

Association of Lipoprotein (a) and Coronary Artery Lesion and In-hospital Outcomes in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Baoquan Wu

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Hanjun Zhao

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Changhua Liu

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Hao Lu

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Ruishuang Liu

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Juan Long

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Zhiling Zhang

Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital

Fanfang Zeng (✉ zengfanfang123@tom.com)

Shenzhen Sun Yat-sen Cardiovascular Hospital

Research

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Abstract

Background: Current study was to evaluate association of Lipoprotein (a) [Lp(a)] and coronary artery lesion and in-hospital outcomes in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI).

Methods: Baseline characteristics, characteristics of coronary artery lesion, medications use, and cardiovascular events during hospitalization were collected. Based on Lp(a) level, patients were divided into low (< 30 mg/dL) and high (≥ 30 mg/dL) groups.

Results: Compared to those with low Lp(a), patients with high Lp(a) had larger numbers of coronary arteries $\geq 70\%$ stenosis and longer coronary artery lesion ($P < 0.05$). Patients with high Lp(a) were more likely to have left anterior descending artery lesion, pre-PCI TIMI flow grade 0 and post-PCI TIMI flow grade 2, and type C coronary lesion ($P < 0.05$). After adjustment, high Lp(a) remained associated with higher odds of having coronary artery $\geq 70\%$ stenosis, type C coronary lesion and pre-PCI TIME flow grade 1/0. Compared to those with low Lp(a), patients with high Lp(a) had a higher unadjusted odds of acute stent thrombosis (odds ratio [OR] 1.10 and 95% confidence interval [CI] 1.01-2.27), congestive heart failure (OR 1.24 and 95% CI 1.15-2.38) and composite in-hospital outcomes (OR 1.28 and 95% CI 1.18-2.42). After adjustment, patients with high Lp(a) remained had a higher odds of congestive heart failure (OR 1.08 and 95% CI 1.01-1.78) and composite in-hospital outcomes (OR 1.12 and 95% CI 1.04-1.81).

Conclusion: High Lp(a) was associated with more severe coronary artery lesion, and higher risk of congestive heart failure and composite in-hospital outcomes.

Background

Coronary heart disease (CHD) remains a leading cause of morbidity and mortality worldwide despite advancements in invasive and medication treatments have been achieved in the past three decades [1–3]. Dyslipidemia is a major risk factor for CHD and lowering serum low-density lipoprotein cholesterol (LDL-C) level with statins treatment is beneficial to reduce cardiovascular events after percutaneous coronary intervention (PCI) treatment [3, 4]. However, numerous studies have shown that despite receiving intensive statins treatment, a substantial proportion of patients remain experience cardiovascular events including myocardial infarction, stent thrombosis and cardiovascular death, indicative of a significant residual cardiovascular risk in these populations [5–8].

Traditional therapies such as statins targeting LDL-C have been unsatisfactory, and many studies found that increased lipoprotein (a) [Lp(a)] level was associated with cardiovascular events [9–12]. Lp(a) is a LDL-like particle synthesized in the liver [13]. Serum Lp(a) level is predominantly dependent on the number of repeats in the kringle IV type 2 protein domain [13]. Numerous studies have shown that increased serum Lp(a) level portends a higher cardiovascular risk [9–12]. Unfortunately, statins treatment has no effects on Lp(a) reduction [13, 14]. Of note, Lp(a) gene expression varies substantially between different racial/ethnic groups [15, 16], and results of prior observational and epidemiological studies are

almost from Caucasian populations. How are the effects of increased serum Lp(a) level on clinical outcomes in Chinese Han populations with acute coronary syndrome (ACS) have not been fully elucidated yet. In last several years, accumulating evidence have consistently shown that Lp(a) could be reduced with PCSK9 inhibitor, which in turn was associated with a lower incidence of cardiovascular events [17, 18]. Therefore, Lp(a) is increasingly recognized as a modifiable cardiovascular risk factor currently, and it is speculated that Lp(a) reduction may further reduce residual cardiovascular risk.

Herein, using a retrospective design, we collected data of ACS patients undergoing PCI in our hospital, and the aims of current analysis was to evaluate: 1) the association of Lp(a) and coronary artery lesion, 2) the association of Lp(a) and in-hospital outcomes.

Methods

Study participants

Current study was approved by the Institution Review Board of our hospital and since this was a retrospective study, no written consent form was required. Patients who were diagnosed as CHD between January of 2017 and December of 2019 were screened, and the inclusion criteria were as follows: \geq 18 years old; an admission diagnosis of ACS; undergoing PCI; received intensive statins treatment during hospitalization; and had Lp(a) measurement at admission. The exclusion criteria were as follows: undergoing coronary artery bypass grafting; critically ill patients that required mechanical circulatory support or ventilation; failed to have coronary artery stenting; or died before PCI (Fig. 1).

Data collection

All data were collected from electronic health record by three independent investigators. Data, including vital signs (blood pressure and heart rate at admission), anthropometrics (height and weight), demographics (age and sex), socioeconomic status (highest educational attainment), cardiovascular risk factor (smoking status and obesity), comorbidities (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, congestive heart failure, CHD, prior myocardial infarction, prior PCI, prior coronary artery bypass grafting, ischemic stroke/transient ischemic stroke (TIA), peripheral vascular disease [PVD] and chronic kidney disease [CKD]), were collected. Body mass index (BMI) was calculated using weight in kilograms divided by height in squared meters and $\text{BMI} \geq 28 \text{ kg/m}^2$ was defined as obesity in accordance to the WHO criterion for Asian populations. Laboratory parameters included lipid panel, glycated hemoglobin A1c (HbA1c), serum levels of creatinine, C-reactive protein (CRP), high-sensitivity cardiac troponin-I (Hs-cTNI), and N-terminal pro-B natriuretic peptide (NT-proBNP). Creatinine was used to calculate estimated glomerular filtration rate (eGFR). Procedural characteristics included duration of symptom onset to undergo PCI, arterial access site, number of coronary arteries $\geq 70\%$ stenosis, lesion location and lesion length, TIMI flow grade of pre- and post-PCI treatment, minimum lumen diameter of pre- and post-PCI treatment in the lesion vessel, type and number of stent implanted, volume of contrast

and antiplatelet loading used during PCI. Medication use before admission were reconciled by physicians and medication use during hospitalization was extracted from electronic health record. The SYNTAX score was calculated by an independent interventional cardiologist using dedicated software (www.SYNTAXscore.com). All these data were entered to the encrypted excel dataset.

In-hospital outcomes

In-hospital cardiovascular events were identified and adjudicated by independent cardiologists who did not involve in the current study. All the cardiovascular events were adjudicated based on clinical symptoms/signs, laboratory tests, and imagining studies rather than based on ICD-9 code, and the cardiovascular events included acute stent thrombosis, myocardial infarction, ischemic stroke/TIA, congestive heart failure and cardiovascular mortality. In specific, acute stent thrombosis was diagnosed based on coronary angiography with evidence of thrombotic occlusion of the implanted coronary stent and all the diagnosis was definite acute stent thrombosis based on the Academic Research Consortium criteria [19]. Myocardial infarction was diagnosed based on clinical symptoms (e.g. substernal chest pain), electrocardiographic exam (e.g. ST-segment elevation or depression) and plasma concentration of cardiac troponin I above the 99th percentile upper normal limit [20]. Patients with MI due to acute stent thrombosis was defined as the event of acute stent thrombosis. Ischemic stroke/TIA was diagnosed based on neurologic deficits plus cerebrovascular imaging evidence (e.g. computed tomography) [21]. Congestive heart failure was diagnosed by clinical manifestations including cardiac dyspnea, pink frothy sputum, and crackles in bilateral lung as well as a supporting examination such as echocardiogram or chest X-ray [22]. Cardiovascular mortality was defined as death due to cardiac etiologies.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation (SD) or median (interquartile range; IQR), and categorical variables were presented as number and frequency. Participants were divided into low Lp(a) (< 30 mg/dL) and high Lp(a) (≥ 30 mg/dL) groups based on recommendation [23]. Between-group differences were evaluated by Student t test or Mann-Whitney-Wilcoxon test for continuous variables, and chi-squared test for categorical variables. Low Lp(a) group was served as the reference group in unadjusted and adjusted models. Logistic regression analysis was performed to evaluate the association of Lp(a) and coronary artery lesion and in-hospital outcomes with adjustment for potential covariates. In specific, in the regression model, age, gender and covariates that were significantly different at baseline were included.

Since the SYNTAX score was included in regression model, and in order to avoid collinearity, the individual component of coronary lesion (e.g. number of arteries $\geq 70\%$ stenosis) was not included in the regression model. All analyses were conducted using the SPSS 23.0 statistical software and a two-sided P value < 0.05 was considered as statistical significance.

Results

Baseline characteristics comparisons

Baseline characteristics comparisons were shown in Table 1. Compared to those with low Lp(a), patients with high Lp(a) were more likely to be men; had higher BMI and higher prevalence of diabetes mellitus and dyslipidemia ($P < 0.05$). Serum levels of Lp(a), Hs-cTNI and NT-proBNP were higher, while eGFR was lower in high Lp(a) group ($P < 0.05$).

Table 1
Baseline characteristics comparisons

Variables	Lp(a) < 30 mg/dL (n = 566)	Lp(a) ≥ 30 mg/dL (n = 726)	P-value
Age (years)	55.9 ± 11.8	57.1 ± 13.2	0.87
Men, n (%)	355 (62.7)	540 (74.4)	< 0.001
≥ High school, n (%)	337 (59.5)	412 (56.7)	0.63
Systolic blood pressure (mm Hg)	128 ± 14	130 ± 16	0.41
Diastolic blood pressure (mm Hg)	73 ± 10	75 ± 11	0.33
Heart rate (beat per minute)	86 ± 19	88 ± 18	0.19
Body mass index (kg/m ²)	24.1 ± 6.3	25.7 ± 6.6	0.007
Current smoker, n (%)	248 (43.8)	315 (43.4)	0.28
Obesity, n (%)	175 (30.9)	238 (32.9)	0.75
Hypertension, n (%)	382 (67.5)	475 (65.4)	0.69
Diabetes mellitus, n (%)	163 (28.8)	251 (34.6)	< 0.001
Dyslipidemia, n (%)	278 (49.1)	398 (54.8)	< 0.001
Atrial fibrillation, n (%)	52 (9.2)	75 (10.3)	0.90
Congestive heart failure, n (%)	63 (11.1)	81 (11.2)	0.98
Coronary heart disease, n (%)	118 (20.8)	166 (22.9)	0.62
Prior myocardial infarction, n (%)	60 (10.6)	85 (11.7)	0.80
Prior PCI, n (%)	82 (14.5)	102 (14.0)	0.93
Prior CABG, n (%)	9 (1.6)	13 (1.8)	0.77
Ischemic stroke/TIA, n (%)	38 (6.7)	55 (7.6)	0.38
Peripheral vascular disease, n (%)	30 (5.3)	49 (6.7)	0.50
Chronic kidney disease, n (%)	78 (13.4)	104 (14.3)	0.68
HbA1c (%)	5.8 ± 0.5	5.9 ± 0.6	0.91
Total cholesterol (mmol/L)	4.9 ± 0.9	5.0 ± 1.1	0.55

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; HbA1c, glycated hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B type natriuretic peptide; Hs-CTnI, high sensitivity cardiac troponin-I; eGFR, estimated glomerular filtration rate

Variables	Lp(a) < 30 mg/dL (n = 566)	Lp(a) ≥ 30 mg/dL (n = 726)	P-value
LDL-C (mmol/L)	3.0 ± 0.5	3.1 ± 0.5	0.49
HDL-C (mmol/L)	1.2 ± 0.4	1.1 ± 0.4	0.73
Triglyceride (mmol/L)	1.8 (0.7–2.7)	1.9 (0.6–2.8)	0.16
Lipoprotein (a) (mg/dL)	17.6 (10.5–26.8)	73.6 (41.4-137.9)	< 0.001
C-reactive protein (mg/dL)	6.9 ± 2.0	8.2 ± 2.3	0.03
NT-proBNP (pg/mL)	366.7 (142.8-632.2)	394.2 (170.9-756.4)	0.01
Hs-CTnl (ng/mL)	7.3 ± 3.1	9.5 ± 3.3	0.009
Creatinine (umol/L)	96.4 ± 18.5	97.1 ± 19.2	0.48
eGFR (ml/min/1.73 m ²)	69.6 ± 13.6	67.3 ± 11.8	0.004
PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; HbA1c, glycated hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B type natriuretic peptide; Hs-CTnl, high sensitivity cardiac troponin-I; eGFR, estimated glomerular filtration rate			

Procedural characteristics comparisons

As shown in Table 2, compared to those with low Lp(a), patients with high Lp(a) had larger numbers of coronary arteries ≥ 70% stenosis and had longer coronary artery lesion ($P < 0.05$). In addition, patients with high Lp(a) were more likely to have left anterior descending artery lesion, pre-PCI TIMI flow grade 0 and post-PCI TIMI flow grade 2, and type C coronary lesion ($P < 0.05$). The use of glycoprotein IIb/IIIa inhibitor during PCI was also higher in patients with high Lp(a) ($P < 0.05$). In addition, the SYNTAX score was also higher in patients with high versus low Lp(a) (21.2 ± 5.7 vs 17.7 ± 4.6). No differences in other procedural characteristics were observed.

Table 2
Procedural characteristics comparisons

Variables	Lp(a) < 30 mg/dL (n = 566)	Lp(a) ≥ 30 mg/dL (n = 726)	P-value
Duration of symptom onset to PCI (day)	1.9 (0.5–2.8)	2.0 (0.6–2.9)	0.37
ST-segment elevation MI, n (%)	178 (31.4)	237 (32.6)	0.44
Non-ST-segment elevation MI, n (%)	157 (27.7)	204 (28.1)	0.61
Unstable angina, n (%)	231 (40.9)	285 (39.3)	0.19
Femoral artery access, n (%)	265 (46.8)	343 (47.2)	0.53
Number of arteries ≥ 70% stenosis	1.4 ± 0.5	1.6 ± 0.6*	0.008
Lesion length, mm	25.3 ± 6.5	27.6 ± 6.8*	0.01
Lesion locations			
Left main, n (%)	89 (15.7)	116 (16.0)	0.72
LAD, n (%)	286 (50.5)	450 (62.0)*	< 0.001
LCX, n (%)	198 (35.0)	275 (37.9)	0.36
RCA, n (%)	247 (43.6)	308 (42.4)	0.22
Pre-PCI TIMI flow grade			
Grade 3	0	0	-
Grade 2	0	0	-
Grade 1	369 (65.2)	427 (58.8)	0.71
Grade 0	197 (34.8)	299 (41.2)*	0.03
Post-PCI TIMI flow grade			
Grade 3	543 (95.9)	703 (90.4)	0.92
Grade 2	23 (4.1)	70 (9.6)*	0.006
Grade 1	0	0	-
Grade 0	0	0	-
Pre-PCI minimum lumen diameter, mm	0.78 ± 0.12	0.76 ± 0.10	0.28

PCI, percutaneous coronary intervention; MI, myocardial infarction; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; * P < 0.05 versus Lp(a) < 30 mg/dL group

Variables	Lp(a) < 30 mg/dL (n = 566)	Lp(a) ≥ 30 mg/dL (n = 726)	P-value
Post-PCI minimum lumen diameter, mm	2.32 ± 0.63	2.31 ± 0.61	0.85
Type C coronary lesion, n (%)	138 (24.4)	245 (33.7)	0.07
Antiplatelet medication loading, n (%)	524 (92.6)	674 (92.8)	0.69
Glycoprotein IIb/IIIa inhibitor, n (%)	40 (7.1)	89 (12.3)*	0.03
Volume of contrast (ml)	164.5 ± 39.6	162.7 ± 40.3	0.54
Number of stents implanted	1.8 ± 0.6	1.9 ± 0.7	0.96
Drug-eluting stent, n (%)	548 (96.8)	704 (97.0)	0.80
SYNTAX score	17.7 ± 4.6	21.2 ± 5.7*	0.002

PCI, percutaneous coronary intervention; MI, myocardial infarction; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; * P < 0.05 versus Lp(a) < 30 mg/dL group

Comparisons of medication use at admission and during hospitalization

As presented in Table 3, the use of statins and anti-diabetes were higher in patients with high versus low Lp(a) (P < 0.05). During hospitalization, compared to admission, the use of guideline recommended medication was significantly increased in both groups. The use of ticagrelor, anti-diabetes and low molecular-weight heparin was also higher in patients with high Lp(a) (P < 0.05).

Table 3
Medications use at admission and during hospitalization

Medications	Lp(a) < 30 mg/dL (n = 566)	Lp(a) ≥ 30 mg/dL (n = 726)
At admission		
Aspirin, n (%)	303 (53.5)	397 (54.7)
Clopidogrel, n (%)	37 (6.5)	50 (6.9)
Ticagrelor, n (%)	12 (2.1)	16 (2.2)
Statins, n (%)	249 (44.0)	368 (50.7)*
Beta-blocker, n (%)	231 (40.8)	302 (41.6)
ACEI/ARB, n (%)	285 (50.4)	384 (82.9)
Calcium channel blocker, n (%)	186 (32.9)	243 (33.5)
Anti-diabetes, n (%)	134 (23.7)	232 (32.0)*
During hospitalization		
Aspirin, n (%)	566 (100)	726 (100)
Clopidogrel, n (%)	518 (91.5)	626 (86.2)
Ticagrelor, n (%)	48 (8.5)	100 (13.8)*
Statins, n (%)	538 (95.1)	687 (94.6)
Beta-blocker, n (%)	465 (82.3)	602 (82.9)
ACEI/ARB, n (%)	421 (74.4)	530 (73.0)
Calcium channel blocker, n (%)	134 (23.7)	183 (25.2)
Anti-diabetes, n (%)	162 (25.1)	246 (33.9)*
Low molecular-weight heparin, n (%)	34 (6.0)	74 (10.2)*
ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker;		
* P < 0.05 versus Lp(a) < 30 mg/dL group		

Association of Lp(a) and coronary artery lesion

Association of Lp(a) level and coronary artery lesion were evaluated and shown in Table 4. In reference to low Lp(a), high Lp(a) was associated with higher unadjusted odds of having coronary artery ≥ 70% stenosis, type C coronary lesion, and pre- and post-PCI TIME flow grade 1/0. After adjusted for potential covariates, high Lp(a) remained associated with higher odds of having coronary artery ≥ 70% stenosis,

type C coronary lesion and pre-PCI TIMI flow grade 1/0. It is noted that additionally adjusted for glycoprotein IIb/IIIa inhibitor use during PCI, high Lp(a) was associated with higher odds of having post-PCI TIMI flow grade 1/0, suggesting that the use of glycoprotein IIb/IIIa inhibitor might attenuate the adverse effect of Lp(a).

Table 4
Association of Lp(a) and coronary artery lesion

High Lp(a) versus low Lp(a)	Odds ratio	95% Confidence interval
Number of arteries \geq 70% stenosis		
Unadjusted	1.95	1.46–2.84
Adjusted	1.34	1.09–2.01
Type C coronary lesion		
Unadjusted	1.67	1.34–2.22
Adjusted	1.24	1.09–1.83
Pre-PCI TIMI flow grade 1/0		
Unadjusted	1.63	1.30–2.18
Adjusted	1.22	1.04–1.72
Post-PCI TIMI flow grade 1/0		
Unadjusted	1.59	1.24–1.93
Adjusted	1.13	0.98–1.36
Additionally adjusted to glycoprotein IIb/IIIa inhibitor	1.19	1.02–1.48
Adjusted for age, gender, smoking status, hypertension, diabetes mellitus, dyslipidemia, C-reactive protein, estimated glomerular filtration rate, and statins use at admission		

Association of Lp(a) and in-hospital outcomes

As shown in Table 5, compared to patients with low Lp(a), patients with high Lp(a) had a higher unadjusted odds of acute stent thrombosis (odds ratio [OR] 1.10 and 95% confidence interval [CI] 1.01–2.27), congestive heart failure (OR 1.24 and 95% CI 1.15–2.38) and composite in-hospital outcomes (OR 1.28 and 95% CI 1.18–2.42). After adjustment for potential covariates, patients with high Lp(a) remained had a higher odds of congestive heart failure (OR 1.08 and 95% CI 1.01–1.78) and composite in-hospital outcomes (OR 1.12 and 95% CI 1.04–1.81).

Table 5
Association of Lp(a) and in-hospital outcomes

Cardiovascular events	Lp(a) < 30 mg/dL (n = 566)	Lp(a) ≥ 30 mg/dL (n = 726)	Unadjusted	Adjusted
	n (%)		Odds ratio (95% confidence interval)	
Acute stent thrombosis, n (%)	4 (0.7)	12 (1.7)	1.10 (1.01–2.27)	1.01 (0.78–1.70)
Myocardial infarction, n (%)	15 (2.7)	32 (4.4)	1.16 (0.94–2.25)	1.05 (0.83–1.57)
Ischemic stroke/TIA, n (%)	6 (1.1)	10 (1.4)	1.19 (0.90–2.23)	1.03 (0.80–1.74)
Congestive heart failure, n (%)	54 (9.5)	94 (12.9)	1.24 (1.15–2.38)	1.08 (1.01–1.78)
Cardiovascular mortality, n (%)	10 (1.8)	14 (1.9)	1.08 (0.84–2.11)	1.00 (0.65–1.42)
Composite, n (%)	89 (15.7)	162 (22.3)	1.28 (1.18–2.42)	1.12 (1.04–1.81)
TIA, transient ischemic attack; Adjusted for age, gender, body mass index, diabetes mellitus, dyslipidemia, C-reactive protein, N-terminal pro-brain natriuretic peptide, high sensitivity cardiac troponin-I, estimated glomerular filtration rate, SYNTAX score, statins and anti-diabetes use at baseline, ticagrelor and low molecular weight heparin use during hospitalization				

Discussion

To our knowledge, this is the first few studies to evaluate the impact of Lp(a) on coronary artery lesion and in-hospital outcomes in ACS patients undergoing PCI in China. There are two main findings of our current analyses: 1) increased Lp(a) was associated with a more severe coronary artery lesion as reflected by numbers of coronary arteries $\geq 70\%$ stenosis, type C coronary lesion and pre-PCI TIME flow grade 1/0; 2) after adjustment for potential covariates, increased Lp(a) was associated with a higher risk of congestive heart failure and composite in-hospital outcomes. These findings highlight the importance of measuring Lp(a) in ACS patients, which might help to improve cardiovascular risk stratification. With respect to the efficacy of PCSK9 inhibitor on Lp(a) reduction, future researches are needed to evaluate whether PCSK9 inhibitor can reduce in-hospital cardiovascular events in ACS patients with high Lp(a) in Chinese populations.

In ACS patients after PCI treatment, intensive statins has been recommended as the cornerstone treatment. Nonetheless, numerous studies have reported that despite adherence to intensive statins treatment, a substantial proportion of patients remain experience stent thrombosis, myocardial infarction, ischemic stroke/TIA and cardiovascular death. The reasons for the residual cardiovascular risks are likely multifactorial [7, 8, 13, 18], which included systemic inflammation, uncontrolled other risk factors (e.g.

hypertension and diabetes), poor adherence to antiplatelet medications, and among others. Importantly, prior studies also have shown that increased Lp(a) is associated with a variety of cardiovascular diseases such as CHD and congestive heart failure [24–26]. The pathophysiological effects of increased Lp(a) on cardiovascular systems are two folds, that is pro-atherosclerosis and pro-thrombosis. Through binding to circulating oxidized phospholipid and apoprotein B100 (OxPL/ApoB100), Lp(a) exerts potent inflammatory and oxidative effects on endothelial cells, causing endothelial dysfunction, macrophages migration and proliferation, foams cells accumulation, and necrotic core expansion [13, 23]. On the other hand, Lp(a) also plays an important role in impairing endogenous fibrinolysis, promoting platelet aggregation and thrombosis formation [13, 23, 27]. These two pathophysiological functions of Lp(a) predispose patients with high Lp(a) at substantial high residual cardiovascular risks. Indeed, prior studies showed that compared to those with low Lp(a), high Lp(a) was associated with more severe coronary artery stenosis as detected by angiography [28], and was also associated with less coronary collateral circulation in patients with acute myocardial infarction [29]. In addition, one study reported that increased Lp(a) at baseline was associated with a higher risk of stent restenosis and revascularization [11]. Two additional studies also showed that plasma Lp(a) concentration was an independent predictor of stent restenosis [30, 31]. Consistent to prior reports, results of our current study also suggest that in ACS patients undergoing PCI, compared to those with low Lp(a), patients with high Lp(a) had a higher unadjusted risk of acute stent thrombosis, which might be due to the less optimal post-PCI TIMIE flow in these ACS populations. As shown in Table 4 that high Lp(a) was associated with post-PCI TIMI flow grade 1/0, and after adjustment for glycoprotein IIb/IIIa inhibitor, the association was attenuated into statistical insignificance, suggesting that in ACS patients with high Lp(a), use of glycoprotein IIb/IIIa inhibitor during PCI might mitigate the potential thrombotic risk of Lp(a). Future studies are needed to corroborate our findings.

Few studies have reported that increased Lp(a) was associated with a higher risk of congestive heart failure in Caucasian populations. For example, Kamstrup et al reported that elevated Lp(a) level was associated with an increased risk of congestive heart failure [32]. Steffen et al also found that Lp(a)-related risks of congestive heart failure were only evident in Caucasian populations but not in Black or Asian populations [24]. Interestingly and importantly, our current study for the first time showed that compared to those with low Lp(a), patients with high Lp(a) had higher risk of congestive heart failure even after adjustment for potential covariates. The underlying mechanisms are likely multifactorial, and we considered that the higher incidence of congestive heart failure might be due to more severe ischemic injury in ACS patients with high Lp(a). Indeed, patients with high Lp(a) had larger number of coronary stenosis $\geq 70\%$, were more likely to have type C lesion and left anterior descending coronary stenosis, and poorer coronary perfusion pre- and post-PCI treatment. Further studies are needed to corroborate our current findings and if confirmed, Lp(a) might be used to predict the incidence of congestive heart failure.

There are some limitations of our current study. First, this is a retrospective and observational study, and findings from current study cannot be drawn causal relationship. Second, due to the difference in Lp(a) gene expression between different racial/ethnic populations, current findings might not be extrapolated to other populations. Third, although extensive adjustment for potential covariates, unmeasured and

undetected covariates might still exist and influence the association of Lp(a) and outcomes. Fourth, we only evaluated the association of Lp(a) and in-hospital outcomes and whether these observations extended to long-term outcome was unknown. Last but not the least, the modest sample size might not be able to find significant association of high Lp(a) and other cardiovascular events such as myocardial infarction.

Conclusion

In conclusion, our current study shows that in ACS patients undergoing PCI, high Lp(a) was associated with more severe coronary artery lesion. In addition, high Lp(a) was also associated with higher risk of congestive heart failure and composite in-hospital outcomes. Future studies are needed to corroborate our current findings, and also needed to evaluate how to mitigate the cardiovascular risk associated with increased Lp(a).

Abbreviations

Coronary heart disease (CHD)

Low-density lipoprotein cholesterol (LDL-C)

Percutaneous coronary intervention (PCI)

Lipoprotein (a) [Lp(a)]

Acute coronary syndrome (ACS)

Transient ischemic stroke (TIA)

Peripheral vascular disease (PVD)

Chronic kidney disease (CKD)

Body mass index (BMI)

Glycated hemoglobin A1c (HbA1c)

C-reactive protein (CRP)

High-sensitivity cardiac troponin-I (Hs-cTNI)

N-terminal pro-B natriuretic peptide (NT-proBNP)

Estimated glomerular filtration rate (eGFR)

Standard deviation (SD)

Interquartile range (IQR)

Declarations

Ethics approval and consent to participate

The study design was approved by the Clinical and Basic Research Ethic Committee of Fuwai Hospital. This was a retrospective study and no written informed consent was required.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

None.

Funding

Not Applicable.

Author Contributions

BQU and FFZ conceived the study, participated in the design and drafted the manuscript; BQW and HJZ performed the statistical analyses; BQW, HJZ, CHL, HL, RSL, JL, ZLJ and FFZ collected the data. All authors read and approved the final manuscript.

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Figures

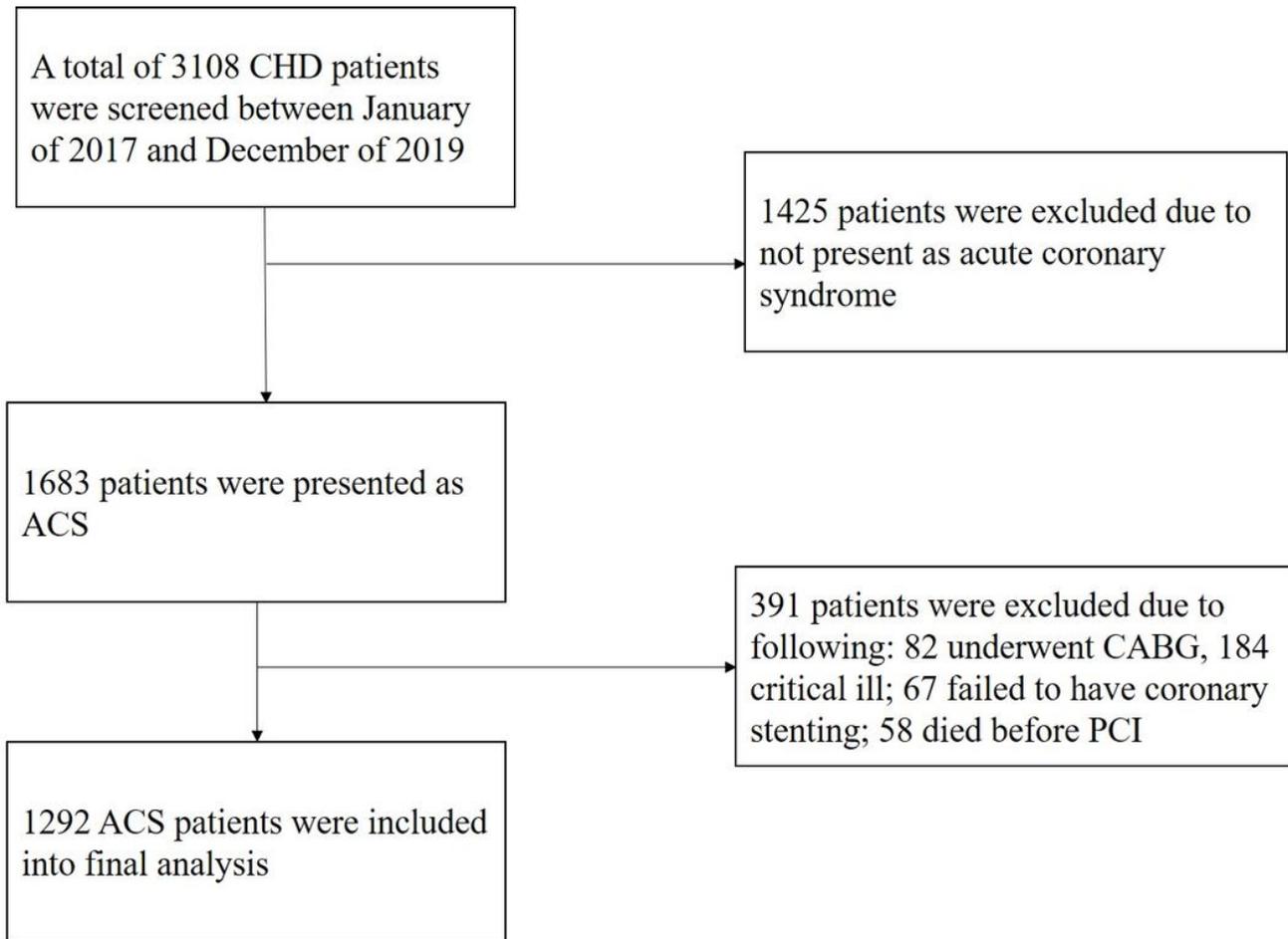


Figure 1

Figure 1

Study flowchart