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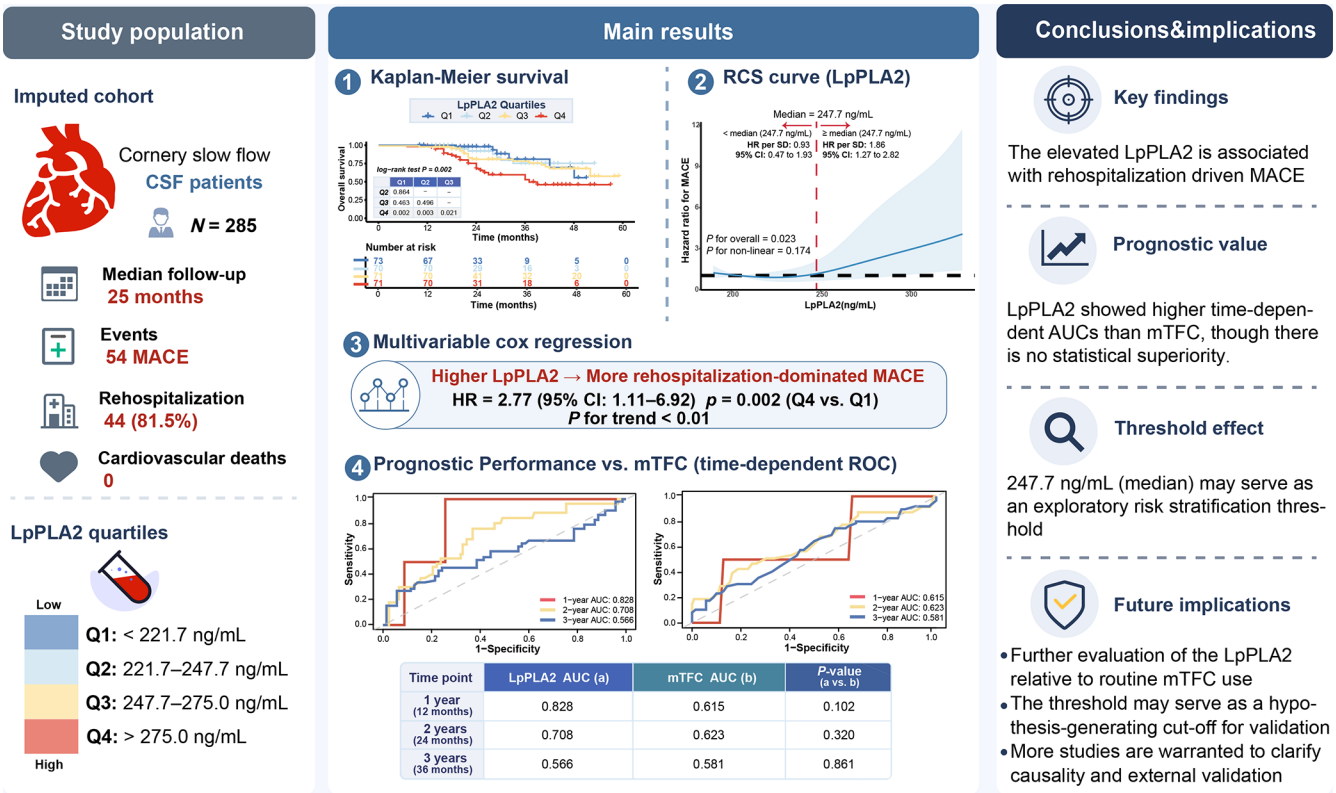
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Elevated plasma lipoprotein-associated phospholipase A2 levels are associated with poor prognosis in patients with coronary slow flow

A retrospective study

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Graphical abstract



Time point	LpPLA2 AUC (a)	mTFC AUC (b)	P-value (a vs. b)
1 year (12 months)	0.828	0.615	0.102
2 years (24 months)	0.708	0.623	0.320
3 years (36 months)	0.566	0.581	0.861

Supplemental Digital Content is available for this article.

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Abstract

Background: Coronary slow flow (CSF) is characterized by reduced coronary circulation and delayed contrast media opacity during angiography. Inflammatory responses have been observed in CSF. The correlation between lipoprotein-associated phospholipase A2 (LpPLA2) as a vascular inflammatory factor and the prognosis of CSF patients remains unclear. This study aims to investigate the potential correlation between plasma LpPLA2 levels and the occurrence of major adverse cardiovascular events (MACE) in CSF patients.

Methods: A retrospective study was conducted on 285 patients with CSF who were admitted to Anqing Municipal Hospital from January 2019 to March 2023. LpPLA2 plasma levels and baseline data were collected from hospital records; the mean thrombolysis in myocardial infarction frame count (mTFC) was calculated for each patient. Follow-up was conducted by telephone call or cardiology clinic data, and the occurrence and timing of MACE were recorded.

Results: The median follow-up duration was 25 (95% confidence interval [CI]: 23–27) months. During follow-up, MACE occurred in 54 patients (18.9%), including 4 individuals who had nonfatal myocardial infarction, 6 who had arrhythmias (4 with atrial fibrillation, 2 with frequent ventricular premature beats), and 44 who had rehospitalizations due to unstable angina pectoris. No cardiac deaths or cerebrovascular events occurred during follow-up. We categorized LpPLA2 into quartiles, and multivariable adjusted Cox models showed an association between LpPLA2 levels and MACE incidence among CSF patients. Compared with the lowest quartiles, the hazard ratios for the highest quartiles of LpPLA2 levels were 2.77 (95% CI: 1.11–6.92) (P-trend < 0.01). Though the restricted cubic spline curve indicates a linear relationship between LpPLA2 and MACE incidence in patients with CSF (P for nonlinearity = 0.174), the risk of MACE was relatively flat until 247.7 ng/mL of predicted LpPLA2 levels and increased afterward, with an HR of 1.86 (95% CI: 1.27–2.82) per standard deviation. Kaplan–Meier survival assessments revealed that patients in the highest LpPLA2 quartile exhibited a worse prognosis for MACE compared with those in the lower quartiles of LpPLA2 levels (log-rank P = 0.002). Additionally, multivariable Cox regression analyses identified mTFC, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and diabetes as other factors associated with the occurrence of MACE in patients with CSF.

Conclusion: Elevated plasma LpPLA2 levels were associated with MACE (rehospitalization-dominated MACE) in patients with CSF after multivariable adjustment. In addition to LpPLA2, dyslipidemia, diabetes, and mTFC may also be correlated with the prognosis of CSF.

Trial registration: ChiCTR2400086042, June 24, 2024 (Retrospectively registered).

Keywords: coronary artery disease, coronary slow flow, lipoprotein-associated phospholipase A2, major adverse cardiovascular events

Nonstandard Abbreviations and Acronyms

CSF	coronary slow flow
CX	circumflex
eGFR	estimated glomerular filtration rate
HDL-C	high-density lipoprotein cholesterol
LAD	left anterior descending
LDL-C	low-density lipoprotein cholesterol
LpPLA2	lipoprotein-associated phospholipase A2
MACE	major adverse cardiovascular events
mTFC	mean thrombolysis in myocardial infarction frame count
RCA	right coronary artery
TFC	thrombolysis in myocardial infarction frame count

Highlights

- LpPLA2 is associated with MACE (rehospitalization-dominated MACE) in patients with coronary slow flow (CSF).
- The mTFC, LDL-C, HDL-C, and diabetes are also correlated with the prognosis of CSF.
- The prognostic threshold for LpPLA2 (about 247.7 ng/mL) requires external validation before clinical application.
- LpPLA2 demonstrates good diagnostic value for CSF (AUC = 0.851).

1. Introduction

Coronary slow flow (CSF) is characterized by a slow progression of coronary flow velocity following the injection of a contrast agent with normal or near-normal coronary vessels during coronary angiography.[1,2] This phenomenon was initially documented by Tambe et al.[3] The incidence rate of CSF in coronary angiograms ranges from 1% to 7% and is frequently observed in male individuals, smokers, and patients at high cardiovascular risk.[2] Historically, CSF patients were considered to have favorable prognoses due to the absence of significant coronary artery stenosis. However, some observational studies have indicated an association between CSF and major adverse cardiovascular events (MACE), such as myocardial infarction, sudden death, arrhythmias, cerebrovascular events, and rehospitalization due to unstable angina, suggesting a poor prognosis.[4–6] Despite being well-established clinical

and angiographic findings, the precise pathogenic mechanisms underlying CSF remain unclear. Numerous studies have proposed that subclinical atherosclerosis, endothelial dysfunction, and microvascular abnormalities may be involved in its pathogenesis.[1] Furthermore, inflammatory responses have been observed in CSF and are implicated in the pathological processes of CSF.[1,7]

Lipoprotein-associated phospholipase A2 (LpPLA2), a novel vascular-specific inflammatory cytokine and enzyme involved in stress reaction, has also been reported to be associated with the presence and severity of CSF.[8,9] LpPLA2 is secreted by macrophage cells, often detected in unstable coronary plaques,[10] and has been shown to mediate the inflammatory process within the vascular wall.[11] Its proinflammatory properties make LpPLA2 an independent predictive biomarker for future cardiovascular events among patients with atherosclerotic cardiovascular disease.[12–14] It remains unknown whether this inflammatory biomarker predicts MACE in patients with CSF. Therefore, the present study aimed to investigate the prognostic value of LpPLA2 for MACE in patients with CSF, extending prior observations beyond diagnosis and severity assessment to long-term clinical risk stratification.

2. Methods

2.1. Study population

This retrospective cohort study, conducted at Anqing Municipal Hospital in Anhui Province, China, from January 1, 2019 through March 31, 2023, enrolled a total of 8,780 consecutive patients. Among them, 315 patients were identified as having CSF confirmed by angiography using the thrombolysis in myocardial infarction frame count (TFC) and exhibiting normal or near-normal coronary vessels (angiographic stenosis < 40%).[15] Patients were diagnosed with CSF if at least one major epicardial coronary artery had a Thrombolysis in Myocardial Infarction (TIMI) frame count exceeding the normal range in the absence of significant obstructive stenosis. Those with single-vessel or multivessel involvement were included, and the number of affected vessels was recorded for subsequent analysis. Exclusion criteria included incomplete angiography recordings, angiographic stenosis ≥ 40%, history of coronary revascularization, left ventricular ejection fraction < 40%, pulmonary heart disease, organic heart disease (e.g., congenital heart disease, severe valvular heart disease, cardiomyopathy), coronary ectasia, coronary myocardial bridge, coronary artery spasm, atrial fibrillation, severe liver or kidney dysfunction, cancer, missing LpPLA2 data, and loss to follow-up at the beginning (Fig. 1). To assess the diagnostic value of LpPLA2 for CSF, we conducted additional analyses on a control group comprising 215 consecutive patients with complete baseline data. All of these patients underwent coronary angiography during the same period and were confirmed to have normal coronary flow (NCF) with normal or only mildly stenotic arteries (stenosis < 40%); the results are presented in the additional file.

Demographic data, including age, sex, body mass index (BMI), smoking status, post-discharge medication, and diagnosed medical conditions (hypertension and diabetes), were collected at the time of angiography. Post-discharge medication was defined as pharmacological agents prescribed at hospital discharge and reported by the patient as still being taken at the first follow-up assessment. The following medication classes were recorded: antiplatelet therapy (aspirin, $P2Y_{12}$ inhibitors); vasodilators (nitrates, including both short-acting and long-acting formulations); and lipid-lowering agents (statins, with atorvastatin and rosuvastatin being the most frequently prescribed). Echocardiogram data pertaining to left ventricular ejection fraction (LVEF), interventricular septal thickness (IVST), left ventricular end-diastolic dimension (LVEDD), left atrial anteroposterior diameter (LAAP),

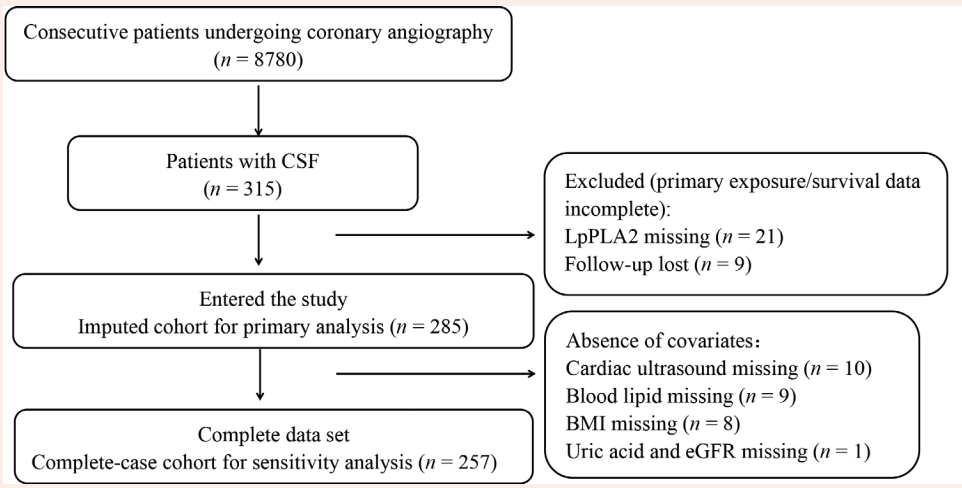


Figure 1. The flow chart depicts the procedure for patient enrollment and follow-up. BMI = body mass index; CSF = coronary slow flow; eGFR = estimated glomerular filtration rate; LpPLA2 = lipoprotein-associated phospholipase A2.

and the value of the E/A ratio of the mitral annulus were recorded. Laboratory data obtained at the time of angiography from electronic medical records included triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and estimated glomerular filtration rate (eGFR). Uric acid, urea, creatinine, triglyceride, total cholesterol, LDL-C, and HDL-C levels were measured using a chemiluminescence method with a Roche Diagnostics Cobas analyzer Cobas8000, c702 module. The eGFR was calculated using the Chinese modified MDRD equations.[16] Plasma LpPLA2 activity was measured using a chemiluminescence immunoassay (Hotgen Biology Technology Co., Ltd., Beijing, China).

The study received approval from the Ethics Committee of Anqing Municipal Hospital (Approval No.: Medical Ethics Review [2024] No. 42) on January 9, 2024, and was conducted in compliance with relevant guidelines and regulations.

All research activities adhered to the principles outlined in the Declaration of Helsinki. Additionally, informed consent was obtained from all patients or their legal guardians through the signing of the required documentation.

2.2. Coronary angiography

All patients underwent coronary angiography using the standard Judkins technique with either a radial or femoral artery approach. Coronary blood flow was evaluated using thrombolysis in TFC, which is considered an objective and quantitative measure. TFC was originally defined by Gibson and refers to the number of film frames required for the contrast agent to reach distal landmarks. The first frame was determined when the contrast agent completely filled the entrance of the coronary artery. Distal landmarks included the distal left anterior descending (LAD) artery bifurcation (known as the "tail of the whale"), distal circumflex (CX) artery bifurcation (the longest lateral left ventricular wall artery branch), and distal right coronary artery bifurcation (the first posterolateral artery branch) (Fig. 2). CSF was operationally defined as TFC > 27 frames in the absence of obstructive epicardial coronary artery disease. Given the longer length of the LAD compared with other coronary arteries, its TFC value was adjusted by dividing it by 1.7 to derive a corrected TFC (cTFC). Since the criteria for TFC values were counted at a speed of 30 frames per second during angiography, we multiplied our study's acquisition rate of 15 frames/s by two when calculating TFC values. The mean TFC (mTFC) calculated from averaging LAD, CX, and right coronary artery TFCs was recorded. Finally, all TFC measurements were performed by two experienced interventional cardiologists blinded to clinical data and Lp-PLA_2 levels. Each operator independently assessed TFC in all three major coronary arteries using the standardized method. Discrepancies were resolved through joint review to reach a consensus value for each vessel. Although interobserver variability was not formally quantified, the consensus-based assessment by two experienced operators minimizes the likelihood of significant measurement bias.

2.3. Follow-up

After completing the collection of demographic and coronary angiographic data from medical records, patients initially diagnosed with CSF were followed up through phone call invitations or available outpatient cardiology clinic data. The follow-up evaluation focused on the occurrence of MACE and recorded the date when MACE occurred. In our study, MACE was defined as nonfatal myocardial infarction, cardiac death, severe arrhythmias (e.g., sick sinus syndrome, second-degree or higher atrioventricular block, frequent ventricular premature beats, ventricular tachycardia or ventricular fibrillation, and

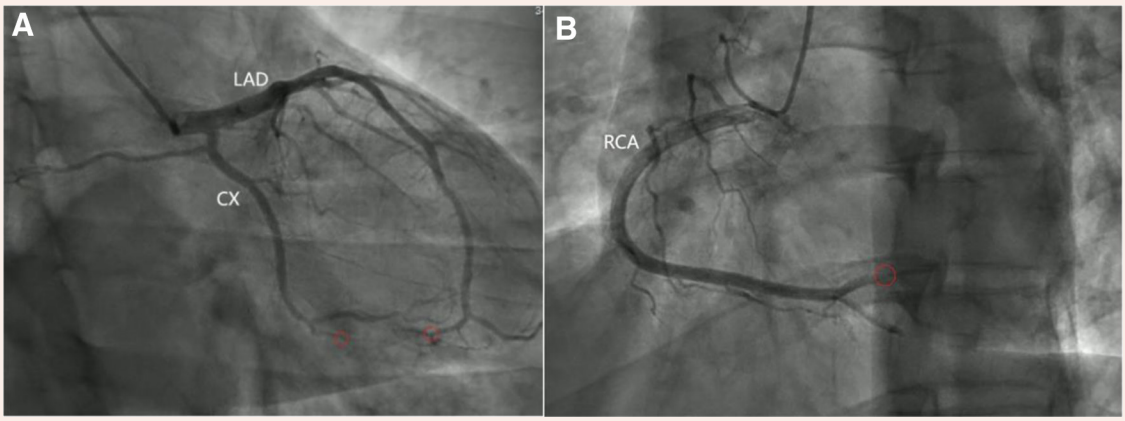


Figure 2. Schematic illustration of distal landmarks for major coronary artery bifurcations. (A) The illustration depicts the distal landmarks for LAD bifurcation, also known as the "tail of the whale," and CX bifurcation, which represents the longest branch of the lateral left ventricular wall artery. (B) The illustration depicts the distal landmark of the RCA bifurcation, defined as the first posterolateral arterial branch. CX = circumflex; LAD = left anterior descending; RCA = right coronary artery.

paroxysmal or persistent atrial fibrillation), rehospitalization due to unstable angina, and cerebrovascular events. Rehospitalization due to unstable angina was defined as admission during follow-up for unstable angina symptoms confirmed by the attending physician, meeting all of the following criteria: Typical ischemic ECG changes during symptoms (new or transient ST-segment depression ≥ 0.5 mV or T-wave inversion ≥ 0.2 mV in ≥ 2 contiguous leads); High-sensitivity troponin I/T levels below the 99th percentile upper reference limit, or only minor fluctuations not meeting the diagnostic threshold for myocardial infarction; Symptoms requiring hospitalization, with exclusion of admissions for elective percutaneous coronary intervention (PCI), heart failure, or other noncardiovascular causes.

2.4. Statistical analysis

All analyses were performed using R statistical software version 3.6.1 (R Foundation). Data were described as means and SDs for continuous variables. The Shapiro–Wilk test was conducted to determine the distribution of quantitative variables. Categorical variables were described using frequency with percentage. To clinically examine the association between plasma LpPLA2 levels and incident MACE in CSF patients, LpPLA2 levels were divided into quartiles. Baseline characteristics are summarized according to LpPLA2 quartiles and compared using analysis of variance, the Kruskal–Wallis test, or the chi-square test, depending on data types and distributions.

We calculated the person-time of follow-up for each participant included in the study from the date of CSF diagnosis (January 1, 2019 to March 31, 2023) survey until the occurrence of MACE, loss to follow-up, or the end of follow-up (March 31, 2024), whichever came first. Incidence rates of MACE per 100 person-years were calculated based on LpPLA2 quartiles. Cox regression analysis was conducted to calculate hazard ratios with 95% confidence intervals (CIs), using LpPLA2 as the exposure variable and considering the lowest quartiles as the reference. To minimize overfitting, we selected candidate variables with $P < 0.1$ in univariate analysis for multivariable Cox regression, then retained only statistically significant covariates to streamline the model. To assess robustness, we constructed three multivariable models with progressively fewer covariates: Model 1: Adjusted for age and sex only (minimally adjusted model). Model 2: Adjusted for age, sex, and significant covariates from multivariable analysis. Model 3: Adjusted exclusively for significant covariates (most parsimonious model). The trend test utilized median values from each LpPLA2 quartile as a continuous variable within the model. Kaplan–Meier curves depicted MACE rates across LpPLA2 quartiles assessed via log-rank testing. Additionally, potential nonlinear relationships were explored through 4-knotted restricted cubic spline (RCS) regression (the knots being determined by Akaike information criterion between 3 and 7). The reference value (HR = 1) was set at the 10th percentiles, while knots corresponded to 5th, 35th, 65th, and 95th percentiles. Meanwhile, univariate and multivariate Cox proportional hazards regression were performed to determine predictive variables for the occurrence of MACE among CSF patients. In multivariable analyses, only those variables with $P \leq 0.1$ based on univariate testing were taken into account, and LpPLA2 was handled as an unprocessed continuous variable in these models. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of LpPLA2 for the diagnosis of CSF. To evaluate the incremental predictive value, we compared the time-dependent areas under the curve (AUCs) of LpPLA2 and mTFC for MACE at 1, 2, and 3 years. However, due to substantial censoring and limited events beyond 3 years, stable ROC curves could not be constructed for 4- and 5-year follow-up. Of the 285 patients who completed follow-up, 28 (9.8%) had missing covariate information pertaining to echocardiographic data, blood lipids, body mass index, eGFR, and uric acid. Missing data were assumed to be missing at random and were handled using multiple imputation with chained equations, based on pooled results from five replications. The imputed dataset ($n = 285$) was defined as the primary analysis population, with results from this population presented as the main findings throughout the manuscript. Complete-case analysis ($n = 257$) was performed as a sensitivity analysis to assess the robustness of the findings. Two-sided $P < 0.05$ was deemed statistically significant.

3. Results

315 patients were identified as having CSF from 8,780 patients evaluated, resulting in an incidence rate of 3.59%. We excluded patients with missing LpPLA2 data or complete loss to follow-up, as LpPLA2 is the primary exposure variable and follow-up information is essential for survival analysis. After excluding 21 patients with missing LpPLA2 data and 9 patients lost to follow-up, 285 patients were included in the final analysis.

Table 1 presents the comparison of baseline data across LpPLA2 quartiles (Quartile 1: < 221.7 ng/mL, Quartile 2: 221.7–247.7 ng/mL, Quartile 3: 247.7–275.0 ng/mL, Quartile 4: > 275.0 ng/mL). Among the 285 patients, 194 (68.1%) were male, with a mean age of 54.1 years and a mean mTFC of 31.2 frames. Statistically significant differences were observed in left ventricular end-diastolic dimension, mTFC, LDL-C, and triglyceride levels among different LpPLA2 quartiles.

Following a median follow-up period of 25 (95% CI: 23–27) months calculated using the reverse Kaplan–Meier method, MACE occurred in 54 patients (18.9%). This included nonfatal myocardial infarction in four individuals, arrhythmias in six individuals (four with atrial fibrillation and two with frequent ventricular premature beats), and rehospitalization due to unstable angina pectoris in 44 patients. No cardiac deaths or cerebrovascular events occurred during the CSF patient follow-up period in our study. Among the 54 patients who suffered MACE during follow-up, 5 patients underwent repeat coronary

Table 1

Baseline characteristics of 285 participants according to LpPLA2 quartiles.

Variables	Quartile 1 (< 221.7 ng/mL) (*N* = 73)	Quartile 2 (221.7–247.7 ng/mL) (*N* = 70)	Quartile 3 (247.7–275.0 ng/mL) (*N* = 71)	Quartile 4 (> 275.0 ng/mL) (*N* = 71)	*P*
Clinical characteristics					
Age (year)	60.12 ± 11.71	57.63 ± 8.48	59.62 ± 10.58	58.85 ± 12.56	0.516
Male	46 (63%)	47 (67.1%)	48 (67.6%)	53 (74.6%)	0.511
BMI (kg/m^2)*	24.78 ± 5.22	24.41 ± 3.51	24.48 ± 2.99	24.83 ± 2.65	0.640
Hypertension	23 (31.5%)	28 (40%)	28 (39.4%)	30 (42.3%)	0.568
Diabetes	7 (9.6%)	10 (14.3%)	9 (12.7%)	5 (7%)	0.517
Smoking history	25 (34.2%)	19 (27.1%)	21 (29.6%)	25 (35.2%)	0.695
Laboratory parameters					
LVEF (%)*	63.80 ± 7.23	61.89 ± 8.06	61.78 ± 7.74	60.56 ± 8.90	0.226
LAAP (mm)*	33.70 ± 5.74	33.84 ± 7.17	33.71 ± 5.70	35.89 ± 8.00	0.246
IVST (mm)*	9.30 ± 1.68	9.27 ± 0.96	9.20 ± 1.31	9.26 ± 1.29	0.916
LVEDD (mm)*	45.83 ± 4.60	46.33 ± 6.19	46.57 ± 5.40	48.97 ± 5.85	0.010
E/A ratio*	1.00 ± 0.47	1.13 ± 0.58	1.04 ± 0.44	1.05 ± 0.48	0.780
Platelet-to-lymphocyte ratio	124.71 ± 51.03	113.89 ± 46.45	123.93 ± 54.13	127.92 ± 71.84	0.675
Neutrophil-to-lymphocyte ratio	2.50 ± 1.80	2.31 ± 1.14	2.50 ± 1.19	3.36 ± 3.16	0.548
Uric acid (μmol/L)*	338.33 ± 87.44	336.37 ± 89.62	340.15 ± 99.28	361.55 ± 94.16	0.413
Triglyceride (mmol/L)*	1.45 ± 0.81	1.59 ± 0.74	1.41 ± 0.73	1.62 ± 0.77	0.031
Total cholesterol (mmol/L)*	3.95 ± 0.87	4.16 ± 0.80	4.24 ± 0.90	4.21 ± 0.85	0.161
HDL-C (mmol/L)*	1.27 ± 0.33	1.16 ± 0.25	1.18 ± 0.30	1.14 ± 0.32	0.066
LDL-C (mmol/L)*	1.96 ± 0.70	2.27 ± 0.77	2.37 ± 0.72	2.36 ± 0.81	0.003
eGFR (mL/min)*	93.21 ± 19.37	98.83 ± 21.15	94.93 ± 22.41	90.39 ± 22.60	0.127
CSF vessels number	1.85 ± 0.86	2.20 ± 0.79	2.13 ± 0.77	2.01 ± 0.82	0.063
mTFC (frames)	29.92 ± 4.55	31.07 ± 4.92	32.02 ± 4.83	32.00 ± 4.38	0.034
Discharge cardiovascular medications					
Nitrates	26 (35.6%)	31 (44.3%)	40 (56.3%)	36 (50.7%)	0.076
Antiplatelet agents	41 (56.2%)	37 (52.9%)	33 (46.5%)	31 (43.7%)	0.419
Statins	59 (80.8%)	56 (80%)	53 (74.6%)	49 (69%)	0.317

CSF = coronary slow flow; E/A = the value of E/A ratio of mitral annulus; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; IVST = interventricular septal thickness; LAAP = left atrial anteroposterior diameter; LDL-C = low-density lipoprotein cholesterol; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction.
*Missing data exist (refer to the flowchart for details).

angiography. These included 4 patients with myocardial infarction; all 4 were found to have developed obstructive lesions requiring percutaneous coronary intervention, and one patient with rehospitalization for unstable angina. This patient had single-vessel coronary slow flow at baseline, with the affected vessel showing approximately 30% stenosis on initial angiography. Repeat angiography revealed persistent slow flow in the same vessel, with mild progression of the preexisting lesion from approximately 30% to 40% stenosis, while other vessels remained angiographically normal without slow flow. The composite endpoint was dominated by rehospitalization for unstable angina (44 out of 54 events, 81.5%), with no cases of cardiovascular death or stroke observed during follow-up. Therefore, the term "rehospitalization-dominated MACE" (as noted in the Abstract conclusion) is used to describe this outcome, acknowledging the predominance of rehospitalization events and the absence of hard clinical endpoints. Due to the predominance of rehospitalization for unstable angina (44/54 events) and the insufficient number of remaining events (n = 10, including only 4 myocardial infarctions and no cardiac deaths or cerebrovascular events) to support meaningful analysis, separate subgroup analyses were not performed.

The associations between plasma LpPLA2 levels and incident MACE in CSF patients are presented in Table 2. In models 1 to 3, statistically significant associations were observed when comparing the highest versus the lowest quartiles of LpPLA2 levels, with multivariate-adjusted hazard ratios (95% CIs) of 4.12 (95% CI: 1.67–10.17), 3.04 (95% CI: 1.22–7.60), and 2.77 (95% CI: 1.11–6.92), respectively. Across all three models, LpPLA2 levels were associated with MACE in CSF patients, supporting the robustness of our findings despite the limited number of events. The P values for trend tests were all significant ($P < 0.01$). The incidence rates of MACE ranged from 4.13 to 15.76 per 100 person-years across the quartiles of LpPLA2 levels. Similar results were obtained when analyzing the complete-case cohort (eTable 1, Supplemental Digital Content, https://links.lww.com/CARES/A20). Kaplan–Meier survival curves showed that CSF patients in the highest LpPLA2 quartile experienced more rehospitalization-dominated MACE than those in the lower quartiles (log-rank test $P = 0.002$) (Fig. 3A). Estimates beyond 48 months should be interpreted with caution due to the small number of at-risk participants in all groups.

An RCS analysis, based on a multivariable corrected model identical to model 3, was employed to visually represent the relationship between plasma LpPLA2 levels and incident MACE in CSF patients. The risk of MACE incidence remained relatively stable until around a predicted LpPLA2 level of 247.7 ng/mL, after which it began

Table 2

LpPLA2 quartiles and the hazard ratio of MACE in 285 participants.

LpPLA2 (ng/mL, median [range])	Cases	Person years	Model 1*		Model 2†		Model 3‡	
			HR (95% CI)	*P* for trend	HR (95% CI)	*P* for trend	HR (95% CI)	*P* for trend
Q1 (208.3 [< 221.7])	6	145.25	Reference		Reference		Reference	
Q2 (234.3 [221.7–247.7])	7	145.08	1.23 (0.41–3.67)		0.71 (0.23–2.21)		0.66 (0.21–2.04)	
Q3 (260.3 [247.7–275.0])	17	195.58	1.66 (0.64–4.26)		0.91 (0.34–2.41)		0.92 (0.34–2.45)	
Q4 (289.2 [> 275.0])	24	152.33	4.12 (1.67–10.17)	< 0.001	3.04 (1.22–7.60)	0.001	2.77 (1.11–6.92)	0.002

*Model 1 was adjusted for age and sex.
†Model 2 was adjusted for age, sex, mTFC, HDL-C, LDL-C, and diabetes.
‡Model 3 was adjusted for mTFC, HDL-C, LDL-C, and diabetes.

to increase, though with a linear trend overall (*P* for non-linearity = 0.174); above this threshold, the hazard ratio per standard deviation higher predicted LpPLA2 level was found to be 1.86 (95% CI: 1.27–2.82) (Fig. 3B). Similar results were obtained when the analysis was performed on the complete-case cohort (eFigure 1, Supplemental Digital Content, https://links.lww.com/CARES/A20).

The occurrence of MACE among patients with CSF was investigated using univariate and multiple Cox regression analyses to identify independent predictors. The multiple Cox regression analyses, which included variables with $P \leq 0.1$ based on the univariate analysis, revealed that the incidence of MACE was associated with levels of LpPLA2 (as an unprocessed continuous variable analyzed in the model) (HR: 1.01, 95% CI: 1.00–1.02, $P = 0.012$), mTFC (HR: 1.13, 95% CI: 1.03–1.23, $P = 0.012$), LDL-C (HR: 1.51, 95% CI: 1.04–2.18, $P = 0.043$), HDL-C (HR: 0.33, 95% CI: 0.11–0.99, $P = 0.049$), and diabetes (HR: 2.83, 95% CI: l.38–5.84, $P = 0.006$) (Table 3). To evaluate incremental value, we compared time-dependent AUCs of LpPLA2 and mTFC for MACE at 1 to 3 years. Beyond three years, stable ROC curves were not feasible due to limited events and censoring. LpPLA2 showed higher AUCs in the first 2 years, but differences were not significant. Thus, LpPLA2 did not demonstrate superior prognostic value over mTFC in CSF patients (Fig. 4).

Comparison between the CSF group (n = 285) and the NCF group (n = 215) revealed that LpPLA2 levels were significantly higher in CSF patients than in those with normal flow ($P < 0.001$) (eTable 2, Supplemental Digital Content, https://links.lww.com/CARES/A20). ROC curve analysis demonstrated that LpPLA2 had good predictive value for the diagnosis of CSF (AUC = 0.851, $P < 0.001$) (eFigure 2, Supplemental Digital Content, https://links.lww.com/CARES/A20).

4. Discussion

In our study, 315 patients were identified with CSF out of 8,780 patients who underwent angiography, resulting

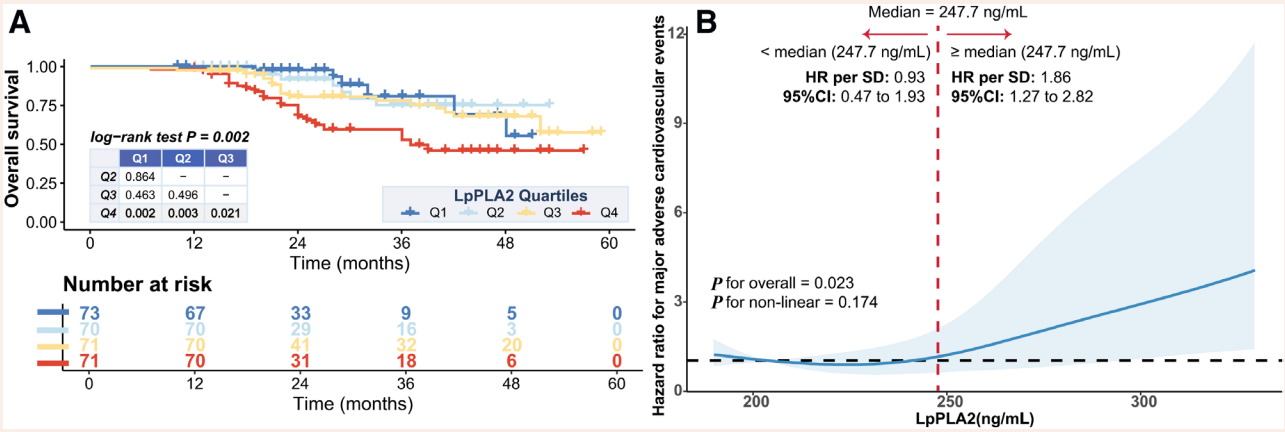


Figure 3. Association between LpPLA2 levels and incident MACE in CSF patients, analyzed by quartile stratification and restricted cubic spline (RCS) regression. (A) Kaplan–Meier curves of MACE rates in 285 CSF patients across LpPLA2 quartiles. (B) Association of predicted LpPLA2 levels with incident MACE in 285 CSF patients through a 4-knotted RCS curve adjusted for covariates in model 3. Hazard ratio is indicated by a solid line and 95% confidence intervals by the shaded area. The reference point was set at the tenth percentile, while knots corresponded to the 5th, 35th, 65th, and 95th percentiles. The standard deviation for LpPLA2 levels was 37.88 ng/mL. LpPLA2 = lipoprotein-associated phospholipase A2.

Table 3

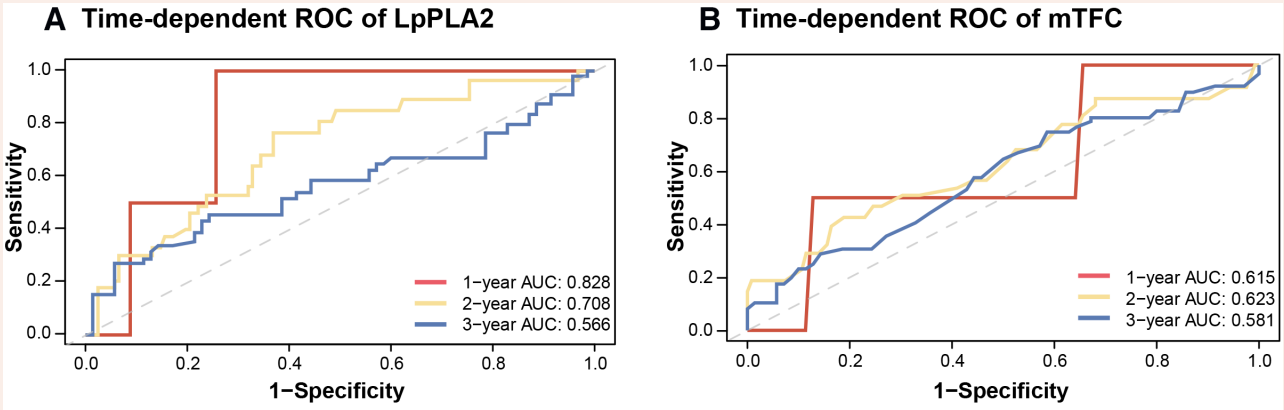
Univariate and multivariate predictors of incident MACE in CSF patients.

	Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.02 (1.00–1.05)	0.103		
Male	1.32 (0.67–2.58)	0.420		
BMI	0.96 (0.88–1.05)	0.379		
Hypertension	1.17 (0.68–2.04)	0.571		
Diabetes	2.06 (1.03–4.13)	0.041	2.83 (1.38–5.84)	0.006
Smoking history	1.71 (0.98–2.97)	0.057	1.64 (0.91–2.96)	0.101
LVEF	1.00 (0.97–1.03)	0.961		
LAAP	1.01 (0.97–1.05)	0.629		
IVST	1.01 (0.82–1.25)	0.925		
LVEDD	1.01 (0.96–1.07)	0.600		
E/A ratio	0.95 (0.54–1.67)	0.849		
Platelet-to-lymphocyte ratio	1.01 (1.00–1.01)	0.019	1.01 (0.99–1.01)	0.117
Neutrophil-to-lymphocyte ratio	1.19 (1.04–1.35)	0.009	1.05 (0.87–1.27)	0.596
Uric acid	1.00 (1.00–1.00)	0.922		
Triglyceride	1.22 (0.91–1.63)	0.186		
Total cholesterol	1.21 (0.87–1.67)	0.258		
HDL-C	0.42 (0.16–1.06)	0.067	0.33 (0.11–0.99)	0.049
LDL-C	1.54 (1.08–2.21)	0.017	1.51 (1.04–2.18)	0.043
eGFR	0.99 (0.98–1.00)	0.072	0.99 (0.98–1.00)	0.103
mTFC	1.12 (1.05–1.19)	< 0.001	1.13 (1.03–1.23)	0.012
CSF vessels number	1.42 (1.00–2.03)	0.052	0.85 (0.48–1.53)	0.588
LpPLA2	1.01 (1.01–1.02)	< 0.001	1.01 (1.00–1.02)	0.012
Nitrates	1.35 (0.77–2.35)	0.294		
Antiplatelet agents	0.82 (0.47–1.41)	0.470		
Statins	1.36 (0.69–2.64)	0.373		

BMI = body mass index; CSF = coronary slow flow; E/A = the value of E/A ratio of mitral annulus; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; IVST = interventricular septal thickness; LAAP = left atrial anteroposterior diameter; LDL-C = low-density lipoprotein cholesterol; LpPLA2 = lipoprotein-associated phospholipase A2; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; mTFC = mean thrombolysis in myocardial infarction frame count.

in an incidence rate of 3.59%, consistent with the previously reported range of 1% to 7%.[1] Following a median follow-up period of 25 months, CSF patients meeting the inclusion criteria exhibited a high incidence rate (18.9%) of MACE, with rehospitalization due to unstable angina accounting for the majority (15.4%). Our analysis suggests that LpPLA2 may predict the occurrence of MACE during follow-up in CSF patients. According to consensus recommendations, LpPLA2 levels > 200 ng/mL indicate increased cardiovascular risk,[17] with 235 ng/mL (the 50th percentile) also proposed as a conservative cut point.[18] These thresholds are intended for risk stratification rather than as therapeutic targets. In our study of CSF patients, RCS analysis demonstrated a linear relationship between LpPLA2 and MACE risk (*P* for nonlinearity = 0.174). However, visual inspection suggested that the risk curve began to rise more appreciably around the median value (about 247.7 ng/mL). Therefore, we exploratorily selected this median as a potential cutoff to facilitate clinical interpretation, and we acknowledge that external validation in independent cohorts is necessary before clinical application. Moreover, the hazard ratio for LpPLA2 as a continuous variable was 1.01 (95% CI: 1.00–1.02) per ng/mL, indicating a very modest absolute effect size per unit increase. Consequently, the observed association should not be overinterpreted as reflecting large individual risk variations. Our exploratory threshold of 247.7 ng/mL is slightly higher than the established consensus cut points of 200 or 235 ng/mL. This difference may reflect the unique characteristics of our CSF population or the specific outcome measure (MACE) examined. Consistent with prior recommendations, we emphasize that this threshold is proposed for risk stratification purposes rather than as a therapeutic target. Despite its exploratory nature, identifying a potential threshold may offer the following advances: It provides a preliminary reference point for clinicians to identify CSF patients at potentially higher risk of adverse outcomes; It may inform the design of future prospective studies by suggesting a cutoff for risk stratification or patient enrollment. In addition to LpPLA2, multiple Cox regression analyses indicated that mTFC, LDL-C, HDL-C, and diabetes were also associated with the occurrence of MACE in CSF patients.

Common characteristics of CSF were usually identified by comparing clinical data between patients with CSF and those with normal coronary artery flow through several observational studies. Most studies have reported a higher prevalence of CSF in men, smokers, and patients with high CV risks.[2] A cross-sectional study involving 124 patients revealed that CSF patients were predominantly male, had a history of smoking and hypertension, as well as elevated laboratory indicators such as lipids



C Comparison between LpPLA2 AUC and mTFC AUC

Time point	LpPLA2 AUC (a)	mTFC AUC (b)	*P*-value (a vs. b)
1 year (12 months)	0.828	0.615	0.102
2 years (24 months)	0.708	0.623	0.320
3 years (36 months)	0.566	0.581	0.861

Figure 4. Rehospitalization-dominated ROC curve comparison: time-dependent AUC of (A) LpPLA2, (B) mTFC, (C) LpPLA2 versus mTFC for MACE at different time points. AUC = areas under the curve; LpPLA2 = lipoprotein-associated phospholipase A2; mTFC = mean thrombolysis in myocardial infarction frame count; ROC = receiver operating characteristic.

and mean platelet volume. Furthermore, these subjects displayed subtle declines in diastolic function alongside an overall reduction in longitudinal strain during cardiac ultrasound assessments.[19] Notably highlighted by Yilmaz et al.,[20] within the context of suspected atherosclerotic heart disease necessitating coronary angiography procedures, those affected by CSF exhibited an increased likelihood of presenting metabolic syndrome hallmarked by hyperglycemia, hyperlipidemia, and overweight when compared with counterparts demonstrating normal coronary blood flow velocities. A recent study found that decreased retinal microvascular density may serve as a potential biomarker for the diagnosis of CSF.[21]

Cohort studies have shown that around two-thirds of patients with CSF present with acute coronary syndrome,[2] typically characterized by recurrent chest pain, mainly at rest, and accompanied by electrocardiogram changes. While most CSF patients have a favorable prognosis in terms of major cardiovascular events, the persistent episodes of chest pain can significantly impact their quality of life. Additionally, several cases have reported that clinical manifestations of CSF also include malignant arrhythmias and sudden death.[5,22] Further studies have identified CSF as a risk predictor for myocardial ischemia, myocardial infarction, arrhythmia, and sudden cardiac death.[23–25]

Although CSF has been found to be associated with vascular endothelial dysfunction, microvascular disease, insulin resistance, oxidative stress, and adipocytokines, the exact mechanisms remain unclear.[1] Inflammation plays a crucial role in the human immune response, serving dual functions in defense mechanisms. Initially, it protects physiological homeostasis against infection and tissue damage, but should be promptly resolved once infectious agents are eliminated or initial tissue injuries are repaired. Failure to resolve inflammation can lead to tissue dysfunction and other adverse consequences.[26,27] Studies have confirmed that inflammation is a risk factor for various cardiovascular diseases,[28] and inflammatory responses have also been observed in CSF.[1,7] Plasma soluble adhesion molecules and inflammatory markers were found to be significantly elevated in CSF patients, including C-reactive protein,[29] interleukin-6,[29] platelet-to-lymphocyte ratio,[30] neutrophil-to-lymphocyte ratio,[31] matrix metalloproteinase-9, and soluble CD40 ligand.[32]

LpPLA2 has been proposed as a novel independent inflammatory marker and has been associated with various vascular diseases in epidemiological studies.[12,33] Numerous studies have established LpPLA2 activity as an independent predictor of CHD outcomes in the general population.[14,34] Recent research has shown that elevated plasma LpPLA2 levels are also linked to the onset and severity of CSF.[8,9] Our study suggests that LpPLA2 can function as a prognostic indicator for rehospitalization-dominated MACE in CSF patients. LpPLA2, originally known as platelet-activating factor acetylhydrolase due to its hydrolytic activity on platelet-activating factor,[35] is primarily secreted by macrophages and circulates in the bloodstream bound to LDL and HDL.[36] LpPLA2 has the

ability to hydrolyze and oxidize LDL into two biologically active products, oxidized nonesterified fatty acids and lysophosphatidylcholine, which act as proinflammatory substances derived from LpPLA2, inducing immune responses and oxidative stress.[37] As CSF has been found to be associated with vascular endothelial dysfunction and oxidative stress,[1] this may provide a link between LpPLA2 activity and CSF pathogenesis. There is evidence indicating that LpPLA2 plays a role in the initiation and progression of atherosclerosis; the proatherogenic function of LpPLA2 is believed to stem from its proinflammatory byproducts, which may facilitate the development of atherosclerotic plaques and ultimately contribute to the formation of a necrotic core.[14,37] Studies have confirmed that early atherosclerosis is involved in the occurrence and development of CSF,[1,38] which might be another link between LpPLA2 and CSF pathogenesis. In our study, when LpPLA2 was divided into quartiles, the results of multimodel Cox regression indicated that the highest level of LpPLA2 was associated with a higher incidence of MACE compared with the lowest level in CSF patients. When considered as a continuous variable, although the RCS curve suggests an overall linear relationship between LpPLA2 and MACE rate, the linear relationship becomes more pronounced when plasma levels of LpPLA2 exceed 247.7 ng/mL. The mechanisms underlying the association between LpPLA2 and rehospitalization-dominated MACE in CSF are not fully understood. The most plausible hypothesis suggests that unresolved inflammatory responses mediated by LpPLA2 may contribute to vascular endothelial dysfunction, oxidative stress, and early atherosclerosis, thereby playing a role in the initiation and progression of CSF.

In addition to LpPLA2, multiple Cox regression analyses have shown that mTFC, LDL-C, HDL-C, and diabetes are associated with the occurrence of MACE in CSF patients. Previous studies have found that dyslipidemia[6,39] and mTFC[39] are associated with the occurrence of MACE in CSF patients, which is consistent with our findings. Isik et al.[40] identified diabetes as a potential predictor of CSF. Yu et al.[4] demonstrated that diabetes was an independent prognostic predictor of MACE in patients with normal coronary arteries during a mean of 3.5 years of follow-up. Our study suggests that diabetes is linked to poor prognosis in CSF patients. Previous studies have indicated that hypertension independently predicts MACE in patients with CSF,[6,39] leading to a certain number of cardiovascular deaths over a relatively long follow-up period. However, our study suggests that there is no significant correlation between hypertension and the occurrence of MACE in patients with CSF; this may be due to insufficient follow-up time and a limited number of cases of cardiovascular death.

Despite suggesting that LpPLA2 may have predictive value for clinical outcomes in CSF patients, several limitations should be acknowledged when interpreting our findings. First, this was a single-center retrospective study primarily relying on telephone follow-up, which may result in incomplete information, recall bias, and omission of crucial details regarding clinical outcomes. The retrospective design and modest sample size ($n = 285$) limit generalizability and require validation in larger, multicenter prospective cohorts. Second, the limited number of hard clinical endpoints (cardiovascular death, myocardial infarction, stroke) precluded robust analysis of LpPLA2's predictive value for these outcomes. Our findings are primarily driven by rehospitalization for unstable angina (44/54 events). Due to substantial censoring and limited events beyond three years, stable ROC curves could not be constructed for longer follow-up. Additionally, the short follow-up period (initiated in 2019 when testing became available at our institution) may affect statistical power. Third, LpPLA2 was measured only at baseline, and we lack data on its dynamic changes during follow-up, which might provide additional prognostic insight. Although we included inflammatory indicators such as platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio as confounders, other inflammatory markers (e.g., CRP, interleukin-6) were not systematically collected due to data limitations. Fourth, unmeasured confounding cannot be excluded. While smoking status was included in multivariable models, other lifestyle-related factors, such as physical activity, alcohol consumption, and socioeconomic status, were not systematically collected. These unmeasured confounders may have influenced the observed association between LpPLA2 and cardiovascular outcomes. Accordingly, we explicitly acknowledge that the modest sample size and event count, together with potential residual confounding, preclude any definitive predictive claims. Thus, our findings should be interpreted as demonstrating an association rather than providing evidence for a causal mechanism. Fifth, prognostic outcome data for the 215 NCF patients and the remaining > 8,000 patients who underwent angiography were unavailable, which represents a significant limitation of our study. Furthermore, as coronary artery stenosis is often not apparent in CSF patients, only a small subset of MACE patients ($n = 5$) underwent repeated angiography, limiting the assessment of stenosis progression across LpPLA2 levels. Finally, although LpPLA2 was associated with outcomes, the time-dependent AUC analysis showed that its prognostic performance did not differ significantly from that of mTFC ($P > 0.05$). This finding suggests that, in clinical practice, the added value of measuring LpPLA2 beyond the readily available angiographic index mTFC may be limited, and its routine use should be weighed against cost and availability, and the exploratory threshold identified in our RCS analysis (about 247.7 ng/mL) requires external validation before clinical application.

In conclusion, elevated LpPLA2 levels were associated with MACE in CSF patients. Additionally, dyslipidemia, diabetes, and mTFC may also be associated with CSF prognosis. However, further investigation is needed to elucidate the exact pathophysiological mechanism of LpPLA2 in CSF, and prospective multicenter studies with larger sample sizes are required to validate our findings.

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Ethical statements

The study received approval from the Ethics Committee of Anqing Municipal Hospital [Approval No.: Medical Ethics Review (2024) No. 42]. Written informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki.

Conflicts of interest

All authors declare that there are no conflicts of interest.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AI statement

During the preparation of this work, the author used AI tools for language and grammar polishing. After using the tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

References

[1] Chalikias G, Tziakas D. Slow coronary flow: pathophysiology, clinical implications, and therapeutic management. *Angiology*. 2021;72:808–18.

[2] Aparicio A, Cuevas J, Morís C, Martín M. Slow coronary blood flow: pathogenesis and clinical implications. *Eur Cardiol*. 2022;17:e08.

[3] Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries--a new angiographic finding. *Am Heart J*. 1972;84:66–71.

[4] Yu J, Yi D, Yang C, et al. Major adverse cardiovascular events and prognosis in patients with coronary slow flow. *Curr Probl Cardiol*. 2024;49:102074.

[5] Wozakowska-Kapłon B, Niedziela J, Krzyzak P, Stec S. Clinical manifestations of slow coronary flow from acute coronary syndrome to serious arrhythmias. *Cardiol J*. 2009;16:462–8.

[6] Zhu X, Shen H, Gao F, et al. Clinical profile and outcome in patients with coronary slow flow phenomenon. *Cardiol Res Pract*. 2019;2019:9168153.

[7] Wang X, Nie SP. The coronary slow flow phenomenon: characteristics, mechanisms and implications. *Cardiovasc Diagn Ther*. 2011;1:37–43.

[8] Liang Q, Lei X, Huang X, Fan L, Yu H. Elevated lipoprotein-associated phospholipase A2 is valuable in prediction of coronary slow flow in non-ST-segment elevation myocardial infarction patients. *Curr Probl Cardiol*. 2021;46:100596.

[9] Ding YD, Pei YQ, Wang R, et al. Increased plasma lipoprotein-associated phospholipase A2 levels are associated with coronary slow flow. *BMC Cardiovasc Disord*. 2020;20:248.

[10] Li J, Wang H, Tian J, Chen B, Du F. Change in lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndrome. *Medicine (Baltimore)*. 2018;97:e11517.

[11] Silva IT, Mello AP, Damasceno NR. Antioxidant and inflammatory aspects of lipoprotein-associated phospholipase A_2(Lp-PLA_2): a review. *Lipids Health Dis*. 2011;10:170.

[12] Münzel T, Gori T. Lipoprotein-associated phospholipase A(2), a marker of vascular inflammation and systemic vulnerability. *Eur Heart J*. 2009;30:2829–31.

[13] White HD, Simes J, Stewart RA, et al.; LIPID Study Investigators. Changes in lipoprotein-associated phospholipase A2 activity predict coronary events and partly account for the treatment effect of pravastatin: results from the Long-Term Intervention with Pravastatin in Ischemic Disease study. *J Am Heart Assoc*. 2013;2:e000360.

[14] Thompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet (London)*. 2010;375:1536–44.

[15] Beltrame JF. Defining the coronary slow flow phenomenon. *Circ J*. 2012;76:818–20.

[16] Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol*. 2006;17:2937–44.

[17] Davidson MH, Corson MA, Alberts MJ, et al. Consensus panel recommendation for incorporating lipoprotein-associated phospholipase A2 testing into cardiovascular disease risk assessment guidelines. *Am J Cardiol*. 2008;101:51F–7F.

[18] Lanman RB, Wolfert RL, Fleming JK, et al. Lipoprotein-associated phospholipase A2: review and recommendation of a clinical cut point for adults. *Prev Cardiol*. 2006;9:138–43.

[19] Seyyed Mohammadzad MH, Khademvatani K, Gardeshkhah S, Sedokani A. Echocardiographic and laboratory findings in

coronary slow flow phenomenon: cross-sectional study and review. *BMC Cardiovasc Disord*. 2021;21:230.
[20] Yilmaz H, Demir I, Uyar Z. Clinical and coronary angiographic characteristics of patients with coronary slow flow. *Acta Cardiol*. 2008;63:579–84.
[21] MozafaryBazargany M, Khalili Pour E, Shamsedini A, et al. Chorioretinal microvascular changes in slow flow coronary phenomenon: a multi-center study. *Sci Rep*. 2024;14:31090.
[22] Saya S, Hennebry TA, Lozano P, Lazzara R, Schechter E. Coronary slow flow phenomenon and risk for sudden cardiac death due to ventricular arrhythmias: a case report and review of literature. *Clin Cardiol*. 2008;31:352–5.
[23] Zhu Q, Wang S, Huang X, et al. Understanding the pathogenesis of coronary slow flow: recent advances. *Trends Cardiovasc Med*. 2024;34:137–44.
[24] Sen T. Coronary slow flow phenomenon leads to ST elevation myocardial infarction. *Korean Circ J*. 2013;43:196–8.
[25] Amasyali B, Turhan H, Kose S, et al. Aborted sudden cardiac death in a 20-year-old man with slow coronary flow. *Int J Cardiol*. 2006;109:427–9.
[26] Buckley CD, Gilroy DW, Serhan CN. Proresolving lipid mediators and mechanisms in the resolution of acute inflammation. *Immunity*. 2014;40:315–27.
[27] Katkenov N, Mukhatayev Z, Kozhakhmetov S, et al. Systematic review on the role of IL-6 and IL-1β in cardiovascular diseases. *J Cardiovasc Dev Disease*. 2024;11:206.
[28] Sprague AH, Khalil RA. Inflammatory cytokines in vascular dysfunction and vascular disease. *Biochem Pharmacol*. 2009;78:539–52.
[29] Li JJ, Qin XW, Li ZC, et al. Increased plasma C-reactive protein and interleukin-6 concentrations in patients with slow coronary flow. *Clin Chim Acta*. 2007;385:43–7.
[30] Qiu Z, Jiang Y, Jiang X, et al. Relationship between platelet to lymphocyte ratio and stable coronary artery disease: meta-analysis of observational studies. *Angiology*. 2020;71:909–15.
[31] Yılmaz M, Korkmaz H, Bilen MN, Uku O, Kurtoğlu E. Could neutrophil/lymphocyte ratio be an indicator of coronary artery disease, coronary artery ectasia and coronary slow flow? *J Int Med Res*. 2016;44:1443–53.
[32] Zhang X, Ding J, Xia S. A preliminary study of MMP-9 and sCD40L in patients with coronary slow flow. *Ann Palliat Med*. 2021;10:657–63.
[33] Siddiqui MK, Kennedy G, Carr F, et al. Lp-PLA(2) activity is associated with increased risk of diabetic retinopathy: a longitudinal disease progression study. *Diabetologia*. 2018;61:1344–53.
[34] Corsetti JP, Rainwater DL, Moss AJ, Zareba W, Sparks CE. High lipoprotein-associated phospholipase A2 is a risk factor for recurrent coronary events in postinfarction patients. *Clin Chem*. 2006;52:1331–8.
[35] Dennis EA, Cao J, Hsu YH, Magrioti V, Kokotos G. Phospholipase A2 enzymes: physical structure, biological function, disease implication, chemical inhibition, and therapeutic intervention. *Chem Rev*. 2011;111:6130–85.
[36] Tellis CC, Tselepis AD. Pathophysiological role and clinical significance of lipoprotein-associated phospholipase A2(Lp-PLA2) bound to LDL and HDL. *Curr Pharm Des*. 2014;20:6256–69.
[37] Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. *Arterioscler Thromb Vasc Biol*. 2005;25:923–31.
[38] Pekdemir H, Cin VG, Ciçek D, et al. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. *Acta Cardiol*. 2004;59:127–33.
[39] Aksoy S, Öz D, Öz M, Agirbasli M. Predictors of long-term mortality in patients with stable angina pectoris and coronary slow flow. *Medicina (Kaunas, Lithuania)*. 2023;59:763.
[40] Isik T, Ayhan E, Uyarel H, et al. Increased mean platelet volume associated with extent of slow coronary flow. *Cardiol J*. 2012;19:355–62.