Clin. Lab. 2025;71:XXX-XXX

ORIGINAL ARTICLE

Predictive Value of Lp-PLA2 Combined with Leukocyte-Derived Markers for Heart Failure After Acute Myocardial Infarction

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SUMMARY

Background: **We aimed to evaluate the value of lipoprotein-associated phospholipase A2 (Lp-PLA2) in the serum plus leukocyte-derived markers such as platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) for predicting heart failure (HF) after acute myocardial infarction (AMI).**
Methods: **A total of 80 AMI patients (case group) hospitalized between June 2019 and July 2022 and 80 healthy subjects (healthy group) were selected. An HF group and a non-HF group were established for the case group. The general data, serum Lp-PLA2 concentration, PLR, and NLR were compared between the two subgroups. Analysis of the risk factors for HF in AMI patients was performed.**
Results: **The case group, compared with the healthy group, had higher serum Lp-PLA2 concentration, PLR, and NLR ($p < 0.05$). HF occurred in 10 cases (12.50%) in the case group. In comparison to the non-HF group, increases of serum Lp-PLA2 concentration, PLR, and NLR were detected in the HF group ($p < 0.05$). Elevated serum Lp-PLA2 concentration, PLR, and NLR served as risk factors for HF in AMI patients ($OR > 1$, $p < 0.05$). NLR, PLR, serum Lp-PLA2, and combination of the three had the areas under the curves of 0.734, 0.731, 0.719, and 0.910, respectively, in predicting HF in AMI patients.**
Conclusions: **NLR, PLR, and serum Lp-PLA2 concentration were elevated in AMI patients, that were associated with HF. Combined determination of NLR, PLR, and serum Lp-PLA2 can effectively predict the risk of HF in AMI patients.**
(Clin. Lab. 2025;71:xx-xx. DOI: 10.7754/Clin.Lab.2024.240735)

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Manuscript accepted September 6, 2024

KEYWORDS

acute myocardial infarction, heart failure, leukocyte, lipoprotein, lymphocyte, neutrophil, platelet

INTRODUCTION

Being a damaging cardiovascular disease characterized by sudden onset and high mortality, acute myocardial infarction (AMI) seriously threatens the health of patients [1]. Percutaneous coronary intervention (PCI) is the major treatment means for AMI currently, which can quickly dredge the infarcted vessels and restore blood perfusion. However, heart failure (HF) still occurs in some patients following PCI, becoming a leading contributor to death at present [2]. Therefore, it is of important significance to develop a rapid and efficient

biomarker for forecasting HF risk in AMI patients. As a biomarker with high vascular specificity, lipoprotein-associated phospholipase A2 (Lp-PLA2) can induce the activation of monocyte-macrophages and make monocyte-macrophages aggregate to the intima and bind to oxidized low-density lipoprotein to become foam cells, which has intimate associations with AMI onset and progression and possesses certain predictive value for adverse coronary events [3]. Platelet-to-lymphocyte ratio (PLR) together with neutrophil-to-lymphocyte ratio (NLR) belongs to leukocyte-derived markers. Their associations with the regulation of glycolipid metabolism and expression of endothelial inflammatory factors have been verified recently, which work as important risk factors for the onset and progression of AMI [4,5]. Therefore, serum Lp-PLA2 and leukocyte-derived markers are closely associated with the occurrence and development of AMI, and they are potential biomarkers for predicting HF in AMI patients.

In this study, the predictive value of serum Lp-PLA2 and leukocyte-derived markers for HF in AMI patients was analyzed, aiming to provide valuable clinical evidence.

MATERIALS AND METHODS

Subjects

This study was approved by the ethics committee of our hospital. A total of 80 AMI patients (case group) hospitalized herein during June 2019 and July 2022 and 80 healthy subjects (healthy group) were selected. In the case group, there were 51 males and 29 females aged 40 - 71 years, with an average age of (59.32 ± 3.28) years. The body mass index (BMI) was 22 - 26 kg/m^2, with an average BMI of (24.24 ± 0.35) kg/m^2. The systolic blood pressure of 128 - 155 mmHg and diastolic blood pressure of 82 - 103 mmHg, with an average of (135.20 ± 5.16) mmHg and (96.60 ± 3.05) mmHg, respectively, were measured at admission. In the healthy group, 46 males and 34 females had an age between 38 - 72 years and a mean of (58.86 ± 3.46) years; the BMI was 22 - 26 kg/m^2, with a mean of (24.26 ± 0.38) kg/m^2, and the systolic blood pressure and diastolic blood pressure at admission were 125 - 156 mmHg and 80 - 105 mmHg, with a mean of (135.50 ± 5.10) mmHg and (96.65 ± 3.02) mmHg, respectively. For the healthy and case groups, the gender, age, BMI, and blood pressure were all well-balanced and comparable ($p > 0.05$).

Inclusion and exclusion criteria

The following inclusion criteria were utilized: 1) patients clinically diagnosed with AMI, 2) those who consented and cooperated with the study, 3) those with normal mental state and communication ability, and 4) those who were given long-term secondary preventive medication for coronary heart disease after successful PCI.

The exclusion criteria included: 1) patients with coronary bifurcation, severe calcification, coagulation disorders, malignant tumor, congenital heart disease, pulmonary heart disease, connective tissue disease, autoimmune disease, uncontrolled communicable or infectious diseases, or severe liver or kidney dysfunction, and 2) those with a recent history of using glucocorticoid or nonsteroidal anti-inflammatory drugs.

Collection of blood samples

Fasting blood (5 mL) was drawn from the median cubital vein of each participant in a quiet state on the day of physical examination in the healthy group and after admission before PCI in the case group. The blood samples were subjected to 30 minutes of standing at room temperature before 10-minute centrifugation at 2,500 r/min (centrifugal radius: 10 cm). Then the resulting upper serum was collected into a centrifuge tube and stored in a refrigerator at -80°C for up to one month before being thawed for the subsequent assays. All measurements were performed in a single batch to minimize variability.

Measurement of Lp-PLA2 concentration in the serum, NLR, and PLR

The serum was taken out from the refrigerator and thawed at room temperature. Then enzyme-linked immunosorbent assay with corresponding kit [MBL, Jinpin Chemical Technology (Shanghai) Co., Ltd., China] was conducted to determine the serum Lp-PLA2 concentration. Neutrophil, lymphocyte, and platelet counts were measured in EDTA whole blood samples and performed on the day of blood collection using XN series automatic blood fluid analyzer (Sysmex Corporation, Japan). Then NLR and PLR were calculated.

Determination of HF

The patients in the case group were followed up for one year after treatment, and those who met the following criteria were determined as HF: 1) symptoms and/or signs of HF [6], 2) increase in N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration (NT-pro BNP ≥ 450 pg/mL in patients aged < 50 years old, NT-proBNP ≥ 900 pg/mL in patients aged 50 - 70 years old, and NT-proBNP > 1,800 pg/mL in patients aged > 75 years old), and 3) oral or intravenous administration of diuretics.

Collection of general data

Demographic data: gender (male, female), smoking history (smoking index ≥ 400) (yes, no), drinking history (blood alcohol concentration ≥ 0.08 g/dL) (yes, no), obesity (BMI ≥ 24 kg/m^2) (yes, no), history of statin use (yes, no), history of β-blocker use (yes, no), age, number of diseased vessels, and diastolic and systolic blood pressure (examined by an electronic sphygmomanometer before PCI).

Laboratory indicators: glycosylated hemoglobin (Hb A1c) measurement was made in EDTA whole blood samples and performed on the day of blood collection

Table 1. Serum Lp-PLA2 concentration, NLR, and PLR in healthy and case groups ($\bar{x} \pm s$).

Group	n	Lp-PLA2 (U/L)	NLR	PLR
Healthy	80	120.80 ± 12.13	2.82 ± 0.20	100.15 ± 10.25
Case	80	220.55 ± 15.20	4.50 ± 0.35	135.24 ± 11.28
t		45.879	35.276	20.592
p		< 0.001	< 0.001	< 0.001

by high-performance liquid chromatography (Bio-Rad-10, Hercules, USA). The serum was taken out from the refrigerator and thawed at room temperature. Then the peak concentration of troponin I was measured by the colloidal gold method using a kit (Xiamen Boson Biotech Co., Ltd., China). Fasting plasma glucose (FPG) concentration was measured with the oxidizing electrode method using Biosen C-Line blood glucose analyzer (EKF Diagnostics, Germany). AU5811 automatic biochemical analyzer (Beckman, USA) was employed to detect total cholesterol (TC) together with triglyceride (TG).

Electrocardiogram indicators: Prince-180D 24-hour dynamic electrocardiography (Shanghai Minchen Medical Equipment Co., Ltd., China) was used to identify fragmented QRS wave (an rSr' pattern of two related leads but no typical bundle branch block waveform) (detected or not detected). Sonos 5000 color Doppler ultrasound system (HP, USA) was utilized for measurement of left ventricular ejection fraction (LVEF).

Statistical analysis

SPSS 23.0 software was applied to implement statistical analysis. The measurement data in normal distribution were described by mean ± standard deviation ($\bar{x} \pm s$) and underwent the *t*-test. The risk factors for HF in AMI patients were explored by logistic regression analysis. The values of serum Lp-PLA2, PLR, NLR, and combination of the three for predicting HF in AMI patients were analyzed through receiver operating characteristic (ROC) curves. $p < 0.05$ suggested a difference of statistical significance.

RESULTS

Serum Lp-PLA2 concentration, NLR, and PLR in healthy and case groups

The case group, compared with the healthy group, had raised serum Lp-PLA2 concentration, PLR, and NLR ($p < 0.05$) (Table 1).

Incidence of HF

It was found by post-treatment follow-up that HF occurred in 10 cases (12.50%) in the case group, and the remaining 70 patients (87.50%) developed no HF.

General data of HF and non-HF groups

By contrast to those in the non-HF group, increases of serum Lp-PLA2 concentration, PLR, and NLR were detected in the HF group ($p < 0.05$). No intergroup differences of statistical significance were observed in other data ($p > 0.05$) (Table 2).

Risk factors for HF in AMI subjects

The presence or absence of HF in AMI subjects were set as a dependent variable (1 = presence, 0 = absence), and the abovementioned indicators with statistically significant differences were determined as independent variables for logistic regression analysis. It was found that elevated serum Lp-PLA2 concentration, PLR, and NLR served as risk factors for HF in AMI patients (*OR* > 1, $p < 0.05$) (Table 3 and Figure 1).

Value of serum Lp-PLA2, PLR, NLR, and combination of the three for HF prediction in AMI subjects

The plotting of ROC curves was accomplished using the present or absent HF in AMI patients as a dependent variable (1 = presence, 0 = absence) and the serum Lp-PLA2 concentration, PLR, and NLR as test variables. The areas under the ROC curves (AUCs) of NLR, PLR, serum Lp-PLA2, and combination of the three in predicting HF in AMI patients were 0.734, 0.731, 0.719, and 0.910, respectively (Table 4 and Figure 2).

DISCUSSION

AMI is a heart disease in which atherosclerosis causes stenosis and obstruction of coronary artery, giving rise to hypoxia, myocardial ischemia, and even necrosis. It is one of the most important cardiovascular diseases threatening the life health of Chinese residents [7]. With effective medication and PCI and the establishment of chest pain centers, great progress has been made in the treatment of AMI, significantly decreasing its mortality. However, HF still occurs in some AMI patients after blood perfusion is restored by PCI, emerging as a leading contributor to unplanned readmission and death after PCI [8,9]. Therefore, it is of great clinical significance to search for biomarkers that can effectively predict post-AMI HF for early prevention and intervention and prognostic improvement in AMI patients.

Lp-PLA2 is primarily synthesized and expressed by macrophages, lymphocytes, monocytes, and mastocytes, which can hydrolyze oxidized phospholipids in plaques, and produce pro-inflammatory and pro-atherosclerotic products, participating in multiple stages of AMI [10, 11]. Leukocyte-derived markers can effectively reflect immunity, immediate anti-inflammatory capacity, and thrombosis risk. Among them, NLR and PLR have been proven to be closely related to the progression and prognosis of atherosclerosis [12,13]. Therefore, it is specu-

Table 2. General data of HF and non-HF groups.

Item		HF group (n = 10)	Non-HF group (n = 70)	Statistical value	p
Gender [n (%)]	male	4 (40.00)	47 (67.14)	1.739	0.187
	female	6 (60.0)	23 (32.86)		
Smoking history [n (%)]	yes	3 (30.0)	5 (7.14)	2.857	0.091
	no	7 (70.00)	65 (92.86)		
Drinking history [n (%)]	yes	3 (30.00)	7 (10.00)	1.633	0.201
	no	7 (70.00)	63 (90.00)		
Obesity [n (%)]	yes	6 (60.00)	40 (57.14)	0.029	0.864
	no	4 (40.00)	30 (42.86)		
History of statin use [n (%)]	yes	4 (40.00)	30 (42.86)	0.029	0.864
	no	6 (60.00)	40 (57.14)		
History of β-blocker use [n (%)]	yes	7 (70.00)	38 (54.29)	0.0356	0.551
	no	3 (30.00)	32 (45.71)		
Fragmented QRS wave [n (%)]	detected	6 (60.00)	39 (55.71)	0.007	0.932
	not detected	4 (40.00)	31 (44.29)		
Age (years)		59.33 ± 5.05	59.32 ± 5.02	0.006	0.995
Number of diseased vessels (n)		2.32 ± 0.36	2.24 ± 0.35	0.674	0.502
Peak concentration of troponin I (μg/L)		18.23 ± 2.26	18.26 ± 2.24	0.040	0.969
Systolic blood pressure (mmHg)		138.65 ± 5.01	135.69 ± 5.03	1.742	0.086
Diastolic blood pressure (mmHg)		97.65 ± 3.46	96.66 ± 3.48	0.842	0.402
Serum FPG (mmol/L)		8.29 ± 0.30	8.30 ± 0.28	0.105	0.917
HbA1c (%)		9.20 ± 0.25	9.22 ± 0.24	0.245	0.807
Serum TC (mmol/L)		6.73 ± 0.21	6.76 ± 0.19	0.461	0.646
Serum TG (mmol/L)		3.25 ± 0.68	3.32 ± 0.70	0.297	0.767
LVEF (%)		35.59 ± 3.92	35.52 ± 4.00	0.052	0.959
Serum Lp-PLA2 (U/L)		235.89 ± 16.24	218.36 ± 10.29	4.278	< 0.001
NLR		4.95 ± 0.38	4.44 ± 0.22	6.186	< 0.001
PLR		145.25 ± 12.27	133.81 ± 11.05	3.022	0.003

Table 3. Logistic regression analysis results of risk factors for HF in AMI patients.

Variable	B	Standard error	Wald	p	Odds ratio	95% confidence interval
NLR	0.157	0.048	10.698	0.001	1.170	1.065 - 1.285
PLR	0.026	0.009	8.346	0.004	1.026	1.008 - 1.045
Serum Lp-PLA2	0.015	0.007	4.592	0.032	1.015	1.001 - 1.029

Table 4. Value of serum Lp-PLA2, PLR, NLR, and combination of the three for predicting HF in AMI patients.

Item	Optimal cutoff-value	Area under the curve	Standard error	p	95% confidence interval
NLR	4.58	0.734	0.048	< 0.001	0.639 - 0.829
PLR	140.26	0.731	0.051	< 0.001	0.631 - 0.830
Serum Lp-PLA2	230.56 U/L	0.719	0.050	< 0.001	0.621 - 0.818
Combination	-	0.910	0.028	< 0.001	0.856 - 0.964

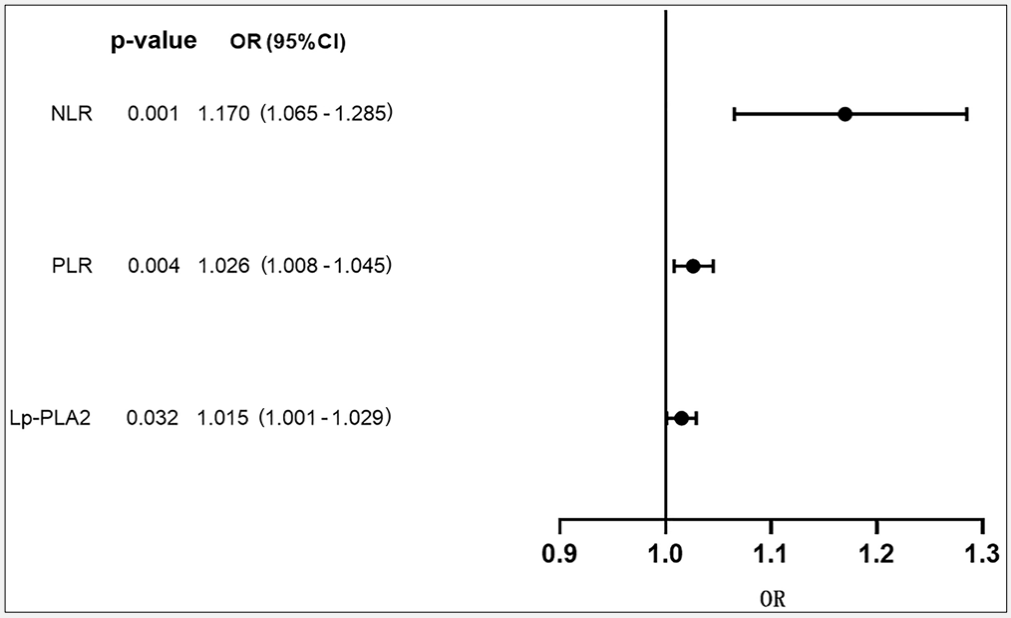

Figure 1. Forest plot of clinical characteristics based on multivariate logistic regression analysis.

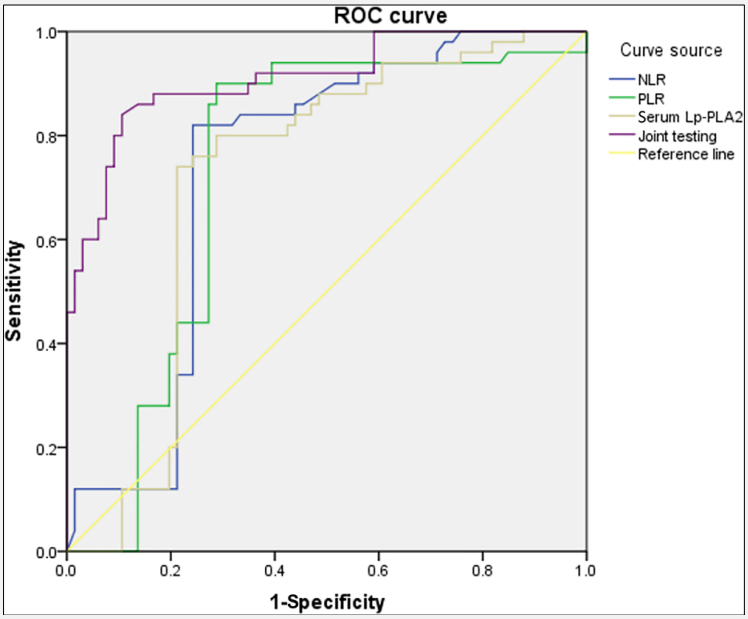

Figure 2. ROC curves for predicting HF in AMI patients.

lated that NLR, PLR, and Lp-PLA2 have the potential to participate in the onset and development of HF in AMI patients. In this study, by contrast to the healthy group, the case group exhibited increases in NLR, PLR, and serum Lp-PLA2 concentration, suggesting that these indicators were raised in AMI patients. Furthermore, according to multivariate logistic regression analysis, elevated NLR, PLR, and serum Lp-PLA2 concentration were risk factors for HF in AMI patients. The possible reasons are as follows:

First, Lp-PLA2 can hydrolyze oxidized phospholipids in coronary intima into two bioactive products (lysophosphatidylcholine and oxidized free fatty acids), which can induce endothelial infiltration of macrophages by stimulating endothelial cells to express adhesion molecules plus cytokines and trigger transformation of macrophages into foam cells by being phagocytized by macrophages, constantly damaging coronary vascular endothelial function and increasing the risk of HF [14,15]. In addition, a high expression of Lp-PLA2 can trigger an inflammatory cascade reaction during the atherosclerosis process, and then activated inflammatory cells can produce more Lp-PLA2, creating a self-reinforcing cycle, and ultimately leading to the deposition of more lysophosphatidylcholine and oxidized free fatty acids under coronary intima and promoting the development of plaque lipid core. As a result, a heavy heart burden is imposed on patients and cardiac vascular microcirculation is affected, causing myocardial ischemia and hypoxia, and continuously increasing the risk of HF [16, 17]. Second, as leucocyte-derived markers, NLR, and PLR can reflect ongoing non-specific inflammatory response and hypercoagulable state, which are independent risk factors for HF in AMI patients [18,19]. Therefore, elevated NLR and PLR indicate a stronger inflammatory response and higher risk of thrombosis in AMI patients, which may worsen coronary endothelial injury and myocardial damage, further increasing HF risk [20, 21]. As revealed by the present study, the AUCs of NLR, PLR, serum Lp-PLA2, and combination of the three in predicting HF in AMI patients were 0.734, 0.731, 0.719, and 0.910, respectively. It can be seen that the pre-PCI NLR, PLR, and serum Lp-PLA2 concentration should be closely monitored in AMI patients, and effective measures should be taken to decrease these indicators to reduce the risk of HF.

In conclusion, NLR, PLR, and serum Lp-PLA2 concentration are elevated in AMI patients, which are associated with HF. Combined determination of NLR, PLR, and serum Lp-PLA2 can effectively predict the risk of HF in AMI patients. Nevertheless, this study is limited. The data are based only on a small number of cases and therefore need confirmation in a larger study.

Declaration of Interest:

None.

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