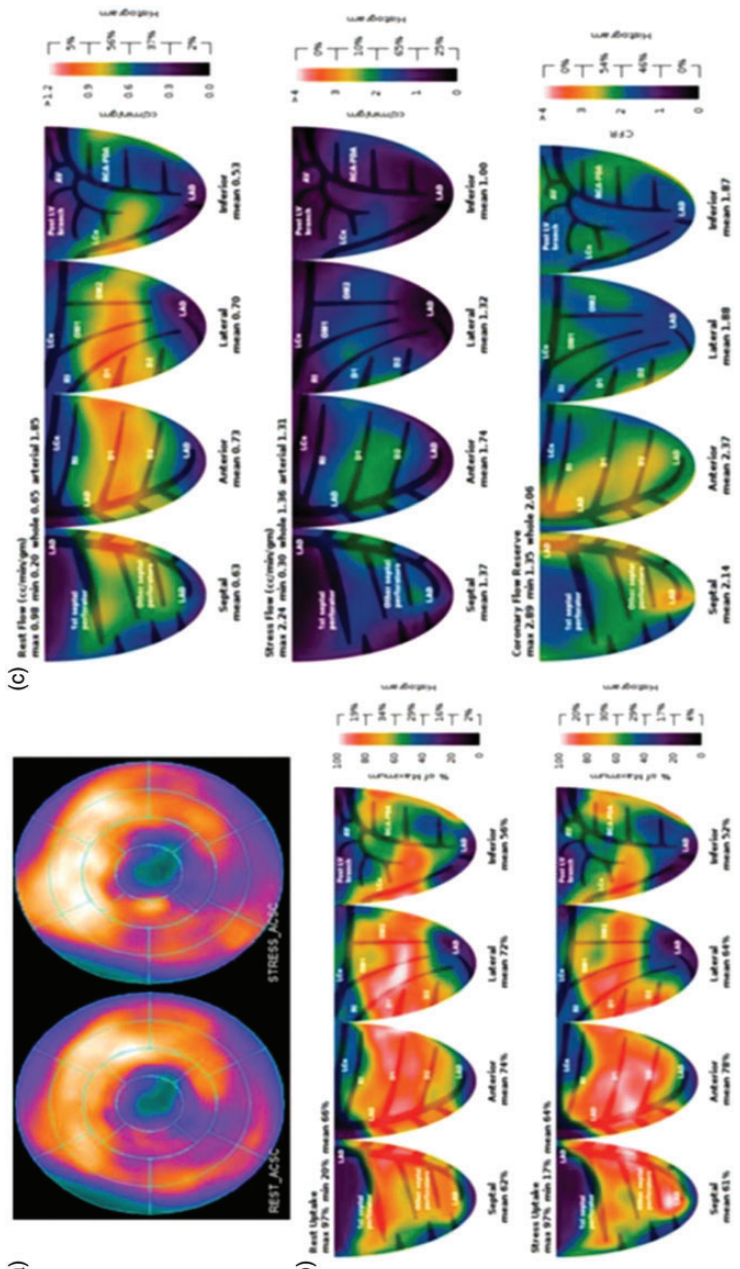

Figure 2. (a) Myocardial bovine eye diagram; (b) rest/stress uptake; and (c) rest/stress flow and coronary flow reserve (CFR). Resting and ATP-stressed PET/CT myocardial perfusion images in a 54-year-old woman showing showed extensive severe ischemia. The overall CFR was 2.06, and the CFRs of the septal, anterior, lateral, and the inferior walls were 2.14, 2.37, 1.88, and 1.87, respectively.

Table 1. Baseline demographic characteristics.

Variable	Subgroup		*P* value
	CMVD (n = 20)	OCAD (n = 20)	
Demographic characteristics			
Age, years, (mean± SD)	58±13	58±13	>0.95
Sex (%)			>0.95
Male	8 (40)	8 (40)	>0.95
Female	12 (60)	12 (60)	>0.95
Symptoms (%)			
Chest pain	10 (50)	12 (60)	0.34
Chest tightness	9 (45)	4 (20)	0.04*
Combined	1 (5)	4 (20)	0.15
Smoking (%)	1 (5)	5 (25)	0.34
Alcohol (%)	1 (5)	5 (25)	0.34
Hypertension (%)	7 (35)	15 (75)	<0.001*
Diabetes mellitus (%)	0 (0)	9 (45)	0.001*
SBP, mmHg (mean±SD)	125±13.4	126±15.9	0.88
DBP, mmHg (mean±SD)	79.5±11.1	78±11	0.86
Laboratory parameters			
LDL-C, mmol/L	2.53±0.63	1.76±0.97	<0.001*
HDL-C, mmol/L	1.25±0.39	1.09±0.25	0.67
RDW, median (range)	13.6 (11.9–18.5)	13.8 (12.1–16.4)	0.13
Troponin I, pg/mL	12.75 (10.1–32)	26 (12.1–87)	0.01*
HbA1c, %	5.79±1.71	6.79±1.72	0.09
BNP, pg/mL	33.8±25.4	48.7±23.4	0.64
Electrocardiography (%)			
Anterior wall ST-changes	5 (25)	10 (50)	0.19
Inferior wall ST-changes	12 (60)	5 (25)	0.025*
Lateral wall ST-changes	2 (10)	4 (20)	0.66
Posterior wall ST-changes	1 (5)	1 (5)	>0.95

CMVD, coronary microvascular dysfunction; OCAD, obstructive coronary artery disease; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; RDW, red cell distribution width; HbA1c, hemoglobin A1c.

while troponin I levels were significantly higher in the OCAD subgroup, but were still within the normal range (P=0.01) (Figure 3). Electrocardiography showed nonspecific ST-T changes, while inferior wall ST-changes were significantly more common in the CMVD subgroup compared with the OCAD subgroup (P=0.025).

LDL-C was a strong predictor of CMVD

The above results identified significant differences in four risk factors (hypertension, diabetes mellitus, troponin I, and LDL-C) between patients with CMVD and OCAD. We, therefore, conducted a logistic regression analysis including hypertension, troponin I, and LDL-C, but excluding diabetes mellitus to avoid bias because it was only observed in the OCAD subgroup. The results identified LDL-C as a strong predictor for developing CMVD, with an odds ratio of 5.24 (Table 2), while hypertension and troponin I had odds ratios of 0.12 and 0.91, respectively.

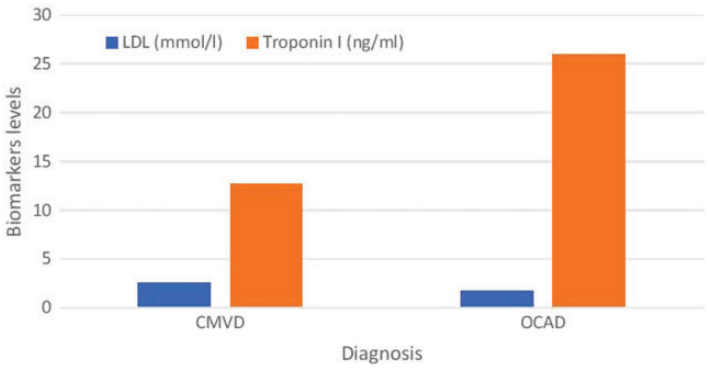

Figure 3. LDL-C and troponin-I levels in CMVD and OCAD subgroups. CMVD, coronary microvascular dysfunction; OCAD, obstructive coronary artery disease; LDL-C, low-density lipoprotein-cholesterol.

Table 2. Logistic regression of potential predictive factors of CMVD.

Factor	OR	Lower 95% CI	Upper 95% CI	*P* value
Hypertension	0.12	0.19	0.735	0.022*
hsTNI	0.91	0.84	0.985	0.019*
LDL-C	5.24	1.40	19.64	0.014*

OR, odds ratio; CI, confidence interval; hsTNI, highly sensitive troponin I; LDL-C, low-density lipoprotein-cholesterol.

Discussion

Normal coronary arteries and NOCAD are common findings in women with signs and symptoms of ischemia.[8] The Coronary Artery Surgery Study (CASS) demonstrated that the constellation of symptoms associated with typical angina (substernal pain precipitated by emotional or physical stress, relieved within 10 minutes by rest or nitroglycerin) predicted CAD in both men and women. However, the prevalence of NOCAD was higher among women compared with men in CASS, suggesting that symptoms were less diagnostic in women. The Women Ischemia Syndrome Evaluation (WISE) study found that a classification of "typical" angina missed 65% of women with CAD. However, women without CAD might experience symptoms of microvascular ischemia or ischemia related to coronary constriction.[9] This suggests that there might be a difference in clinical presentations between men and women in terms of typical compared with atypical angina, and concentrating on one might result in some patients being missed, especially women with CMVD.

LDL-C is one of the most significant reversible risk factors for cardiovascular morbidity and mortality. A meta-analysis indicated that reducing LDL-C by 1 mmol/L could reduce the cardiovascular risk by one-fifth because a similar linear phenomenon is likely to occur at any baseline LDL-C level.[10] Kauffman et al.[11] showed that LDL-C, but not total cholesterol, was inversely correlated with CFR in patients with hypercholesterolemia, and they concluded that LDL-C-induced CMVD could play an important part in the pathogenesis of CAD and its complications. Moreover, Mangiacapra et al.[12] found a significant correlation between serum cholesterol levels and CMVD. These results suggest that LDL-C is a potentially significant risk factor for developing cardiovascular disease, including CMVD and that it is involved in the pathogenesis of disease progression.

Several trials have aimed to improve the prognosis and reduce MACE, including the SATURN trial,[13] in which rosuvastatin reduced LDL-C, increased HDL, and improved the LDL-to-HDL ratio compared with atorvastatin. The Scandinavian Simvastatin Survival Study (4S) demonstrated reductions in all-cause mortality, fatal events, and myocardial revascularization procedures.[14–16] The current study found significantly higher mean LDL-C levels in patients with CMVD compared with OCAD. However, LDL-C remains a risk factor in both subgroups, and emphasis should be placed on reducing LDL-C to reduce the risks of MACE.

CFR is the ratio of absolute global myocardial blood flow at peak stress compared with at rest,[17] and it is emerging as a potential quantitative imaging marker of vascular age and clinical risk. CFR can be measured invasively by quantitative CAG, and noninvasively by echocardiography, cardiac magnetic resonance imaging (CMR), and PET/CT. PET quantitative analysis is more accurate than single photon computed tomography (ECT), which tends to produce false-positive results. Lansky and Pietras investigated non-atherosclerotic contributors to the adverse prognosis associated with the abnormal CFR that was observed in the WISE study.[18] Both men and women with abnormal CFR had strikingly higher rates of events compared with patients with normal CFR. Women with normal stress echocardiograms and a normal CFR had an annual event rate of 0.5% compared with 8.2% among those with an abnormal CFR.[19] A CFR <2 was consistent with worsening diastolic function, showing a decrease in e′ and E/e′. Impaired CFR was independently associated with diastolic dysfunction and adverse events, particularly in hospitalized heart failure with preserved ejection fraction (HFpEF) patients.[20] Moreover, CFR provides prognostic information, especially in asymptomatic patients with type 2 diabetes mellitus without overt CAD, and patients with a CFR <2.5 tended to have worse long-term outcomes.[21] A CFR <2 also had a prognostic value for future cardiovascular events in nondiabetic patients with chest pain without myocardial perfusion defects.[22] Most studies found that a lower CFR was associated with a poor prognosis, which explains the complications of CMVD including myocardial infarction, congestive heart failure, stroke, and sudden cardiac death. In our study, CMVD was diagnosed based on a CFR of <2.6, as determined by Löffler and Bourque,[7] who combined different research studies to produce the following classifications: CFR >2.6 and no CMVD; CFR 2.6–1.5 and borderline CMVD; and CFR <1.5 and definite CMVD.

CMVD poses a management challenge because of the lack of uniform diagnostic criteria and the multiple mechanistic pathways that contribute to the pathophysiology of the disease. The goals of treatment include controlling the symptoms, improving quality of life, reducing the incidence of hospitalization, and improving event-free survival. A multidisciplinary approach is often required. Some treatment strategies, including nitric oxide modulators, angiotensin-converting enzyme inhibitors, and transcutaneous electrical nerve stimulation, had beneficial effects on their endpoints in a systematic review by Marinescu et al.,[4,7] while other drugs, including calcium channel blockers, alpha-blockers, and statins showed no improvements in their respective endpoints. Other studies of treatment options for CMVD investigated drugs such as calcium channel blockers (verapamil and diltiazem), sublingual nitrates, nicorandil, and phosphodiesterase inhibitors (sildenafil) in women, and angiotensin-converting enzyme inhibitors, statins, ranolazine, and trimetazidine, with some improvement.[22,23] Limited evidence also suggests that some Chinese medicines could improve CMVD, which is caused by

slow coronary flow.[24] CMVD is easy to overlook, and emphasis should be placed on obtaining a correct diagnosis and administering the appropriate drugs, with regular follow-up.

This study was limited by the small sample size, and the sample size was limited by the high cost of PET/CT. Further studies with more patients are required to verify these results.

The current study demonstrated that there are many similarities between CMVD and OCAD in terms of their clinical presentations and laboratory biomarkers. However, the results highlight the use of CFR measurements that were obtained by non-invasive PET/CT for differentiating between these subgroups and as a prognostic indicator. It is important to establish a correct diagnosis of CMVD to prevent future MACE.

Availability of data and materials

Data are available upon request to the authors.

Author contributions

All authors drafted the manuscript and performed critical revision. All authors read and approved the final manuscript.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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