Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Glycolipid dysregulation mediated Left ventricular diastolic dysfunction in coronary microvascular disease pathogenesis

Yanjiang Jin
Heilongjiang University of Chinese Medicine
Wei Wen
Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine
Yi Chi
The People's Hospital Medical Group of Xiangzhou Zhuhai
Fuhai Zhao
China Academy of Chinese Medical Sciences
Li Liu
2763258815@qq.com

Heilongjiang University of Chinese Medicine

Article

Keywords: coronary microvascular disease, glycolipid dysregulation, left ventricular diastolic dysfunction, angiographic microvascular resistance.

Posted Date: August 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10420371/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background: Ischemic heart disease (IHD) from coronary microvascular disease (CMVD) is key in non-obstructive coronary heart disease, and left ventricular diastolic dysfunction (LVDD) may link to CMVD via glycolipid dysregulation.

Objective: To explore LVDD-CMVD association and mediation by glycolipid dysregulation.

Methods: This study enrolled patients with chest pain and no obstructive coronary artery disease to explore glycolipid dysregulation -mediated LVDD triggers CMVD. Logistics regression model and linear correlation analysis were constructed to explore the associations between LVDD and CMVD. Restricted cubic splines were applied to further the associations of LVDD with CMVD. Given glycolipid dysregulation as intermediary factor, we investigate the mediating effects of LVDD on CMVD.

Results: 376 patients were eventually recruited and 222 patients were diagnosed with CMVD. In the multivariable-adjusted model, LVDD and glycolipid dysregulation including the triglyceride-glucose (TyG), triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) and triglyceride/high-density lipoprotein (TG/HDL)were positively related to CMVD (Odds Ratio (OR)=2.18, 95% CI=1.03-4.60; OR=1.10, 95% CI=0.83-1.45; OR=0.82, 95% CI=0.58-1.14, respectively). Mediation analysis indicated that TyG mediated 4% of the association of LVDD with CMVD.

Conclusion: LVDD positively associates with CMVD, with TyG mediating this link, highlighting glycolipid dysregulation’s role in CMVD pathogenesis.

Introduction

In 2019, the European Society of Cardiology (ESC) stated that approximately 112 million patients with ischemic heart disease (IHD) worldwide seek medical attention for chest pain, and nearly 70% of them have no significant coronary stenosis detected after undergoing coronary angiography (CAG) [1]. Therefore, IHD caused by microvascular lesions is recognized as a crucial pathophysiological mechanism underlying non-obstructive coronary heart disease (CHD). Coronary microvascular disease (CMVD) is a syndrome characterized by myocardial ischemia resulting from structural and/or functional impairments of the coronary microvasculature, which includes pre-arterioles, arterioles, and capillaries. Unlike epicardial lesions, CMVD may involve microvasculature damage caused by multiple risk factors at an earlier stage, and it can trigger heart failure with preserved ejection fraction (HFpEF) [2], which may be closely associated with ischemia-induced left ventricular diastolic dysfunction (LADD). LVDD is characterized by impaired ventricular relaxation and increased chamber stiffness during diastole, resulting in increased left ventricular filling pressures [3]. It is also recognized as a key mechanism in the pathophysiology of HFpEF, which accounts for approximately 50% of all heart failure (HF) cases and is associated with significant complication rates, mortality, and healthcare burdens [4, 5].

Previous studies have shown that numerous risk factors, such as diabetes mellitus, hyperlipidemia, and insulin resistance (IR), can cause damage to coronary endothelial cells and induce microcirculatory dysfunction [6]. The triglyceride-glucose (TyG) index is a marker for assessing insulin resistance. It evaluates the body's insulin sensitivity by combining two biomarkers: triglycerides and fasting blood glucose [7, 8], and is often closely associated with cardiovascular diseases [9]. Similarly, the triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio and total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio were initially recognized as indicators of atherosclerosis [10]. Moreover, the triglyceride/high-density lipoprotein (TG/HDL) ratio is more valuable than other single lipid indicators, as it more strongly reflects the complex interactions in lipoprotein metabolism and better predicts the progression of atherosclerosis [11]. And these indicators can more comprehensively reflect the body's glucose and lipid metabolism levels. Higher values of these indicators are most likely to damage small microvessels and induce CMVD.

The aim of this study is to investigate the association between LVDD and CMVD, and to further analyze whether this association is mediated by key glycolipid dysregulation pathways—specifically, changes in the TyG index, TC/HDL-C ratio, and TG/HDL-C ratio. By elucidating these mechanisms, this study intends to provide a scientific basis for the clinical prevention and treatment of CMVD.

Methods

Data Source

This study is a prospective one, aiming to explore the correlation between LVDD mediated by glycolipid dysregulation and CMVD. The clinical data of all patients included in this study were obtained from those hospitalized in the First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine and the People's Hospital Medical Group of Xiangzhou from January 2023 to May 2025. The patient screening process was shown in Fig. 1 (Flowchart of study participants). The study passed the ethics committee of Ethical approval was granted by the hospital's ethics committee. Furthermore, all methods were performed in accordance with the relevant guidelines and regulations.

Diagnostic criteria for CMVD

Diagnostic criteria for CMVD adhered to the Chinese Multidisciplinary Expert Consensus on the Diagnosis and Treatment of Microvascular Diseases (2020) [12], encompassing myocardial ischemia symptoms, objective evidence of myocardial ischemia, non-obstructive coronary artery disease (< 50% stenosis on CTA/CAG), and impaired coronary microcirculatory function, involving impaired coronary flow reserve (CFR) < 2.5 or < 2.0, or the slow coronary flow phenomenon (TIMI frames > 25), the index of microvascular resistance index (IMR) > 25.

Inclusion criteria

CMVD group: (□)no significant stenosis in 3 coronary arteries including left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) by coronary angiography (CAG) (stenosis < 50%); (□)3 coronary arteries with normal quantitative flow ratio (QFR) > 0.8, and the angiographic microvascular resistance (AMR) > 250 mmHg*s/m [13];

Control group (non-CMVD): (□)no significant stenosis of coronary artery shown by CAG; (□)3 coronary arteries measured by QFR, QFR > 0.8, AMR < 250 mmHg*s/m;

Furthermore, all recruited patients aged over 20, regardless of gender.

Exclusion criteria

(□)Undergoing coronary revascularization within 1 month before this CAG, including Percutaneous Coronary Intervention (PCI), Percutaneous Transluminal Coronary Angioplasty (PTCA) and coronary artery bypass grafting (CABG); (□)organic heart disease, such as severe heart failure (HF), malignant arrhythmia, valvular disease, etc.; (□)acute and chronic inflammation, immune diseases or malignant tumors; (□)severe renal insufficiency: glomerular filtration rate < 45 mL/min; (□)severe coagulation disorders or bleeding; (□)allergy to contrast media. In addition, the exclusion criteria of CAG included poor visualization during or overlapping of the contrasted vessels

AMR examination

Patients who meet the inclusion criteria underwent QFR examination. Real-time CAG images were conducted to the QFR instrument (Pulse Medical, Shanghai) and analyzed under a single angle of a single vessel using the software AngioPlus Core (version V2). The process is performed by a trained cardiologist, who performed the analysis. After selecting the optimal contrast view with minimal vessel overlap, the software automatically outlined the detected vessel lumen. The contrast flow rate is derived by dividing the vessel length by the contrast fill time, which is then converted to the filling flow rate [14]. Subsequently, frames in which the lumen contour was fully exposed were selected as analysis frames to determine the main

and side branches of the analyzed vessels. According to Murray's bifurcation-principle, the reference vessel diameter needs to be reconstructed [15]. Finally, according to fluid dynamics, AMR was calculated following the blow equations [16–20].

$$\varvec{AMR} = \frac{\mathbf{Pd}}{\mathbf{Velocity_{hyp}}} = \frac{\varvec{Pa} \times \varvec{Qflow}}{\mathbf{Velocity_{hyp}}}$$

1

Note

Pa is aortic pressure at baseline; Pd is distal coronary artery pressure; Velocityhyp indicates coronary blood flow velocity in the hyperemic status.

Echocardiography examination

Well-trained echocardiographers performed routine transthoracic echocardiography and interpreted all echocardiograms: left ventricle internal dimension measured at end-diastole, left ventricle internal dimension measured at end-systole measured with M-mode, and early diastolic mitral inflow velocity/late diastolic mitral inflow velocity, early diastolic mitral inflow velocity/peak early diastolic mitral septal annular velocity (E/e'), and tricuspid regurgitation velocity (TR) measured [21].

The echocardiography-based diagnosis of LVDD was published in 2016 by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [22]: (i) mitral annulus e' velocity (septal e'<7 cm/s or lateral e'<10 cm/s) [25]: (ii) average E/e' >14; (iii) left atrial volume index > 34 ml/m^2; and (iv) maximum tricuspid regurgitant velocity > 2.8 m/s.

Diagnosis of LVDD: A positive result for two or more of the above indicators suggests LVDD, and a negative result for two or more suggests non-LVDD.

Definition of glycolipid dysregulation

The TyG index is a direct and effective indicator for evaluating insulin resistance (IR). As a comprehensive measure of triglycerides (TG) and fasting blood glucose, its specific calculation formula is as follows [23]:

$$\varvec{Tyg} = \mathrm{LN}\left[\frac{\varvec{TG} \ast \varvec{FBG})}{2}\right]$$

2

TG/HDL is used to characterize lipid metabolism levels, and it is expressed as serum triglycerides/ serum high-density lipoprotein [24].

TC/HDL is also used to characterize lipid metabolism levels, and it is expressed as serum total cholesterol/ serum high-density lipoprotein [25].

Statistical analysis

All data were analyzed via R statistical (version 4.2.2) and python (version 3.12.7). According to the normal distribution, all continuous variables do not follow normal distribution, and thus were presented in the form of medians and interquartile ranges. Whereas, categorical variables were expressed as frequencies and percentages. A statistically significant result was determined as a two-sided P value < 0.05.

Logistics regression models were employed to estimate the associations of glycolipid dysregulation, LVDD and CMVD, and to calculate Odds ratios (OR) and 95% confidence interval (CI). Model 1 was unadjusted. Model 2 was adjusted for gender, smoking, and drinking; Model 3 was additionally modified to account for gender, age, smoking, drinking, hypertension,

hyperlipidemia, diabetes, creatine kinase isoenzyme-MB, brain natriuretic peptide, troponin, myoglobin. The restricted cubic spline (RCS) model was applied to investigate the non-linear relationship of glycolipid dysregulation, LVDD and CMVD. Furthermore, to clarify the correlation of LVDD and CMVD, we conducted a linear analysis. And the violin plots were applied to characterize the differences in these indicators of LVDD between the CMVD and non-CMVD group. Afterwards, the receiver operating characteristic (ROC) curve with the area under the curve (AUC) was used to explore the cutoff value of LVDD, Average E/e' and TR to identify CMVD. Eventually, the presence of a mediating effect was defined as existing a significant indirect effect, direct effect and total effect [26].

Results

Baseline characteristic

Intergroup comparative analysis revealed that the prevalence of abnormal left ventricular end-diastolic diameter (LVDD) and the incidence of electrocardiographic ischemic manifestations were significantly higher in the CMVD group. In terms of risk factors, the proportion of smokers in the CMVD group was notably higher. Regarding medication use, more patients in the CMVD group received proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. At the level of laboratory indicators, the levels of uric acid (UA), triglyceride, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), TyG, total cholesterol-high-density lipoprotein ratio (TC/HDL), and triglyceride-high-density lipoprotein ratio (TG/HDL) in the CMVD group were significantly higher than those in the non-CMVD group ($P<0.05$). Coronary functional examination results showed that the three-vessel coronary stenosis rate and coronary blood flow velocity in the non-CMVD group were higher than those in the CMVD group; however, the levels of microvascular resistance (AMR) and quantitative flow ratio (QFR) were higher in the CMVD group ($P<0.05$). Echocardiographic examination indicated that the average E/e' ratio and tricuspid regurgitation (TR) level in the CMVD group were significantly higher, while the septal early diastolic peak velocity (Septal e') and lateral early diastolic peak velocity (Lateral e') were significantly lower than those in the non-CMVD group ($P<0.05$). No statistically significant differences were observed in other indicators between the two groups ($P>0.05$), as shown in Table 1.

Table 1
Characteristics of the study population

Variables	Total (n = 376)	Non-CMVD (n = 154)	CMVD (n = 222)	*P*
Baseline characteristic				
Gender				0.10
Male, n (%)	219 (58.24)	82 (53.25)	137 (61.71)	
Female, n (%)	157 (41.76)	72 (46.75)	85 (38.29)	
LVDD, n (%)				< 0.01
NO, n (%)	110 (60.77)	64 (86.49)	46 (42.99)	
YSE, n (%)	71 (39.23)	10 (13.51)	61 (57.01)	
ECG, n (%)	189 (50.27)	49 (31.82)	140 (63.06)	< 0.01
Risk factors				
Smoking, n (%)	118 (31.38)	36 (23.38)	82 (36.94)	< 0.01
Drinking, n (%)	107 (28.46)	38 (24.68)	69 (31.08)	0.18
Hypertension, n (%)	263 (69.95)	111 (72.08)	152 (68.47)	0.45
Diabetes, n (%)	141 (37.50)	54 (35.06)	87 (39.19)	0.42
Hyperlipidemia, n (%)	206 (54.79)	88 (57.14)	118 (53.15)	0.44
Hyperuricemia, n (%)	26 (6.91)	7 (4.55)	19 (8.56)	0.13
Medication during perioperation				
Aspirin, n (%)	366 (97.34)	150 (97.40)	216 (97.30)	1.00
Clopidogrel, n (%)	349 (92.82)	147 (95.45)	202 (90.99)	0.10
Statin, n (%)	318 (84.57)	130 (84.42)	188 (84.68)	0.94
Ezetimibe, n (%)	72 (19.15)	31 (20.13)	41 (18.47)	0.69
PSK9, n (%)	19 (5.05)	2 (1.30)	17 (7.66)	< 0.01
Nitroglycerin, n (%)	106 (28.19)	41 (26.62)	65 (29.28)	0.57
Beta blockers, n (%)	165 (43.88)	69 (44.81)	96 (43.24)	0.76
CCB, n (%)	153 (40.69)	65 (42.21)	88 (39.64)	0.62
Physical examination				
Systolic pressure (mmHg)	133.00 [121.00, 146.00]	135.00 [120.25, 148.75]	133.00 [122.00, 145.00]	0.33
Diastolic pressure (mmHg)	82.00 [74.00, 89.25]	80.00 [73.00, 88.00]	83.00 [75.00, 90.00]	0.10
Heart rate (bpm)	74.00 [65.00, 82.00]	73.00 [65.00, 81.75]	74.50 [66.00, 82.00]	0.71

Abbreviation: *LVDD* Left ventricular diastolic dysfunction; *ECG* Electrocardiogram; *PSK9* Proprotein Convertase Subtilisin/Kexin Type 9; *CCB* Calcium channel blockers; *CK-MB* creatine kinase isoenzyme-MB; *BNP* brain natriuretic peptide; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *BUN* blood urea nitrogen; *UA* uric acid; *HDL* high-density lipoprotein cholesterol; *LDL*: low density lipoprotein; *HBA1c* hemoglobin A1c; *LAD* the left anterior descending coronary artery; *LCX* circumflex branch of left coronary artery; *RCA* right coronary artery; *QFR* quantitative flow ratio; *AMR* angiographic microvascular resistance; V_{min} the minimum velocity; *AMRmax* the maximum angiographic microvascular resistance; *E* mitral valve E wave; *A* mitral valve A wave; *TR* Tricuspid regurgitation velocity; *Tyg* triglyceride-glucose index; *TC/HDL* Total Cholesterol/high-density lipoprotein; TG/HDL Triglycerides/ high-density lipoprotein.

Variables	Total (n = 376)	Non-CMVD (n = 154)	CMVD (n = 222)	*P*
Laboratory indexes				
Troponin (ng/mL)	0.01 [0.01, 0.01]	0.01 [0.01, 0.01]	0.01 [0.01, 0.01]	0.98
CKMB, (ng/mL)	1.69 [1.19, 2.35]	1.69 [1.28, 2.27]	1.69 [1.12, 2.39]	0.61
Myoglobin (ng/mL)	30.30 [25.10, 38.32]	30.60 [25.02, 39.55]	30.19 [25.12, 38.00]	0.59
BNP (pg/mL)	62.03 [29.17, 146.25]	66.60 [29.34, 179.75]	59.18 [28.18, 117.00]	0.18
AST (U/L)	19.25 [13.40, 27.02]	18.90 [14.10, 25.10]	19.85 [13.22, 27.58]	0.77
ALT (U/L)	20.20 [16.38, 25.13]	20.55 [16.35, 25.85]	19.75 [16.41, 24.80]	0.30
Bun (mg/mL)	14.56 [12.04, 17.92]	14.56 [11.48, 18.13]	14.70 [12.34, 17.92]	0.37
Creatinine (umol/L)	72.00 [62.00, 82.00]	72.00 [61.00, 82.00]	72.00 [64.00, 81.75]	0.50
UA (umol/L)	322.00 [265.00, 374.50]	312.00 [242.25, 366.00]	328.00 [274.00, 380.50]	0.02
Glucose (mmol/L)	5.80 [5.20, 6.72]	5.76 [5.21, 6.69]	5.83 [5.18, 6.74]	0.89
Cholesterol (mmol/L)	3.90 [3.22, 4.69]	3.86 [3.09, 4.62]	3.97 [3.28, 4.76]	0.33
Triglyceride (mmol/L)	1.31 [0.95, 1.85]	1.13 [0.86, 1.54]	1.41 [1.06, 2.09]	< 0.01
HDL (mmol/L)	1.11 [0.93, 1.31]	1.15 [0.98, 1.36]	1.08 [0.92, 1.28]	0.04
LDL (mmol/L)	2.15 [1.62, 2.75]	2.03 [1.58, 2.70]	2.21 [1.67, 2.79]	0.10
HbA1c (%)	6.20 [5.80, 6.90]	6.20 [5.80, 6.88]	6.20 [5.80, 7.00]	0.86
Tyg, M [Q_1, Q_3]	8.74 [8.40, 9.18]	8.62 [8.24, 9.00]	8.88 [8.52, 9.25]	< 0.01
TC/HDL, M [Q_1, Q_3]	3.53 [2.86, 4.15]	3.32 [2.80, 3.84]	3.68 [2.93, 4.35]	< 0.01
TG/HDL, M [Q_1, Q_3]	1.23 [0.81, 1.81]	0.93 [0.71, 1.55]	1.33 [0.94, 2.02]	< 0.01
Coronary artery examination				
Diameter stenosis %				
LAD	29.43 ± 9.03	31.46 ± 7.16	28.01 ± 9.90	< 0.01
LCX	28.95 [22.48, 37.00]	31.80 [23.83, 39.30]	27.00 [21.60, 34.22]	< 0.01
RCA	23.60 [16.28, 31.00]	26.55 [19.10, 32.70]	21.15 [15.33, 28.00]	< 0.01
QFR				
LAD	0.93 [0.87, 0.96]	0.88 [0.85, 0.93]	0.94 [0.91, 0.97]	< 0.01
LCX	0.94 [0.89, 0.97]	0.91 [0.85, 0.95]	0.96 [0.93, 0.98]	< 0.01
RCA	0.98 [0.94, 0.99]	0.96 [0.92, 0.98]	0.98 [0.96, 0.99]	< 0.01
AMR (mmHg*s/m)				

Abbreviation: *LVDD* Left ventricular diastolic dysfunction; *ECG* Electrocardiogram; *PSK9* Proprotein Convertase Subtilisin/Kexin Type 9; *CCB* Calcium channel blockers; *CK-MB* creatine kinase isoenzyme-MB; *BNP* brain natriuretic peptide; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *BUN* blood urea nitrogen; *UA* uric acid; *HDL* high-density lipoprotein cholesterol; *LDL*: low density lipoprotein; *HBA1c* hemoglobin A1c; *LAD* the left anterior descending coronary artery; *LCX* circumflex branch of left coronary artery; *RCA* right coronary artery; *QFR* quantitative flow ratio; *AMR* angiographic microvascular resistance; V_{min} the minimum velocity; *AMRmax* the maximum angiographic microvascular resistance; *E* mitral valve E wave; *A* mitral valve A wave; *TR* Tricuspid regurgitation velocity; *Tyg* triglyceride-glucose index; *TC/HDL* Total Cholesterol/high-density lipoprotein; TG/HDL Triglycerides/ high-density lipoprotein.

Variables	Total (n = 376)	Non-CMVD (n = 154)	CMVD (n = 222)	*P*
LAD	271.50 [225.00, 307.25]	223.00 [201.25, 242.00]	299.50 [283.00, 322.00]	< 0.01
LCX	251.00 [234.00, 312.25]	236.00 [219.25, 246.00]	303.00 [271.00, 335.75]	< 0.01
RCA	248.50 [227.75, 286.00]	230.00 [211.25, 243.00]	278.00 [250.25, 309.75]	< 0.01
AMR_{max}	293.50 [247.00, 337.25]	246.00 [239.00, 249.00]	330.00 [306.25, 359.00]	< 0.01
Simulated-hyperemic velocity (cm/s)				
LAD	13.50 [11.20, 16.80]	17.05 [14.90, 19.70]	11.55 [10.30, 13.00]	< 0.01
LCX	14.00 [11.40, 16.70]	16.50 [14.62, 19.30]	12.05 [9.80, 14.00]	< 0.01
RCA	15.65 [13.50, 19.30]	18.55 [16.40, 20.58]	14.30 [12.00, 16.45]	< 0.01
V_{min}	12.05 [9.80, 14.50]	14.90 [13.90, 16.30]	10.35 [8.80, 11.67]	0.01
Echocardiography				
EF, (%)	63.00 [60.00, 66.00]	63.00 [59.00, 65.00]	63.50 [60.00, 66.00]	0.05
E, (m/s)	0.68 [0.57, 0.80]	0.69 [0.57, 0.80]	0.68 [0.57, 0.80]	0.95
A, (m/s_3)	0.86 [0.69, 1.00]	0.88 [0.70, 1.00]	0.84 [0.67, 0.99]	0.29
Septal e', (cm/s)	6.00 [5.00, 7.25]	7.00 [5.00, 8.00]	6.00 [4.85, 7.00]	< 0.01
Lateral e', (cm/s)	8.00 [6.50, 10.00]	9.25 [7.00, 11.75]	8.00 [6.00, 10.00]	< 0.01
Average E/e', M (Q_1, Q_3)	9.07 [7.27, 12.04]	8.21 [7.00, 10.00]	9.68 [7.70, 14.09]	< 0.01
TR, (cm/s)	2.20 [0.00, 2.90]	1.30 [0.00, 2.60]	2.40 [1.55, 2.90]	< 0.01

Abbreviation: *LVDD* Left ventricular diastolic dysfunction; *ECG* Electrocardiogram; *PSK9* Proprotein Convertase Subtilisin/Kexin Type 9; *CCB* Calcium channel blockers; *CK-MB* creatine kinase isoenzyme-MB; *BNP* brain natriuretic peptide; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *BUN* blood urea nitrogen; *UA* uric acid; *HDL* high-density lipoprotein cholesterol; *LDL*: low density lipoprotein; *HBA1c* hemoglobin A1c; *LAD* the left anterior descending coronary artery; *LCX* circumflex branch of left coronary artery; *RCA* right coronary artery; *QFR* quantitative flow ratio; *AMR* angiographic microvascular resistance; V_{min} the minimum velocity; *AMRmax* the maximum angiographic microvascular resistance; *E* mitral valve E wave; *A* mitral valve A wave; *TR* Tricuspid regurgitation velocity; *Tyg* triglyceride-glucose index; *TC/HDL* Total Cholesterol/high-density lipoprotein; TG/HDL Triglycerides/ high-density lipoprotein.

Table 2
The associations of LVDD with CMVD

	OR (95% CI)		
	Model 1	**Model 2**	**Model 3**
LVDD	8.49 (3.94, 18.30)	9.43 (4.24, 20.98)	12.37 (5.00, 30.61)
Lateral e'	0.82 (0.75, 0.91)	0.82 (0.74, 0.90)	0.81 (0.73, 0.89)
Septal e'	0.84 (0.78, 0.91)	0.84 (0.78, 0.91)	0.82 (0.75, 0.89)
Average E/e'	1.16 (1.08, 1.24)	1.17 (1.09, 1.25)	1.19 (1.11, 1.29)
TR	1.51 (1.28, 1.78)	1.55 (1.31 ~ 1.84)	1.62 (1.36, 1.94)
Model 1 was unadjusted.			
Model 2 was adjusted for gender, smoking, and drinking.			
Model 3 was additionally modified to account for gender, age, smoking, drinking, hypertension, hyperlipidemia, diabetes, creatine kinase isoenzyme-MB, brain natriuretic peptide, troponin, myoglobin.			
Abbreviation: *LVDD* Left ventricular diastolic dysfunction; *TR* Tricuspid regurgitation velocity.			

Associations of LVDD with CMVD

(1) Logistic regression

Results of Logistic regression analysis indicated that left ventricular end-diastolic diameter (LVDD) was positively associated with coronary microvascular disease (CMVD) (odds ratio [OR] = 8.49, 95% confidence interval [CI] = 3.94–18.30). After adjusting for other variables, the analytical results of Model 2 and Model 3 still remained statistically significant ($P < 0.05$).

Further correlation analysis of LVDD-related echocardiographic indicators revealed that both lateral early diastolic peak velocity (Lateral e') and septal early diastolic peak velocity (Septal e') were negatively correlated with CMVD, with corresponding OR values and 95% CIs of 0.82 (0.75–0.91) and 0.84 (0.78–0.91), respectively. In contrast, the average E/e' ratio (Average E/e') and tricuspid regurgitation (TR) were positively correlated with CMVD, with OR values and 95% CIs of 1.16 (1.08–12.4) and 1.51 (1.28–1.78), respectively. After multivariable adjustment, the associations between the aforementioned indicators and CMVD remained statistically significant ($P < 0.05$).

(2) Linear correlation analysis

The maximum microvascular resistance (AMRmax) of the three coronary arteries and the minimum hyperemic blood flow velocity (Vmin) of the three coronary arteries were used as indicators to characterize coronary microvascular disease (CMVD). Meanwhile, the lateral early diastolic peak velocity (Lateral e'), septal early diastolic peak velocity (Septal e'), and average E/e' ratio were used as indicators to characterize the function related to left ventricular end-diastolic diameter (LVDD). Linear correlation analysis was performed on the above indicators.

The results showed that AMRmax was positively correlated with the average E/e' ratio, and negatively correlated with both Lateral e' and Septal e' (all $P < 0.05$); Vmin was negatively correlated with the average E/e' ratio, and positively correlated with both Lateral e' and Septal e' (all $P < 0.05$). See Fi. 2 for detailed results.

(3) Results of nonlinear of LVDD's indicators and CMVD

Analysis via restricted cubic spline (RCS) models revealed an L-shaped association between lateral early diastolic peak velocity (Lateral e'), septal early diastolic peak velocity (Septal e'), and coronary microvascular disease (CMVD). In contrast, a mirrored L-shaped association was observed between the average E/e' ratio, tricuspid regurgitation (TR), and CMVD, with detailed results presented in Fig. 3.

(4) The difference results of LVDD indicators across CMVD

The violin plots show that the levels of Lateral e' and Septal e' in the CMVD group are lower, while the levels of TR and average E/e' are higher compared to the control group, with detailed results presented in Fig. 4.

(5) The recognition efficiency of LVDD for CMVD

The ROC results show that the area under the curve for LVDD in diagnosing CMVD is 0.72, while those for average E/e' and TR are 0.71 and 0.74, respectively, with detailed results presented in Fig. 5.

Associations of glycolipid dysregulation with LVDD

Results from Logistic regression analysis indicated a positive correlation between the TyG and CMVD (odds ratio [OR] = 2.18, 95% confidence interval [CI]: 1.03–4.60). After adjusting for relevant variables, the associations of the total cholesterol/high-density lipoprotein cholesterol ratio TC/HDL and TG/HDL with CMVD remained statistically non-significant, detailed data are presented in Table 3. Further RCS analysis revealed that the association curves between Tyg, TG/HDL, TC/HDL and the incidence of abnormal LVDD exhibited an "inverted J-shape". For detailed trends and statistical details, please refer to the supplementary files.

Table 3
The associations of glycolipid dysregulation with LVDD

	OR (95% CI)		
	Model 1	**Model 2**	**Model 3**
Tyg	2.18 (1.03, 4.60)*	1.87 (0.86, 4.06)	1.49 (0.61, 3.61)
TC/HDL	1.10 (0.83, 1.45)	1.13 (0.85, 1.50)	1.13 (0.83, 1.53)
TG/HDL	0.82 (0.58, 1.14)	0.88 (0.62, 1.25)	1.00 (0.66, 1.51)
Model 1 was unadjusted.			
Model 2 was adjusted for gender, smoking, and drinking.			
Model 3 was additionally modified to account for gender, age, smoking, drinking, hypertension, hyperlipidemia, diabetes, creatine kinase isoenzyme-MB, brain natriuretic peptide, troponin, myoglobin.			
Abbreviation: *LVDD* Left ventricular diastolic dysfunction; *Tyg* triglyceride-glucose index; *TC/HDL* Total Cholesterol/high-density lipoprotein; TG/HDL Triglycerides/ high-density lipoprotein.			

Associations of glycolipid dysregulation with CMVD

The results demonstrated that TyG (OR = 1.90, 95%CI = 1.34–2.70), TG/HDL (OR = 1.86, 95%CI = 1.31–2.66), and TC/HDL (OR = 1.84, 95%CI = 1.26–2.68) were positively associated with CMVD. These associations remained robust after multivariate adjustment, with detailed data presented in Table 4. Further RCS analysis revealed that the association curves between TyG, TG/HDL, TC/HDL and the incidence of CMVD exhibited an "inverted J-shape". For detailed trends and statistical parameters, please refer to the supplementary materials.

Table 4
Associations of glycolipid dysregulation with CMVD

	OR (95% CI)		
	Model 1	**Model 2**	**Model 3**
Tyg	1.90 (1.34, 2.70)*	1.86 (1.31, 2.66) *	1.84 (1.26, 2.68) *
TC/HDL	1.21 (1.01, 1.46) *	1.20 (0.99, 1.45)	1.22 (1.01, 1.49) *
TG/HDL	1.45 (1.16, 1.80) *	1.41 (1.14, 1.75) *	1.40 (1.12, 1.75) *
Model 1 was unadjusted.			
Model 2 was adjusted for gender, smoking, and drinking.			
Model 3 was additionally modified to account for gender, age, smoking, drinking, hypertension, hyperlipidemia, diabetes, creatine kinase isoenzyme-MB, brain natriuretic peptide, troponin, myoglobin.			
Abbreviation: *LVDD* Left ventricular diastolic dysfunction; *Tyg* triglyceride-glucose index; *TC/HDL* Total Cholesterol/high-density lipoprotein; TG/HDL Triglycerides/ high-density lipoprotein.			

Mediating role of inflammatory indexes

Figure 6 shows that LVDD mediated 3% of the association between TG/HDL and CMVD, the TC/HDL mediated 1% of the association between TG/HDL and CMVD, and the TyG mediated 4% of the association between TG/HDL and CMVD. (Fig. 5 Analysis of the mediation by left ventricular end - diastolic diameter (Figure a), total cholesterol to high - density lipoprotein cholesterol ratio (Figure b) and triglyceride - glucose index (Figure c) of the associations of TG/HDL with CMVD. CMVD Coronary microvascular disease, TG/HDL triglycerides to high - density lipoprotein cholesterol ratio). However, the indirect effects of TG/HDL and TC/HDL on LVDD were not significant.

Discussions

In this study, we found a positive association of LVDD with CMVD, and after the comprehensively adjusted model, these results remained significantly. Given that the positive correlations of index of glucose and glycolipid dysregulation with LVDD and CMVD were uncovered by logistic regression, we performed the mediation analysis to identify the significant roles of TyG, TG/HDL and TC/HDL in linking LVDD with CMVD, further expounding glucose and glycolipid dysregulation as a potential underlying mechanism to trigger CMVD. Therefore, LVDD may be a potent approach for the onset of CMVD and this process may be mediated by glycolipid dysregulation.

In general, epicardial arteries primarily serve a conductive function and exhibit minimal resistance to coronary blood flow under normal conditions. In contrast, pre-arterioles and arterioles act as the resistance vessels of the coronary circulation, responsible for regulating and distributing coronary blood flow to meet the dynamic metabolic demands of local tissues [27, 28]. Thus, CMVD is primarily characterized by a significant increase in microcirculatory resistance and a reduction in coronary flow reserve, resulting in the inability to meet myocardial oxygen demand during peak metabolic states. In this study, we found that the microcirculatory resistance index (AMR) of the three coronary arteries was significantly higher in patients in the CMVD group than in those in the control group. A higher microcirculatory resistance leads to a decrease in coronary blood flow velocity. Consistently, our study found that the coronary blood flow velocity of the three coronary arteries was significantly reduced in patients in the CMVD group. flow velocity (V) can be used as direct functional indicators of the coronary arteries to characterize microcirculatory lesions. In addition, the TIMI frame count (TFC) is also an important indicator for characterizing CMVD, and multiple guidelines explicitly highlight its crucial role in the diagnosis of CMVD [29, 30]. Studies have shown that the corrected TIMI frame count is linearly correlated with the peak and mean coronary diastolic flow velocities [31]. Consistent with these findings, our study also demonstrated that the TIMI frame count of the three coronary arteries was significantly higher in patients of the CMVD group than in the control population.

Previous studies have shown that CMVD is influenced by a variety of risk factors, such as smoking, alcohol consumption, hypertension, diabetes mellitus, and hyperlipidemia [32]. Consistent with these findings, our study also revealed that the proportion of smokers was higher in the CMVD group (36.94% vs. 23.38%). Additionally, patients in the CMVD group had a higher serum uric acid level (median: 328 μmol/L). Regarding lipid profiles, the CMVD group exhibited higher levels of triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C), lower levels of high-density lipoprotein cholesterol (HDL-C), and a higher proportion of patients taking PCSK9 inhibitors. These results suggest that metabolic abnormalities are an important mechanism underlying the pathogenesis of CMVD [33].

Our study found that compared with healthy individuals, patients with coronary microvascular dysfunction (CMVD) had a significantly higher rate of electrocardiographic (ECG) ischemic manifestations (63.06% vs. 31.82%). This suggests that structural and functional impairments affecting the entire coronary circulation—particularly the microcirculation, which has an extensive distribution and thus leads to more severe myocardial ischemia—act as key mediators of patients' symptoms and prognosis [34]. Furthermore, long-term subendocardial ischemia induces myocardial inflammation, fibrosis, and increased myocardial stiffness, ultimately resulting in left ventricular end-diastolic dysfunction (LVDD). Consistent with this mechanism, our study also revealed that the prevalence of LVDD was significantly higher in CMVD patients than in the control group (57.01% vs. 13.51%).

Our study found that compared with healthy individuals, patients with CMVD had a significantly higher rate of electrocardiographic (ECG) ischemic manifestations (63.06% vs. 31.82%). This suggests that structural and functional impairments affecting the entire coronary circulation—particularly the microcirculation, which has an extensive distribution and thus contributes to more severe myocardial ischemia—act as key mediators of patients' symptoms and prognosis [32]. Furthermore, long-term subendocardial ischemia induces myocardial inflammation, fibrosis, and increased myocardial stiffness, ultimately leading to LVDD. Consistent with this pathological pathway, our study revealed that the prevalence of LVDD was significantly higher in CMVD patients than in the control group (57.01% vs. 13.51%). In addition, logistic regression analysis revealed a positive correlation between LVDD and CMVD. Regarding LVDD-related echocardiographic parameters, violin plots vividly demonstrate that the mean E/e' ratio and tricuspid regurgitation (TR) velocity were higher in the CMVD group than in the control group; in contrast, the lateral e' velocity and septal e' velocity were lower in the CMVD group. Studies have shown that the mean E/e' ratio can be used to estimate left ventricular filling pressure (LVFP) [34]; a higher E/e' ratio indicates elevated LVFP, which impairs ventricular filling during diastole [35]. In addition, the CMVD group had significantly reduced e' velocities at the interventricular septum and lateral wall, reflecting a decrease in left ventricular myocardial perfusion during diastole and confirming the presence of left ventricular diastolic dysfunction. Notably, some studies have proposed that a mean E/e' ratio > 14 indicates elevated LVFP [36], which can directly characterize LVDD. LVDD is defined as an abnormality in myocardial mechanical function [37], where the ventricle fails to accept blood at low pressure in early diastole, resulting in slow or incomplete ventricular filling [38]. Consequently, the blood flow velocity in the left ventricular walls (lateral wall and interventricular septum) decreases during diastole. The E/e' ratio is calculated as the ratio of the early diastolic transmitral flow velocity (E wave) to the average e' velocity measured at the left ventricular septum and lateral wall [39]. Linear correlation analysis revealed a positive correlation between the AMR and the mean E/e' ratio, as well as a negative correlation between AMR and the lateral e' velocity and septal e' velocity. This indicates that increased microcirculatory resistance leads to elevated left ventricular wall stiffness and reduced annular velocity. Additionally, previous studies have suggested a positive correlation between the mean E/e' ratio and microcirculatory resistance [40]. So we can conclude that microcirculatory resistance indices serve as target variables for left ventricular diastolic dysfunction (LVDD). Similarly, results from CS curve analysis showed that the mean E/e' ratio and TR velocity exhibited an inverted J-shaped curve relationship with CMVD, while the lateral e' velocity and septal e' velocity showed an L-shaped relationship with CMVD.

In this study, patients in the CMVD group had higher levels of the TyG, TG/HDL, and TC/HDL than those in the control group. Furthermore, logistic regression analysis revealed a positive correlation between the TyG, TG/HDL, TC/HDL and CMVD (odds ratio [OR] > 1). Previous studies have indicated that the TG/HDL shows greater potential than individual lipid molecules in predicting insulin resistance and atherosclerosis. Liping Liao et al. [41] found that the TG/HDL is an independent risk factor for CMVD (OR = 1.826). Similarly, the TC/HDL also plays a crucial role in predicting coronary artery plaques [42]. In addition, the TyG is recognized as an important tool for assessing insulin resistance and is closely associated with various cardiovascular

diseases, including chronic coronary syndromes and ischemia with non-obstructive coronary arteries (INOCA) [43]. Wen Zhang et al. [44] demonstrated that the TyG index is an independent predictor of CMVD (OR = 1.436) and is closely correlated with the risk of major adverse cardiovascular events. Furthermore, glucose and glycolipid dysregulation can lead to abnormal myocardial substrate utilization, neurohormonal activation, interstitial fibrosis, and CMVD, which in turn result in adverse cardiac remodeling and myocardial dysfunction. This is particularly evident in patients with metabolic syndrome, who often present with LVDD [45]. Finally, our mediation effect analysis revealed that the TyG mediates LVDD ($P < 0.05$), thereby contributing to the development of CMVD.

This prospective cohort study yields three principal findings: (1) It provides novel epidemiological evidence supporting the positive correlation between LVDD and CMVD; (2) Mediation analysis confirms the intermediary role of TyG (mediated proportion: 4%, $P < 0.01$) in the LVDD-CMVD pathway; (3) Longitudinal monitoring of lipid ratios may serve as a cost-effective strategy for early CMVD risk stratification. Notably, the observational design precludes causal inference, and the single-center recruitment limits generalizability of findings.

Conclusions

This study provided evidence for the positive associations of LVDD with CMVD, while also indicating the significant mediating role of Glycemic and glycolipid dysregulation indices in this association.

Declarations

Acknowledgements

No Applicable

Author contributions

W.W., Y.C., and J-Y. J collected the data and drafted the manuscript, F-H.Z and L.L reviewed the manuscript, provided feedback, and comprehensively led the research.

Found

This work was supported by Guangdong Province Project Proposal (NO. 20251355).

Availability of data and materials

We have uploaded the raw data to Figshare via the website:

[https://figshare.com/s/ac02ca82182362eeeb8b](https://link.wtturl.cn/?target=https%3A%2F%2Ffigshare.com%2Fs%2Fac02ca82182362eeeb8b&scene=im&aid=497858&lang=zh)

The identical data availability statement will also be filled in the system accordingly.

Ethics approval and consent to participate

This study was approved by the Ethics Committee from Heilongjiang University of Chinese Medicine, Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine, Xiyuan Hospital of China Academy of Chinese Medical Sciences and the People's Hospital Medical Group of Xiangzhou.

We informed the patient that the clinical data would be used for publication and obtained consent from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References

1. Knuuti, J. et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [J]. *Eur. Heart J.* **41** (3), 407–477 (2020).
2. Chen, S. et al. Effect of sodium-glucose Co-transporter 2 inhibitors on coronary microcirculation. *Front. Pharmacol.* **16**, 1523727. 10.3389/fphar.2025.1523727. (2025). PMID: 40093320; PMCID: PMC11906428.
3. Kosmala, W. & Marwick, T. H. Asymptomatic Left Ventricular Diastolic Dysfunction: Predicting Progression to Symptomatic Heart Failure. *JACC Cardiovasc. Imaging*. **13** (1 Pt 2), 215–227. 10.1016/j.jcmg.2018.10.039. (2020). Epub 2019 Apr 17. PMID: 31005530.
4. Zile, M. R., Baicu, C. F. & Gaasch, W. H. Diastolic Heart Failure—Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle. *N Engl. J. Med.* **350**, 1953–1959. 10.1056/NEJMoa032566 (2004).
5. Faerch, K. et al. Natural history of insulin sensitivity and insulin secretion in the progression from normal glucose tolerance to impaired fasting glycemia and impaired glucose tolerance: the Inter99 study. *Diabetes Care*. **32** (3), 439–444. 10.2337/dc08-1195 (2009).
6. Labazi, H. & Trask, A. J. Coronary microvascular disease as an early culprit in the pathophysiology of diabetes and metabolic syndrome. *Pharmacol. Res.* **123**, 114–121. 10.1016/j.phrs.2017.07.004. (2017). Epub 2017 Jul 9. PMID: 28700893; PMCID: PMC5599173.
7. Lee, J. et al. Lipid indices as simple and clinically useful surrogate markers for insulin resistance in the U.S. population. *Sci. Rep.* 10.1038/s41598-021-82053-2 (2021).
8. Simental-Mendía, L. E., Rodríguez-Morán, M. & Guerrero-Romero, F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab. Syndr. Relat. Disord*. **6** (4), 299–304. 10.1089/met.2008.0034 (2008).
9. Dang, K. et al. The association between triglyceride-glucose index and its combination with obesity indicators and cardiovascular disease: NHANES 2003–2018. *Cardiovasc. Diabetol.* **23** (1), 8. 10.1186/s12933-023-02115-9. (2024). PMID: 38184598; PMCID: PMC10771672.
10. Gaziano, J. M., Hennekens, C. H., O'Donnell, C. J., Breslow, J. L. & Buring, J. E. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation* **96** (8), 2520–2525. 10.1161/01.CIR.96.8.2520 (1997).
11. Sambuceti, G., L'Abbate, A. & Marzilli, M. Why should we study the coronary microcirculation? *Am. J. Physiol. Heart Circ. Physiol.* **279** (6), H2581–H2584. 10.1152/ajpheart.2000.279.6.H2581 (2000).
12. Chen Hao, G. & Tao, W. Expert Consensus on Diagnosis and Treatment of Multidisciplinary Microvascular Diseases in China. *Chin. J. Circulation*. **35** (12), 1149–1165 (2020).
13. Zhang, Y. et al. B. Automatic coronary blood flow computation: Validation in quantitative flow ratio from coronary angiography. *Int. J. Cardiovasc. Imaging*. **35**, 587–595 (2019).
14. Nguyen, H. H. et al. TG/HDL-C Ratio Is a Risk Factor Associated with CKD: Use in Assessing the Risk of Progression of CKD. *Pathophysiology* **29** (3), 374–382. 10.3390/pathophysiology29030029. (2022). PMID: 35893599; PMCID: PMC9326757.
15. Suda, A. et al. Coronary functional abnormalities in patients with angina and nonobstructive coronary artery disease. *J. Am. Coll. Cardiol.* **74**, 2350–2360 (2019).
16. Shaw, L. J. et al. Impact of Ethnicity and Gender Differences on Angiographic Coronary Artery Disease Prevalence and In-Hospital Mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation* **117**, 1787–1801 (2008).
17. Zhang Yun, C. & Yundai Fu Xianghua, etc. Chinese expert consensus on the diagnosis and treatment of coronary microvascular disease [J]. *Chin. J. Circulation*. **32** (05), 421–430 (2017).

18. Mileva, N., Nagumo, S. & Mizukami, T. etc. Prevalence of Coronary Microvascular Disease and Coronary Vasospasm in Patients With Nonobstructive Coronary Artery Disease: Systematic Review and Meta-Analysis. J Am Heart Assoc. ;11(7): e023207. (2022). 10.1161/JAHA.121.023207. Epub 2022 Mar 18. PMID: 35301851; PMCID: PMC9075440.
19. Huang, F-Y., Huang, B-T. & Lv, W-Y. etc. The prognosis of patients with nonobstructive coronary artery disease versus normal arteries determined by invasive coronary angiography or computed tomography coronary angiography: a systematic review. Medicine ;95: e3117. (2016).
20. Geng, L. et al. Association of quantitative flow ratio-derived microcirculatory indices with anatomical-functional discordance in intermediate coronary lesions. *Int. J. Cardiovasc. Imaging*. **37** (10), 2803–2813. 10.1007/s10554-021-02292-2. (2021). Epub 2021 May 31. PMID: 34059977.
21. Cai, J., Liang, Z., Feng, W. & Long, H. Correlation between left atrial strain and left ventricular diastolic function in hypertensive patients. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. **48** (6), 846–851. 10.11817/j.issn.1672-7347.2023.220301 (2023). English, Chinese.
22. Nagueh, S. F. et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. ;29(4):277–314. (2016). 10.1016/j.echo.2016.01.011. PMID: 27037982.
23. Zhang, P., Mo, D., Zeng, W. & Dai, H. Association between triglyceride-glucose related indices and all-cause and cardiovascular mortality among the population with cardiovascular-kidney-metabolic syndrome stage 0–3: a cohort study. *Cardiovasc. Diabetol.* **24** (1), 92. 10.1186/s12933-025-02642-7. (2025). PMID: 40022225; PMCID: PMC11871745.
24. Kosmas, C. E. et al. The Triglyceride/High-Density Lipoprotein Cholesterol (TG/HDL-C) Ratio as a Risk Marker for Metabolic Syndrome and Cardiovascular Disease. *Diagnostics (Basel)*. **13** (5), 929. 10.3390/diagnostics13050929. (2023). PMID: 36900073; PMCID: PMC10001260.
25. Ma, T. et al. The predictive value of TG/HDL and TC/HDL for risk of mortality and cardiovascular events in incident peritoneal dialysis patients. *Clin. Kidney J.* **18** (6), sfaf165. 10.1093/ckj/sfaf165. (2025). PMID: 40567496; PMCID: PMC12188193.
26. Xu, B. et al. Is systemic inflammation a missing link between cardiometabolic index with mortality? Evidence from a large population-based study. *Cardiovasc. Diabetol.* **23** (1), 212. 10.1186/s12933-024-02251-w. (2024). PMID: 38902748; PMCID: PMC11191290.
27. Camici, P. G. & Crea, F. Coronary microvascular dysfunction. *N Engl. J. Med.* **356**, 830–840 (2007).
28. Chilian, W. M. Coronary microcirculation in health and disease. Summary of an NHLBI workshop. *Circulation* **95**, 522–528 (1997).
29. Li, Y. et al. Coronary microvascular dysfunction in post-PCI target vessels: a systematic review and meta-analysis of prevalence and associated outcomes. *Front. Cardiovasc. Med.* **12**, 1620204. 10.3389/fcvm.2025.1620204. (2025). PMID: 40832144; PMCID: PMC12358399.
30. Padro, T. et al. ESC Working Group on Coronary Patho-physiology and Microcirculation position paper on 'coronary microvascular dysfunc-tion in cardiovascular disease' [J]. *Cardiovasc. Res.* **116** (4), 741–755 (2020).
31. Nie, S. P. et al. Can transthoracic Doppler echocardiography be used to detect coronary slow flow phenomenon [J]? *Chin. Med. J. (Engl)*. **123** (24), 3529–3533 (2010).
32. Reynolds, H. R. & Smilowitz, N. R. Ischaemia with non-obstructive coronary arteries in the 2024 European Society of Cardiology guidelines for the management of chronic coronary syndromes. Eur Heart J Acute Cardiovasc Care. ;14(3):173–177. (2025). 10.1093/ehjacc/zuaf005. PMID: 39820976.
33. McCallinhart, P. E., Chade, A. R., Bender, S. B. & Trask, A. J. Expanding landscape of coronary microvascular disease in co-morbid conditions: Metabolic disease and beyond. *J. Mol. Cell. Cardiol.* **192**, 26–35. 10.1016/j.yjmcc.2024.05.004. (2024). Epub 2024 May 10. PMID: 38734061; PMCID: PMC11340124.
34. Taqueti, V. R. & Di Carli, M. F. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **72** (21), 2625–2641. 10.1016/j.jacc.2018.09.042. (2018). PMID: 30466521; PMCID: PMC6296779.

35. Michelsen, M. M. et al. Overlap between angina without obstructive coronary artery disease and left ventricular diastolic dysfunction with preserved ejection fraction. *PLoS One*. **14** (5), e0216240. 10.1371/journal.pone.0216240. (2019). PMID: 31120897; PMCID: PMC6532855.
36. Zhang, X., Li, K., Cardoso, C., Moctezuma-Ramirez, A. & Elgalad, A. Interpreting Diastolic Dynamics and Evaluation through Echocardiography. *Life (Basel)*. **14** (9), 1156. 10.3390/life14091156. (2024). PMID: 39337939; PMCID: PMC11433582.
37. Deswal, A. Diastolic dysfunction and diastolic heart failure: mechanisms and epidemiology. *Curr. Cardiol. Rep.* **7**, 178–183 (2005).
38. Gaasch, W. H. & Zile, M. R. Left ventricular diastolic dysfunction and diastolic heart failure. *Annu. Rev. Med.* **55**, 373–394 (2004).
39. Lanspa, M. J. et al. Grissom C.K. Application of a simplified definition of diastolic function in severe sepsis and septic shock. *Crit. Care*. **20**, 243. 10.1186/s13054-016-1421-3 (2016).
40. Hong, D. et al. Prognostic Impact of Cardiac Diastolic Function and Coronary Microvascular Function on Cardiovascular Death [J]. *J. Am. Heart Assoc.* **12** (3), e027690 (2023).
41. Liao, L. P., Wu, L. & Yang, Y. The relationship between triglyceride/high-density lipopro-tein cholesterol ratio and coronary microvascular disease [J]. *BMC Cardiovasc. Disord*. **23** (1), 228 (2023).
42. Wang, L. L. et al. Sex Differences in the Relationship Between Lipid Ratios and the Risk of Carotid Plaque. Angiology. Feb **14**:33197251316624. doi: 10.1177/00033197251316624. (2025). Epub ahead of print. PMID: 39949279.
43. Wu, Z. et al. Triglyceride-glucose index in the prediction of adverse cardiovascular events in patients with premature coronary artery disease: a retrospec-tive cohort study [J]. *Cardiovasc. Diabetol.* **21** (1), 142 (2022).
44. Zhang, W. et al. Association between the triglyceride-glucose index and the presence and prognosis of coronary microvascular dysfunction in patients with chronic coronary syndrome [J]. *Cardiovasc. Diabetol.* **22** (1), 113 (2023).
45. Zhou, D. et al. Metabolic syndrome, left ventricular diastolic dysfunction and heart failure with preserved ejective fraction. *Front. Endocrinol. (Lausanne)*. **16**, 1544908. 10.3389/fendo.2025.1544908 (2025).

Figures

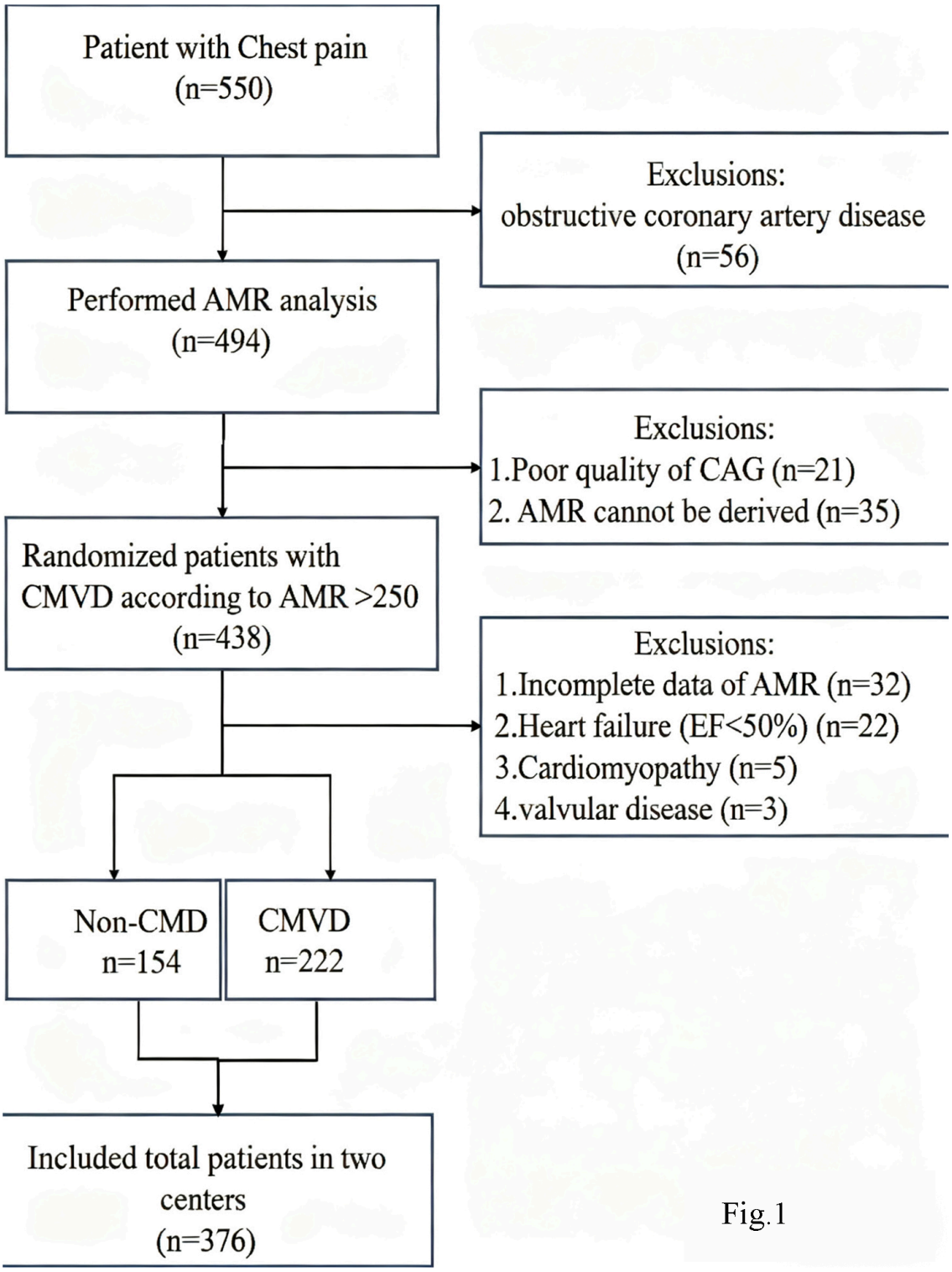


Figure 1

flowchart.

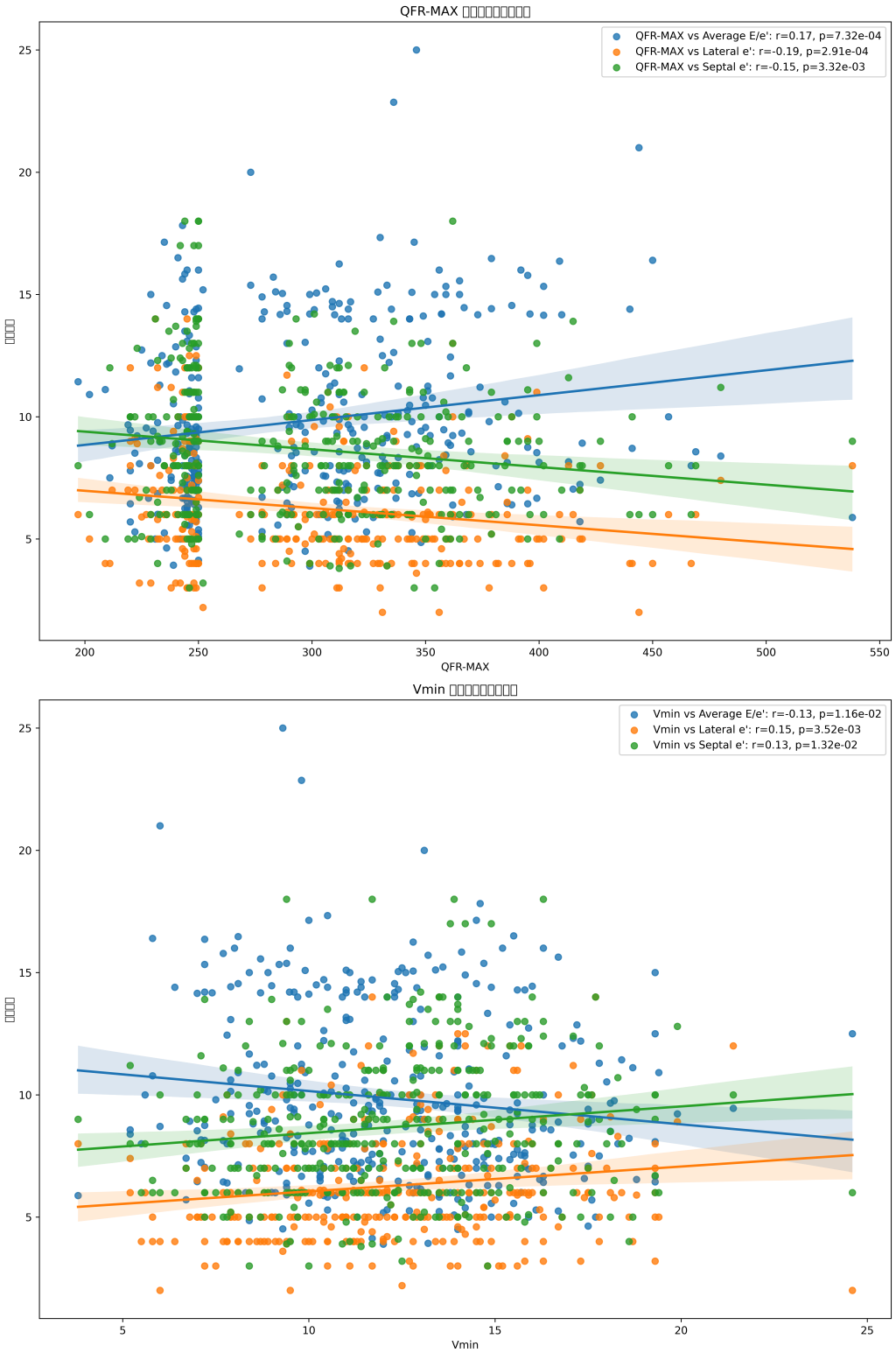


Figure 2

Linear correlation analysis. The upper graph shows the linear correlation between AMRmax and the average E/e', lateral e', and septal e'. The lower graph shows the linear correlation between Vmin and the average E/e', lateral e', and septal e'.

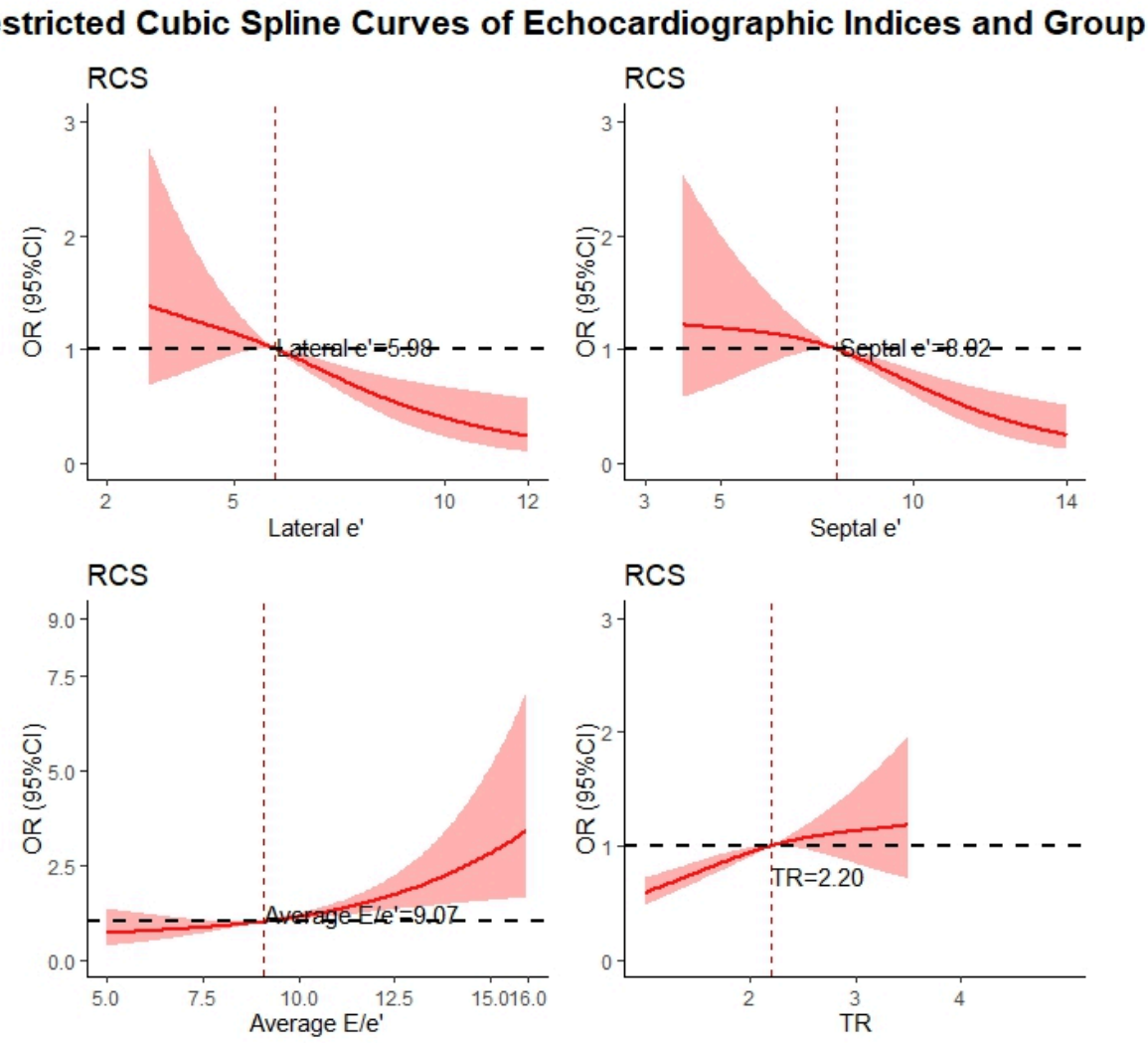


Figure 3

restricted cubic spline (RCS). The vertical axis represents the odds ratio (OR) value of CMVD as the outcome variable.

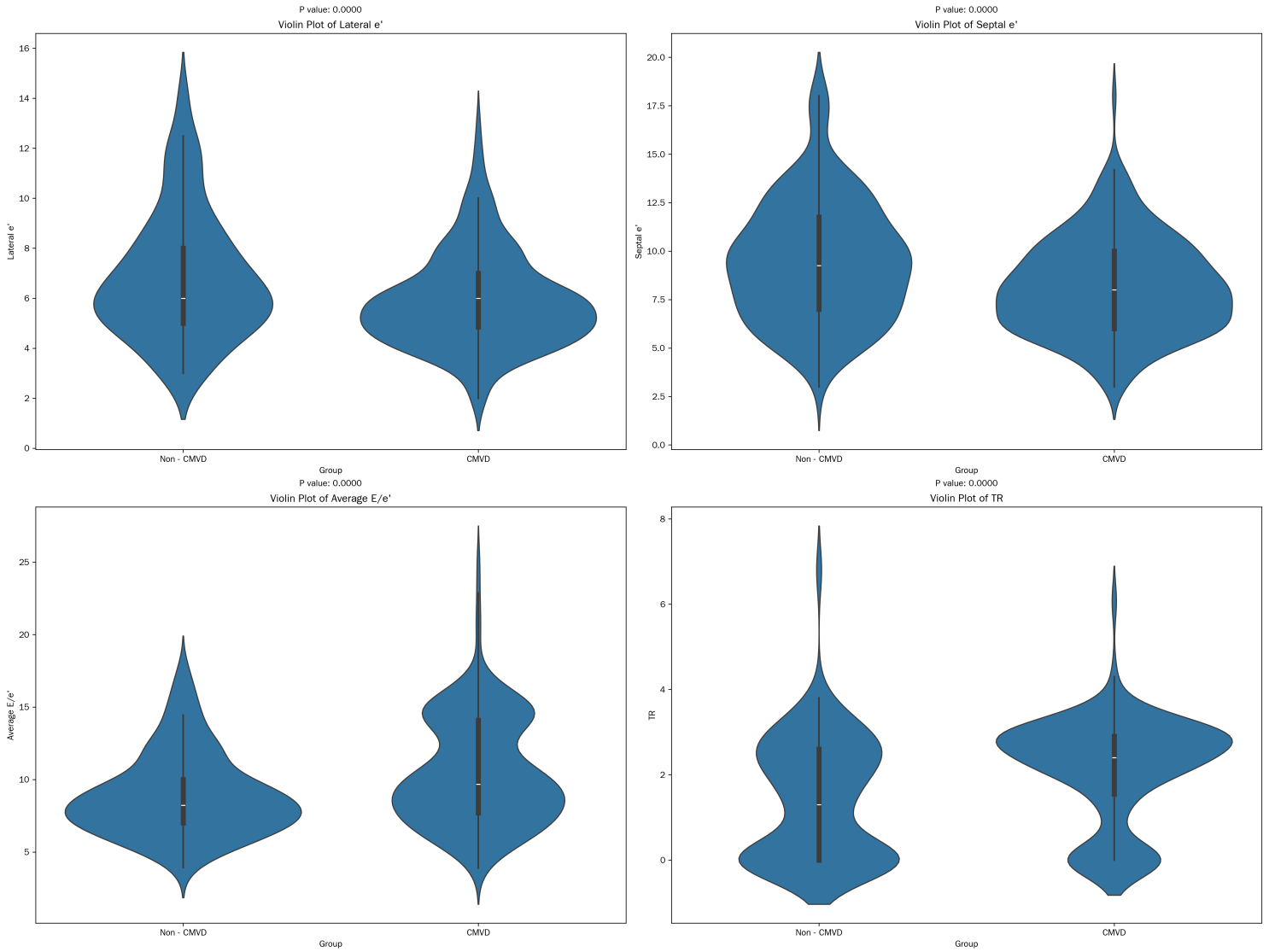


Figure 4

violin plot.

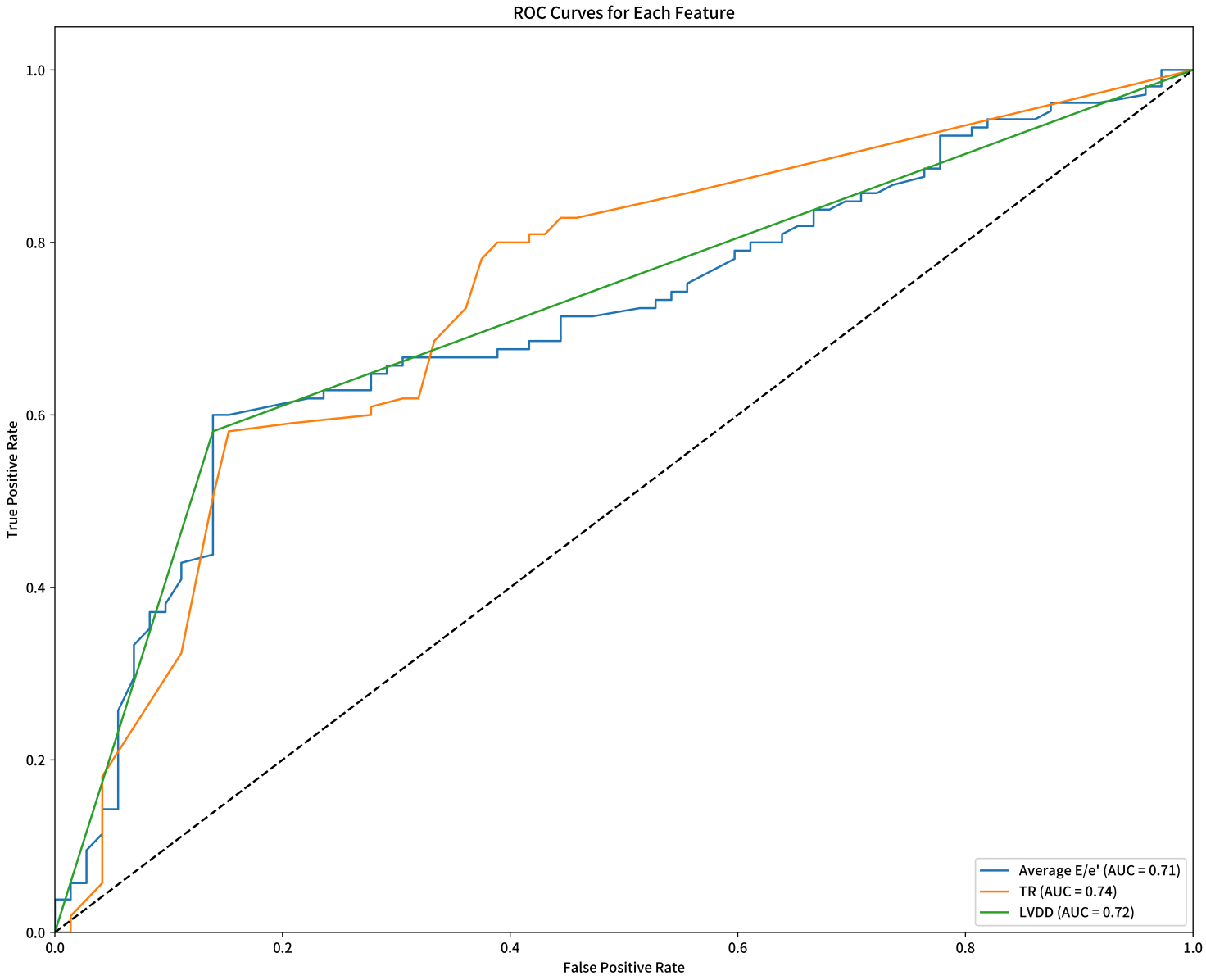


Figure 5

Receiver Operating Characteristic. AUC: area ynder curve.

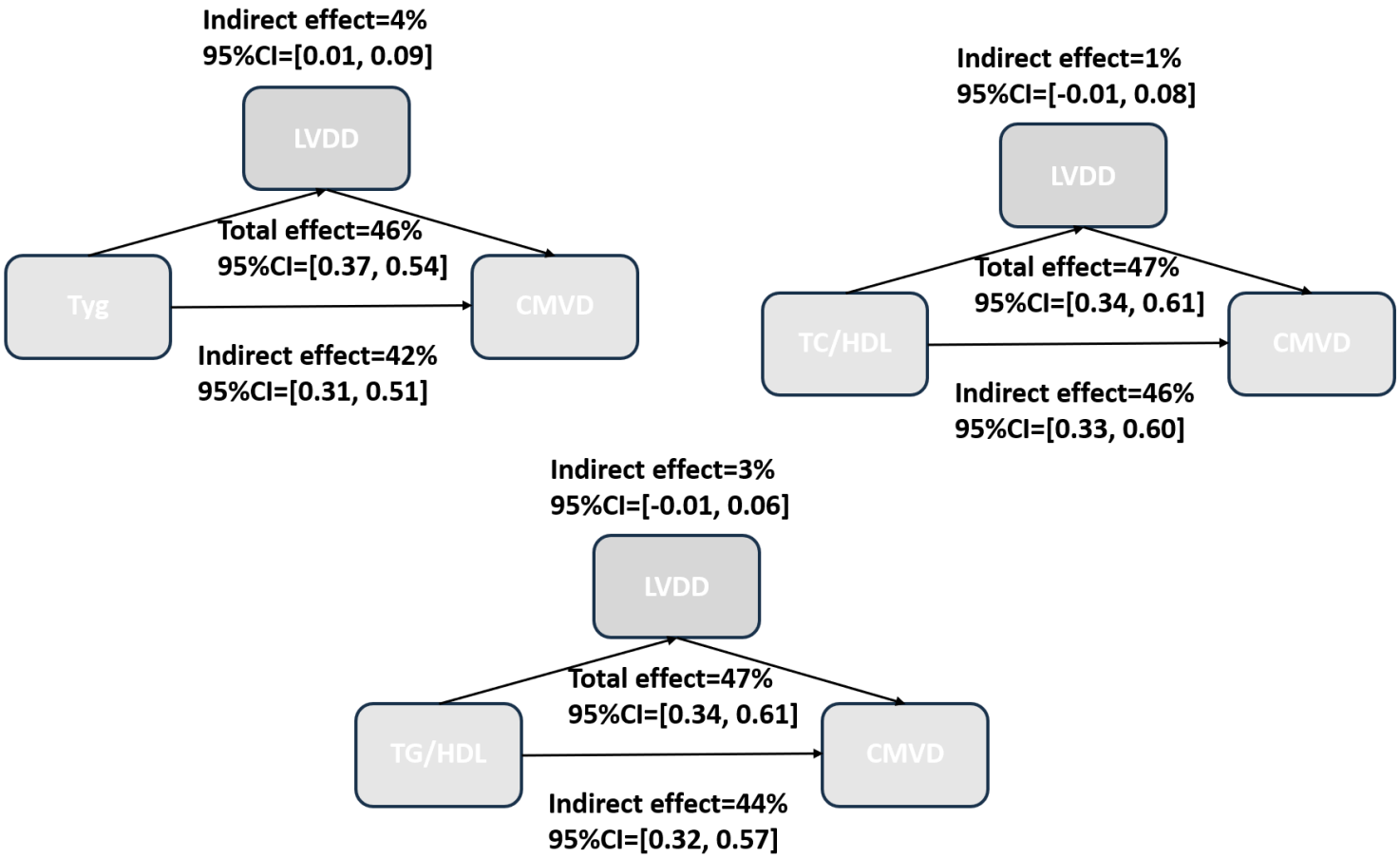


Figure 6

Legend not included with this version.

Supplementary Files

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

- file.csv