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Original Article

Association between serum lipoprotein (a) levels and major adverse cardiovascular events in Chinese patients with ST-segment elevation myocardial infarction

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Abstract: Background: Our study investigated the association between circulating levels of lipoprotein (a) [Lp(a)] and the incidence of major adverse cardiovascular events (MACE). Materials and Methods: Primary percutaneous coronary intervention was conducted in 175 Chinese patients diagnosed with ST-segment elevation myocardial infarction (STEMI) and were followed prospectively for one year. Based on their serum Lp(a) levels, these patients were categorized into two groups: low Lp(a) group (<30 mg/dL) and high Lp(a) group (≥30 mg/dL). MACE was described as cardiovascular mortality/death, new onset of or worsening heart failure, coronary revascularization, non-fatal myocardial infarction, acute stent thrombosis, and serious arrhythmia. Results: One-year mortality was significantly greater in the high Lp(a) group (P=0.016). Receiver operating characteristic curve analysis identified that a value of 17.6 mg/dL of Lp(a) predicted MACE. Serum Lp(a) levels could predict MACE as shown by Multivirate Cox regression analysis (P<0.001). Kaplan-Meier MACE survival analysis showed that the risk of MACE was significantly greater among patients in the high Lp(a) group (log rank P<0.001). Conclusions: Serum levels of Lp(a) is a useful biomarker for STEMI patients undergoing percutaneous intervention and can be assessed for risk stratification in this patient population.

Keywords: Cardiac arrhythmia, cardiovascular abnormalities, percutaneous coronary intervention, myocardial infarction, heart failure

Introduction

Several genetic studies have suggested a causal role of lipoprotein (a) (Lp(a)) in atherosclerosis [1-3]. In a Canadian study, genetic polymorphisms in the LPA locus, mediated by Lp(a) levels, were associated with aortic-valve calcification and the incidence of clinical aortic stenosis in White Europeans, African Americans, and Hispanic Americans [4]. Clarke and colleagues identified two LPA variants that were correlated with increased levels of serum Lp(a) and also with an increased risk of coronary disease [3].

In 2008, a study investigated the risk of myocardial infarction (MI) corresponding with Lp(a) levels, discovering that the risk of MI increased 3-4 fold when levels of Lp(a) were extremely high [5]. Further, the study revealed a trend towards a stronger association between Lp(a) and cardiovascular (CV) events in patients with higher non-high-density lipoprotein cholesterol levels [6], a finding that has been observed for low-density lipoprotein (LDL) cholesterol in other studies [7, 8]. Professional societies, such as the European Atherosclerosis Society Consensus Panel and the National Lipid Association Biomarkers Expert Panel, have recommended screening for Lp(a) levels, in order to identify those at intermediate or high risk of cardiovascular disease (CVD). A target level of <50 mg/dL was established as a function of global cardiovascular risk, along with recommendations for intervention with niacin to lower Lp(a) and by extension CVD risk [9].

Major adverse cardiovascular events (MACE) are frequent in patients after MI, therefore novel therapeutic strategies could be helpful in

preventing their recurrence [10, 11]. The discovery of novel biomarkers could be valuable for screening and prevention of adverse clinical outcomes in post-MI patients. In this study we investigated the risk of MACE in Chinese patients with STEMI, based on their serum Lp(a) levels.

Materials and methods

Study population

One hundred and seventy five patients with STEMI were admitted to the Department of Cardiology of Wuhan General Hospital of the Guangzhou Military Command. 133 patients were allocated to low Lp(a) group (<30 mg/dL) and 42 patients in low Lp(a) group (≥30 mg/dL) as previously suggested by Konishi et al (2015) [12]. Approval was obtained from the ethics committee of the hospital as well as written informed consent from the patients, who were enrolled in this prospective study.

Inclusion criteria: Patients with STEMI, whose duration of symptoms was less than 24 hours and who were candidates for percutaneous coronary intervention (PCI) treatment were included in this prospective study. STEMI was diagnosed by ischemic-type chest pain, new ST-segment elevation measured from the J-point in ≥ 2 contiguous leads of at least 0.2 mV in leads V1, V2, and V3 or at least 0.1 mV in the remaining leads, and greater than 2-fold elevation of creatine kinase levels.

Exclusion criteria: Patients with severe liver disease, autoimmune disease, known malignancy, hematological disorders, severe valvular heart disease, known cases of hypothyroidism, inflammatory or infectious diseases, histories of bleeding diatheses, patients not undergoing PCI, or patients who presented more than 24 h after the onset of symptoms were excluded from the study.

Blood sample collection and serum Lp(a) measurements

Fasting venous blood samples were obtained within 24 h of primary PCI from all participants. The samples collected were centrifuged at 3000×*g* for 15 min at 4°C to isolate the plasma. Plasma samples were stored at -80°C for future analysis. The particle-enhanced turbidimetric immunoassay was used to determine Lp(a) concentrations [Lp(a) Latex (DAIICHI), Sekisui Medical Co., Ltd., Tokyo, Japan]. Apolipoprotein A and B were measured in a turbidimetric inhibition immunoassay, total cholesterol was measured by a cholesterol oxidase-peroxidase assay; low-density lipoprotein and high-density lipoprotein cholesterol were measured directly and triglyceride was measured by GPO-PAP (Olympus AU-5400 Automation Chemistry system instrument, Olympus Corporation, Tokyo, Japan).

Follow-up and assessment of clinical outcomes

Every three months, we did anthropometric measurements, clinical characteristics, and clinical events recording at planned follow-up clinic visits from questionnaires, medical records, and telephone calls for up to 1 year from the date of enrollment of each individual patient. The Ethics Committee of Wuhan General Hospital of Guangzhou Military Command approved the investigations and it conformed to the provisions of the Declaration of Helsinki.

Study endpoints

The MACE was described as cardiovascular mortality/death, the new onset of or worsening heart failure, coronary revascularization, non-fatal myocardial infarction, acute stent thrombosis, and serious arrhythmia. Serious arrhythmia was classified as ventricular fibrillation, ventricular flutter, persistent ventricular tachycardia, serious sinus bradycardia or AV block requiring a transient pacemaker, or atrial fibrillation with a mean heart rate ≥150 beats per minute.

Statistical analysis

Wilcoxon two-sample test and Chi-Squared test were applied to data analyses. Mean values ± standard deviation (SD) were used for continuous variables and numbers and/or percentages for categorical variables. To determine the individual predictors of MACE, a hazard ratio with 95% confidence interval (CI) was calculated through the use of a Cox proportional hazard model. For multivariate analysis, the variable in the univariate analysis with *P*-value <0.10 was incorporated and the analysis was adjusted for that variable. The optimal Lp(a) cut-off value for

Table 1. Baseline characteristics of the study groups

Characteristics	Low Lp(a) group (*n*=133)	High Lp(a) group (*n*=42)	*P* value
Men (%)	115 (86.5%)	30 (71.4%)	0.043*
Age (years)	59.55 ± 12.58	59.79 ± 14.90	0.919
BMI (Kg/m^2)	26.60 ± 2.71	25.88 ± 2.39	0.071
Smoking status (%)	66 (49.6%)	15 (35.7%)	0.162
Systolic blood pressure (mmHg)	131.73 ± 30.31	119.21 ± 27.99	0.019*
Diastolic blood pressure (mmHg)	79.08 ± 17.23	73.88 ± 15.47	0.123
Heart rate (beats per min)	78.07 ± 14.98	78.19 ± 17.37	0.549
Diabetes (%)	29 (21.8%)	12 (28.6%)	0.488
Hypertension (%)	56 (42.1%)	14 (33.3%)	0.406
Hyperlipidemia (%)	47 (35.3%)	19 (46.3%)	0.278
LAD lesion (%)	93 (69.9%)	27 (64.3%)	0.620
Multi vessel disease (%)	30 (22.6%)	13 (31.7%)	0.327
Anterior wall MI (%)	93 (69.9%)	27 (64.3%)	0.620
Hs CRP (mg/L)	4.70 ± 3.35	5.18 ± 3.33	0.464
S Cr (μmol/L)	90.82 ± 36.49	99.14 ± 56.11	0.387
cTnT (ng/ml)	4.80 ± 3.04	4.82 ± 3.19	0.919
NTproBNP (ng/L)	2534.81 ± 3678.13	3214.83 ± 6500.47	0.848
Medication			
Asprin	133 (100%)	42 (100%)	-
Statin	133 (100%)	42 (100%)	-
ACE inhibitors	120 (90.2%)	40 (95.2%)	0.487
Beta blockers	112 (84.2%)	36 (85.7%)	1.000
Clopidogrel	133 (100%)	42 (100%)	-

Data are expressed as means ± SD or percentages, *P<0.05 statistically significant. BMI; body mass index, LAD; left anterior descending, hs CRP; high-sensitivity C-reactive protein, S Cr; serum creatinine, cTnT; cardiac troponin T, NT pro BNP; N-terminal pro-brain natriuretic peptide.

Table 2. Serum lipid levels

Characteristics	Low Lp(a) group (*n*=133)	High Lp(a) group (*n*=42)	*P* value
TG (mmol/l)	1.41 ± 0.91	1.35 ± 0.90	0.692
TC (mmol/l)	4.94 ± 1.47	4.87 ± 1.21	0.507
LDL-C (mmol/l)	2.55 ± 0.74	2.62 ± 0.85	0.776
HDL-C (mmol/l)	1.14 ± 0.29	1.10 ± 0.32	0.289
Apolipoprotein A1 (g/L)	1.11 ± 0.28	1.12 ± 0.23	0.312
Apolipoprotein B (g/L)	1.09 ± 0.20	1.14 ± 0.19	0.183
Lp (a) (mg/dL)	10.82 ± 6.91	51.53 ± 21.68	<0.001*

Data are expressed as means ± SD. TG, triacylglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a). *P<0.05.

MACE prediction was identified through Receiver Operating Characteristic (ROC) curve analysis. A Kaplan-Meier survival analysis with a log-rank test was applied to determine the MACE-free rates in both groups. Odds ratios were calculated to compare the major clinical events between the two groups. All statistical analyses were performed using R version 3.2.1 software, and the *P* value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study groups

Table 1 shows the baseline characteristics of patients in the two groups. No statistically significant differences were found in age, body mass index, and known CVD risk factors, except that the proportion of male participants in the high Lp(a) group was lower (*P*=0.043). The patients in the high Lp(a) group also had lower systolic blood pressure (*P*=0.019). Medication profiles were similar in both groups. In order to confirm correctly allocation and establish the mean levels of Lp(a) in the high and low Lp(a) groups, we calculated

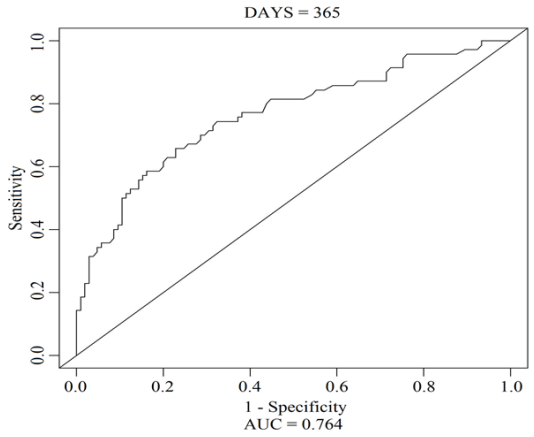

Figure 1. Receiver operating characteristic (ROC) curve showing the ability of Lp(a) to predict MACE.

average (mean ± SD) Lp(a) levels (**Table 2**). Patients in the high Lp(a) group had serum Lp(a) levels of 51.53 ± 21.68 mg/dL compared with (10.82 ± 6.91 mg/dL) in the low Lp(a) group (P<0.001). Other serum lipid levels showed no significant differences in the two groups.

Lipoprotein(a) levels and predictor of MACE

ROC curve analysis (**Figure 1**) identified that a value of 17.6 mg/dL of Lp(a) predicted MACE, with a maximum area under the curve of 0.764 (sensitivity 65.71% and specificity 77.14%). To identify individual predictors of MACE, univariate and multivariate Cox regression analyses were performed (**Table 3**). Univariate Cox regression analyses identified Lp(a) levels (P< 0.001), total cholesterol (P=0.008), smoking (P=0.001), systolic blood pressure (P<0.001), and diastolic blood pressure (P=0.001) as significant factors. Multivariate analysis, on the other hand identified only Lp(a) levels (P<0.001), smoking (P=0.033), and total cholesterol (P=0.013) as predictors of MACE.

The Kaplan-Meier survival analysis showed the that the risk of MACE was significantly greater for patients in high Lp(a) group (log rank P<0.001) (**Figure 2**). Similarly, cumulative hazard estimates based on the univariate Cox regression model showed the higher rate of MACE occurrence was associated with high Lp(a) group (P<0.001) (**Figure 3**).

Clinical events

Table 4 shows the comparisons of the clinical events or endpoints between the two groups. The cardiovascular mortality/death (P=0.016), the new onset or worsening heart failure (P=0.004), non-fatal MI (P=0.024), and coronary revascularization (P=0.043) were significantly greater in the high Lp(a) group. However, no statistically significant difference was found for serious arrhythmias between the two groups (**Table 4**).

Discussion

Circulating levels of Lp(a) are determined predominately by genetic variations in the LPA gene coding for apo (a) [13]. Variation in the LPA gene includes the kringle IV type 2 repeat polymorphism, which determines the size of the expressed apo (a). The size of this protein is inversely correlated with Lp(a) levels [13]. Two tag single-nucleotide polymorphisms, rs-10455872 and rs3798220 tagging the kringle IV type 2 polymorphism, were also strongly associated with Lp(a) levels [3].

Several research studies have implicated Lp(a) as major risk factor contributing to cardiovascular diseases, but the physiological role of LP(a) is not completely understood. According to some experimental reports, Lp(a) inactivates plasmin formation by restricting adherence of plasminogen to fibrin. Lp(a) also accelerates atherogenic and pro-inflammatory activities-atherothrombotic activity is markedly increased in the presence of Lp(a) and apo(a) [1, 14-19].

Multiple studies have suggested an association between elevated Lp(a) levels and CV risk in primary prevention [20-25]. A secondary prevention study revealed that the risk of long term adverse events in patients after coronary stenting were significantly correlated to Lp(a) levels [26]. Another study identified that baseline levels of Lp(a) (30 mg/dL) were associated with higher risk of sudden cardiac death in post MI patients, whereas only 7.9 mg/dL of Lp(a) was associated with cardiac death in patients with unstable angina [27]. Berq and colleagues reported the significant relationship between high Lp(a) levels and major coronary events and CV death [28]. Similarly, a study recording adverse clinical events in patients with unstable angina found a greater frequency of rehospitalization and increased risk of cardiac death and myocardial infarction amongst those with increased Lp(a) levels [26].

Table 3. Univariate and multivariate Cox proportional hazards regression analyses

	Univariate				Multivariate			
Variables	HR	95% CI		*p* value	HR	95% CI		*P* value
Male (%)	0.606	0.347	1.059	0.079	1.219	0.638	2.326	0.549
Age (years)	1.009	0.991	1.027	0.353	1.001	0.979	1.023	0.947
Smoking (%)	0.434	0.262	0.720	0.001*	0.532	0.298	0.951	0.033*
Hypertension (%)	0.830	0.511	1.348	0.452				
Hyperlipidemia (%)	1.580	0.773	3.217	0.206				
DM (%)	1.378	0.813	2.334	0.234				
SBP (mmHg)	0.983	0.975	0.991	<0.001*	0.991	0.974	1.008	0.307
DBP (mmHg)	0.974	0.960	0.989	0.001*	0.996	0.966	1.026	0.771
HR (beats/minute)	1.009	0.993	1.026	0.262				
TC (mmol/l)	1.228	1.054	1.429	0.008*	1.225	1.044	1.438	0.013*
LDLc (mmol/l)	1.187	0.889	1.584	0.245				
HDLc (mmol/l)	1.477	0.648	3.366	0.354				
TG (mmol/l)	0.997	0.971	1.024	0.823				
Lp(a) (mg/dL)	1.002	1.001	1.003	<0.001*	1.002	1.001	1.002	<0.001*
HsCRP (mg/L)	1.031	0.961	1.107	0.391				
SCr (μmol/L)	1.003	1.000	1.007	0.077	1.003	0.999	1.007	0.141
cTnT (ng/ml)	1.038	0.962	1.119	0.334				
BMI (Kg/m^2)	0.946	0.868	1.031	0.205				

HBP, high blood pressure; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; LDLc, low-density cholesterol; HDLc, high-density cholesterol; TG, triglyceride; Lp(a), lipoprotein(a), hsCRP, high-sensitivity C-reactive protein; SCr, serum creatinine; cTnT; cardiac troponin T, BMI, body mass index. *P<0.05 statistically significant.

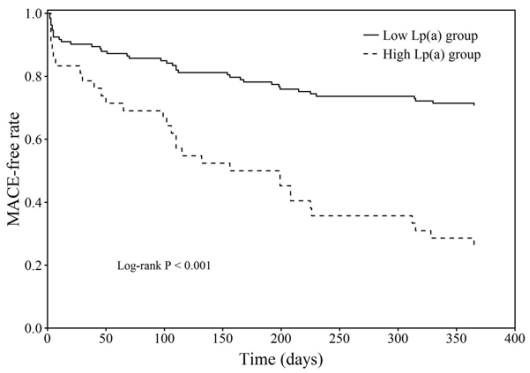

Figure 2. Kaplan-Meier survival analysis for MACE-free rate based on serum Lp(a) levels.

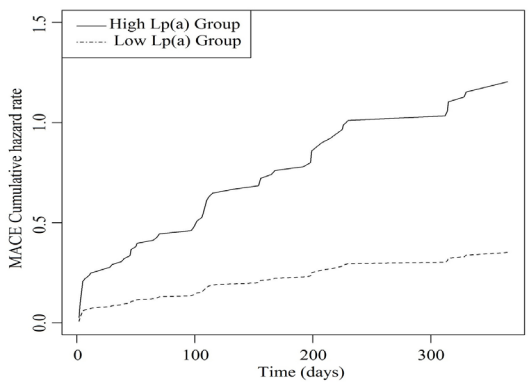

Figure 3. Cumulative hazard estimates based on univariate Cox regression model on the Lp (a) groups.

The randomized, blinded, placebo-controlled Heart and Estrogen/progestin Replacement Study revealed that Lp(a) was independently associated with recurrent coronary heart disease in postmenopausal women [29]. Lp(a) levels were correlated with baseline disease severity, disease progression, and event rate, but the risk as significantly reduced when LDL-cholesterol was reduced [30]. However, a small-scale study of post-coronary-artery bypass grafting (CABG) patients failed to show any association between Lp(a) levels and cardiac mortality or CHD events in younger subjects (<55 years) or subjects with high LDL [31]. Another study identified Lp(a) as a useful biomarker for predicting vascular events in non-diabetic patients with coronary artery disease [32]. Furthermore, Lp(a) could be useful in predicting cardiovascular events in patients with known atherothrombotic cardiovascular disease [33]. A study investigating the prognostic role of Lp(a) in Japanese STEMI patients suggested that Lp(a) levels was useful in predicting secondary vascular events [34]. Our results also indicated the Lp(a) levels as a predictor of MACE,

Table 4. Clinical events (composite and the components)

Major Events/Endpoints	Low Lp(a) group (*n*=133)	High Lp(a) group (*n*=42)	OR	95% CI		*P* value
Death	6 (4.5%)	7 (16.7%)	4.233	1.326	13.938	0.016*
Nonfatal myocardial infarction	5 (3.8%)	6 (14.3%)	4.267	1.219	15.584	0.024*
New onset or worsening heart failure	21 (15.8%)	16 (38.1%)	3.282	1.500	7.166	0.004*
Coronary revascularization	1 (0.8%)	3 (7.1%)	10.154	1.261	208.453	0.043*
Serious Arrhythmia	8 (6.0%)	6 (14.3%)	2.604	0.811	7.979	0.163
MACE	37 (27.8%)	30 (71.4%)	6.406	2.83	15.302	<0.001*

*The total MACE number is not equal to added components, few events may occur in individual patients. CV; cardiovascular, MACE; major adverse cardiovascular events. Data are expressed as percentages. **P*<0.05 statistically significant.

further confirming the prognostic role of circulating Lp(a) levels in this study population.

Limitations

Drawbacks to the current study include the relatively small sample size, short follow-up time period, and the fact that it was a single-center study. Future studies including larger sample sizes from different regions and a longer follow-up time period are needed to confirm our results.

Conclusions

This study found serum Lp(a) levels are a useful biomarker for identifying the risk of MACE in Chinese patients with STEMI and thus may assist in the monitoring and management of such patients, at least in the first year of treatment.

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Disclosure of conflict of interest

None.

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