Elevated Lipoprotein-Associated Phospholipase A2 is Valuable in Prediction of Coronary Slow Flow in Non-ST-Segment Elevation Myocardial Infarction Patients

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Abstract: ***Background*** **Coronary flow is a determinative factor of non-ST-segment elevation myocardial infarction (NSTEMI) patients. Lipoprotein-Associated Phospholipase A2(Lp-PLA2) as a vascular specific inflammatory cytokine might relate to coronary slow flow in these patients.** ***Methods*** **105 NSTEMI patients and 83 UAP patients were enrolled. Another group division was made by Lp-PLA2 tertile data. Corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) was adopted to represent coronary flow condition. Correlation analysis was made between CTFC and other clinical indicators. Multivariable regression analysis was used to identify the influential factors of coronary flow in NSTEMI patients. ROC curve was used to determine the diagnostic value of Lp-PLA2 with coronary slow flow (CSF).** ***Results*** **High sensitive C reactive protein (hsCRP, $P < 0.01$), Lp-PLA2($P < 0.01$), N-terminal pro-brain natriuretic peptide (NT-proBNP, $P < 0.05$), mean platelet volume (MPV, $P<0.05$), CTFC($P < 0.05$) was higher in NSTEMI than UAP patients. hsCRP($P < 0.01$), MPV ($P < 0.01$), NT-proBNP($P < 0.01$) CTFC($P < 0.01$)**

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was higher in high-Lp-PLA2 group. Lp-PLA2 and hsCRP ($r = 0.22$, $P < 0.01$), MPV ($r = 0.21$, $P < 0.05$), CTFC ($r = 0.69$, $P < 0.01$) had a positive correlation in NSTEMI group. Multivariable regression analysis showed that Lp-PLA2 could explain most part changes of CTFC in NSTEMI patients, CTFC = 0.55*Lp-PLA2 +0.03*hsCRP+0.005*NT-proBNP+15.843. Lp-PLA2 was specific and sensitive in diagnosis of CSF in NSTEMI group, AUC = 0.851(95% confidence interval (CI): 0.771-0.924, $P < 0.01$), Cutoff=196.96ng/ml, sensitivity = 84%, specificity = 81%. *Conclusions* Lp-PLA2 is closely correlated with coronary flow in NSTEMI patients. Lp-PLA2 over 196.96ng/ml could be used to predict CSF in NSTEMI patients. (Curr Probl Cardiol 2021;46:100596.)

Introduction

Coronary flow is a crucial factor in the prognosis of Non-ST-segment elevation myocardial infarction (NSTEMI) patients, which is mainly influenced by inflammatory cytokine disorder, platelet activation, and intracoronary thrombosis. Abnormal coronary flow is frequently due to erosion of the atherosclerotic plaque cap, it was the result of plaques instability or plaques rupture,[1] and deteriorated by platelet aggregation and thrombosis intracoronary. Occurrence of coronary slow flow (CSF) might directly lead to high incidence of cardiac events or even cardiac death. Lp-PLA2 is a novel vascular specific inflammatory cytokine, a stress reaction related enzyme, may express at high level in emergency conditions and then gradually remained stable,[2,3] takes part in the development of atherosclerotic plaques, Lp-PLA2 is secreted by macrophage cells detected in the unstable coronary plaques.[4] Lp-PLA2 could also hydrolyze oxidized phospholipids and produce non-esterified fatty acids, resulting in endothelia dysfunction. Lp-PLA2 was considered as a predictor of cardiac events.[5] Due to its pathophysiological background, Lp-PLA2 may be a coronary flow related factor.

Unlike ST-segment- elevation myocardial infarction (STEMI) patients with an apparently occluded coronary artery and blocked coronary flow. NSTEMI is more prevalent in clinical and showed as with wide range of coronary flow disorders, NSTEMI provided a good example in studying the coronary flow condition in practical work. In clinical, risk stratification of NSTEMI is still according to conventional factors, the

recommended window of invasive interventional therapy is by the risk stratification of these patients, in fact, coronary flow disorder is a determinative factor in making percutaneous coronary intervention (PCI) strategy to these patients, indicators reflecting coronary flow condition might be useful in these conditions. Lp-PLA2 as a vascular specific inflammatory cytokine, relating to stability status of coronary lesions, might have close relationship with coronary flow. We aimed to explore value of Lp-PLA2 in different coronary flow conditions in NSTEMI patients.

Methods

Study Population and Group Division

We recorded the data of consecutive patients who went to our hospital to make a retrospective study. 188 patients met the inclusion and exclusion criteria were enrolled. According to the clinical diagnosis, they were categorized into NSTEMI ($n = 105$) and UAP group ($n = 83$). Second group division was made by Lp-PLA2 tertile data of NSTEMI patients, the patients were regrouped into three Lp-PLA2 tertile groups, showed as low-Lp-PLA2 (<180.4 ng/ml)group, middle-Lp-PLA2 (≥ 180.4, <204.8 ng/ml)group and high-Lp-PLA2(>204.8 ng/ml) group.

Inclusion and Exclusion Criteria

Inclusion criteria: NSTEMI and UAP diagnostic standard was according to the WHO criterion for the coronary artery disease (CAD). They all received coronary angiography (CAG). Indication of CAG was according to "unstable angina pectoris and ST-segment elevation myocardial infarction: guidelines for diagnosis and treatment".

Diagnosis of NSTEMI requires an electrocardiogram and a careful review for signs and symptoms of cardiac ischemia. 1, Electrocardiographic abnormality include T-wave tenting or inversion, ST-segment depression. 2, Patients with chest pain Troponin T or I are the most sensitive determinant of NSTEMI. Early markers include myoglobin and creatine kinase−MB subforms (or isoforms). 3, former CTA, if necessary (at least 1 epicardium coronary artery or its main branch stenosis in diameters $\geq 50\%$).

Diagnosis standard of diabetes mellitus (DM) was according "World Health Organization and the International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia:

report of a WHO/IDF consultation. Geneva: World Health Organization, 2006".

Exclusion criteria: (1). Age≤18 and≥80 years old. (2). Not suitable for the coronary artery interventional therapy, such as acute infectious disease or hemorrhage status. (3). Patients with serious hepatobiliary, kidney, pancreas, pulmonary and peripheral vascular disease, which would affect inflammatory conditions. (4). Tumor of blood system disease, other heart diseases (cardiomyopathy, heart valve disease, myocarditis).

Demographic Data and Clinical Features

Data of demographic (age, gender), smoking history, diabetes mellitus history, hypertension history were recorded, BMI was calculated by $kg.cm^{-2}$.

Hypertension was diagnosed by systolic BP≥140 mmHg and diastolic BP≥90 mmHg, or they were under treatment with antihypertension medications.

Diabetes mellitus was defined as a state with a fasting plasma glucose level≥126 mg/dL, HBA1c>6.5%, a random glucose level≥200 mg/dL or receiving the medicine treatment of diabetes mellitus.

Laboratory Analysis

Patients enrolled would be fasting 8 hours before blood samples were collected. Blood biochemical indicators including hemoglobin A1c (HBA1c), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), lipoprotein A(LPA), hypersensitive C reactive protein (hsCRP), N-terminal pro brain natriuretic peptide (NT-proBNP). They were tested and recorded.

Blood routine test results including white blood cells (WBC), neutrophilic granulocyte (NEUT), mean platelet volume (MPV). They were tested and recorded.

The concentration of plasma Lp-PLA2 was determined by immunoturbidimetric assay with PHOMO scattering analyzer (Autobio Biology Technology Co., Ltd. Zhengzhou, China).

Calculation of CTFC

Coronary angiograms (CAG) was carried out in the catheterization department with standard protocols. Coronary flow could be quantitatively represented by corrected TIMI frame count (CTFC, frames). CAG video was recorded, CTFC was carefully counted, the first

CTFC frame was according to the contrast across more than 70% of the arterial with anterograde perfusion and touching both borders of the lumen. The final frame was according to the leading edge of the contrast column reached the distal end. Left anterior descending (LAD) coronary artery may have 1.7 times greater than the mean value of the left circumflex coronary artery (LCX) and the right coronary artery (RCA), the frame could result of the LAD was divided by 1.7 and then could be calculated with the LCX and RCA.

CTFC for analysis was calculated by two independent operators. The mean CTFC for each subject was calculated by totaling of CTFCs for the LAD, LCX, and RCA, and then divided by 3.[6]

Definition of Coronary Slow Flow (CSF)

Coronary slow flow (CSF) was defined by CTFC data from coronary angiography. Higher level of CTFC in the CAG video represents the lower perfusion rate of contrast in the coronary arteries, was an indirect coronary flow parameter. CTFC was from the strict data of CAG, separately calculated by 2 experienced operators, especially in determine of coronary slow flow. CTFC cumulative frequency was made in SPSS software, 75% cumulative frequency data of CTFC ($\geq$26.9 frames) was used to represent CSF.

Statistical Analysis

SPSS19.0 statistical program package for Windows (SPSS Inc., Chicago, IL) was used to analyze the research data. The kolmogorov-Smirnov test was used to test normality of distribution. Continuous variables with normal distribution were expressed as mean $\pm$ standard deviation ($\overline{X} \pm S$). Student's t-test was used to test variable with normal distribution. Continuous variables without normal distribution were showed as percentiles 50(25,75). The Mann-Whitney U test, Kruskal-Wallis test was used to test differences in variables without normal distribution. Categorical variables were compared by the Chi-square test or post hoc Fisher exact test. Spearman correlation coefficient and Pearson correlation coefficient were used to show correlations of Lp-PLA2 with coronary flow related factors. To determine the factors affecting CTFC, multivariate linear regression analysis was adopted. ROC curve analysis was adopted to determine diagnostic value of Lp-PLA2 to CSF, Youden index method was used to calculate cutoff data of Lp-PLA2. Value of two-tailed $P < 0.05$ was considered having a significant statistical difference.

Results

Coronary Flow Influential Factors Comparison between NSTEMI and UAP Group

LDL-C (3.4±1.3 vs 2.8±1.0 mmol/L, $P<0.05$), Lp-PLA2(192.7±23.1 vs 170.3±22.6 ng/ml, $P<0.01$), NT-proBNP (589.8 (259.3, 769.9) vs 302.3 (238.7, 731.1) pg/mL, $P<0.05$), MPV(11.1±2.5 vs 10.2±2.3fL, $P<0.05$), CTFC (25.9±3.1 vs 23.6±3.7frames, $P<0.05$), hsCRP (3.9 (3.1, 4.9) vs 2.9 (2.1,3.9) mg/L, $P<0.01$) was higher in NSTEMI group than in UAP group. Gender (male), age, hypertension history, smoking history, BMI, HBA1c, TC, HDL-C, TG, LPA, WBC, NEUT didn't have significant statistical differences (Table 1, Fig 1).

Comparison of Coronary Flow Influential Factors in Lp-PLA2 Tertile Groups by NSTEMI Patients

hsCRP was higher in high-LP-PLA2 group than in low-LP-PLA2 group (4.4(3.3, 5.2) vs 3.3(2.6, 4.4) mg/L, $P < 0.05$), higher in high-LP-

TABLE 1. Coronary flow influential factors comparison between NSTEMI and UAP group.

Items	NSTEMI (n = 105)	UAP (n = 83)	*P*
Male (n, %)	75 (71.4)	68 (81.9)	0.09
Age (years, $\overline{X} \pm S$)	61.2±4.5	59.5±3.3	0.6
Hypertension (n, %)	83 (60.0)	66 (79.5)	0.9
Smoking (n, %)	78 (45.7)	51 (61.4)	0.06
BMI ($kg*m^{-2}$)	25.5±6.8	26.4±7.1	0.3
HBA1C (%)	6.7 (5.9, 7.6)	6.4 (5.6, 7.1)	0.5
TC (mmol/L)	4.1±1.8	4.0±1.8	0.6
LDL-C(mmol/L)	3.4±1.3	2.8±1.0	<0.05
HDL-C(mmol/L)	0.9±0.1	0.9±0.2	0.2
TG (mmol/L)	2.1±0.4	1.9±0.4	0.2
LPA (mmol/L)	201.9±11.3	199.3±11.4	0.1
hsCRP(mg/L)	3.9 (3.1, 4.9)	2.9 (2.1,3.9)	<0.01
LP-PLA2(ng/ml)	192.7±23.1	170.3±22.6	<0.01
NT-proBNP(pg/mL)	589.8 (259.3, 769.9)	302.3 (238.7, 731.1)	<0.05
WBC (10^9)	8.4±2.2	8.2±2.1	0.4
NEUT (%)	67.1±7.1	67.3±6.4	0.7
MPV (fL)	11.1±2.5	10.2±2.3	<0.05
CTFC(frames)	25.9±3.1	23.6±3.7	<0.05

Abbreviations: BMI, body mass index; CKMB, MB isoenzyme of creatine kinase; CTFC, corrected thrombolysis in myocardial infarction (TIMI) frame count; HBA1c, hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; hsCRP, hypersensitive C reactive protein; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; LPA, lipoprotein A; N-terminal pro brain natriuretic peptide (NT-proBNP); WBC, white blood cells; MPV, mean platelet volume; NEUT, neutrophilic granulocyte percentage; RDW, Red cell distribution width.

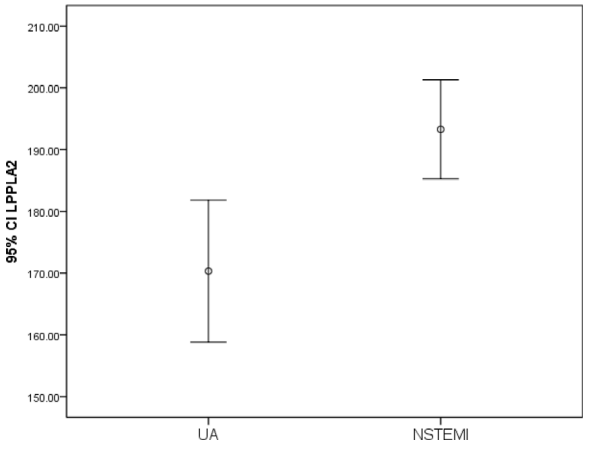

FIG 1. Error bar (CI 95%) of Lp-PLA2 between UAP and NSTEMI group, $P < 0.01$.

PLA2 group than in middle-LP-PLA2 group (4.4(3.3, 5.2) vs 3.8(3.2, 4.9) mg/L, $P < 0.01$). MPV was higher in high-LP-PLA2 group than in low-LP-PLA2 group (11.6±2.5 vs 10.2±2.3fL, $P < 0.05$), higher in middle-LP-PLA2 group than in low-LP-PLA2 group (11.7±2.4 versus 10.2±2.3 fL, $P < 0.05$). NT-proBNP was higher in middle-LP-PLA2 group than in low-LP-PLA2 group (550.1(262.6, 680.1) vs 287.9(225.5, 362.1) pg/mL, $P < 0.01$), higher in high-LP-PLA2 group than in low-LP-PLA2 group (680.3(275.8, 781.2) vs 287.9(225.5, 362.1) pg/mL, $P < 0.01$). CTFC was higher in middle-LP-PLA2 group than in low-LP-PLA2 group (25.1±3. 5 vs 19.5±3.4 frames, $P < 0.01$), higher in high-LP-PLA2 group than in middle-LP-PLA2 group (29.1±3.5 vs 25.1±3.5 frames, $P < 0.01$) (Table 2, Fig 2).

Correlation Analysis Results of Lp-PLA2 and hsCRP, NT-proBNP, MPV, CTFC

Correlation analysis was made between Lp-PLA2 and hsCRP, MPV, NT-proBNP, CTFC in NSTEMI patients. Lp-PLA2 and hsCRP had a positive relationship ($r = 0.22$, $P < 0.01$). Lp-PLA2 and MPV had a positive relationship ($r = 0.21$, $P < 0.05$). Lp-PLA2 correlated with NT-proBNP ($r = 0.35$, $P < 0.01$). Lp-PLA2 and CTFC had a positive relationship ($r = 0.69$, $P < 0.01$).

Correlation analysis in UAP group showed that Lp-PLA2 and hsCRP had no correlation ($P = 0.25$). Lp-PLA2 correlated with MPV ($r = 0.21$,

TABLE 2. Comparison of coronary flow influential indicators in different Lp-PLA2 tertile groups by NSTEMI patients.

Items	Low-LP-PLA_2 (n=22)	Middle-LP-PLA_2 (n=46)	High-LP-PLA_2 (n=37)	*F/ H*	*P*
hsCRP(mg/L)	3.3 (2.6, 4.4)	3.8 (3.2, 4.9)	4.4 (3.3, 5.2)*,!	11.6(*H*)	<0.01
LDL-C(mmol/L)	3.1±1.1	3.3±1.3	3.8±1.5	1.9	0.15
MPV (fL)	10.2±2.3	11.7±2.4*	11.6±2.5*	3.6	<0.05
NT-proBNP (pg/mL)	287.9 (225.5, 362.1)	550.1 (262.6, 680.1)$	680.3 (275.8, 781.2)*	12.2(*H*)	<0.01
CTFC(frames)	19.5±3.4	25.1±3.5$	29.1±4.1$,!	45.8	<0.01

*Compared with Low LP PLA_2 group, $P < 0.05$.
$Compared with Low LP PLA_2 group, $P < 0.01$.
!Compared with middle LP PLA_2 group, $P < 0.01$.
Abbreviations: CTFC, corrected thrombolysis in myocardial infarction(TIMI) frame count; hsCRP, hypersensitive C reactive protein; LDL-C, low density lipoprotein cholesterol; MPV, mean platelet volume; N-terminal pro brain natriuretic peptide (NT-proBNP).

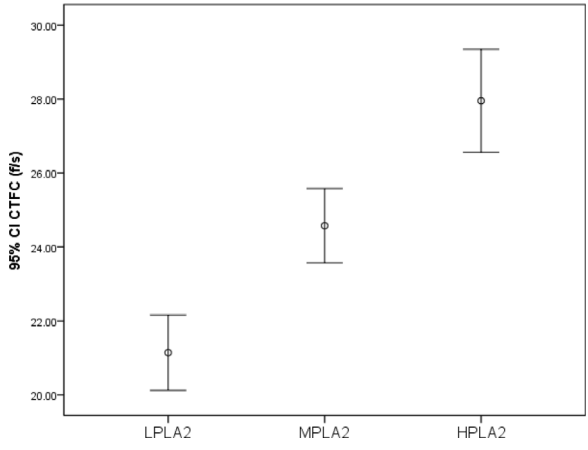

FIG 2. Error bar (CI 95%) of CTFC among Lp-PLA2 groups, $P < 0.01$.

$P < 0.05$). Lp-PLA2 correlated with NT-proBNP ($r = 0.31$, $P < 0.01$). Lp-PLA2 had no correlation with CTFC ($P = 0.24$) (Table 3, Figs 3 and 4).

Multivariable Linear Regression Analysis of Coronary Flow in NSTEMI Group

CTFC was in line with cluster of changes in NSTEMI patients, In order to investigate the factors affected CFTC, CTFC as dependent variable, CKMB, LDL-C, MPV, Lp-PLA2, hsCRP, NT-proBNP as independent

TABLE 3. Correlation coefficients of Lp-PLA2 with items between NSTEMI and UAP groups

Items	NSTEMI		UAP	
	r	*p*	*r*	*p*
hsCRP	0.22	<0.01	NA	0.25
MPV	0.21	<0.05	0.21	<0.05
NT-proBNP	0.35	<0.01	0.31	<0.01
CTFC	0.69	<0.01	NA	0.24

Abbreviations: CTFC, corrected thrombolysis in myocardial infarction(TIMI) frame count; hsCRP, hypersensitive C reactive protein; LDL-C, low density lipoprotein cholesterol; MPV, mean platelet volume; N-terminal pro brain natriuretic peptide (NT-proBNP).

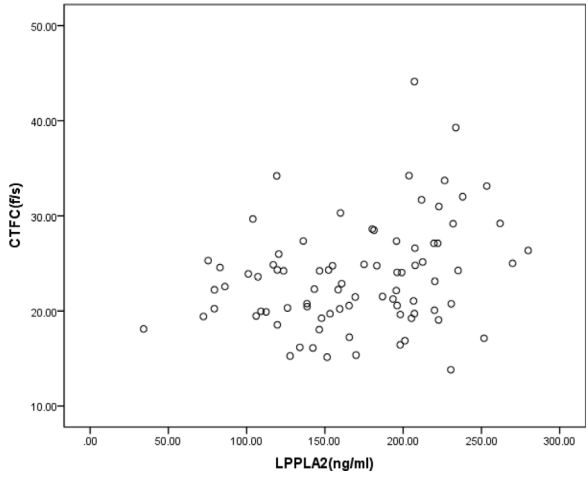

FIG 3. Correlation analysis of Lp-PLA2 and CTFC in UAP group, $P > 0.01$.

variables were analyzed. All the independent variables were taken into regression analysis by SPSS software. Finally, Lp-PLA2, hsCRP, NT-proBNP could explain the changes of CTFC in NSTEMI patients. The regression equation was CTFC=0.55*Lp-PLA2+0.03*hsCRP+ 0.005*NT-proBNP+15.843. Regression coefficients were tested with significant statistical differences. (Reference Table 4).

ROC Analysis of Lp-PLA2 with Coronary Slow Flow Separately in NSTEMI and UAP Patients

ROC analysis was adopted to evaluate the diagnostic value of Lp-PLA2 with CSF. CTFC≥26.9 frames (75% cumulative frequency) was defined as CSF. ROC analysis was separately performed in NSTEMI and

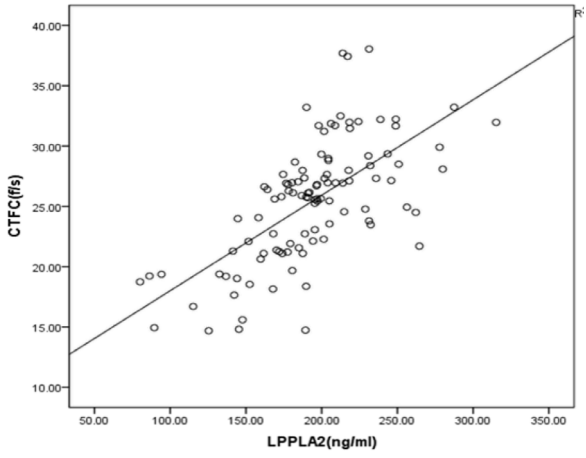

FIG 4. Correlation analysis of Lp-PLA2 and CTFC In NSTEMI group. $r = 0.69$, $P < 0.01$.

TABLE 4. Multivariable linear regression analysis of CTFC in NSTEMI group.

Variables	β	*t*	*P* value
Constant	15.843	10.554	0.000
Lp-PLA2	0.55	2.05	0.004
HsCRP	0.03	3.31	0.001
NT-proBNP	0.005	3.08	0.002

Abbreviations: CTFC, corrected thrombolysis in myocardial infarction (TIMI) frame count; hsCRP, hypersensitive C reactive protein; N-terminal pro brain natriuretic peptide (NT-proBNP).

UAP patients. Area under the curve (AUC) of Lp-PLA2 with CSF was in UAP patients 0.585 (95% confidence interval (CI): 0.463-0.708, $P < 0.01$). AUC of Lp-PLA2 with CSF in NSTEMI group was 0.851(95% confidence interval (CI): 0.771-0.924. $P < 0.01$), Cutoff=196.96ng/ml, sensitivity = 84%, specificity = 81%. (Figs 5 and 6). Lp-PLA2 in definition of CSF was more sensitive and specific in NSTEMI patients.

Discussion

NSTEMI represents an emergency cardiovascular condition in clinical, closely related to coronary flow status, coronary slow flow (CSF) is a factor of poor prognosis in these patients. In clinical, coronary flow is influenced by many factors, inflammatory cytokine is the most important one among them,[7,8] vascular specific inflammatory cytokine such as Lp-PLA2 might be the promising one related to instability of coronary plaques, perhaps even initiative factor of CSF. In NSTEMI patients, unstable

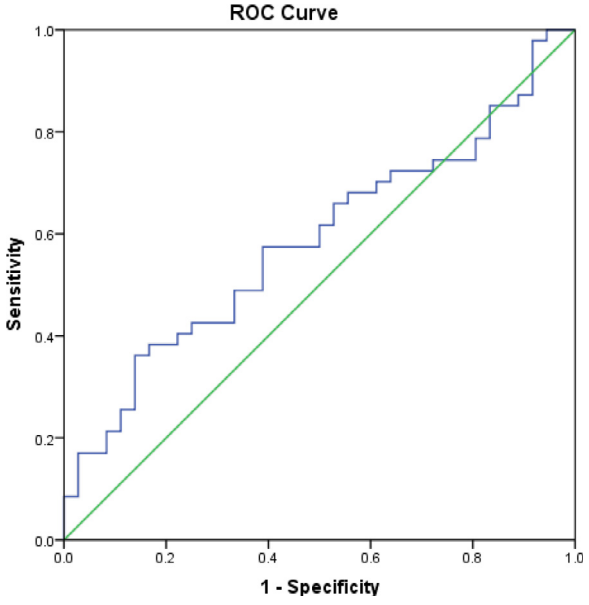

FIG 5. Area under the curve (AUC) of Lp-PLA2 with CSF in UAP patients was 0.585 (95% confidence interval (CI): 0.463-0.708, $P < 0.01$).

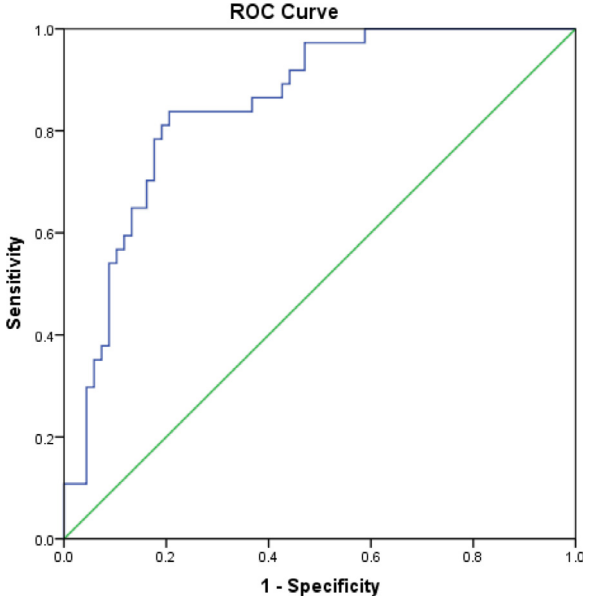

FIG 6. Area under the curve (AUC) of Lp-PLA2 with CSF in NSTEMI patients was 0.851(95% confidence interval (CI): 0.771-0.924, $P < 0.01$). Cutoff = 196.96ng/ml, sensitivity = 84%, specificity = 81%.

coronary plaque may induce coronary flow disorder, and the coronary flow is exacerbated by consequent platelet activation and intracoronary thrombosis. But in practical, CSF is not easily identified, CSF is often acquired by coronary angiography (CAG), it is defined as delayed progression of contrast agent in coronary artery, it is through an invasive procedure and sometime not suitable for all the patients. Thrombolysis in myocardial infarction (TIMI) grade 2 or lower flow phenomenon was once an accepted criterion of CSF. With the advantages in cardiovascular disease, the occurrence of Corrected TIMI frame count (CTFC) made the coronary flow quantitatively comparable, reproducible and the definition of CSF more scientific. And CSF draws more attention than before. CSF was reported be associated with instability of coronary plaques and related with major adverse cardiovascular events (MACE).[9] Cardiac events such as cardiomyocyte ischemia, myocardial infarction, severe cardiac arrhythmia, or even sudden death all had close relationship with CSF. But CSF is a complicated result in CAD patients, In addition to inflammatory factors, endothelial dysfunction,[10] platelet activation was all contributors of CSF.[11,12] CSF is more prevalent in NSTEMI patients and difficult to identify if without invasive procedure as aforementioned, accurate detection of CSF might be important to these patients. Prediction of CSF through clinical indicators had gradually become a highlighted subject.[13–15]

NSTEMI as an acute stress response may induce a cluster changes of inflammatory cytokine in the body, such as hsCRP and Lp-PLA2. hsCRP is an unspecific acute phase inflammatory cytokine, synthesized in liver and influenced by many other factors, such as body mass index (BMI), plasma lipid levels, blood glucose, hyperinsulinemia and insulin resistance. hsCRP was reported having an elevated trend in acute coronary syndrome(ACS) patients.[16–18] Unlike hsCRP, Lp-PLA2 is considered as a vascular specific inflammatory cytokine, secreted mainly by macrophages in coronary plaques.[19] Lp-PLA2 expressed highly in unstable coronary plaques than in stable ones,[20] elevated Lp-PLA2 was related to instability of coronary plaques.[3,21] Lp-PLA2 was also reported having close relationship with cardiovascular events in ACS patients.[22–26] Lp-PLA2 may be used as a clinical risk stratification factor in cardiovascular disease.[27] Lp-PLA2 was sensitive in identification of patients with high atherosclerotic risk.[28–30] Lp-PLA2 perhaps might be a promising indicator of coronary flow in NSTEMI patients, and not reported before.

In addition to Lp-PLA2, coronary flow is also related to platelet activation and cardiac dysfunction, and CSF might also be influenced by those factors. In the present study, LDL-C, hsCRP, Lp-PLA2, NT-proBNP,

MPV, CTFC was higher in NSTEMI patients. Elevated MPV is an indicator of platelet activation, large platelet would have more pseudopods and more platelet particles, resulting in platelet aggregation and intracoronary thrombosis. NT-proBNP is considered as a cardiac function indicator in clinical, elevated NT-proBNP represents ischemic cardiomyocyte dysfunction, also a sign of coronary hypoperfusion. In the second group division, hsCRP, MPV, NT-proBNP was also discovered highly expressed in high-Lp-PLA2 group, in line with elevated CTFC. In correlation analysis, Lp-PLA2 and CTFC had positive correlation in NSTEMI group ($r = 0.69$, $P < 0.01$), and this result was not obvious in UAP group. In multivariable regression analysis, Lp-PLA2, hsCRP, NT-proBNP could explain CTFC changes in NSTEMI patients, the weight of Lp-PLA2 in explaining CTFC was more significant than hsCRP and NT-proBNP, as stated in the regression equation. ROC curve analysis was made to determine the diagnostic value of Lp-PLA2 to CSF. Area under the curve (AUC) in NSTEMI group was 0.851(95% confidence interval (CI): 0.771-0.924, $P < 0.01$). In this study, Lp-PLA2 was in accordance with CTFC changes in NSTEMI, especially in diagnosis of CSF in these patients. Lp-PLA2 might be a risk stratification parameter of NSTMI, Lp-PLA2 greater than the cut-off value (over 196.96ng/ml) might be used in diagnosis of CSF, strategy should be adopted in avoiding CSF if Lp-PLA2 was detected over the cutoff data, close correlation of elevated Lp-PLA2 and cardiac events as reported before[25,26] perhaps due to the occurrence of CSF in those patients, making Lp-PLA2 a potential risk factor in cardiovascular and cerebrovascular diseases.[31]

In addition to cardiovascular disease, Lp-PLA2 was also found highly expressed in other fields.[32] Lp-PLA2 antagonist was effective in diabetic macular edema,[33] Lp-PLA2 targeted therapy might be promising in future, a 20-years followed up study showed Lp-PLA2 activity was higher in abdominal aortic aneurysm than the normal contrast, and related to incidence of abdominal aortic aneurysm.[34,35] Lp-PLA2 was also related to progress of obese,[36] Lp-PLA2 antagonist showed excellent result in treating with these disease.[37] Lp-PLA2 was also an earlier marker of dyslipidemia, especially children with abnormal Lp-PLA2.[38] But as a coronary flow related factor, particular in NSTEMI, significance of Lp-PLA2 was not elicited before, our result perhaps extended the field of this vascular specific inflammatory cytokine.

This result might bring the practical use of Lp-PLA2 in decision making of NSTEMI, for instance, invasive strategy of NSTEMI is ranging from immediate invasive strategy(<2 hours), early invasive strategy(<24 hours) and delayed invasive strategy(< 72 hours). The stratification

strategy is still according to the conventional clinical risk factors recommended by 2015 European societies of cardiology (ESC) NSTE-ACS guidelines and 2018 ESC myocardial revascularization guidelines. Besides the conventional risk factors cited by those documents, coronary flow is another crucial factor in NSTEMI patients. Predictive value of Lp-PLA2 in coronary flow disorder might be more accurate and instant than the former parameters, this is beneficial to NSTEMI patients.

Predictive value of Lp-PLA2 to CSF was significant in NSTEMI patients in this study. In clinical, STEMI had the feature of obstructive coronary flow in the culprit vessel, quantitively comparison of coronary flow might be difficult, further investigation still needed in this aspect, non-culprit vessels flow in STEMI patients might be an alternative approach. Another limitation in this study was due to the data from a single center, and data from more centers might be more necessary in the further. Unlike the expensive, complicated procedure such as CAG, Lp-PLA2 is easily acquired and Lp-PLA2 over the cutoff data might also be a mirror of CSF, furthermore, more accurate cut-off data is still needed, inflammatory cytokine and CSF may draw more attentions in the future.

Conclusions

NSTEMI possess high Lp-PLA2 and Lp-PLA2 is closely related to coronary flow in these patients. Lp-PLA2 (over 196.96ng/ml) perhaps is a predictor of coronary slow flow in NSTEMI.

Declarations

Ethics approval and consent to participate: this work was approval by the ethics committee of The First Affiliated Hospital of Xi'anJiaotong University and has a consent to the participation.

Consent for Publication

All the authors have consent for the publication.

Availability of Data and Material

All the data and material were effective.

Authors' Contributions

Qi Liang conceived of the study and participated in its design, coordination, conduct, analysis, and drafted the manuscript. Xinjun Lei

participated in the design of the study, conduct, and the interpretation of results. Lihong Fan participated in the design of the study and performed the statistical analysis. Xin Huang participated in the conception and design of the study and secured funding. All authors revised the manuscript for content and read and approved the final manuscript.

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