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Original Article

Serum lipoprotein(a) predicts 1-year major cardiovascular events in patients after percutaneous coronary intervention

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Abstract: Background: Lipoprotein(a) [Lp(a)], which is predictive of coronary heart disease (CHD), plays an important role in the pathogenesis of atherosclerosis. This study aimed to evaluate the association of Lp(a) with major adverse cardiovascular events (MACEs) and readmission in individuals who had undergone a percutaneous coronary intervention (PCI). Methods: A total of 1,938 patients with CHD who had undergone a PCI from January 2010 to December 2018 were assigned to three groups based on Lp(a) level. Follow-up was performed to assess the 1-year occurrence of MACEs and readmission. Results: Kaplan-Meier survival curves showed that the cumulative hazard incidence rate of MACEs and repeat PCI (re-PCI) significantly increased with Lp(a) level. Multivariate Cox proportional hazards regression analysis further confirmed Lp(a) as a significant independent predictor of MACEs. The area under the curve of the complex index risk score was significantly larger than those of other independent indicators. In individuals with low-density lipoprotein-cholesterol (LDL-C) levels either below 70 mg/dL or between 70 mg/dL and 100 mg/dL, Lp(a) was associated with increased rates of MACEs and readmission. In addition, a nomogram was constructed to predict 1-year MACE. Conclusions: High Lp(a) levels may be a residual risk factor for MACEs in individuals with LDL-C levels under 100 mg/dL. Additionally, the built nomogram could predict 1-year MACEs with high accuracy. Lp(a) independently predicts 1-year MACEs, indicating its importance in risk assessment and the selection of clinical strategies in patients who have undergone a PCI.

Keywords: Lp(a), percutaneous coronary intervention, major cardiovascular event, readmission

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the most prevalent cause of coronary heart disease (CHD) and represents the top cause of mortality in humans around the world [1]. Dyslipidemia constitutes the core mechanism of ASCVD occurrence and development, and is listed as a correctable risk factor [2]. Low-density lipoprotein-cholesterol (LDL-C), an important blood lipid index, is well known as the primary target of blood lipid treatment and control in ASCVD. However, randomized controlled trials and real-world studies have shown there are still residual risks of cardiovascular events even after LDL-C levels are controlled within the ideal range based on current guidelines [3, 4].

Lipoprotein(a) [Lp(a)] is a new target for blood lipid intervention that has attracted attention because of evidence supporting its use as a medicinal target [5]. Lp(a) is an LDL-like molecule synthesized by hepatocytes that promotes atherosclerosis, thrombosis, and foam cell formation by its deposition in the arterial intima [6]. Recently, Lp(a) was recognized as one of the most significant cardiovascular risk factors for cardiovascular disease (CVD) [7]. Substantial evidence from studies including epidemiological study [8], meta-analysis [9], genome-wide study [10], and Mendelian randomization

study [11] suggested that high Lp(a) levels increase CVD risk. Studies have confirmed that plasma Lp(a) levels could independently predict ASCVD as well as calcific aortic valve disease [12]. Lp(a) levels above 30 mg/dL are reported to significantly increase disease risk; thus, reducing Lp(a) levels is an important strategy for reducing the risks of ASCVD and calcific aortic valve disease and improving prognosis [13, 14].

A percutaneous coronary intervention (PCI) is necessary for CHD diagnosis and treatment, to improve patient prognosis [15]. Although employing a PCI has multiple advantages in diagnosis and treatment, it cannot reverse the pathology of atherosclerosis and does not eliminate the occurrence of cardiovascular events. A high rate of recurrent adverse cardiovascular events, including myocardial infarction, angina, heart failure, and sudden cardiac death, occur in patients with CHD after a PCI, seriously impacting their quality of life.

Although the close association of Lp(a) and cardiovascular risk has been reported, the association of serum Lp(a) levels and cardiovascular outcomes, such as coronary artery stent restenosis within 1 year in the Chinese population, has not been assessed. Therefore, a retrospective trial was carried out to evaluate the association of baseline serum Lp(a) levels and MACEs within 1 year in patients administered a PCI.

Methods

Study design

The present retrospective observational trial was approved by the Clinical Research Ethics Committee of Shandong Provincial Hospital, which is affiliated with Shandong First Medical University (SWYX No. 2020-170). The procedures of this study followed the "Declaration of Helsinki". The requirement for informed consent was waived because of the retrospective nature of the trial. The study population was selected from the PCI registry of Shandong Provincial Hospital. Inclusion criteria were patients of at least 18 years of age who had undergone a PCI at Shandong Provincial Hospital with a follow-up 1 year after the PCI at Shandong Provincial Hospital. The exclusion criteria included thyroid disease, infectious disease, immune system disease, moderate to severe rheumatic valvular disease, a recent history of anti-inflammatory or antioxidant use, liver or kidney dysfunction, serious systemic diseases, hematological diseases, mental illnesses, and incomplete patient data. Between January 2010 and December 2018, 1,938 individuals who had undergone a PCI were recruited for the study. This trial was registered at http://www.chictr.org.cn (Chinese clinical trial registry; No. ChiCTR22000597-23). Patients were assigned to three groups based on Lp(a) level: low [Lp(a) < 10.9 mg/dL, 647 cases], mid [10.9 mg/dL < Lp(a) < 27.3 mg/dL, 647 cases], and high [27.3 mg/dL < Lp(a) < 181.7 mg/dL, 644 cases].

Data collection

Peripheral blood samples were collected upon admission, after overnight fasting. All biochemical measurements were conducted in the clinical testing center of Shandong Provincial Hospital. The main testing procedure followed the manufacturer's instructions. Demographic data including age, gender, smoking and drinking status, past medical history, coronary angiography and surgery data, and echocardiography and medication history were retrieved from medical records or collected during follow-up. Plasma levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, Lp(a), creatinine, uric acid, Hcy, and fasting blood glucose (FBG) were quantified using standard laboratory procedures in the clinical testing center. Follow-up duration was from the date of discharge until 1 year after the PCI and was conducted by outpatient examination and/or phone interviews.

Study endpoints

The primary study endpoint was a major adverse cardiovascular event (MACE), including recurrent angina, acute myocardial infarction, severe cardiac arrhythmia, heart failure, nonfatal ischemic stroke, transient ischemic attack, stent restenosis, and death from cardiovascular causes. The secondary outcome was the readmission within 1 year, defined as readmission for all causes from the first admission. All events were evaluated by cardiologists independently. Data extraction was performed by two investigators.

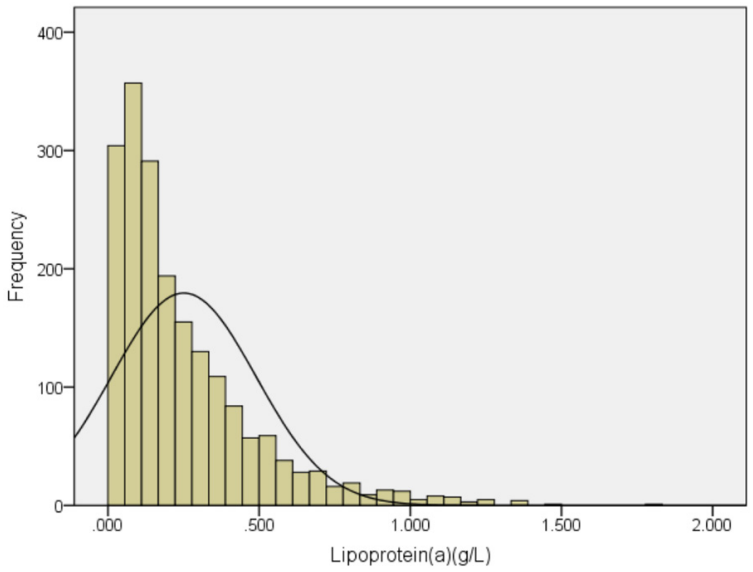

Figure 1. Distribution of lipoprotein(a) levels in the study population.

Statistical analysis

R 3.6.3, Python 3.7 and SPSS 20.0 were utilized for data analysis. Continuous data were presented as mean ± SD or median with interquartile range (IQR), and differences were assessed by one-way ANOVA when normally distributed, Kruskal-Wallis tests for nonparametric variables. Categorical data were expressed as percentages and compared using the χ^2 test. Kaplan-Meier curve analysis was carried out to calculate the cumulative incidence over time, and the log-rank test was utilized for comparisons. Univariate analysis was used to evaluate several values. The association of Lp(a) with incidence of MACEs within 1 year of the PCI was assessed by Cox regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A predictive nomogram was built for predicting MACEs, and its predictive accuracy was measured by the concordance index. Two-sided *P* values less than 0.05 indicated significance.

Results

Study population and Lp(a) distribution

The median level of Lp(a) was 0.170 g/L (IQR = 0.083-0.345 g/L) (**Figure 1**). The baseline clinico-demographic and biochemical characteristics of the patients are summarized in **Table 1**. The patients were assigned to three groups based on Lp(a) levels (< 10.9 mg/dL in tertile 1, 10.9 mg/dL < Lp(a) < 27.3 mg/dL in tertile 2, and 27.3 mg/dL < Lp(a) < 181.7 mg/dL in tertile 3). Significant differences existed in systolic (P = 0.002) and diastolic (P = 0.010) blood pressure levels among the three groups. In addition, patients with Lp(a) levels in tertile 3 had elevated total cholesterol, triglyceride, and LDL-C levels; LDL-C/high-density lipoprotein-cholesterol (HDL-C) and apolipoprotein B (ApoB)/ApoA ratios (P < 0.001); and HDL-C levels (P = 0.005) compared to patients with Lp(a) levels in tertiles 1 and 2.

Predictive value of Lp(a) in incidences of MACEs

As patients underwent angiography for cardiac symptoms, we assessed the association of Lp(a) with the incidence of MACEs, readmission, repeat PCI (re-PCI), and re-angiography. **Figure 2** shows the cumulative HRs for the incidence of MACEs, readmission, re-PCI, and re-angiography at 1 year. The log-rank test revealed overt disparities among the Lp(a) tertile groups in terms of the incidence of MACEs (P = 0.028, **Figure 2A**), re-PCI (P = 0.038, **Figure 2C**), and re-angiography (P = 0.018, **Figure 2D**). The readmission rates were similar for all patients, regardless of Lp(a) level (P = 0.302, **Figure 2B**). Next, to observe whether Lp(a) independently predicted the incidence of MACEs, we performed a univariable Cox proportional hazard regression analysis. Lp(a) as a continuous variable was related to incidence of MACEs (HR = 1.781, 95% CI = 1.136-2.793; P = 0.012). Compared to patients with the lowest Lp(a) levels, there was an association between patients with the highest levels of Lp(a) (tertile 3; HR = 1.407, 95% CI = 1.051-1.884; P = 0.022) and incidence of MACEs, unlike patients with moderate Lp(a) levels (tertile 2; HR = 1.015, 95% CI = 0.743-1.388; P = 0.924) (data not shown). After adjusting for other clinical covariates, Lp(a) level was able to predict the incidence of MACEs in a significant fashion (HR

Table 1. Baseline characteristics of patients

Variable	Lipoprotein(a)			*P* value
	Tertile 1 (n = 647)	Tertile 2 (n = 647)	Tertile 3 (n = 644)	
Age, y	60.42±9.89	60.41±9.50	60.34±10.23	0.988
Male, n (%)	463 (71.6)	467 (72.2)	431 (66.9)	0.079
Heart rate, bpm	69.38±11.04	69.20±11.35	69.83±10.92	0.585
Respiratory rate	17.89±1.33	17.93±1.43	18.02±1.44	0.218
SBP, mmHg	135.67±19.30	132.29±17.77	135.34±19.61	0.002
DBP, mmHg	79.43±12.14	77.87±11.86	79.81±12.37	0.010
Hospital day, d	9.67±4.30	9.84±4.55	9.70±5.57	0.788
Medical history, n (%)				
Hypertension	389 (60.1)	388 (60.0)	396 (61.5)	0.828
Diabetes	220 (34.0)	211 (32.6)	184 (28.6)	0.093
Dislipidemia	20 (3.1)	16 (2.5)	26 (4.0)	0.274
Previous PCI	47 (7.3)	44 (6.8)	53 (8.2)	0.607
Myocardial infarction	231 (35.7)	250 (38.6)	263 (40.8)	0.163
Procedural characteristics, n (%)				
Multivessel	596 (92.1)	585 (90.4)	592 (91.9)	0.487
Vasoocclusion	166 (25.7)	192 (29.7)	182 (28.3)	0.263
Stent number	1.75±0.87	1.66±0.85	1.78±0.94	0.040
Risk factor, n (%)				
Smoking	318 (49.2)	330 (51.0)	306 (47.5)	0.455
Drinking	297 (45.9)	324 (50.1)	292 (45.3)	0.176
Biochemistry				
TC, mmol/L	4.41±1.15	4.40±1.08	4.71±1.16	< 0.001
TG, mmol/L	1.87±1.30	1.65±0.87	1.68±1.01	< 0.001
LDL-C, mmol/L	2.64±0.85	2.65±0.84	2.94±0.95	< 0.001
HDL-C, mmol/L	1.08±0.26	1.12±0.25	1.13±0.26	0.005
LDL-C/HDL-C ratio	2.55±0.98	2.47±0.91	2.73±1.06	< 0.001
Lp(a), g/L	0.06 (0.03-0.08)	0.17 (0.14-0.22)	0.43 (0.35-0.61)	< 0.001
ApoA-I, g/L	1.11±0.20	1.11±0.20	1.12±0.20	0.434
ApoB, g/L	0.91±0.30	0.92±0.30	1.00±0.33	< 0.001
ApoB/ApoA-I ratio	0.84±0.29	0.85±0.31	0.92±0.34	< 0.001
Creatinine, μmmol/L	71.71±17.45	71.99±15.68	71.41±16.25	0.817
Uric acid, μmmol/L	336.92±87.58	330.98±82.88	333.933±82.97	0.451
Hcy, μmmol/L	15.98±7.82	15.09±7.80	15.23±6.72	0.071
FBG, mmol/L	6.37±1.82	6.40±1.93	6.38±2.01	0.956
Discharge medication, n (%)				
Aspirins	643 (99.4)	645 (99.7)	639 (99.2)	0.524
Statins	606 (93.7)	602 (93.0)	603 (93.6)	0.879
Clopidgrel/Ticagrelor	633 (97.8)	637 (98.5)	630 (97.8)	0.647
β-blockers	532 (82.2)	530 (81.9)	527 (81.8)	0.981
Diuretic	94 (14.5)	112 (17.3)	104 (16.1)	0.391

Data are mean ± SD, median (interquartile range), or number (%). SBP, systolic blood pressure; DBP, diastolic blood pressure; PCI, percutaneous coronary intervention; multivessel, number of diseased blood vessels greater than or equal to two; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; Lp(a), lipoprotein(a); Hcy, homocysteine; FBG, fasting blood glucose.

= 1.854, 95% CI = 1.163-2.955; P = 0.009) in model 1. There was still a relationship between patients with the highest levels of Lp(a) (tertile 3) and the incidence of MACEs (HR = 1.391,

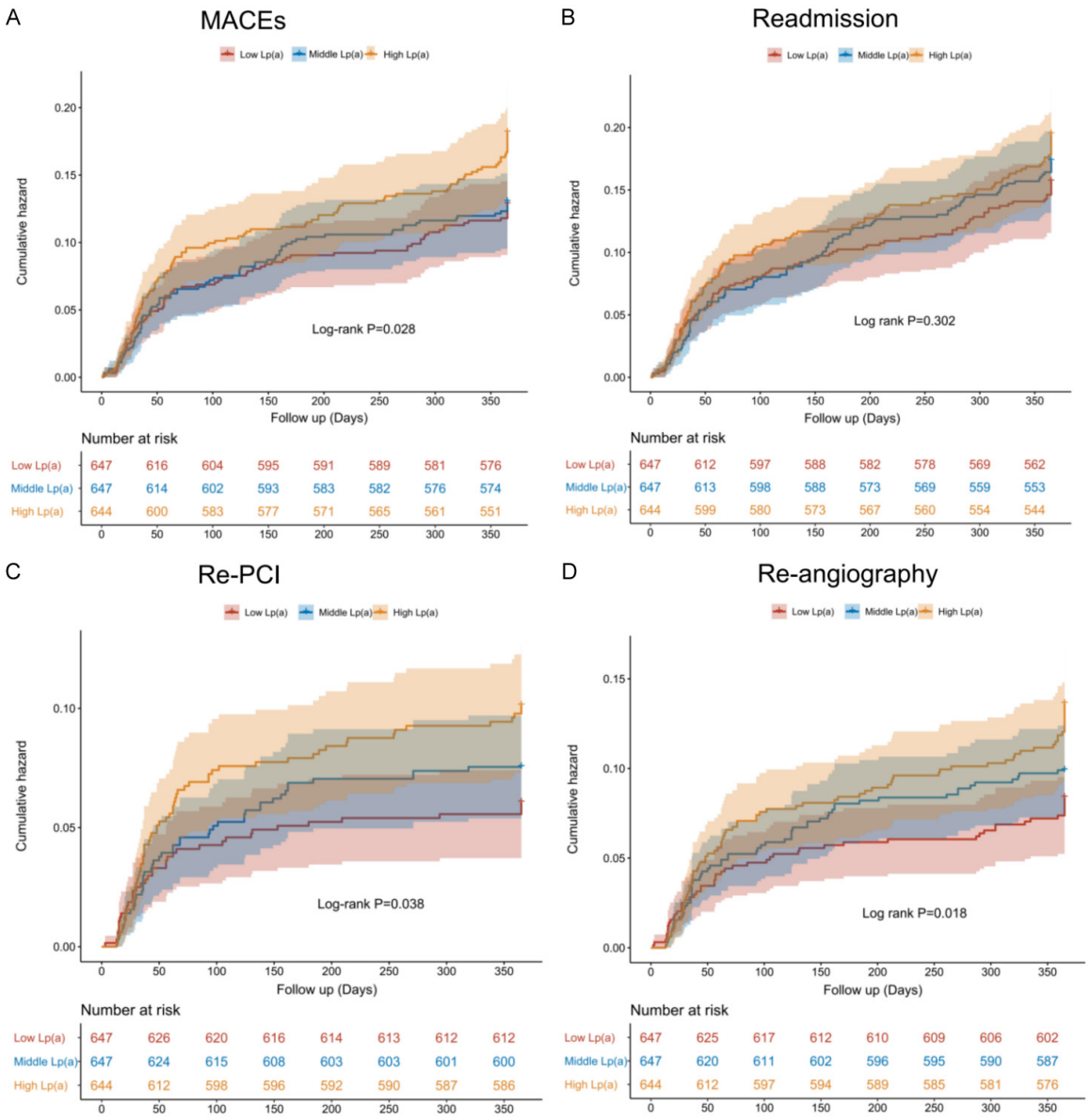

Figure 2. Cumulative hazard curves for incidence of MACEs, readmission rate, re-PCI, and re-angiography according to the tertile of Lp(a) at the 1-year follow-up. A. Cumulative HRs of incidence of MACEs. B. Cumulative HRs of readmission rate. C. Cumulative HRs of re-PCI. D. Cumulative HRs of re-angiography. Major adverse cardiovascular events (MACEs), percutaneous coronary intervention (PCI), hazard ratios (HRs).

95% CI = 1.033-1.871; P = 0.029) in model 2. **Table 2** summarizes the data from the multivariate analysis. The area under the curve of the complex index was significantly larger than those of the other indicators, indicating that the Cox model had better predictive power than other single indicators (Delong test P < 0.001) (**Figure 3A**). The same predictive power was proved by DCA (Decision curve analysis) (**Figure 3B**).

Subgroup analysis

The results of the exploratory subgroup analyses of relationships between different levels of LDL-C and the occurrence of MACEs and readmission are shown in **Figure 4**. Of the entire patient population, cases with LDL-C levels below 70 mg/dL had a 7.3-fold higher risk of MACEs occurrence (HR = 7.291, 95% CI = 1.852-28.702; P = 0.004) and a 4.1-fold higher

Table 2. Multivariable analysis of one-year occurrence of MACEs

Variable	Z	HR	95% CI	*P* value
Model 1: Lp(a) as a continuous variable				
Lp(a)	2.594	1.854	1.163-2.955	0.009
Vaso-occlusion	5.736	2.052	1.605-2.623	< 0.001
Statins	-5.804	0.364	0.258-0.512	< 0.001
Aspirins	-3.334	0.221	0.091-0.537	0.001
Model 2: Lp(a) as a categorical variable				
Low Lp(a)		1.0 (Reference)	1.0 (Reference)	
Medium Lp(a)	-0.133	0.979	0.714-1.341	0.894
High Lp(a)	2.177	1.391	1.033-1.871	0.029
Vaso-occlusion	5.799	2.07	1.619-2.648	< 0.001
Statins	-5.77	0.366	0.26-0.515	< 0.001
Aspirins	-3.194	0.235	0.097-0.572	0.001

In models 1 and 2, the adjusted covariates included age, sex, TC, TG, FBG, and multivessel disease. CI, confidence interval; HR, hazard ratio; the remaining abbreviations as in **Tables 1** and **2**.

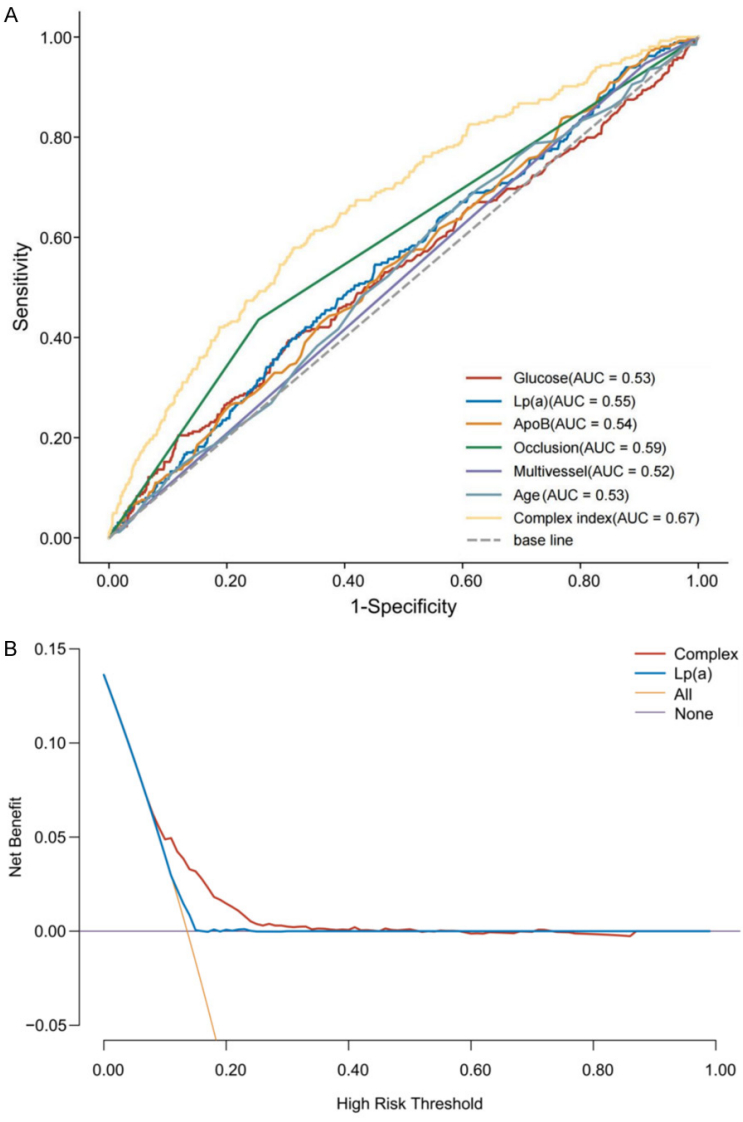

Figure 3. A. Multiple receiver operating characteristic curves for the examined factors. AUC, area under the curve. B. Decision curve analysis.

risk of readmission occurrence (HR = 4.072, 95% CI = 1.048-15.812; P = 0.043) for every SD increment in Lp(a) level. Individuals with LDL-C levels between 70 mg/dL and 100 mg/dL had a 2.7-fold higher risk of MACE occurrence (HR = 2.668, 95% CI = 1.307-5.443; P = 0.007) and a 2.3-fold higher risk of readmission occurrence (HR = 2.301, 95% CI = 1.153-4.594; P = 0.018) for every SD increment in Lp(a) level.

Prognostic nomogram for incidence of MACEs

A nomogram was built using the multivariable Cox regression for predicting the incidence of MACEs based on significant independent factors along with age and gender (**Figure 5**). Diverse prognostic factors had different risk levels, which could be determined by drawing a vertical line upward to the

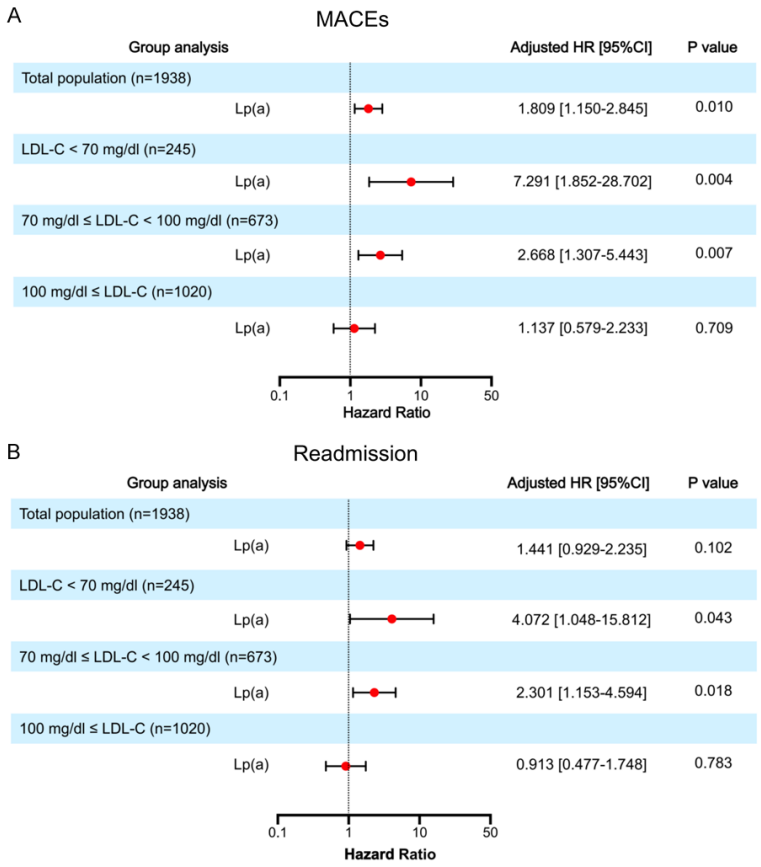

Figure 4. Subgroup analysis by forest plots. A. Risk of MACEs incidence associated with Lp(a) level in stratified samples for different LDL-C groups, adjusted for age and gender. B. Risk of readmission rate associated with Lp(a) level in stratified samples for different LDL-C groups, adjusted for age and gender. Major adverse cardiovascular events (MACEs), low-density lipoprotein-cholesterol (LDL-C).

axis with "dots" through the values for the prognostic factors. The nomogram can be used to assess the incidence of MACEs 1 year after a PCI for a patient from the sum of risk points.

Discussion

Coronary heart disease (CHD) threatens human health more than any other disease. Previous studies have shown that aging, hypertension, elevated LDL-C levels, low HDL-C levels, smoking, and diabetes are all high-risk factors for CHD. LDL-C has been known as the primary target of ASCVD for blood lipid intervention. The majority of patients with CHD after PCI achieved a target LDL-C level below 70 mg/dL after lipid-lowering therapy using statins and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. However, some of these patients still had adverse cardiovascular events after a PCI, including myocardial infarction, stroke, restenosis, and even cardiovascular death [16]. Previous evidence suggests the residual risk after a PCI is also related to increased serum Lp(a) levels [17], but the relationship between Lp(a) levels and clinical outcome after a PCI still deserves further investigation.

Lp(a) is one of the new targets for lipid intervention, accruing more evidence and attention in recent years. The risk of myocardial infarction and rates of cardiovascular and all-cause death increase with elevated Lp(a) level. However, compared to other blood lipid indicators such as HDL-C and LDL-C, plasma Lp(a) levels are affected by genetic factors and are not sensitive to lifestyle changes, including diet and exercise. Plasma Lp(a) levels are generally elevated in the population and vary greatly among individuals [18], findings that are consistent with those of the present study. We also demonstrated that Lp(a) levels in patients with CHD after a PCI positively correlated with the occurrence of MACEs within 1 year. The multivariate Cox regression analysis showed that Lp(a) level was an independent predictor of 1-year MACE incidence in patients with CHD after a PCI.

Current guidelines propose reducing LDL-C levels to prevent the incidence of ASCVD, but clinical trials have noted a residual ASCVD risk even after aggressive LDL-C level reduction. Reduced levels of inflammatory markers, including such non-LDL-C lipid indices as triglycerides, triglyceride-rich lipoprotein, Lp(a), and C-reactive protein, are increasingly considered to reduce residual risk related to LDL-C. One study demonstrated rosuvastatin dosage, age, smoking, drinking, and diabetes to independently predict atrial fibrillation and ischemic

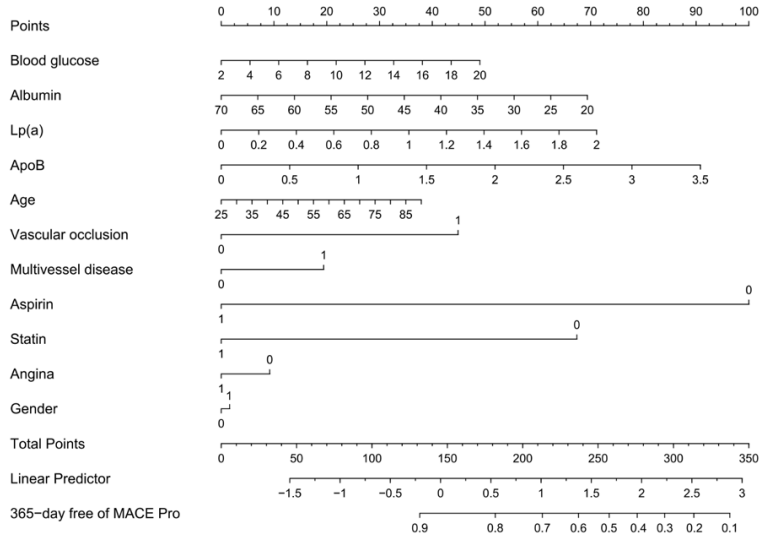

Figure 5. Nomogram based on the multivariate Cox regression analysis for predicting 1-year incidences of MACEs. Major adverse cardiovascular events (MACEs).

events [19]. Another study showed that high Lp(a) levels increase ASCVD risk, even in patients with an LDL-C level below 70 mg/dL [20]. Our study indicated that elevated Lp(a) levels increase the 1-year incidence of MACEs in patients with an LDL-C level less than 100 mg/dL, and the effect was more significant in those with an LDL-C level less than 70 mg/dL.

It is generally believed that the main pathophysiological effect of Lp(a) on CHD is to promote thrombosis and atherosclerosis. Borrelli [21] found that Lp(a) damages the vascular endothelial barrier by promoting adhesion molecule production by endothelial cells, stimulating vascular smooth muscle cell migration and proliferation, and promoting the formation of atherosclerotic plaques. Lp(a) is considered to elicit stronger pro-atherosclerotic effects than LDL. Therefore, it is thought that lowering Lp(a) levels should also be prioritized during conventional LDL-C-lowering therapy. Lowering Lp(a) levels to about 65.7 mg/dL effectively reduces the risk of ASCVD [22], but the ideal control level for Lp(a) remains unclear. Epidemiological studies suggest an Lp(a) level greater than 25 mg/dL raises the risk of developing ASCVD in healthy individuals, whereas an Lp(a) level greater than 50 mg/dL elevates the risk of recurrence in ASCVD patients [23]. The European Atherosclerosis Society (EAS) [24] proposed the ideal Lp(a) level in patients with ASCVD to be less than 50 mg/dL, while China, the United States, and Canada [25] considered the ideal Lp(a) level to be 30 mg/dL. The 2019 European Society of Cardiology/EAS guidelines for the management of dyslipidemia indicates that each adult should have at least one Lp(a) measurement in their lifetime, and patients with an Lp(a) level greater than 180 mg/dL are at high risk for ASCVD compared to individuals with heterozygous familial hypercholesterolemia [16]. As described above, Lp(a) levels independently predict the occurrence of MACE within 1 year after a PCI. Despite the overwhelming effects of statins on decreasing LDL-C levels and preventing ASCVD, statins have no overt effect on Lp(a) level [26]. Recent evidence [27] suggested that PCSK9 inhibitors may decrease Lp(a) levels using a dual mechanism. When used alone, PCSK9 inhibitors block Lp(a) synthesis; in combination with statins, PCSK9 inhibitors enhance LDL receptor activity and accelerate Lp(a) catabolism. Similarly, clinical studies have demonstrated that PCSK9 inhibitors decrease LDL-C and Lp(a) levels by more than 60% and 20%, respectively [28]. Nonetheless, it is unclear whether the reduction in MACE occurrence by PCSK9 inhibitors results from a decrease in Lp(a) levels or a further decrease in LDL-C levels from statin treatment. Although statins generally do not decrease Lp(a) levels, PCSK9 inhibitors can reduce Lp(a) levels and improve cardiovascular outcomes.

In recent years, the understanding of Lp(a) has made great progress. However, multiple issues remain unknown, including the exact synthesis and metabolic pathways of Lp(a) and its effects on pathophysiological characteristics, which need to be gradually explored in future basic and/or clinical research. Nevertheless, a limitation of this study should be mentioned. This was a single-center retrospective study. To minimize bias impact, the researchers used relatively comprehensive records of predictive variables and outcome indicators in the data-

base for analysis and research. Given the significant differences in the distribution of Lp(a) levels in different ethnic groups, epidemiological studies with large samples and populations covering different regions are warranted.

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Disclosure of conflict of interest

None.

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