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ORIGINAL ARTICLE

Impact of Lipoprotein (a) on Long-Term Outcomes in Patients With Acute Myocardial Infarction

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Background: Lipoprotein (a) (Lp(a)) is a complex circulating lipoprotein, and there is increasing evidence it is a risk factor for atherosclerotic cardiovascular disease (ASCVD). This study aimed to investigate the influence of Lp(a) serum levels on long-term outcomes after acute myocardial infarction (AMI).

Methods and Results: Between January 2015 and January 2018, we enrolled 262 patients with AMI who underwent coronary angiography within 24 h of the onset of chest pain and had available Lp(a) data enabling subdivision into 2 groups: high Lp(a) (≥32 mg/dL: n=76) and low Lp(a) (<32 mg/dL: n=186). The primary endpoint was major adverse cardiac events (MACE), which was defined as a composite of cardiac death, nonfatal MI, and readmission for heart failure. Multivariate Cox regression analysis was performed to identify the predictors of MACE. The incidence of MACE was significantly higher in the high Lp(a) group than in the low Lp(a) group (32.8% vs. 19.6%, P=0.004). Multivariate analysis showed that Lp(a) ≥32 mg/dL was an independent predictor of MACE (hazard ratio 2.84, 95% confidence interval 1.25–6.60, P=0.013).

Conclusions: High Lp(a) levels were associated with worse long-term outcomes after AMI, so Lp(a) may be useful for risk assessment.

Key Words: Acute myocardial infarction; Lipoproteins; Outcomes

Cardiovascular disease (CVD) is the leading cause of death worldwide.[1] Furthermore, patients who survive acute myocardial infarction (AMI) are reported to have poor clinical outcomes; even with optimal medical therapy, including aggressive lipid-lowering therapy, the incidence of cardiovascular events after AMI is high,[2–4] and was reported to be twice that in patients with coronary artery disease (CAD) within 1 year after AMI onset.[5] Thus, identification and management of the residual risk factors for major adverse cardiac events (MACE) after AMI is necessary because of the substantial residual CVD risk that remains after AMI despite optimal management.

Lipoprotein (a) (Lp(a)) is an apolipoprotein B-containing lipoprotein bound to a hydrophilic, highly glycosylated protein called apolipoprotein (a) (apo(a)). Lp(a) levels are approximately 70% to ≥90% genetically determined by the LPA gene.[6,7] Although high levels of Lp(a) are considered an independent and causal risk factor for atherosclerotic CVD (ASCVD) through mechanisms associated with increased atherogenesis, inflammation, and thrombosis,[8–14] the influence of Lp(a) on long-term outcomes after AMI remains unknown. Therefore, we aimed to assess the influence of Lp(a) on MACE, comprising cardiac death, nonfatal MI, and readmission for heart failure (HF), after AMI.

Methods

Study Participants

Between December 2015 and January 2018, 397 consecutive patients with AMI underwent primary percutaneous coronary intervention within 24 h of the onset of chest pain at Hiroshima City Hiroshima Citizens Hospital. We enrolled 262 of the surviving patients in whom Lp(a) was measured several days after AMI prior to their discharge. AMI was diagnosed as chest pain consistent with ongoing myocardial ischemia persisting for >30 min with concomitant ECG changes. Additionally, serum creatine kinase was measured every 3 h, and the peak creatine kinase level had to be more

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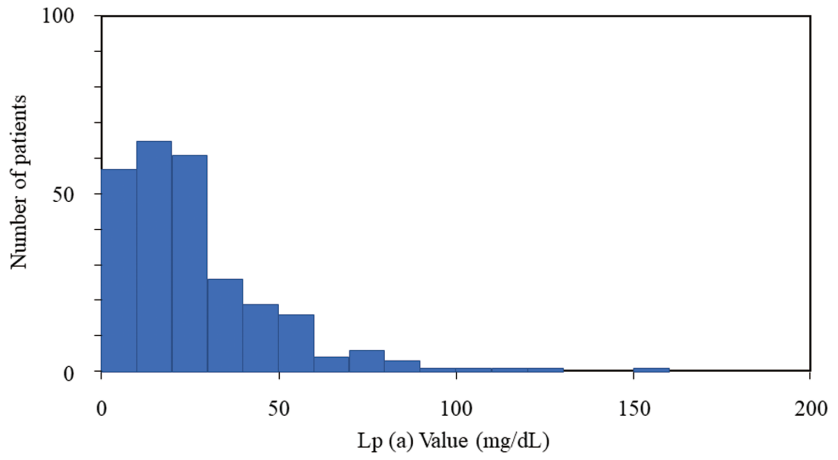

Figure 1. Histogram of lipoprotein (a) (Lp(a)) value. The median (interquartile range) value of Lp(a) was 21 (11–35.25) mg/dL, ranging from 1 to 158 mg/dL.

Table 1. Baseline Characteristics

	Low Lp(a) (n=186)	High Lp(a) (n=76)	P value
Age (years)	67±13	69±14	0.236
Male	141 (76%)	55 (72%)	0.563
Hypertension	123 (66%)	54 (71%)	0.471
Diabetes mellitus	89 (48%)	33 (43%)	0.490
Dyslipidemia	113 (61%)	40 (53%)	0.228
Current smoker	63 (34%)	26 (34%)	0.958
Previous MI	15 (8%)	9 (12%)	0.351
Atrial fibrillation	17 (9%)	15 (20%)	0.023
CKD	61 (33%)	29 (38%)	0.409
Killip Class 2–4	45 (24%)	23 (30%)	0.325
Initial TIMI 0–1 flow	127 (68%)	50 (66%)	0.697
Collateral circulation	37 (20%)	20 (27%)	0.282
Multivessel disease	63 (34%)	33 (44%)	0.127
Final TIMI 3	168 (92%)	72 (95%)	0.601
Peak CK	2,976±2,328	2,867±2,144	0.727
Hgb	14.4±1.9	14.1±1.9	0.152
eGFR	69±21	66±23	0.348
HbA1c	6.3±1.3	6.5±1.4	0.224
NT-proBNP	1,712±3,523	3,075±4,989	0.018
CRP	0.6±2.3	0.8±1.8	0.526
LVEF (%)	57±9	54±12	0.029
Aortic valve stenosis	5 (3%)	0 (0%)	0.326
Medications at discharge			
DAPT	171 (93%)	70 (92%)	0.797
Statins	174 (95%)	70 (92%)	0.571
ACEI/ARB	148 (80%)	56 (75%)	0.309
β-blocker	148 (81%)	63 (83%)	0.764
SGLT2-I	11 (6%)	4 (5%)	>0.999
MRA	23 (13%)	12 (16%)	0.447
Loop diuretics	31 (17%)	20 (27%)	0.072

Patients with high Lp(a) levels had a significantly higher prevalence of atrial fibrillation (AF), higher NT-ProBNP level on admission, and lower LVEF at discharge. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK, creatine kinase; CKD, chronic kidney disease; CRP, C-reactive protein; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; Lp, lipoprotein; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; SGLT2-I, sodium-glucose cotransporter-2; TIMI, Thrombosis in Myocardial Infarction.

Table 2. Serum Lipid and Lp(a) Levels

	Low Lp(a) (n=186)	High Lp(a) (n=76)	P value
Lp(a) (mg/dL)	15±8	54±23	<0.001
Total cholesterol (mg/dL)	181±57	187±54	0.424
Triglycerides (mg/dL)	117±81	110±67	0.521
HDL-C (mg/dL)	50±14	49±14	0.913
LDL-C (mg/dL)	118±46	125±38	0.285
Apolipoprotein A1 (mg/dL)	113±21	112±19	0.743
Apolipoprotein B (mg/dL)	88±25	97±20	0.007
Apolipoprotein E (mg/dL)	4.0±1.1	3.9±1.2	0.625

Patients with high Lp(a) levels had significantly higher apolipoprotein B levels than those with low Lp(a) levels. HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LDL-C, low-density lipoprotein cholesterol.

than twice the normal upper limit.

Emergency coronary angiography was performed as previously described[15] in multiple projections prior to reperfusion therapy, which was initiated immediately after diagnostic angiography, and its allocation was determined by the attending physician. The perfusion status of the infarct-related coronary artery was determined according to the Thrombolysis in Myocardial Infarction (TIMI) classification. The initial TIMI flow grade was assessed before the commencement of reperfusion therapy, and the final TIMI flow grade was assessed using the final angiography image. Coronary stenosis was visually assessed. Multivessel disease (MVD) was defined as the presence of lesions with ≥75% stenosis in ≥1 vessel exclusive of the infarct-related artery. Left main CAD ≥50% was considered to be at least 2-vessel disease. The extent of collateral circulation was evaluated on the pretreatment angiogram and classified using the method described by Rentrop et al.[16] Collateral circulation was considered present if the grade was ≥2.

Several days after the AMI, blood samples were obtained after overnight fasting according to a previously reported procedure.[17] Serum Lp(a) levels were measured using a turbidimetric immunoassay system (BML, Tokyo, Japan). Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) level >140 mg/dL, high-density lipoprotein cholesterol (HDL-C) levels <40 mg/dL, triglycerides (TG) level >150 mg/dL, or treatment with lipid-lowering medication. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 of body surface. The study protocol was reviewed and approved by the Ethics Committee of Hiroshima City Hiroshima Citizens Hospital, and informed consent was given by each patient.

The study patients were divided into 2 groups according to their serum Lp(a) levels: high Lp(a) (≥32 mg/dL: n=76) and low Lp(a) (<32 mg/dL: n=186).

The primary endpoint was MACE. Cardiac death was defined as death from pump failure, sudden cardiac death, or death from arrhythmia. HF was defined as new-onset or worsening of signs and symptoms that required urgent therapy and resulted in hospitalization.[18]

Statistical Analysis

Continuous variables are presented as mean±standard deviation (SD) and were analyzed using Student's t-test. Categorical variables are expressed as frequencies and were analyzed using the chi-square or Fisher's exact test. The receiver-operating characteristic (ROC) curve analyses were performed to determine the optimal cutoff values of Lp(a) for predicting MACE. Event curves after AMI were constructed using the Kaplan-Meier method and compared using the log-rank test. Risk factors associated with the outcomes were determined using univariate analysis. Variables with a P value <0.1 in the univariate analysis were included in the multivariate analysis. Cox proportional hazard regression was used to identify independent predictors of MACE, adjusting for baseline clinical and angiographic variables. We used the JMP statistical package (version 10.0.2 J, SAS Institute, Cary, NC, USA) for all the statistical tests. Statistical significance was set at P<0.05, and two-tailed tests were applied.

Results

The median (interquartile range) value of Lp(a) was 21 (11–35.25) mg/dL, ranging from 1 mg/dL to 158 mg/dL (**Figure 1**). The baseline clinical and angiographic characteristics are shown in **Table 1**. Patients with high Lp(a) levels had a significantly higher prevalence of atrial fibrillation (AF), higher N-terminal pro-hormone B-type natriuretic peptide (NT-ProBNP) level on admission, and lower left ventricular ejection fraction (LVEF) at discharge. **Table 2** shows the serum lipid levels of the 2 groups. Patients with high Lp(a) levels had significantly higher apolipoprotein B levels than those with low Lp(a) levels.

The median (interquartile range) follow-up period was 4.6 (1.9–5.9) years. No significant difference was noted in the follow-up period between the high Lp(a) and low Lp(a) groups (4.0±2.3 vs. 4.1±2.2, P=0.841). ROC curve analyses determined that the optimal cutoff Lp(a) value for predicting MACE was 32.0 mg/dL [area under the curve (AUC) 0.59, sensitivity=50%, specificity=74%]. The Kaplan-Meier curve for MACE is shown in **Figure 2**. The incidence of MACE was significantly higher in patients with high Lp(a) than in those with low Lp(a) (32.8% vs. 19.6%, P=0.004). **Table 3** shows the event rates for each component of MACE. Cardiac death (9.5% vs. 2.1%, respectively; P=0.033) and readmission for HF (19.4% vs. 5.9%, respectively; P=0.003) were significantly higher in patients with high Lp(a) than in those with low Lp(a), although the incidence of nonfatal MI was comparable between groups (18.0% vs. 15.6%, respectively; P=0.196).

Multivariate analysis showed that Lp(a) level ≥32 mg/dL was an independent predictor for MACE (hazard ratio (HR) 2.84, 95% confidence interval 1.25–6.60, P=0.013) (**Table 4**).

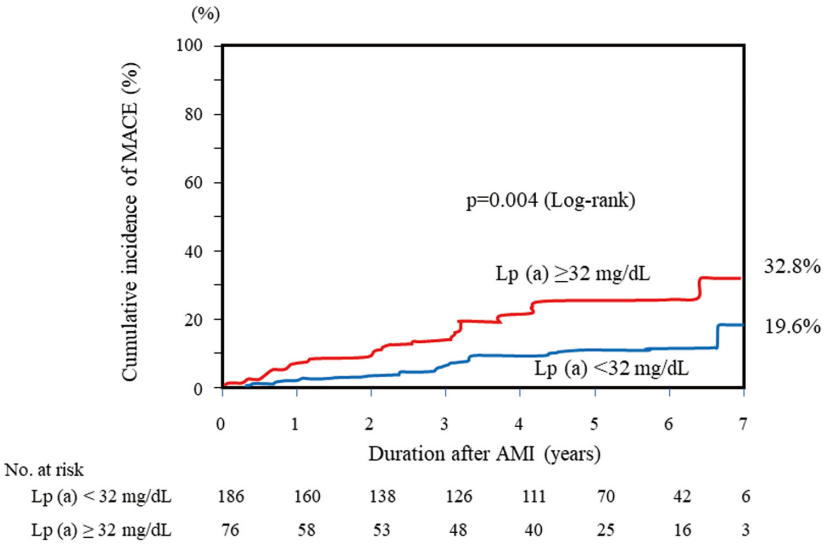

Figure 2. Kaplan-Meier curves for cumulative incidence of major adverse cardiac events (MACE) after acute myocardial infarction (AMI) for patients with high and low Lp(a) levels. The incidence of MACE was significantly higher in patients with high Lp(a) than in those with low Lp(a) (34.7% vs. 18.9%, P=0.004).

Table 3. MACE in Patients With High vs. Low Lp(a)

	Low Lp(a) (n=186)	High Lp(a) (n=76)	P value
Cardiac death (%)	2.1%	9.5%	0.033
Nonfatal MI (%)	15.6%	18.0%	0.196
Readmission for HF (%)	5.9%	19.4%	0.003

Cardiac death (9.5% vs. 2.1%, respectively; P=0.033) and readmission for HF (19.4% vs. 5.9%, P=0.003) were significantly higher in patients with high Lp(a) than in those with low Lp(a), although the incidence of nonfatal MI was comparable between groups. HF, heart failure; Lp(a), lipoprotein (a); MACE, major adverse cardiovascular events; MI, myocardial infarction.

Discussion

This study had 3 major findings: (1) patients with high Lp(a) levels had a significantly higher prevalence of AF, higher NT-ProBNP levels on admission, and lower LVEF at discharge; (2) patients with high Lp(a) levels had a significantly higher incidence of MACE, including cardiac death, nonfatal MI, and readmission for HF, than those with low Lp(a), and (3) Lp(a) level ≥32 mg/dL was an independent predictor for long-term MACE after AMI.

Lp(a) has long been recognized as a genetically determined, independent risk factor for ASCVD.[19] It can become trapped within the arterial wall where it participates in the initiation and progression of atherosclerotic plaques.[20] Particles of Lp(a) may be more atherogenic than other apolipoprotein B-containing lipoproteins, despite carrying less cholesterol, because of their long circulating half-life and high concentration of oxidized phospholipids. Mendelian randomization studies have consistently demonstrated a causal relationship between the plasma concentrations of Lp(a) and the risk of MI, stroke, peripheral arterial disease, and cardiovascular death.[21] Takahashi et al demonstrated that high Lp(a) levels are significantly associated with long-term cardiovascular outcomes, including all-cause death and MI, in patients with acute coronary syndrome, which is consistent with our findings.[22] However, the primary endpoint in our study included readmission for HF, which occurred significantly more frequently in patients with high Lp(a) levels, and to the best of our knowledge, we are the first to report this higher incidence. Kamstrup et al[23] demonstrated that elevated Lp(a) levels were associated with increased risk of HF, consistent with a causal association in the general population. A total of 63% of HF risk was mediated by combined MI and aortic valve stenosis.[23] After exclusion of individuals with MI or aortic valve stenosis, risk estimates were attenuated to approximately two-thirds; however, the association between Lp(a) and HF remained significant. Similarly, the Atherosclerosis Risk in Communities study demonstrated that increased Lp(a) levels were associated with an increased risk of incident HF hospitalization.[24] After excluding patients with a history of MI, the relationship was rendered non-significant. These findings suggest that Lp(a) may be useful for stratifying the risk of HF, especially in patients with AMI. The mechanism behind the atherosclerotic stenotic effect of high Lp(a) levels may be their effect on arterial stiffness, including vascular noncompliance in the aorta, which would increase afterload, and has been strongly associated with an increased risk of HF.[25]

Patients with high Lp(a) levels had a significantly higher prevalence of AF, which might have led to the higher incidence of readmission for HF in this study. Previous studies have shown that patients with AF have a greater risk of HF.[26,27] Using epidemiologic and genetic analyses, Shemirani

Table 4. Cox Proportional Hazard Regression Analyses for Predictors of MACE

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
High Lp(a)	2.65	1.31–5.33	0.007	2.84	1.25–6.60	0.013
Age: 1-year increase	1.03	1.00–1.06	0.058	1.01	0.97–1.06	0.647
Sex (male)	1.33	0.58–3.57	0.519			
Hypertension	1.89	0.86–4.73	0.117			
Diabetes mellitus	1.37	0.68–2.81	0.375			
Dyslipidemia	0.74	0.37–1.51	0.405			
Current smoker	1.32	0.64–2.66	0.444			
Previous MI	4.20	1.66–9.35	0.004	1.93	0.53–5.67	0.291
Atrial fibrillation	2.03	0.81–4.46	0.123			
CKD	1.51	0.73–3.04	0.261			
MVD	1.32	0.64–2.65	0.441			
Killip 2–4	2.89	1.42–5.83	0.004	2.18	0.84–5.54	0.109
LDL-C: 1 mg/dL increase	1.00	0.99–1.00	0.294			
HDL-C: 1 mg/dL increase	1.00	0.97–1.02	0.730			
Triglyceride: 1 mg/dL increase	0.99	0.99–1.00	0.047	1.00	0.99–1.00	0.210
HbA1c: 1% increase	1.24	1.00–1.47	0.051	1.34	1.00–1.72	0.0502
NT-proBNP: 1 pg/mL increase	1.00	0.99–1.00	0.002	1.00	0.99–1.00	0.688
Hgb: 1 g/dL increase	0.83	0.68–1.02	0.074	1.05	0.79–1.40	0.732
β-blocker use	0.83	0.36–2.25	0.697			
Acei/ARB use	0.42	0.20–0.90	0.027	0.86	0.32–2.59	0.770
Statin use	0.42	0.15–1.77	0.205			
Loop diuretic use	3.35	1.61–6.76	0.002	1.24	0.38–3.76	0.711
MRA use	2.46	1.04–5.26	0.042	1.20	0.37–3.59	0.755
SGLT2-I use	0.54	0.03–2.51	0.500			
LVEF: 1% increase	0.95	0.91–0.98	0.002	0.98	0.93–1.03	0.377

Multivariate analysis showed that Lp(a) level ≥35.25 mg/dL was an independent predictor for MACE (hazard ratio 2.46, 95% confidence interval (CI) 1.06–5.66, P=0.037). Hgb, hemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-hormone B-type natriuretic peptide.

et al showed a potentially causal role for Lp(a) in the risk of incident AF in population-scale cohorts that was independent of its effect on ASCVD.[28] Lp(a) particles have additional thrombogenic and inflammatory properties that could provide other mechanisms, independent of ASCVD, by which the effect on AF is mediated.

Therapies with Lp(a)-lowering effects, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or niacin, have been developed. Small interfering ribonucleic acid (RNA) therapeutics[29] and RNA therapeutics that specifically target the hepatic synthesis of apolipoprotein (a) are under development, and include the antisense oligonucleotide, pelacarsen, which is currently being tested in the Lp(a)HORIZON trial.[30] Mendelian randomized studies have demonstrated that elevated Lp(a) levels may be causally associated with an increased risk of atherosclerotic cardiovascular events. Although randomized clinical trials of lipid-lowering therapies that reduced Lp(a) by 20–25% have showed a reduction of the risk of cardiovascular events, it remains unknown whether Lp(a)-lowering therapy reduces the risk of atherosclerotic cardiovascular events beyond what would have expected from the corresponding reduction in low-density lipoprotein and other apolipoprotein B-containing lipoproteins alone.[8,10,31–34] Large-scale randomized controlled studies are warranted to confirm the clinical benefits of Lp(a)-lowering therapy and to identify which patients are likely to benefit most.

Study Limitations

First, this was a single-center retrospective observational study with a small sample size. Second, although we performed multivariate analysis to confirm the independent predictors of long-term outcomes after AMI, other unknown confounding factors might have influenced the outcomes. Third, the samples were obtained 4 days after AMI because almost all patients in this study were discharged within 7 days after AMI. Some reports suggest that the Lp(a) level peaks on the day 5 and then returns to the initial value within 1 week;[35,36] however, Slunga et al showed no clear evidence of elevation in Lp(a) level in the acute phase in a study of 32 AMI patients.[37] Further investigations are needed to confirm the appropriate timing to evaluate the serum Lp(a) level after AMI.

Conclusions

The present study demonstrated that a high Lp(a) level was an independent predictor of long-term MACE after AMI. Measurement of Lp(a) levels after AMI may enable us to identify high-risk patients.

Conflict of Interest Disclosures

There are no conflicts of interest to declare.

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IRB Information

The study protocol was reviewed and approved by the Ethics Committee of Hiroshima City Hiroshima Citizens Hospital. Reference number: 2022-39.

Data Availability

The identified participant data will not be shared.

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