Heart, Lung and Circulation (2019) **28,** 1009–1017
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.05.190

ORIGINAL ARTICLE

Plasma Lipoprotein(a) Concentration Is Associated With the Coronary Severity but Not With Events in Stable Coronary Artery Disease Patients: A Chinese Cohort Study

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Received 26 December 2017; received in revised form 18 April 2018; accepted 13 May 2018; online published-ahead-of-print 8 June 2018

Background Although lipoprotein(a) (Lp(a)) has been regarded as an independent risk factor for atherosclerotic cardiovascular disease (ASCVD), its predictive role in outcomes in stable coronary artery disease (CAD) has been undetermined. The aim of the present study was to investigate the relations of Lp(a) to the coronary severity and events in Chinese patients with angiography-proven stable CAD.

Methods A total of 3,278 patients with stable CAD were consecutively enrolled and the coronary severity was evaluated by the Gensini Score (GS) system. Patients were divided into two groups according to the median of GS: high GS group (n = 1,585) and low GS group (n = 1,693). The associations of continuous Lp(a), Lp(a) ≥300 mg/L, and tertiles of Lp(a) with GS and events were respectively evaluated.

Results Patients in the high GS group had significantly higher concentrations of Lp(a). In addition, the multivariate Cox regression analysis indicated that elevated Lp(a) (odds ratio: 1.164, 95% confidence interval: 1.005–1.349), Lp(a) ≥300 mg/L (odds ratio: 1.200, 95% confidence interval: 1.028–1.401), and the highest tertile of Lp(a) (odds ratio: 1.205, 95% confidence interval: 1.010–1.438) were statistically associated with GS after adjusted for potential confounders. However, although 215 (6.56%) events were established during a median of follow-up over 10,170 patient-years, no relationship between Lp(a) and events was found.

Conclusions In this Chinese cohort study on stable CAD with moderate sample size and follow-up duration, data showed that Lp(a) was significantly associated with the coronary severity while not with cardiovascular events, similar to several studies, suggesting that further study is needed regarding the role of Lp(a) in ASCVD.

Keywords Lipoprotein(a) • Coronary artery disease • Gensini Score • Events

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Introduction

Lipoprotein (a)[Lp (a)] is composed of apolipoprotein (apo) B-100 covalently bound to apolipoprotein a (apo [a]) [1]. The concentration of Lp (a) is genetically determined by LPA gene [2], and is less influenced by diet or life style [3], therefore stable in every individual during the whole life. As we know, Lp (a) is a low-density lipoprotein (LDL)-like lipoprotein [4]. It is this structure that has led to the hypothesis that Lp(a) may be a risk factor for the progression of coronary artery disease (CAD) and future adverse outcomes. Many previous studies have concluded that Lp(a) is associated with the prevalence as well as the severity of CAD [5,6], and future cardiovascular events in the general population [7]. However, the relationship in patients with established CAD is less extensively investigated and significantly weaker than that in the general population [8]. In addition, these previous findings produced conflicting results. Some studies indicated that a higher concentration of Lp(a) might increase the severity of CAD and predict a higher risk of cardiovascular events [9–11], while there existed marked heterogeneity. Several did not find any association of Lp(a) with cardiovascular diseases [12,13]. It is hypothesised that the association between Lp(a) and cardiovascular outcomes may be greatly attenuated by the concentration of LDL-C [14,15].

It is indicated that Lp(a) concentration is highly heterogeneous across different countries, populations, and races [16]. Hence, the study on the role of the plasma Lp(a) levels in predicting the coronary stenosis and events in patients with CAD may clinically be of great interest. Unfortunately, to our knowledge, few studies have explored the potential impact of plasma Lp(a) levels on Chinese stable CAD patients. Even if published, these studies were also limited by small sample sizes and short-term follow-up duration. In fact, no data regarding association of the severity of CAD or the cardiovascular events in large Chinese Han patients with stable CAD are currently available.

Based on this situation, the aim of our current study was to evaluate the value of continuous plasma Lp(a) concentration, Lp(a) $\geq$300 mg/L, and tertiles of Lp(a) respectively on GS and cardiovascular events in Chinese CAD patients. Importantly, the severity of CAD was calculated by the GS system, an exquisite and widely used method in cardiovascular field.

Methods

Study Population

Between November 2011 and January 2015, 4,650 consecutive patients with CAD who were definitely diagnosed by coronary angiography (CAG) were eligible for our current study. Among them, 531 patients with acute myocardial infarction were excluded. In addition, other exclusion criteria included patients without complete clinical and laboratory data, patients with severe heart failure, valvular heart disease, severe liver or renal diseases, systematic inflammatory diseases and malignant systematic diseases. Therefore, in the end, 3,278 consecutive patients with established CAD were enrolled in the present study. The study was in accordance with the principles of the Declaration of Helsinki and informed consent was obtained from every enrolled patient. The flowchart of the present study is shown in Figure 1.

Body mass index (BMI) is equal to weight in kilograms divided by height in metres squared. Hypertension (HTN) was defined as systolic blood pressure (SBP) $\geq$140 mmHg and/or diastolic blood pressure (DBP) $\geq$90 mmHg or currently taking anti-hypertensive medications when patients came to the hospital. Diabetes mellitus (DM) was defined as fasting serum glucose $\geq$7.0 mmol/L or random serum glucose $\geq$11.0 mmol/L or the 2-hour serum glucose of the oral glucose tolerance test $\geq$11.0 mmol/L or using hypoglycaemic medications currently. Dyslipidaemia was defined as total cholesterol $\geq$5.1 mmol/L or triglyceride $\geq$1.7 mmol/L or using lipid-lowering medications at admission.

Laboratory Tests

Blood samples of all enrolled patients were obtained from venous after a 12-hour overnight fast and then tested as soon as possible in laboratory medicine. The lipid profiles including total cholesterol (TC), triglyceride (TG), LDL-C, high density lipoprotein cholesterol (HDL-C), Lp(a) were determined by automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan). And in detail, the concentration of Lp(a) was measured with a latex turbidimetric method (LASAY Lp(a) auto; SHIMA Laboratories, Tokyo). The method for measuring the concentration of Lp(a) has been reported in our previous published papers [17,18]. Lp(a) was determined by immunoturbidimetry method (LASAY Lp(a) auto, SHIMA Laboratories Co. Ltd., Tokyo, Japan). The detection range was 5–1,000 mg/L and the normal range was 0–300 mg/L. The coefficient of variation (CV) value of repetitive measurements was below 10%. Haemoglobin A1c (HbA1c) was tested by Tosoh Automated Glycohemoglobin Analyser (HLC-723G8, Tokyo, Japan). Erythrocyte sedimentation rate (ESR) was tested using Westergren method and high sensitivity C-reactive protein (hs-CRP) was measured through immunoturbidimetry (BeckmannAssay360, Bera, CA, USA).

Gensini Score Assessment

Every patient underwent CAG in our hospital because of angina-like chest pain or significant coronary artery stenosis calculated by coronary computed tomography angiography or positive treadmill exercise test. The results of CAG were evaluated from catheter laboratory records by at least three interventional cardiologists. The coronary severity was assessed by the GS system, which was computed by assigning the severity score to each coronary stenosis. And GS was equal to the scores of luminal narrowing multiplied by the scores of its geographic importance [19].

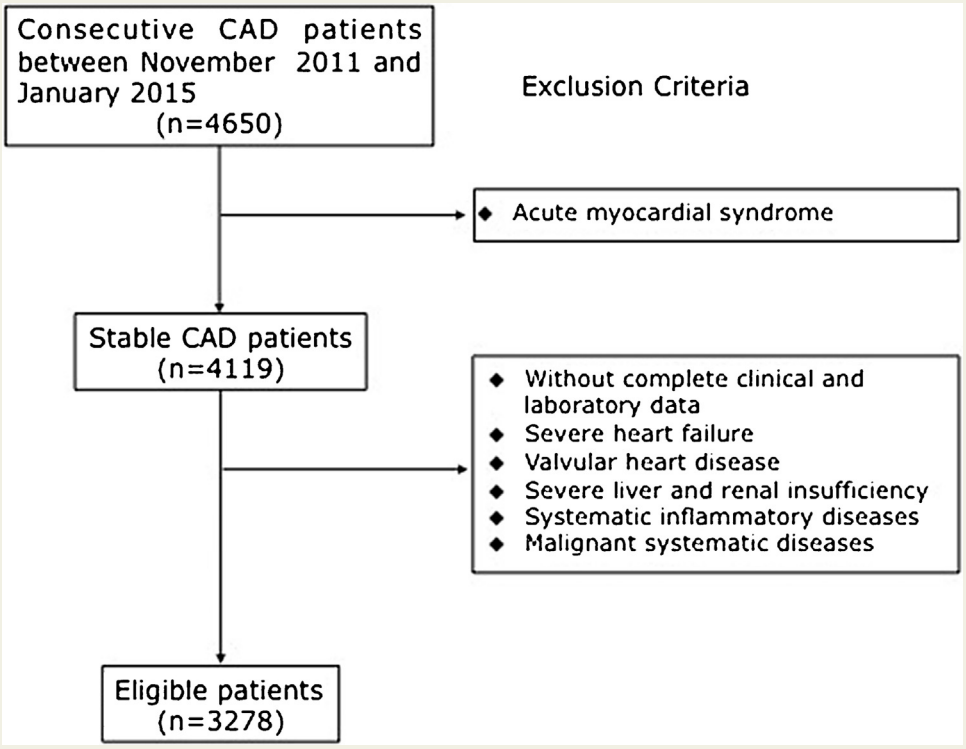

Figure 1 The data flow chart of the current study.

Follow-Up

All enrolled patients were prospectively followed up every 6 months by clinic visit or interview (directly or using telephone). The future events included all cause death, non-fatal myocardial infarction, stroke, unplanned revascularisation including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). All-cause death included cardiac death and non-cardiac death. Non-fatal myocardial infarction was defined as elevated myocardial enzyme along with typical chest pain or typical electrocardiogram changes or new dysfunction of ventricular wall motion. Stroke was defined as acute cerebral infarction diagnosed by the imaging or typical symptoms.

Statistical Analysis

SPSS version 23.0 program (SPSS Inc., Armonk, NY, USA) was used for the analysis of statistical data and two-tailed p values <0.05 was defined as statistically significant. Continuous variables were expressed as mean $\pm$ SD or median with 25th and 75th percentile when appropriate. Student t-test or Mann–Whitney U-test were used for continuous variables to compare the statistical differences between groups. Categorical variables were presented as number (percentage) and analysed by χ^2 statistic test. Univariate and multivariate logistic regression analyses were conducted. Univariate and multivariate Cox regression analyses were conducted. The event-free survival rates among groups of Lp(a) >300 mg/L and Lp(a) ≤ 300 mg/L, and groups of tertiles of Lp(a) were estimated by the Kaplan–Meier method and compared by the log rank test.

Results

Baseline Characteristics of Patients

The concentration of Lp(a) ranged from 1.68 to 1630.4 mg/L (median concentration: 157.06 mg/L, interquartile range from 68.55 to 369.47 mg/L) (Figure 2).

The median of the GS was 24. Gensini Score above the median was defined high GS. Patients were divided into two groups according to the results of GS: high GS group (n = 1,585) and low GS group (n = 1,693). As is shown in Table 1, patients in high GS group were older and had higher BMI. The median of Lp(a) concentration was significantly higher in high GS group than that in low GS group (168.97 vs. 149.75, p = 0.009). Moreover, the incidence of Lp(a) $\geq$300 mg/L was statistically higher in high GS group (33.1% vs. 29.2%, p = 0.018).

During the median follow-up of 37.23 months, a total of 215 (6.56%) events occurred: non-fatal myocardial infarction (n = 27), stoke (n = 54), unplanned revascularisation (n = 101) and all-cause death (n = 33). As is indicated in Table 2, the age in events group was statistically higher than that in non-events group (59.37 $\pm$ 10.54 vs. 57.76 $\pm$ 9.78, p = 0.02). The prevalence of HTN and DM was statistically higher in events group. However, no difference of the Lp(a) concentration was found between the events group and non-events group.

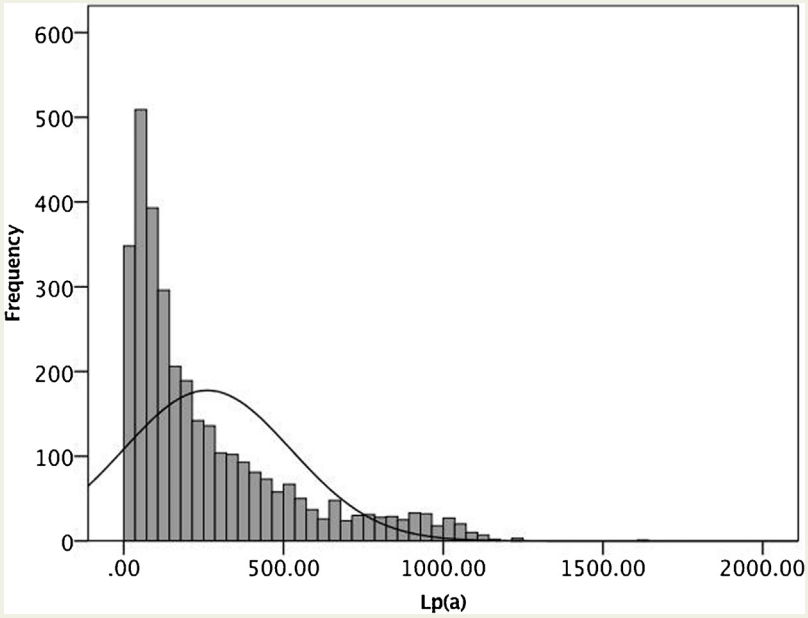

Figure 2 Distribution of lipoprotein(a) [Lp(a)] concentrations.

Table 1 Baseline clinical and biochemical data according to Gensini Score.

Variables	High GS (>24) (n = 1,585)	Low GS (≤24) (n = 1,693)	P
Age (years)	58.22 ± 10.12	57.53 ± 9.56	0.043
Male (n, %)	1,216 (76.7)	1,190 (70.3)	<0.001
BMI (kg/m2)	25.96 ± 3.13	25.75 ± 3.19	0.065
HTN (n, %)	1,011 (63.8)	1,050 (62.0)	0.296
HL (n, %)	1,188 (75.0)	1,256 (74.2)	0.615
DM (n, %)	503 (31.7)	396 (23.4)	<0.001
Family history of CAD (n, %)	245 (15.5)	277 (16.4)	0.480
Current smoker (n, %)	635 (40.1)	653 (38.6)	0.382
TC (mmol/L)	4.19 ± 1.17	4.08 ± 1.02	0.005
LDL-C(mmol/L)	2.58 ± 0.97	2.48 ± 0.98	0.002
HDL-C (mmol/L)	0.98 (0.84–1.16)	1.02 (0.88–1.24)	<0.001
TG (mmol/L)	1.57 (1.16–2.2)	1.52 (1.1–2.08)	0.019
Lp (a) (mg/L)	168.97 (71.12–387.66)	149.75 (66.47–349.66)	0.009
Lp (a) ≥300 mg/L (n, %)	524 (33.1)	495 (29.2)	0.018
HbA1C (%)	6.52 ± 1.21	6.28 ± 1.02	<0.001
ESR (mm/h)	7.00 (3.00–15.00)	7.00 (2.00–12.00)	<0.001
Hs-CRP (mg/L)	1.46 (0.73–3.12)	1.27(0.63–2.65)	<0.001
Prior medication	–	–	
Aspirin (n, %)	956 (60.3)	955 (56.4)	0.023
Statins (n, %)	912 (57.5)	898 (53.0)	0.010
β-blockers (n, %)	551 (34.8)	522 (30.8)	0.017

Data were expressed as mean ± SD, median with 25th and 75th percentile, n (%).

Abbreviations: GS, Gensini Score; BMI, body mass index; HTN, hypertension; HL, hyperlipidaemia; DM, diabetes mellitus; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; Lp(a), lipoprotein(a); HbA1C, haemoglobin A1c; ESR, erythrocyte sedimentation rate; Hs-CRP, high sensitive C-reactive protein.

Table 2 Comparison of clinical and biochemical characteristics among patients with events and without events.

Variables	Events		P
	Yes (n = 215)	No (n = 3063)	
Age (years)	59.37 ± 10.54	57.76 ± 9.78	0.020
Male (n, %)	154 (71.6)	2,252 (73.5)	0.543
BMI (kg/m2)	25.95 ± 3.19	25.84 ± 3.16	0.628
HTN (n, %)	149 (69.3)	1,912 (62.4)	0.044
HL (n, %)	168 (78.1)	2,276 (74.3)	0.212
DM (n, %)	73 (34.0)	826 (27.0)	0.026
Family history of CAD (n, %)	30 (14.0)	492 (16.1)	0.414
Current smoker (n, %)	82 (38.1)	1,206 (39.4)	0.720
TC (mmol/L)	4.23 ± 1.12	4.13 ± 1.09	0.193
LDL-C (mmol/L)	2.52 ± 0.94	2.53 ± 0.98	0.841
HDL-C (mmol/L)	1.01 (0.86–1.27)	1.00 (0.86–1.21)	0.202
TG (mmol/L)	1.62 (1.11–2.21)	1.55 (1.13–2.14)	0.351
Lp (a) (mg/L)	143.9 (71.75–405.52)	158.6 (68.30–368.6)	0.987
Lp (a) ≥300 mg/L (n, %)	67 (31.2)	952 (31.1)	0.980
HbA1C (%)	6.59 ± 1.33	6.38 ± 1.10	0.008
ESR (mm/h)	8.00 (4.00–16.00)	7.00 (3.00–13.00)	0.004
Hs-CRP (mg/L)	1.62 (0.82–3.04)	1.34 (0.67–2.83)	0.034
Prior medication	–	–	
Aspirin (n, %)	113 (52.6)	1,798 (58.7)	0.077
Statins (n, %)	98 (45.6)	1,712 (55.9)	0.003
β-blockers (n, %)	68 (31.6)	1,005 (32.8)	0.721

Data were expressed as mean ± SD, median with 25th and 75th percentile, n (%).

Abbreviations: BMI, body mass index; HTN, hypertension; HL, hyperlipidaemia; DM, diabetes mellitus; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; Lp(a), lipoprotein(a); HbA1C, haemoglobin A1c; ESR, erythrocyte sedimentation rate; Hs-CRP, high sensitive C-reactive protein.

Table 3 Multivariate logistic regression analysis for high Gensini Score.

Variable		OR	95% CI	P
Lg [Lp (a)]	Model 1	1.222	1.062–1.408	0.005
	Model 2	1.252	1.083–1.446	0.002
	Model 3	1.208	1.044–1.398	0.011
	Model 4	1.164	1.005–1.349	0.043
Lp(a) ≥300 mg/L	Model 1	1.216	1.048–1.412	0.010
	Model 2	1.257	1.080–1.464	0.003
	Model 3	1.225	1.051–1.427	0.009
	Model 4	1.200	1.028–1.401	0.021
Lp(a) tertile1 (reference)				
Lp(a) tertile 2	Model 1	1.037	0.876–1.228	0.673
	Model 2	1.042	0.877–1.238	0.641
	Model 3	1.016	0.855–1.209	0.855
	Model 4	0.978	0.821–1.165	0.804
Lp (a) tertile 3	Model 1	1.275	1.076–1.511	0.005
	Model 2	1.312	1.104–1.560	0.002
	Model 3	1.260	1.058–1.501	0.010
	Model 4	1.205	1.010–1.438	0.038

Lp(a), lipoprotein(a); Lg [Lp (a)], lipoprotein(a) was log-transformed; OR, odds ratio; CI, confidence interval.

Model 1: Adjusted for age and male; Model 2: Model 1+hypertension, diabetes mellitus, current smoking, body mass index; Model 3: Model 2+ low density lipoprotein cholesterol; Model 4: Model 3+ erythrocyte sedimentation rate, high sensitive C-reactive protein.

Table 4 **Multivariate Cox regression analysis for cardiovascular events.**

Variable		OR	95% CI	P
Lg[Lp (a)]	Model 1	0.990	0.753–1.301	0.942
	Model 2	1.036	0.782–1.372	0.804
	Model 3	1.040	0.783–1.381	0.787
	Model 4	1.018	0.764–1.356	0.905
Lp(a) ≥300 mg/L	Model 1	0.968	0.724–1.295	0.828
	Model 2	1.021	0.761–1.372	0.888
	Model 3	1.024	0.761–1.377	0.876
	Model 4	1.023	0.759–1.377	0.883
Lp(a) tertile1 (reference)				
Lp(a) tertile 2	Model 1	0.989	0.716–1.367	0.947
	Model 2	0.981	0.704–1.368	0.912
	Model 3	0.983	0.704–1.371	0.918
	Model 4	0.936	0.668–1.311	0.700
Lp(a) tertile 3	Model 1	0.884	0.634–1.233	0.468
	Model 2	0.930	0.664–1.304	0.676
	Model 3	0.933	0.663–1.311	0.688
	Model 4	0.907	0.644–1.278	0.577

Lp(a), lipoprotein(a); Lg [Lp (a)], lipoprotein(a) was log-transformed; OR, odds ratio; CI, confidence interval.
Model 1: Adjusted for age and male; Model 2: Model 1+hypertension, diabetes mellitus, current smoking, body mass index; Model 3: Model 2+ low density lipoprotein cholesterol; Model 4: Model 3+ erythrocyte sedimentation rate, high sensitive C-reactive protein.

Logistic Regression Analysis for the Relationship Between Lp(a) and Gensini Score

After stepwise adjusted for age, male, HTN, DM, current smoking, BMI, LDL-C, ESR and hs-CRP, elevated Lp(a) (odds ratio: 1.164, 95% confidence interval: 1.005–1.349, p = 0.043), Lp(a) ≥300 mg/L (odds ratio: 1.200, 95% confidence interval: 1.028–1.401, p = 0.021), and the highest tertile of Lp(a) (odds ratio: 1.205, 95% confidence interval: 1.010–1.438, p = 0.038) was statistically and significantly related to high GS (Table 3).

Cox Regression Analysis for the Relationship Between Lp(a) and Events

As is shown in Table 4, after adjustment for potential confounders mentioned above, no relationship was found between continuous Lp(a) (odds ratio: 1.018, 95% confidence interval: 0.764–1.356, p = 0.905), Lp(a) ≥300 mg/L (odds ratio: 1.023, 95% confidence interval: 0.759–1.377, p = 0.883), or the highest tertile of Lp(a) (odds ratio: 0.907, 95% confidence interval: 0.644–1.278, p = 0.577) and events in the Cox regression analysis. In Figure 3, the Kaplan–Meier analysis demonstrated no significant differences in the event-free survival rates between Lp(a) <300 mg/L and Lp(a) ≥300 mg/L(p > 0.05) or tertiles of Lp(a).

Discussion

The current prospective study performed in a moderate cohort of Chinese patients with stable CAD indicated that Lp(a) was positively associated with the coronary severity but not with cardiovascular events, which was in accordance with several previous studies [9,12,14,20,21]. Although the present study has several limitations, the data may provide additional information concerning the role of Lp(a) in cardiovascular disease due to the following features: Firstly, the patients were all with stable CAD and the coronary severity was evaluated by the GS system; secondly, we analysed the predictive role of Lp(a) in patients with stable CAD using multiple methods including continuous plasma Lp(a) levels, Lp(a) ≥300 mg/L and Lp(a) tertiles on both the coronary severity and clinical events. Finally, the results of the present study were consistent with several large cohort studies [14], suggesting that a further study may be needed to confirm the relation of Lp(a) and future outcomes in stable CAD.

Many previous studies have demonstrated the association of Lp(a) with the progression of atherosclerosis in the general population. In one study performed in 14,583 individuals who had a health check examination by using cardiac computed tomography to estimate the coronary artery calcium score (CACS) [22], the percentage of CACS >0, which had been indicated as a useful marker of early atherosclerosis, was significantly higher in the highest quartile of Lp(a) concentration when compared with the lowest quartile of Lp(a) concentration. In the multivariate logistic regression analysis, after adjusting for potential confounders, the highest quartile of Lp(a) concentration was found to be positively related to CACS. In addition, many studies have demonstrated that Lp(a) is associated with the prevalence of CAD. Kamstrup PR et al. [23] examined 9,330 individuals from the general population and followed up for 10 years. They found

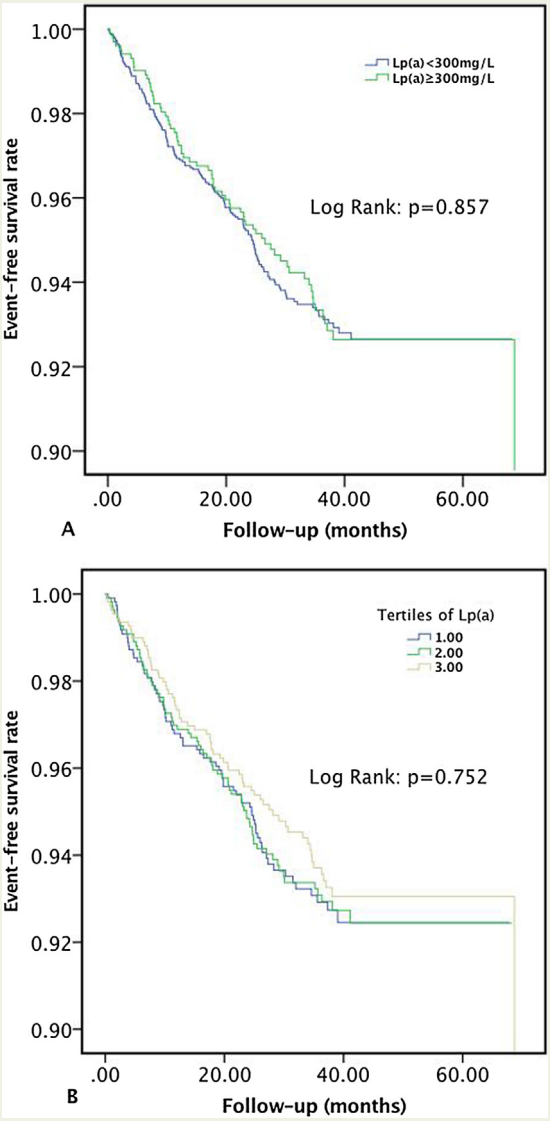

Figure 3 The event-free survival analysis according to lipoprotein(a) [Lp(a)] <300 mg/L and Lp(a) ≥300 mg/L (**A**) and tertiles of Lp(a) (**B**) for cardiovascular events.

that Lp(a) stepwise increased the risk of the incidence of myocardial infarction. And the study showed that a 10 mg/dL increase in the concentration of Lp(a) was associated with a multivariate adjustment hazard ratio of 1.09 for myocardial infarction.

In the second prevention population, several studies have been conducted to explore the relationship between Lp(a) and the severity of coronary artery. Zorio E et al. [24] investigated the value of Lp(a) on the severity of coronary lesions in 222 patients with CAD and found that severer coronary lesion had higher percentage of Lp(a) ≥300 mg/L. The GS method was not used in this study. Several studies evaluated the coronary severity by using the GS system. One study consecutively enrolled 490 individuals scheduled to undergo coronary angiography, among whom 256 were CAD patients [25]. The study indicated that there was a linear relationship between Lp(a) concentration and GS. In addition, multivariate stepwise linear regression analysis demonstrated that Lp (a) was independently associated with GS. There is limited understanding regarding the relationship in Chinese patients. In addition, these studies were limited by a small sample size. In 2016, Zhu L et al. [26] concluded that Lp(a) was related to GS in 679 Chinese Han patients with CAD. Of note, our present study was performed in a relatively large cohort of Chinese patients. To our knowledge, our study was with the largest sample size in estimating the relationship between Lp(a) and cardiovascular diseases in Chinese Han patients. The finding of the present study was in accordance with previous studies that Lp(a) was positively correlated with GS in patients with CAD. Additionally, the GS system was conducted to strictly assess the coronary severity in the present study.

Accordingly, although Lp(a) might be a useful risk marker for the progression of atherosclerosis in the apparently healthy individuals, the role of Lp(a) on cardiovascular outcomes in patients with established CAD remained a separate issue which had controversial results. Researchers hypothesised that the value of Lp(a) on cardiovascular diseases may be weaker in patients with established CAD than in the general population [8,12]. In a meta-analysis with regard to the relationship between Lp(a) and cardiac death and non-fatal myocardial infarction among prospective studies with at least one-year follow-up, they found that the risk ratio for outcomes in the highest tertile of Lp(a) was 1.7 in the general population while only 1.3 in patients with baseline diseases mostly including CAD [8]. Undeniably, several previous studies have found that there is no association of Lp(a) with cardiovascular events in the second prevention population. JS Skinner et al. [13] studied 353 patients who firstly underwent CABG in-hospital and were followed up for 5 years. They found that the Lp(a) concentration had no statistical difference in patients with or without late major cardiac events. And logistic regression analysis indicated that the highest tertile of Lp(a) was not associated with cardiac events. Recently, one study obtained data from 3,313 patients with CAD in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study and then validated the findings in five independent studies involving 10,195 patients with established CAD [12]. This study investigated that the highest tertile of Lp(a) was significantly and positively associated with the incidence of CAD along with the coronary severity, however, not associated with future events in the multivariate Cox regression analysis. Not surprisingly, in agreement with this study, our present study also found the association of Lp(a) with coronary severity but not with events.

The reasons for the disparity among studies were not comprehensively understood. Several studies speculated that the relationship between Lp(a) and cardiovascular events may be affected by LDL-C concentration. One study evaluated the relationship between Lp(a) and the progression of CAD in patients with established CAD after one year intervention of low-diet and daily physical exercise [27]. The findings were that the LDL-C concentration had been

significantly lowered after intervention of diet and exercise, and there was no association of Lp(a) with the progression of cardiovascular disease in the second prevention population. In 2004, O'Donoghue ML et al. [14] assessed the relationship in 6,708 patients with established CAD and indicated that the highest quintile of Lp(a) was statistically and positively correlated with events which included myocardial infarction, stoke and cardiac death in patients with LDL-C concentration over 3.4 mmol/L. However, in patients with lower concentrations of LDL-C, no relationship between Lp(a) and cardiovascular events was found. In addition, in a recent study, 3,251 patients with prior CAD, DM or 10-year Framingham cardiovascular disease risk >20% were enrolled and followed up for over 22 years [15]. The study demonstrated that, in patients with LDL-C <2.6 mmol/L, the highest tertile of Lp(a) was not associated with cardiovascular events. Therefore, the association of Lp(a) with cardiovascular events may be significantly weakened by low LDL-C concentration. In our present study, the mean concentration of LDL-C was less than 2.6 mmol/L, which may strengthen the previous findings on the negative relationship between Lp(a) and events. In addition, the characteristics of our present study including the Chinese population with stable CAD, moderate follow-up duration and sample size, relatively well-controlled LDL-C may influence the predictive role of Lp(a) in cardiovascular events.

The present study reported no differences of LDL-C as well as HDL-C levels between the events group and non-events group. It was not surprising because Table 2 shows the proportion of statins before admission was significantly higher in non-events group (55.9% vs. 45.6%, $p = 0.003$). The concentrations of LDL-C and HDL-C were evaluated immediately after admission to our hospital which meant that, to a large extent, the concentrations might be influenced by use of statins before admission. The real differences of LDL-C and HDL-C levels between events and non-events group might be attenuated by statins used.

There were several limitations in the present study. Firstly, the method we used in our study might be influenced by the apo(a) sizes due to the variable numbers of the KIV type 2 domains. Variations of apo(a) sizes between assay calibrators and patients' samples might overestimate or underestimate the real concentrations of Lp(a). Secondly, data in the current study was from a single-centre. Thirdly, although the sample size was the largest in Chinese patients with stable CAD, more studies with larger sample size and longer follow-up duration are needed to demonstrate our findings.

In conclusion, the current study found that Lp(a) concentration was significantly associated with the coronary severity, but not with events in Chinese patients with established stable CAD.

Acknowledgements

The present study was partially supported by the Capital Health Development Fund (201614035) and CAMS Major Collaborative Innovation Project (2016-I2M-1-011) awarded to Dr. Jian-Jun Li, MD, PhD.

Conflict of Interest

None.

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