

Lipidomic Profiling and Biological Aging in Patients with Coronary Microvascular Dysfunction

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Background: Coronary microvascular dysfunction (CMD) was frequently encountered in patients with angina in the absence of epicardial coronary stenosis. CMD was associated with adverse outcomes while the etiology was unclear.

Objective: In this study, we aimed to investigate the association between lipidomic abnormalities, biological aging and CMD.

Methods: We consecutively enrolled 43 patients with angina exhibiting no epicardial coronary stenosis on angiography. CMD was defined by a coronary angiography-derived index of microvascular resistance (caIMR) >25. Targeted lipidomic profiling quantified 781 lipids. PhenoAge was calculated from clinical parameters. Using machine learning, lipidomic data and clinical characteristics were screened to identify candidate biomarkers.

Results: There were 25 patients having CMD with the mean caIMR of 34.0 (Interquartile range [IQR], 31.0–36.5), in contrast to 23.0 (IQR, 19.0–24.5) in the control group. Patients with CMD had substantially older PhenoAge (61 vs 52, $p = 0.002$). Forty-eight lipid species were dysregulated in patients with CMD, which predominantly belonged to triacylglycerol (TAG). PhenoAge, triglyceride glucose index, hypertension, TAG47:2-FA14:0, TAG48:4-FA18:1 and phosphatidylcholine (18:1/20:3) were independent risk factors of CMD. Incorporating dysregulated lipids significantly improved CMD prediction compared to traditional clinical factors alone (area under the curve, 0.94 vs 0.86, $p < 0.05$).

Conclusion: PhenoAge acceleration and dysregulated lipidome were associated with CMD. Larger-scale studies and external validation are needed in the future.

Keywords: biological aging, lipidomics, index of microcirculatory resistance, coronary microvascular dysfunction

Introduction

Coronary angiography reveals non-obstructive coronary artery disease (CAD) in nearly half of patients presenting with chest pain.¹⁻³ A significant number of symptomatic patients without flow-limiting coronary lesions have structural or functional abnormalities of the coronary microcirculation, resulting in coronary microvascular dysfunction (CMD).⁴ Patients with CMD are at substantially elevated risk of future adverse cardiovascular events.⁵ However, the management of CMD remains challenging due to limited understanding of its etiology and the lack of targeted therapies.

CMD has been invasively assessed using the index of microcirculatory resistance (IMR) through a pressure wire. In recent years, CMD evaluation has been advanced by the development of coronary angiography-derived index of microcirculatory resistance (caIMR), which could conveniently assess CMD based on computational pressure-fluid dynamics and routine coronary angiography.^{6,7} caIMR enables real-time evaluation of CMD in the catheter room without increasing operation time or radiation exposure.

Lipid metabolism is critical for endothelial cells and coronary microvascular homeostasis.⁸ Conventional lipid parameters, such as low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG), are insufficient to characterize the complexity of lipid metabolic processes. Modified lipoproteins may be involved in the development of cardiovascular dysfunction.⁹ The advent of lipidomics allows detailed profiling of lipid species,¹⁰ which is a valuable tool for identifying and quantifying potential biomarkers relevant to disease process.¹¹

Moreover, endothelial dysfunction is a recognized hallmark of panvascular diseases, affecting multiple organs within the circulatory system beyond the heart alone.¹² Cross-organ interactions could accelerate biological aging through inflammatory processes, secretome alterations, metabolic dysregulation.¹³ On the other hand, senescence itself was related with deteriorating endothelial function.¹⁴ Endothelial senescence, characterized by a shift toward a vasoconstrictive, proinflammatory environment, would cause impaired regulation of vascular homeostasis and microvascular dysfunction.¹⁵ The specific association between biological aging and CMD, however, remains unexplored.

In this cross-sectional study, we recruited angina patients without obstructed arteries and assessed coronary microvascular function using caIMR. By integrating machine learning and lipidomic profiling, we investigated the association between lipid metabolic features, biological aging, and CMD. This research aims to enhance the understanding of CMD etiology and identify biomarkers for precise diagnosis and treatment.

Methods

Study Population

A total of 43 patients presenting stable angina pectoris with no coronary stenosis in coronary angiography were consecutively recruited at Shanghai Geriatric Medical Center from 2023 to 2024. Patients were excluded with elevated high-sensitivity cardiac troponin T levels on admission and prior history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Written informed consent was obtained from all participants or their legal representatives. The study protocol was approved by the Ethics Committee of Shanghai Geriatric Medical Center (B2023-007) and conducted according to the guidelines of the Declaration of Helsinki. This trial was registered with the Chinese Clinical Trial Registry (URL: <https://www.chictr.org.cn>; Identifier: ChiCTR2500095360).

caIMR Measurements

caIMR was computed using FlashAngio software (Rainmed Ltd, Suzhou, China). The calculation is based on the assumption that mean diastolic coronary flow velocity is proportional to that in hyperemia. First, a three-dimensional mesh model was reconstructed from the coronary ostium to the distal segment, using ≥ 2 angiographic views separated by $\geq 30^\circ$. Second, angiography-derived FFR (caFFR) was determined through computational pressure-flow dynamics. Finally, caIMR was calculated as:

$$caIMR = Pd_{hyp} \cdot \frac{L}{V_{hyp}}$$

Pd_{hyp} is the mean distal arterial pressure during simulated maximal hyperemia. $Pd_{hyp} = Pa_{hyp} - \Delta P \cdot Pa_{hyp}$ is derived from mean resting aortic pressure via FlashAngio algorithms. ΔP represents the computed pressure gradient along meshed vessels using computational fluid dynamics. L indicates vessel length from the inlet to the distal segment of the target vessel. V_{hyp} is the simulated maximal hyperemic flow velocity. $V_{hyp} = K \cdot V_{diatole}$. K is the constant used to adjust the difference between the resting and hyperemic flow velocity. $V_{diatole}$ is the resting diastolic flow velocity calculated by the software. CMD was defined as caIMR >25.

Sample Collection and Lipidomic Analysis

Venous blood samples were collected after at least 8 hours of fasting. Plasma was separated by centrifugation (1500 g, 15 min, 4°C) within 4 hours and stored at -80°C . Blinded to researchers performed lipid extraction and analysis. 20 μL plasma was spiked with 9 μL internal standard cocktails (Avanti Lipids Polar) and 350 μL pre-cooled isopropanol (-20°C). After vortex-mixing and 10-min incubation at room temperature, samples were stored at -20°C overnight. After vigorous shaking and centrifugation (12,000 rpm, 20 min), supernatants were transferred, re-centrifuged

(12,000 rpm, 10 min), and analyzed in glass tubes via normal-phase liquid chromatography coupled to a QTRAP 5500 mass spectrometer (SCIEX, Framingham, MA, USA) in dual-polarity electrospray ionization mode. 20 μ L aliquots of quality control (QC) samples were prepared by pooling identical volumes of the individual plasma samples. Eight pooled plasma QC samples (20 μ L each) were evenly distributed across each run. Variables with relative standard deviation >20% were excluded, and internal standard peak heights were monitored to ensure stability.

The Q-Trap was operated to scan precursor/product ion pairs. Each test was repeated thrice. Peak area of each pair was processed with MultiQuant™ software (AB Sciex) for further quantification. Additional parameters had been described previously.¹⁶

A total of 781 lipid species were measured in this study including: cholesterol (Cho), cholesterol ester (CE), phosphatidylcholine (PC), lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE), alkylphosphatidylethanolamine [PE(O)], alkenylphosphatidylethanolamine [PE(P)], lysophosphatidylethanolamine (LPE), phosphatidylglycerol (PG), phosphatidylinositol (PI), lysophosphatidylinositol (LPI), phosphatidylserine (PS), ceramide (Cer), GM3 ganglioside, sphingosine (Sph), sphingomyelin (SM), diacylglycerol (DAG) and triacylglycerol (TAG).

Data Preprocessing

Lipid species undetectable in >50% cases were excluded and 691 lipids were left for further analysis. Remaining missing (undetectable) values were replaced by one-fifth of the minimum value of the corresponding lipids in the detected cohort. Then, the lipidomic data was log₁₀ transformed and standardized using Z-score.

PhenoAge Calculation

Biological aging was quantified using PhenoAge adapted from the reported algorithm.^{17,18} PhenoAge was calculated from clinical biomarkers including albumin (g/L), alkaline phosphatase (U/L), ln(C-reactive protein) (mg/dl), creatine (μ mol/L), HbA1c (%), lymphocyte percentage (%), mean corpuscular volume (fl), red blood cell distribution width (%) and white blood cell count ($\times 10^9$ /L). PhenoAge advance was defined as PhenoAge minus chronological age. Biological aging acceleration was defined as PhenoAge advance greater than 0.

Model Development and Validation

Three machine learning (ML) models, including Random Forest (RF), Support Vector Machine (SVM) and eXtreme Gradient Boosting (XGBoost) were implemented for CMD prediction. To optimize the prediction models, the final hyperparameters for each model were tuned based on 50 rounds of 5-fold cross-validation with 80% of the population. Then, the models were refitted on the entire dataset with the optimal hyperparameters. Feature contributions were ranked by descending mean absolute SHAP values.

In order to ensure the robustness of significant lipid species selected from the ML models, 200 rounds of Least Absolute Shrinkage and Selection Operator (Lasso) regression were conducted. In each of the 200 rounds, the dataset was randomly divided into a training set (80%) and a validation set (20%). On the training portion, Lasso regression was conducted with 5-fold cross validation to select the best penalty term (λ). Then we recorded which lipid features had non-zero coefficients—meaning they were selected by the model. Lipid species were then ranked by the frequency of inclusion. Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) was performed to generate Variable Importance in Projection (VIP) scores.

Lipids meeting all three criteria—top 15 features in ML models (mean SHAP), top 15 selection frequency in Lasso regression, and VIP score >1 in OPLS-DA—were integrated with clinical factors into univariable and multivariable logistic regression models (Figure 1).

Statistics

For ML models, model performance was evaluated with area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity and accuracy. AUC comparisons used DeLong's test. The SHapley Additive exPlanations (SHAP) method ranked the importance of inputted features and was used for ML model explanation.¹⁹ Non-linear relationship between the biomarkers and odds ratio of CMD was displayed using restricted cubic splines. Variables with

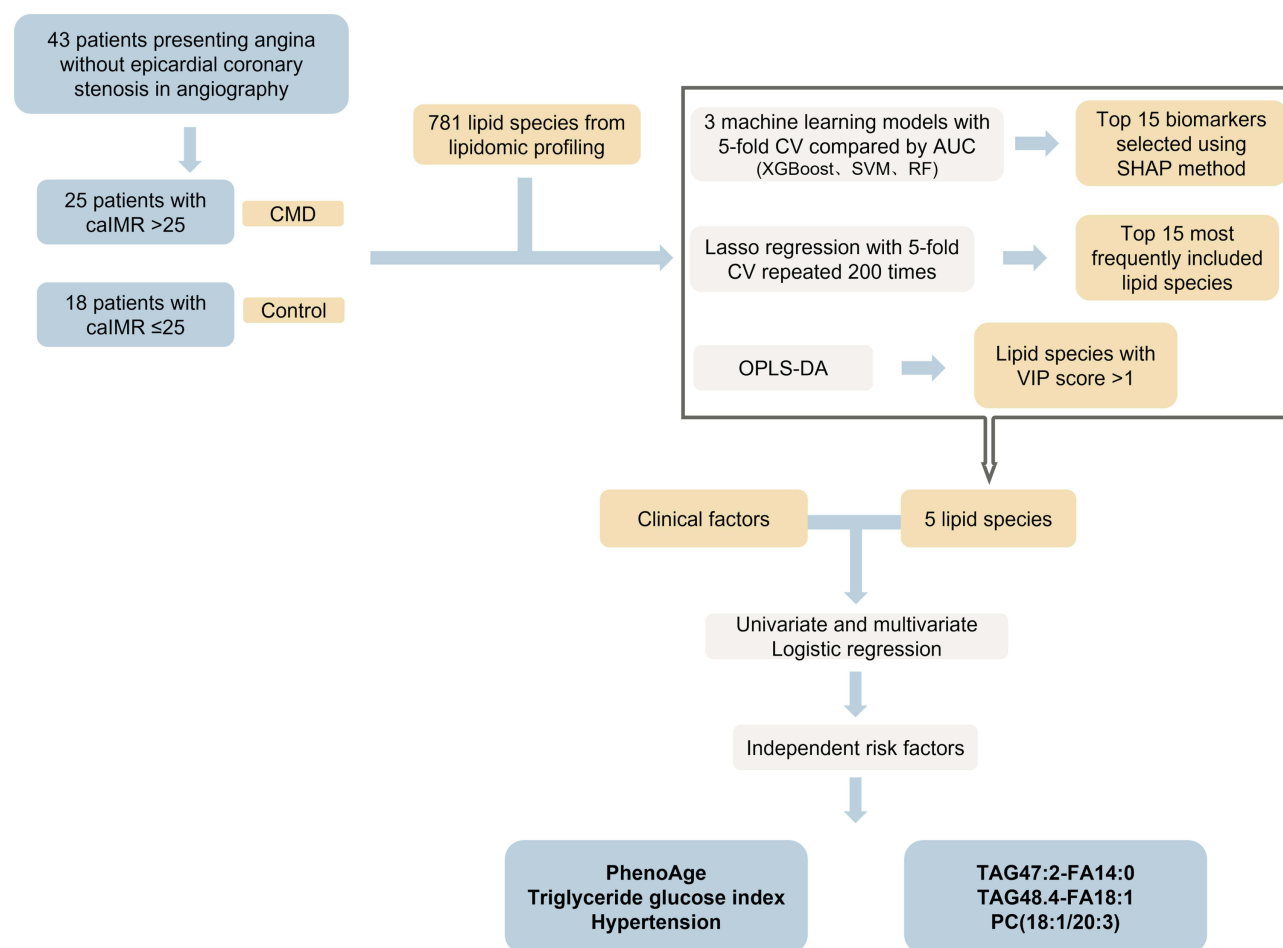


Figure 1 Flow chart of the study.

Abbreviations: AUC, area under the receiver operating characteristic curve; caIMR, coronary angiography–derived index of microcirculatory resistance; CMD, coronary microvascular dysfunction; CV, cross validation; OPLS-DA, orthogonal partial least squares discriminant analysis; PC, phosphatidylcholine; RF, random forest; SHAP, SHapley Additive exPlanations; SVM, support vector machine; TAG, triacylglycerol; TyG, triglyceride glucose index; VIP, variable importance in projection.

$p < 0.05$ in the univariable analysis were subsequently included in the multivariable model for further analysis. The discriminating performance of logistic regression models was evaluated by AUC. Calibration plots, showing the predicted probability versus the observed probability of CMD, were internally validated by 1000 bootstrap resampling. Clinical impact curves visualized net clinical benefits at different risk thresholds.

The study was designed as an exploratory lipidomic investigation in patients with angiography-defined coronary microvascular dysfunction. At study initiation, reliable prior estimates were not available for the expected effect sizes of individual lipid species or PhenoAge in caIMR-defined CMD. For that reason, a conventional power calculation for the lipidomic endpoints was not feasible.

Categorical variables are presented as counts (percentages) and continuous variables as mean $\pm$ standard deviations (SD) or median with interquartile ranges (IQR), accordingly. Comparisons between categorical variables were made by the Chi-squared test, whereas continuous variables were compared by Student's t test (normally distributed) or Mann–Whitney U -test (non-normally distributed). The p -values (two-sided) were corrected for multiple comparisons using the Benjamini–Hochberg method,²⁰ after comparing lipid levels between CMD and control groups. A two-tailed P -value < 0.05 was considered statistically significant. Data were analyzed with R software 4.5.1 and SPSS v25.0 (IBM Corp., Armonk, NY, USA).

Result

Baseline Characteristics

The cohort comprised 43 patients, of whom 28 patients were diagnosed with CMD who had caIMR >25 in at least one vessel. Demographic and clinical characteristics are summarized in [Table 1](#). Smoking history, hypertension, diabetes, conventional lipid parameters, and major lipid-lowering medication categories were assessed at baseline. Most baseline variables were similar between the groups. However, patients with CMD were more likely to be male (78.6% vs 40.0%, $p = 0.011$) and had higher prevalence of hypertension (60.7% vs 26.7%, $p = 0.033$) compared to controls. Additionally, fasting glucose levels and triglyceride glucose index (TyG) were significantly elevated in the CMD group than those in the control group (both $p < 0.05$). No patient was taking omega-3 supplements, fibrates, or PCSK9 inhibitors during the study period. Statin use did not differ significantly between groups, and LDL-C was also comparable between groups ($p = 0.610$). Details of caIMR are presented in [Table 2](#). In brief, the average caIMR of three vessels was substantially higher in CMD patients (34.0 [IQR, 31.0–36.5]) than in controls (23.0 [IQR, 19.0–24.5]) ($p < 0.001$).

Lipidomic Features

After adjustment for multiple comparisons, lipidomic profiling identified 48 lipid species showing differential abundance between the groups (false discovery rate < 0.05. [Supplemental Figure 1](#)). Notably, 36 of these dysregulated lipids (75%)

Table 1 Baseline Demographics and Clinical Characteristics

	Total (n = 43)	CMD [#] (n = 28)	Control (n = 15)	p Value
Age (years)	62(55.5–67.0)	65(60–64)	61(54–64)	0.176
Male	28(65.1)	22(78.6)	6(40.0)	0.011
Hypertension	21(48.8)	17(60.7)	4(26.7)	0.033
Diabetes Mellitus	10(23.3)	6(21.4)	4(26.7)	0.698
Smoking History	5(11.6)	2(7.1)	3(20)	0.210
Laboratory and auxiliary examinations				
hs-CRP (mg/L)	1.10(0.40–2.35)	1.25(0.40–2.70)	1.00(0.40–1.80)	0.808
Platelet ($\times 10^9/L$)	197(171–229)	194(168–231)	197(172–227)	0.601
Hemoglobin (g/L)	132(117–143)	131(118–142)	132(117–140)	0.533
NT-proBNP (pg/mL)	50.60(22.80–103.85)	50.60(20.30–108.90)	49.35(25.90–98.80)	0.789
Cardiac troponin T (ng/mL)	0.006(0.004–0.009)	0.007(0.004–0.009)	0.006(0.004–0.007)	0.442
Total cholesterol (mmol/L)	3.93(3.45–4.51)	3.92(3.23–4.55)	4.04(3.75–4.44)	0.177
Low-density lipoprotein (mmol/L)	2.02(1.56–2.59)	1.98(1.53–2.52)	2.18(1.64–2.65)	0.610
Triglyceride (mmol/L)	1.49(1.02–2.55)	1.49(1.12–2.92)	1.33(0.87–1.75)	0.257
High-density lipoprotein (mmol/L)	1.19(0.92–1.38)	1.16(0.88–1.37)	1.35(0.97–1.72)	0.076
Lp(a) (mg/L)	64(24–180)	64(15–130)	63(29–183)	0.712
Triglyceride glucose index*	9.01(8.42–9.68)	9.34(8.76–9.91)	8.31(8.03–9.01)	0.002
Echocardiography				
Ejection Fraction (%)	65(62–67)	65(62–66)	65(61–69)	0.644
Left atrium (mm)	38(35–43)	39(36–43)	37(34–40)	0.055
LVEDD (mm)	47(44–50)	48(44–49)	47(42–50)	0.474
LVESD (mm)	30(28–32)	31(29–32)	29(27–32)	0.392
SPAP (mmHg)	33(30–36)	33(30–36)	31(30–36)	0.474
IVS (mm)	10(9–11)	10(9–11)	9(9–10)	0.116
PWT (mm)	10(9–10)	10(9–10)	9(8–10)	0.171

Notes: Data are shown as median (interquartile range) or n (%). [#]defined as angiograph-derived index of microcirculatory resistance >25.

*defined as $\ln [\text{triglyceride (mg/dl)} \times \text{blood glucose (mg/dl)}]/2$.

Abbreviations: CMD, coronary microcirculatory dysfunction; hs-CRP, high-sensitivity C-reactive protein; IVS, interventricular septum; Lp(a), lipoprotein (a); LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PWT, posterior wall thickness; SPAP, systolic pulmonary arterial pressure.

Table 2 Angiograph-Derived Index of Microcirculatory Resistance in Coronary Arteries

calMR	Total (n = 43)	CMD [#] (n = 28)	Control (n = 15)	p Value
LAD	33.2(24.1–38.2)	37.6(33.0–40.5)	23.1(18.0–24.1)	<0.001
LCX	30.1(25.0–34.4)	33.1(30.3–38.1)	22.6(20.4–24.7)	<0.001
RCA	25.5(22.7–30.1)	29.1(25.9–36.5)	20.1(17.4–23.2)	<0.001
Average	31.0(24.5–35.0)	34.0(31.0–36.5)	23.0(19.0–24.5)	<0.001

Notes: Data are shown as median (interquartile range). [#]defined as calMR >25.
Abbreviations: calMR, angiograph-derived index of microcirculatory resistance; CMD, coronary microcirculatory dysfunction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

were TAG, all of which were significantly elevated in patients with CMD. Conversely, the CMD cohort had substantially lower circulating levels of several other lipids, including 2 in CE, 3 in SM, 3 in PC and 4 in PE(P).

Further investigation into lipid structural characteristics, specifically the total number of carbon atoms and double bonds, revealed significant correlation with CMD risks (Figure 2). DAG and TAG were generally associated with an increased CMD risk, particularly those with longer carbon chains and greater degrees of unsaturation. In contrast, PE(O), PE(P) and SM were broadly related with a reduced risk profile of CMD.

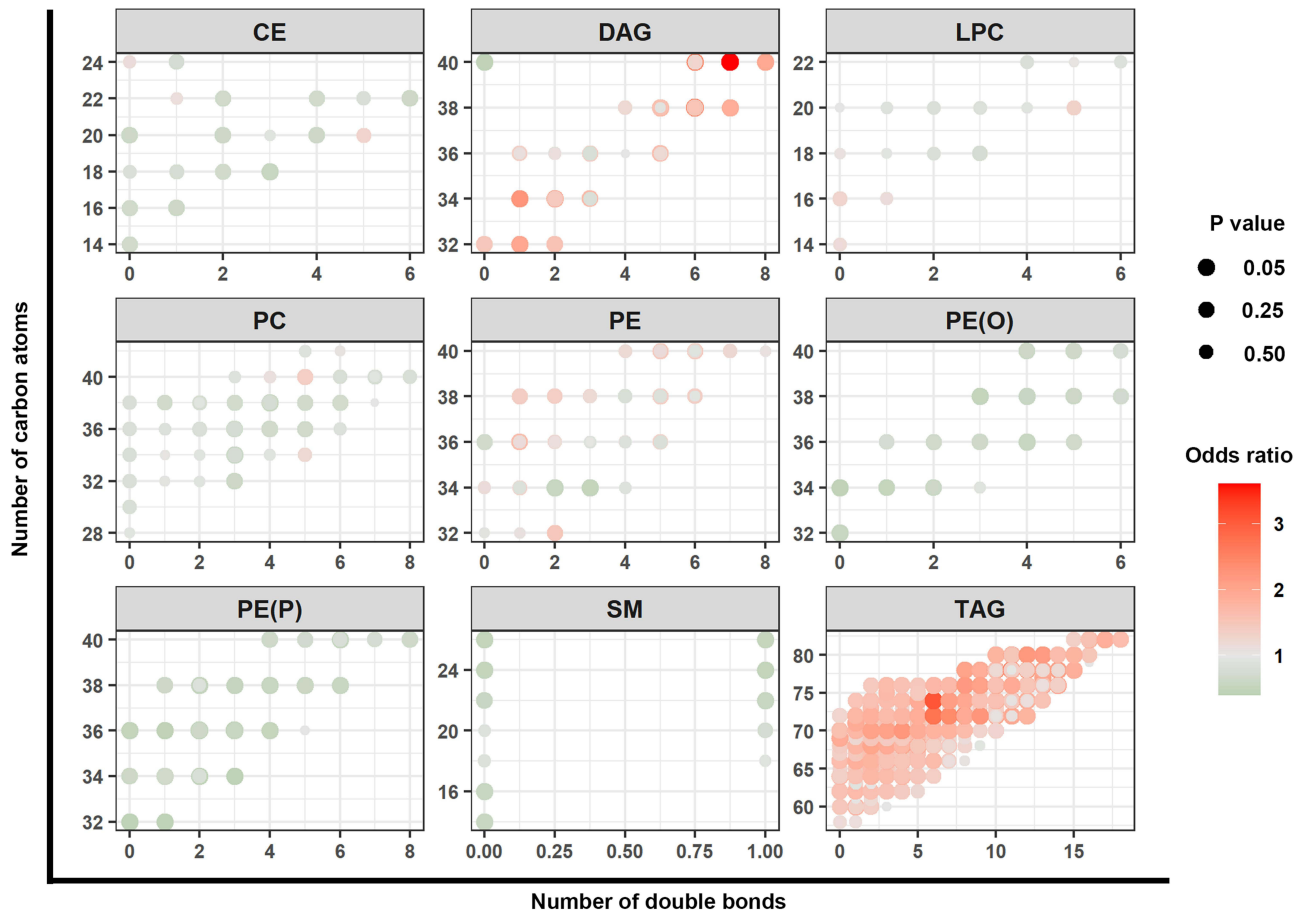


Figure 2 Association between number of carbon atoms, double bonds and CMD risk. Individual lipid species are depicted by filled circles and arranged by lipid class in 9 panels according to the number of total carbon atoms (Y axes) and number of double bonds (X axes). Circle color indicates the magnitude of odds ratio (OR) of coronary microvascular dysfunction (CMD), and circle size corresponds to the significance level.
Abbreviations: CE, cholesterol ester; DAG, diacylglycerol; LPC, lysophosphatidylcholine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PE(O), alkylphosphatidylethanolamine; PE(P), alkenylphosphatidylethanolamine; SM, sphingomyelin; TAG, triacylglycerol.

Table 3 Features in PhenoAge Calculation

Characteristics	Total (n = 43)	CMD [#] (n = 28)	Control (n = 15)	p Value
PhenoAge	60(49–64)	61(58–67)	52(43–58)	0.002
PhenoAge advance*	0.1(–10.6–5.4)	4.3(0.7–7.4)	–11.1(–14.5–8.3)	<0.001
Albumin (g/L)	44(41–46)	45(43–46)	43(40–45)	0.214
Alkaline phosphatase (U/L)	65(59–78)	73(57–82)	64(60–67)	0.157
Ln (C-reactive protein) (mg/dl)	–0.92(–1.39–0.63)	–0.85(–1.39–0.38)	–1.22(–1.39–0.90)	0.148
Creatine (μmol/L)	77(67–89)	78(70–91)	73(63–81)	0.114
HbA1c (%)	5.8(5.4–6.2)	5.9(5.5–6.5)	5.7(5.3–6.0)	0.267
Lymphocyte percentage (%)	28.5(24.6–33.0)	26.7(22.7–31.8)	30.6(27.8–34.8)	0.039
Mean corpuscular volume (fl)	90.0(88.5–93.3)	90.0(88.1–93.3)	90.4(88.5–93.4)	0.789
Red blood cell distribution width (%)	15.1(12.0–16.4)	16.1(15.3–16.7)	11.8(11.4–12.1)	<0.001
White blood cell count (*10 ⁹ /L)	6.54(5.27–7.40)	6.59(5.84–7.57)	5.77(4.30–7.40)	0.262

Notes: Data are shown as median (interquartile range). [#]defined as angiograph-derived index of microcirculatory resistance >25. *defined as PhenoAge - chronological age.

Abbreviation: CMD, coronary microcirculatory dysfunction.

PhenoAge

Details of PhenoAge and related clinical parameters are shown in [Table 3](#). The median PhenoAge was 61 in the CMD group versus 52 in the control group ($p = 0.002$) ([Figure 3](#)). Of note, PhenoAge advance was significantly greater in patients with CMD. 78.4% of the CMD patients had biological aging acceleration in contrast to none in the control group.

Selection of Candidate Biomarkers

We performed fifty rounds of 5-fold cross validation to build three ML models. In comparison with SVM and RF models, the XGBoost model demonstrated superior performance in terms of AUC (0.71; 95% confidence interval [CI], 0.68–0.75) and accuracy (0.68; 95% CI, 0.35–0.91) ([Supplemental Figure 2](#)). The SHAP method was employed to interpret the XGBoost model's decision-making process. Feature contributions were ranked by descending mean absolute SHAP values ([Figure 4A](#)), revealing PhenoAge, TyG index, lymphocyte counts, high-density lipoprotein cholesterol and 11 lipid species as the fifteen most influential predictors. Furthermore, PhenoAge showed a significant positive correlation with SHAP values ([Figure 4B](#)).

Lasso regression with 5-fold cross validation was repeated 200 times, and lipid species were ranked by selection frequency ([Supplemental Table 1](#)). OPLS-DA was performed to generate VIP scores for each lipid ([Supplemental Figure 3](#) and [Supplemental Table 2](#)). To enhance biomarker robustness, lipids meeting all three criteria—top 15 features in XGBoost (mean SHAP), top 15 selection frequency in Lasso regression, and VIP score >1 in OPLS-DA—were integrated with clinical factors into logistic regression models ([Figure 1](#)). Multivariable analyses identified PhenoAge, TyG index, hypertension, PC(18:1/20:3), TAG47:2-FA14:0 and TAG48:4-FA18:1 as independent risk factors of CMD ([Table 4](#)). All these factors were associated with elevated risk of CMD except PC(18:1/20:3) showing protective effect. The correlation between PhenoAge, TyG index and the risk of CMD are displayed in [Figure 5](#). The odds ratio of CMD started to be >1 when PhenoAge was over 60 or Tyg index over 8.57.

Model Performance

The integrated logistic model incorporating both lipid species and clinical factors was compared with a clinical-factor-only model. The combined model demonstrated significantly superior discriminative ability relative to the clinical model (AUC: 0.94 [95% CI, 0.91–0.98] vs 0.86 [95% CI, 0.78–0.96]; $p < 0.05$) ([Figure 6A](#)). As shown in [Figure 6B](#), the combined model exhibited higher consistency between the predicted and observed risks. In clinical impact curves, the model with clinical and lipidomic biomarkers yielded greater net benefits across the entire range of threshold ([Figure 6C](#) and [D](#)).

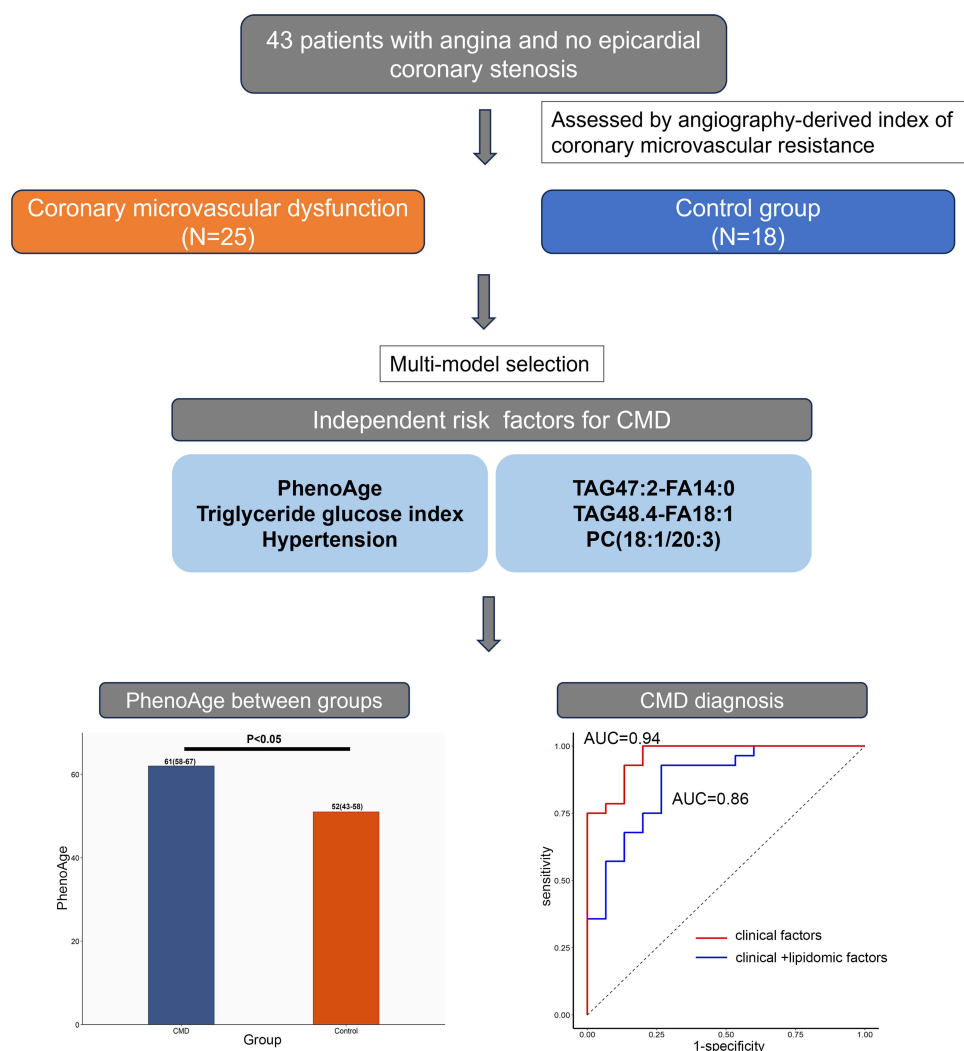


Figure 3 Study workflow. In this study, we investigated the clinical and lipidomic features of patients with coronary microvascular dysfunction. PhenoAge, triglyceride glucose index, hypertension, TAG47:2-FA14:0, TAG48:4-FA18:1 and phosphatidylcholine (18:1/20:3) were independent risk factors of coronary microvascular dysfunction. The diagnosis of coronary microvascular dysfunction was markedly improved by incorporating lipidomic data with clinical factors.

Abbreviations: AUC, area under the receiver operating characteristic curve; CMD, coronary microvascular dysfunction; PC, phosphatidylcholine; TAG, triacylglycerol.

Discussion

In this study, we investigated the lipidomic features of patients with CMD and identified 3 lipids independently associated with CMD. Besides, our findings indicated PhenoAge acceleration was prevalent among CMD patients. PhenoAge, TyG index and hypertension were significant clinical predictors of CMD. Incorporating lipidomic data with clinical factors could provide additional value in the prediction of CMD. These exploratory findings offered novel pathophysiological insights and potential diagnostic strategies for CMD.

Approximately 10% of patients presented non-obstructive coronary arteries despite moderate-to-severe ischemia.²¹ While ischemia and non-obstructive coronary artery disease (INOCA) was historically considered benign,²² contemporary evidence indicated that patients with INOCA often had CMD and elevated risk of adverse outcomes.^{5,23,24} The pathophysiology of CMD involved incompletely understood functional and structural alterations. Functional mechanisms encompassed impaired microvascular relaxation and pathological vasoconstriction.²⁵ Structural changes may include luminal narrowing from vascular remodeling, fibrosis and thrombus plugging, while extraluminal compression due to reduced myocardial elasticity or elevated left ventricular end-diastolic pressure may also impair microcirculatory flow.²⁶

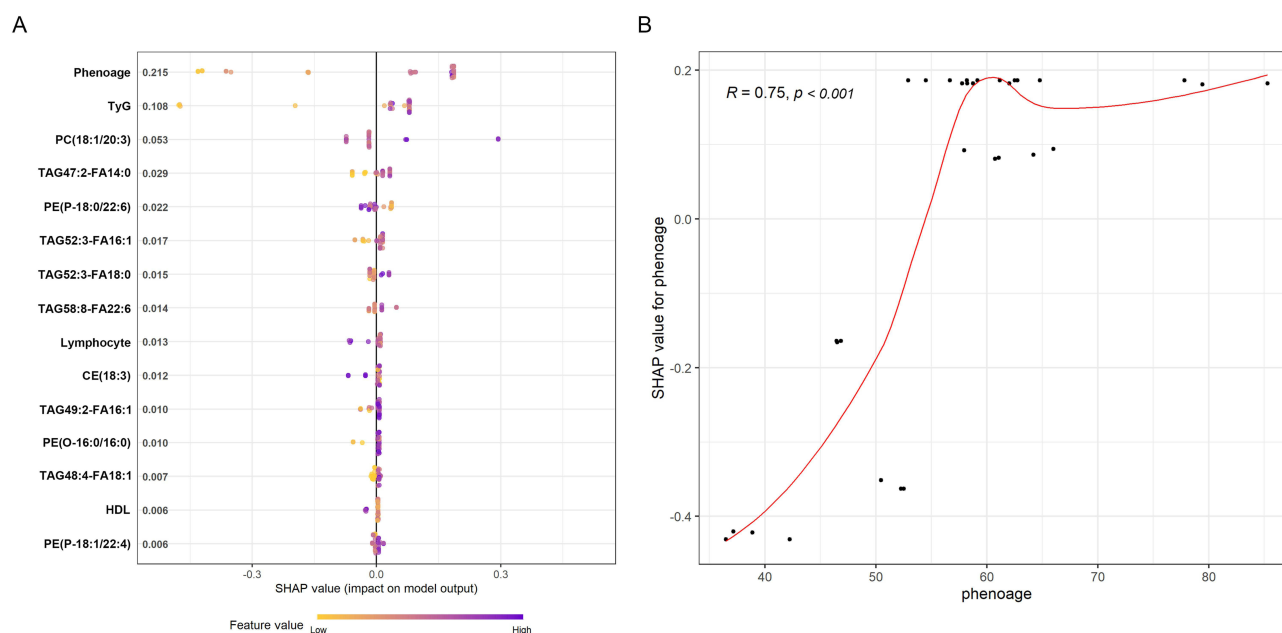


Figure 4 SHAP values of features in the XGBoost model. **(A)** Top 15 features included in the XGBoost model with best discrimination performance. Features are ranked by the importance evaluated through the SHAP method. **(B)** The positive correlation between SHAP values and PhenoAge. **Abbreviations:** CE, cholesterol ester; HDL, high-density lipoprotein cholesterol; PC, phosphatidylcholine; PE(O), alkylphosphatidylethanolamine; PE(P), alkylphosphatidylethanolamine; SHAP, SHapley Additive exPlanations; TAG, triacylglycerol; TyG, triglyceride glucose index.

Although therapeutic lifestyle modifications and anti-anginal medications may benefit CMD management, robust clinical evidence remained lacking. This was partially limited by the fact that the assessment of CMD predominantly relied on invasive methods and provocative tests. The advent of caIMR reduced the complexity of IMR measurement but it still required angiography. Less-invasive evaluation approaches for microcirculatory function are urgently needed.²⁷ Patients with CMD often experienced functional limitation and anxiety, which could cause frequent clinic visits and healthcare resource consumption. Preliminary studies of endothelial/microvascular-targeted therapies show promising vascular functional improvements.²⁸ However, randomized controlled trials are warranted.

Biological aging can be accessed via telomere length, epigenetic clocks, and composite clinical biomarkers. PhenoAge is a composite biological age derived from routine blood biomarkers, requiring no extra cost or specialized equipment. It integrates inflammation, nutrition, metabolism, and hematopoiesis, thereby capturing systemic aging beyond chronological age. Its superior prediction of mortality and cardiovascular events is well validated. Unlike epigenetic clocks, PhenoAge is accessible even in resource-limited settings, making it a practical, versatile tool for cardiovascular risk stratification.

Table 4 Predictors of Coronary Microcirculatory Dysfunction in the Logistic Regression Model

Risk Factors	Adjusted Odds Ratio (95% CI)	p Value
Clinical factors		
Hypertension	8.60(1.05–70.58)	0.045
Triglyceride glucose index*	13.15(2.11–82.04)	0.006
PhenoAge	1.20(1.05–1.37)	0.007
Lipid species		
TAG47:2-FA14:0	4.49(1.37–26.17)	0.031
TAG48:4-FA18:1	9.82(1.95–201.36)	0.038
PC(18:1/20:3)	0.16(0.02–0.67)	0.035

Notes: *Defined as $\ln [\text{triglyceride (mg/dl)} \times \text{blood glucose (mg/dl)} / 2]$.

Abbreviations: PC, phosphatidylcholine; TAG, triacylglycerol.

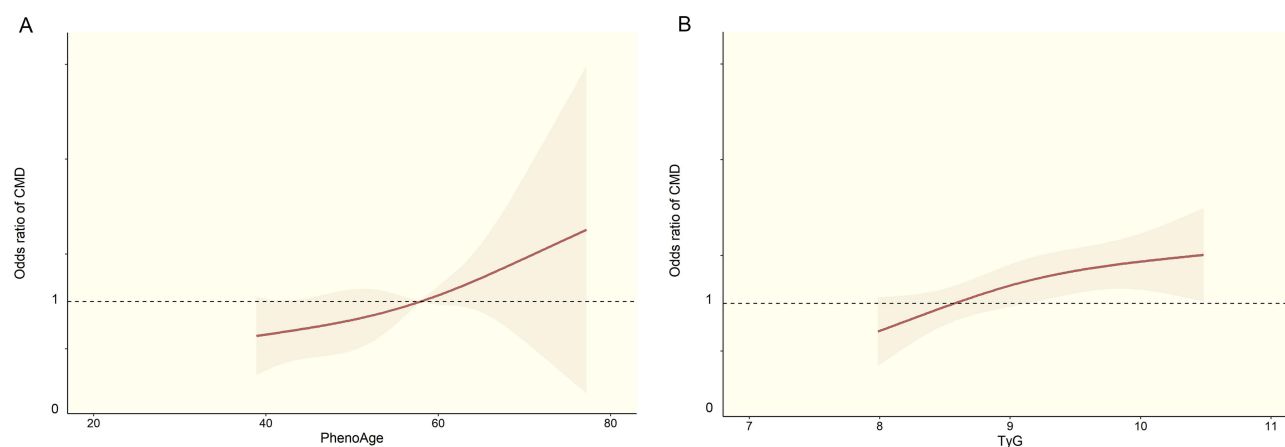


Figure 5 Association between PhenoAge, TyG and CMD risks. Restricted cubic spline curves are plotted to demonstrate the association between PhenoAge (**A**), TyG (**B**) and the odds ratio of CMD.

Abbreviations: CMD, coronary microvascular dysfunction; TyG, triglyceride glucose index.

This study demonstrated a novel association between PhenoAge acceleration and CMD, which could help to understand the microvascular pathophysiology. Although the chronological age was comparable between the groups, CMD patients had significantly elevated PhenoAge. To our knowledge, this was the first study revealing biological aging acceleration specifically in patients with coronary microcirculatory impairment. These findings aligned with emerging evidence linking cellular senescence to endothelial dysfunction and extended prior researches on vascular aging.²⁹ Exposure to hemodynamic forces of blood flow and circulating stimuli could induce endothelium cellular senescence. Senescent cells accumulated in vascular tissues could release pro-inflammatory cytokines, leading to endothelial barrier disruption and impaired nitric oxide bioavailability, which were core mechanisms in microvascular dysfunction.^{30,31} The absence of PhenoAge acceleration in non-CMD controls suggested its potential as a sensitive indicator of vascular vulnerability. The systemic aging phenotype may also explain the elevated cerebrocardiovascular risk in CMD patients despite patent epicardial arteries.^{32–34} However, CMD may also accelerate biological aging through chronic inflammation, oxidative stress, and metabolic dysregulation within the microvasculature. This bidirectional interplay creates a vicious cycle yet remains underexplored. Elucidating this relationship could inform novel therapeutic strategies targeting both CMD and aging pathways.

In this study, control subjects showed no PhenoAge acceleration. Their median PhenoAge advance was substantially negative (–11.1 years), indicating a biologically healthy profile consistent with their clinical status. This reflected the fact that our control group, though symptomatic, comprised patients with genuinely preserved microvascular function. This clear separation implied that accelerated aging was specifically associated with CMD in our cohort, rather than being a common trait in all patients with chest pain. This finding may be limited by the relatively modest sample size and the selective inclusion of symptomatic patients undergoing angiography. Further research is needed to validate this relationship in larger, multi-center cohorts.

Even though traditional lipid parameters were similar between CMD patients and controls, lipidomic analyses revealed profound alterations in the plasma lipidome of CMD patients. 75% of the dysregulated lipids belonged to the TAG class. This TAG predominance was consistent with recent evidence implicating triglyceride-rich lipoproteins (TRL) involvement in vascular inflammation.^{35–37} Some identified lipid species contained highly unsaturated fatty acids. Unsaturated lipids are prone to oxidative damage. Their oxidized products can trigger endothelial dysfunction and inflammation, which are key drivers of CMD. The abundance of such lipids in our CMD cohort suggests that oxidative lipid injury may contribute to microvascular pathology. Direct measurement of oxidized lipid species is warranted to confirm this pathway. Elevated TRL was a risk factor for both CAD and endothelial dysfunction,³⁸ and demonstrated a causal association with increased mortality risk.³⁹ Reduction of remnant lipoprotein cholesterol could possibly ameliorate endothelial dysfunction.⁴⁰ Conversely, PE and related lipids were generally associated with a decreased

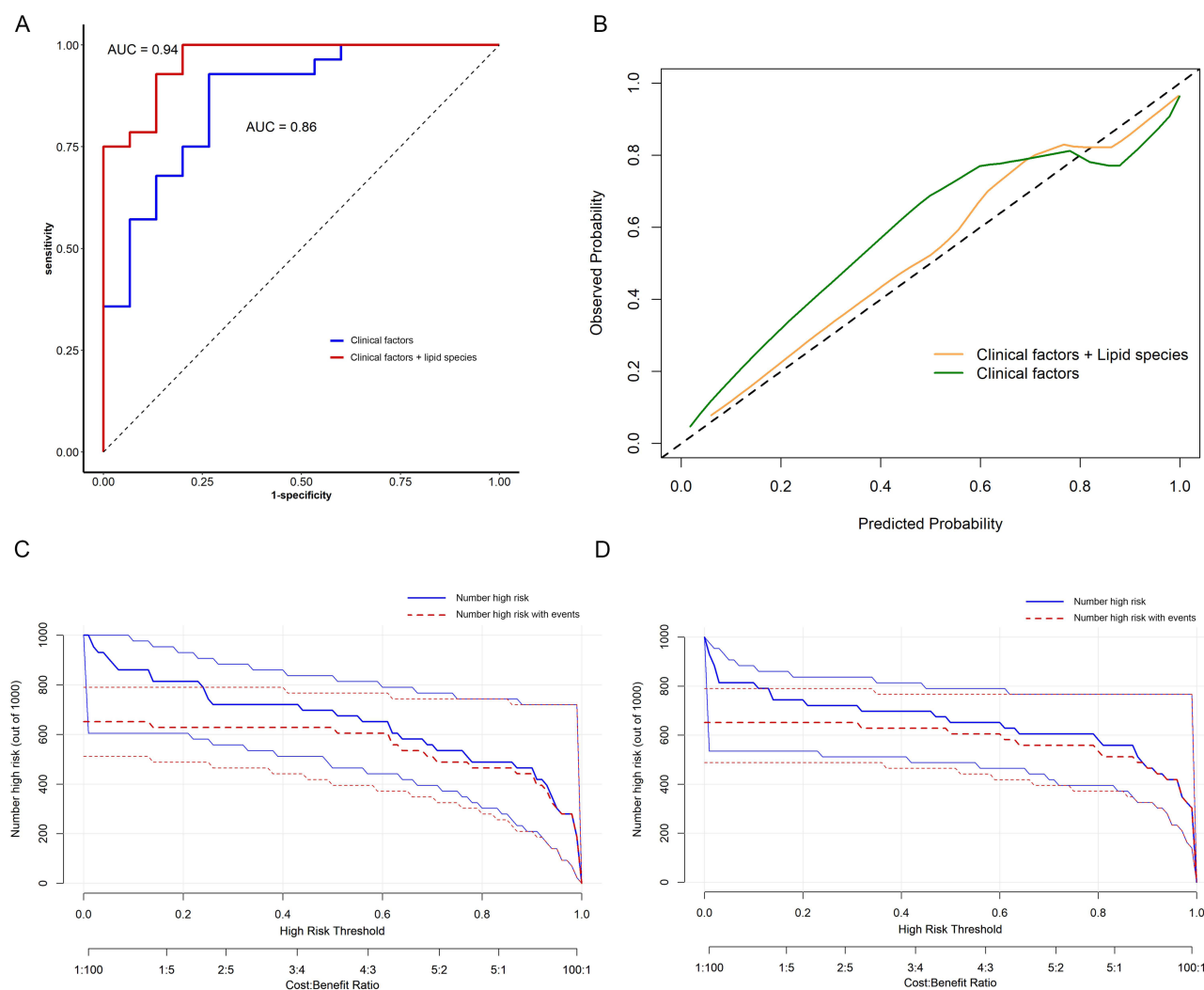


Figure 6 Performance of the predicting models. **(A)** The receiver operating characteristic curve of the clinical and integrated models. AUC was significantly improved in the integrated model (from 0.86 to 0.94, $p < 0.05$). **(B)** The calibration curves of the clinical and integrated models. Perfect prediction is shown by the diagonal black dashed line. The model incorporating clinical and lipidomic factors is closer to the observed probabilities indicating better calibration. The clinical impact curves of the clinical and integrated models are shown in **(C and D)**. The integrated model brought better clinical benefits over most of the risk thresholds, as indicated by the number of high-risk patients with CMD closer to the number of high-risk patients. AUC, are under the receiver operating characteristic curve.

CMD risk. As previously reported, PE and its derivatives were endogenous antioxidant with critical membrane-stabilizing function,^{41,42} which may prevent the microvasculature from oxidative injury. These lipidomic findings extended beyond conventional lipid metrics (eg, LDL-C and TG) by identifying molecular species that may serve as both biomarkers and therapeutic targets of CMD. These hypothesis-generating lipidomic signatures should be validated in multicenter cohorts before these markers can be considered for clinical use.

Beside the lipidomic alterations, we found that TyG index was also substantially higher in the CMD group. TyG index was regarded as a marker of insulin resistance, which could trigger endothelial damage and vasomotor dysfunction within the microvasculature.^{43,44} The elevated TyG index and dyslipidemia thus implicated an impaired cardiometabolic milieu which could directly lead to CMD and cardiovascular outcomes.^{45,46} In patients with chronic coronary syndrome, TyG index was closely correlated with caIMR, and an independent risk predictor for CMD.⁴⁷ Notably, Zhang et al reported that the TyG-CMD correlation was even stronger in non-diabetic patients and females, which suggested its utility in identifying early microvascular injury prior to overt diabetes. Integrating TyG assessment into clinical practice could enhance risk stratification, guide early interventions targeting microvascular injury, and potentially mitigate subsequent adverse events in high-risk cohorts.

A significant imbalance in sex distribution was observed between groups. Sex imbalance was an important limitation, given the known effects of sex hormones and menopausal status on lipid metabolism and vascular biology. The current cohort was too small for reliable sex-stratified analyses. Such analyses would have produced unstable estimates and increased the risk of overfitting. Menopausal status and sex-hormone-related variables were not systematically collected, which prevents us from distinguishing CMD-associated lipidomic differences from sex-related metabolic differences.

Despite its promise, routine clinical implementation of lipidomic profiling would face several hurdles. The need for high-resolution mass spectrometry and specialized bioinformatics expertise may limit accessibility in most hospital laboratories. Data processing is computationally intensive, and standardized reference ranges across different platforms are lacking. Besides, the turnaround time for lipidomics is often longer than conventional lipid tests, and per-sample costs remain substantial. Moreover, results require careful interpretation against clinical context. These challenges currently restrict lipidomics to research settings, but targeted panels based on research evidence and streamlined workflows may facilitate future translation.

Limitation

Several limitations must be acknowledged. First, this was an exploratory study of modest sample size. This constrained the statistical power for subgroup analyses. Validation in larger cohorts would be essential. Because both groups were symptomatic, the observed differences may be more specific to CMD, although they may be smaller than differences observed against healthy individuals. The findings should not be generalized to differences between CMD patients and the general healthy population. Second, as a single-center study, selection bias may limit the conclusions' application to broader populations. Machine learning analyses were not intended to establish a ready-to-use clinical prediction model. Their role was to support exploratory feature screening and to identify lipidomic signals that merit further testing. Feature selection in ML models, while rigorously validated through SHAP, Lasso, and OPLS-DA, still required external validation to ensure generalizability. Third, while caIMR offered practical advantages over invasive IMR, provocative tests were not performed. This made it impossible to confirm whether coronary microvascular spasm coexisted. Fourth, lipidomic profiling relied on a single-timepoint sampling, which precluded the assessment of dynamic lipid changes in response to interventions or disease progression. Additionally, the mechanisms linking specific lipid species to microvascular dysfunction required experimental validation. Fifth, PhenoAge quantification utilized clinical biomarkers rather than direct cellular senescence markers, potentially underrepresenting tissue-level aging mechanisms. Moreover, the cross-sectional design precluded causal inferences regarding observed associations between TyG index, accelerated aging, lipidomic alterations and CMD pathogenesis. Finally, unmeasured confounders such as physical activity patterns, dietary components, and genetic predispositions may further influence the results. The impact of lipid-lowering medications on lipidomic and CMD is still unclear. Future longitudinal work is needed to integrate multi-omics approaches to elucidate mechanistic links between metabolic dysregulation, accelerated aging, and microvascular pathology.

Conclusion

This study demonstrated the association between accelerated biological aging and CMD and delineated a CMD-specific, hypothesis-generating lipidomic signature characterized by TAG enrichment. The integration of lipidomic biomarkers with clinical factors improved CMD diagnosis. Future studies should validate these biomarkers and explore targeted interventions to mitigate microvascular senescence and lipid-mediated endothelial injury.

Data Sharing Statement

The data used in this study would be available upon reasonable request by contacting the corresponding authors (Dr. You Zhou).

Ethical Approval

The study protocol was approved by the Ethics Committee of Shanghai Geriatric Medical Center (B2023-007) and conducted according to the guidelines of the Declaration of Helsinki. This trial was registered with the Chinese Clinical Trial Registry (URL: <https://www.chictr.org.cn>; Identifier: ChiCTR2500095360).

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Disclosure

The authors declare that they have no competing interests in this work.

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