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Inverse Association of Lipoprotein(a) on Long-Term Bleeding Risk in Patients with Coronary Heart Disease: Insight from a Multicenter Cohort in Asia

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Abstract

Background Lipoprotein(a), or Lp(a), has been recognized as a strong risk factor for atherosclerotic cardiovascular disease. However, the relationship between Lp(a) and bleeding remains indistinct, especially in the secondary prevention population of coronary artery disease (CAD). This investigation aimed to evaluate the association of Lp(a) with long-term bleeding among patients with CAD.

Methods Based on a prospective multicenter cohort of patients with CAD consecutively enrolled from January 2015 to May 2019 in China, the current analysis included 16,150 participants. Thus, according to Lp(a) quintiles, all subjects were divided into five groups. The primary endpoint was bleeding at 2-year follow-up, and the secondary endpoint was major bleeding at 2-year follow-up.

Keywords
- lipoprotein(a)
- bleeding
- inverse association
- L-shaped association
- prognosis

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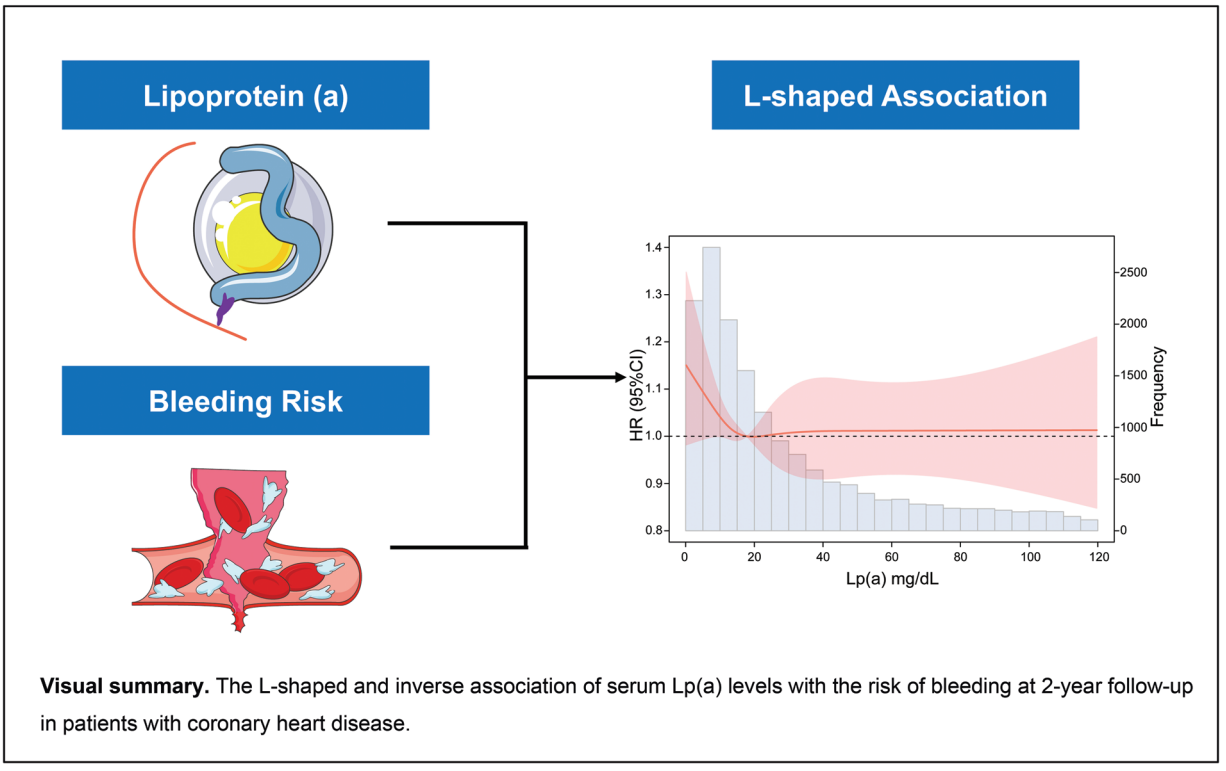

Visual summary. The L-shaped and inverse association of serum Lp(a) levels with the risk of bleeding at 2-year follow-up in patients with coronary heart disease.

Results A total of 2,747 (17.0%) bleeding and 525 (3.3%) major bleeding were recorded during a median follow-up of 2.0 years. Kaplan–Meier survival analysis showed the highest bleeding incidence in Lp(a) quintile 1, compared with patients in Lp(a) quintiles 2 to 5 ($p < 0.001$), while the incidence of major bleeding seemed similar between the two groups. Moreover, restricted cubic spline analysis suggested that there was an L-shaped association between Lp(a) and 2-year bleeding after adjustment for potential confounding factors, whereas there was no significant association between Lp(a) and 2-year major bleeding.

Conclusion There was an inverse and L-shaped association of Lp(a) with bleeding at 2-year follow-up in patients with CAD. More attention and effort should be made to increase the clinician awareness of Lp(a)'s role, as a novel marker for bleeding risk to better guide shared-decision making in clinical practice.

Introduction

Lipoprotein(a), or Lp(a), is an atherogenic lipoprotein containing a low-density lipoprotein (LDL) cholesterol-like particle whose protein moiety has a complex structure of apolipoprotein(a) [Apo(a)] bounding covalently to a single copy of apolipoprotein B-100, and circulating Lp(a) concentrations are dominantly determined by heredity.[1,2] Considerable pieces of evidence from epidemiologic studies, mendelian randomization investigations, and current guidelines have demonstrated that elevated levels of Lp(a) are causally related to increased cardiovascular risk and adverse ischemic events.[3–5] Therefore, Lp(a) has been regarded as a novel therapeutic target of mitigating residual cardiovascular risk in both primary and secondary prevention settings.[5,6] Remarkably, elevated Lp(a) levels have been shown to exert physiological implications in the mechanisms underlying wound healing and tissue repairing, suggesting that Lp(a) might potentially serve as a protective factor against bleeding events.[7] This hypothesis is further supported by a growing body of previous studies indicating an inverse association between Lp(a) and bleeding events in certain clinical settings.[8–10]

Antiplatelet therapy is considered the cornerstone for the management of patients with coronary artery disease (CAD) due to its ability to reduce the incidence of thrombotic events.[11] However, the use of antiplatelet agents is also related to an increased risk of bleeding, whether it is iatrogenic or spontaneous.[12] Achieving a balance between the bleeding risk and the ischemic risk in CAD patients remains an important challenge in contemporary clinical practice. In recent years, advances in

interventional technologies and pharmacology have significantly reduced the occurrence of ischemic events in CAD patients.[13,14] Therefore, growing attention has turned toward the optimized management of bleeding risk without compromising the benefits of ischemic prevention, particularly in East Asian patients, who are usually at a higher risk of bleeding than their European or American counterparts.[15] Against this background, it is clinically relevant to identify CAD patients at a higher risk of bleeding and individualize antiplatelet strategies to improve their prognosis. Ongoing randomized clinical trials (RCTs) are investigating the potential benefit of novel therapies in lowering Lp(a) levels in patients with atherosclerotic cardiovascular disease (ASCVD).[16,17] However, it remains unclear whether low Lp(a) levels would increase the occurrence of bleeding events concomitantly, particularly in treated CAD patients who might be at an increased risk of bleeding.

In the light of the above, based on a national prospective multicenter cohort of East Asian population, we sought to assess the association of Lp(a) with long-term bleeding risk in patients with CAD.

Methods

Cohort Sample

We conducted a post-hoc analysis of data from the PROMISE cohort study (The PRospective Observational Multicenter cohort for ISchemic and hEmorrhage risk in coronary artery disease patients). PROMISE is a prospective, multicenter cohort study aiming to develop risk scores to quantify ischemic and bleeding risks in patients with CAD in China. The PROMISE study was conducted at Fuwai Hospital (National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China) and other eight regional tertiary medical centers across mainland China, including the First Affiliated Hospital of Zhejiang University (Hangzhou, Zhejiang Province), Xinxiang Central Hospital (Xinxiang, Henan Province), the First Hospital of Qinhuangdao (Qinhuangdao, Hebei Province), Peking University Third Hospital (Beijing), Peking Union Medical College Hospital (Beijing), the First Hospital of Lanzhou University (Lanzhou, Gansu Province), Guangdong Cardiovascular Institute (Guangzhou, Guangdong Province), General Hospital of Northern Theater Command of Chinese People's Liberation Army (Shenyang, Liaoning Province). From January 2015 to May 2019, a total of 18,701 individuals with CAD hospitalized for coronary angiography or percutaneous revascularization in cardiology wards at nine centers were recruited in the PROMISE cohort. Patients meeting the exclusion criteria were excluded: (1) lack of Lp(a) data ($n = 1,781$); (2) missing medications at discharge data ($n = 68$); (3) lost to follow-up ($n = 602$). Finally, 16,150 participants were included in the current analyses (►**Fig. 1**). This real-world, prospective, multicenter investigation followed the Strengthening the Reporting of Observational Studies in Epidemiology

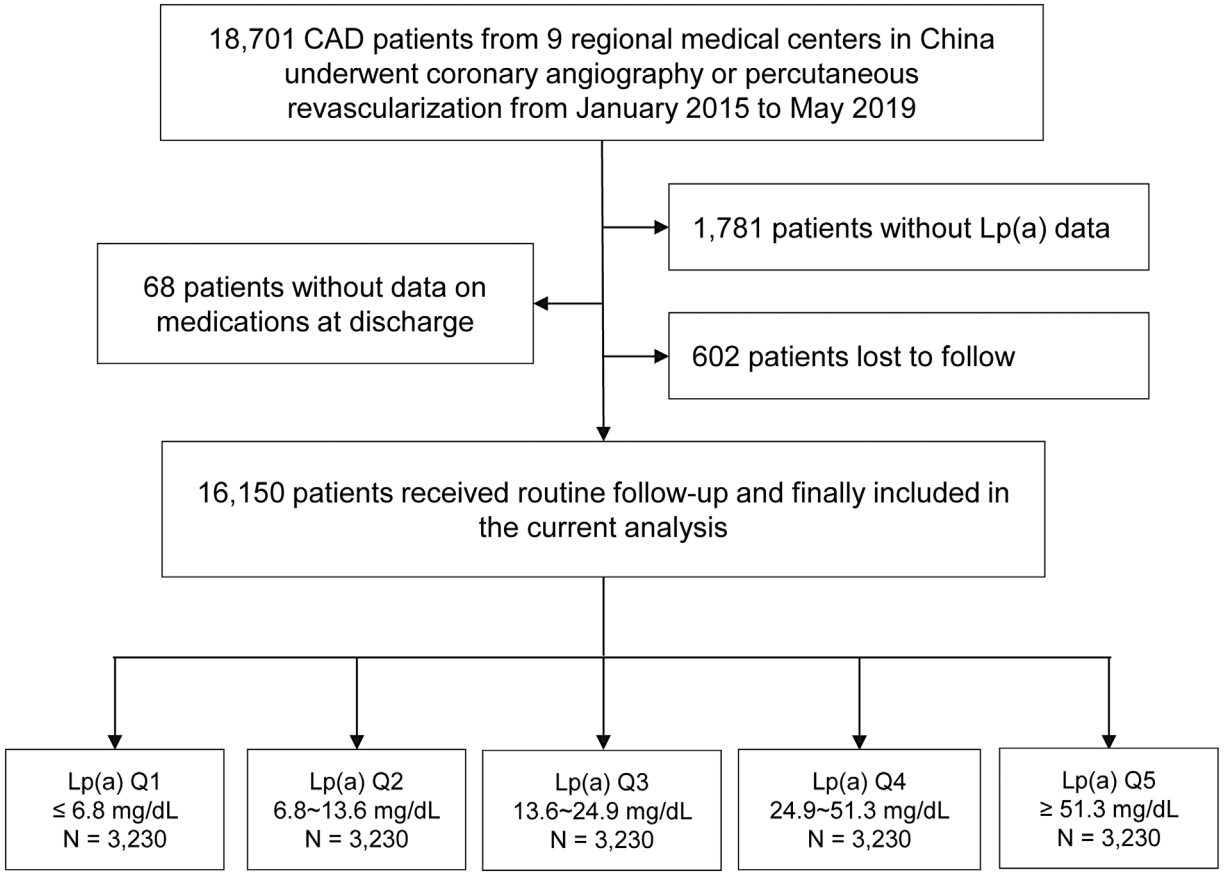

Fig. 1 Flowchart of study. CAD, coronary artery disease; Lp(a), lipoprotein(a).

(STROBE) reporting guideline for cohort studies, whose protocol was complied with the Declaration of Helsinki and endorsed by the Fuwai Hospital Ethics Review Committee. All subjects provided written informed consent before enrollment.

Data Collection, Definitions, and Laboratory Analysis

Data on patients' demographic characteristics, clinical histories, coronary procedural information, laboratory findings, and medications at admission were collected from electronic medical record system. Body mass index (BMI) was calculated with the formula: weight (kg)/[height (m)]2. Diabetes mellitus was defined as previous diagnosis of diabetes, or fasting blood glucose $\geq$7.0 mmol/L, or hemoglobin A1c levels $\geq$6.5%.[18] Hypertension was recorded if the participant had known hypertension with antihypertensive treatment, or new confirmation more than twice on different days by systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg.[19] Family history of CAD, prior medical history of stroke, myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass grafting, current smoking, drinking history, diagnosis on admission, and medication information were collected from self-reported data and rechecked by relevant medical records.

Standard hospital assays were used on fresh plasma samples to measure laboratory indices. The measurement of Lp(a) protocol was mandated. Lp(a) was determined by immunoturbidimetry assay (LASAY Lipoprotein(a) auto; SHIMA laboratories Co., Ltd) containing polyclonal anti-human Lp(a) antibodies from goat. The assay was calibrated by Lp(a) protein-validated lyophilized methods with a 5-point calibrator. Serum LDL cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglyceride levels were measured by an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan) in an enzymatic assay. High-sensitivity C-reactive protein (hsCRP) was measured by using immunoturbidimetry (Beckmann Assay, Bera, California, United States). Based on the modified Simpson's rule, left ventricular ejection fraction (LVEF) was measured by two-dimensional echocardiography.

Coronary procedural information was analyzed and recorded by two independent experienced operating specialists who were blinded to the participant's baseline data. According to the coronary angiography, left main (LM) disease was determined by stenosis of $\geq$50% in LM coronary artery and three-vessel disease was defined as stenosis of $\geq$50% in all three main coronary arteries (right coronary artery, left anterior descending branch, and left circumflex branch).[20]

Follow-Up and Study Outcomes

Regular follow-up was achieved through telephone interview and medical records at 30 days, 6 months, 1 year, and 2 years after discharge. The primary endpoint was bleeding at 2-year follow-up, and the secondary endpoint included major bleeding at 2-year follow-up. The bleeding endpoint was defined by the Bleeding Academic Research Consortium (BARC), and BARC type 2, 3, or 5 bleeding was regarded as major bleeding.[21] To capture bleeding systematically during the follow-up, information was collected from all the enrolled patients about the cause (procedural or nonprocedural), site (intraocular, intracranial, visceral, peritoneal, access site, etc.), and severity (quantified by impact on laboratory data and clinical status) of bleeding, and then they were classified by two independent cardiologists, based on the BARC definitions. Bleeding related to surgery was included in the event. All endpoint events were adjudicated centrally by two independent cardiologists, who were blinded to the protocol of this study, and possible disagreement was resolved by consensus.

Statistical Analysis

Categorical variables were described as frequency with percentage, and continuous variables were presented as median with interquartile range (IQR) based on variable distribution. Differences of categorical and continuous variables in baseline characteristics across Lp(a) score categories were compared by using the chi-square test and the Kruskal–Wallis test, as appropriate. The risks of bleeding and major bleeding among two groups based on Lp(a) quintiles and Lp(a) quartiles were compared by the log-rank test and illustrated by Kaplan–Meier survival curves. Cox proportional hazard models were constructed to evaluate the association between Lp(a) level and long-term bleeding risk. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for BMI, hypertension, family history of CAD, and drinking history. Model 3 was further adjusted for LDL cholesterol, total cholesterol, hsCRP, LVEF, dual antiplatelet therapy (DAPT), β-blocker, calcium-channel blocker (CCB) and oral anticoagulants, which were selected based on statistical significance in univariate analysis ($p < 0.05$) and clinical experience (►**Supplementary Table S1**, in the online version>). Also, all the coefficients for model 3 were shown in ►**Supplementary Table S2** (available in the online version). Moreover, according to the Akaike information criterion, restricted cubic splines (RCSs) with four knots were used to evaluate the predictive ability of Lp(a) for the risk of bleeding on a continuous scale. Knots for RCS were fixed at the 5th, 35th, 65th, and 95th percentiles of Lp(a) and the reference value was median concentration of Lp(a) (18.2 mg/dL). Furthermore, exploratory subgroup analysis was performed to assess the predictive utility of Lp(a) on the primary endpoint in specific subsets using model 3, stratified by age, sex, BMI, hypertension, family history of CAD, drinking history, and use of oral anticoagulants, and was shown as the forest plot. Potential subgroup difference was interpreted by testing interactions between Lp(a) and covariates mentioned above. Statistical analyses were performed using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). Two-tailored *p*-values of <0.05 were considered statistically significant.

Results

Baseline Characteristics

A total of 16,150 participants were enrolled in the current analysis. At baseline, the median (IQR) age was

61.3 (54.0–68.0) years and 74.8% were men. The distribution of Lp(a) was right-skewed with a median level of 18.2 mg/dL (IQR: 8.2–41.9 mg/dL). Thus, all participants were separated into five groups based on Lp(a) quintiles. Patients in the Lp(a) quintile 1 group were tended to be older, men, and higher BMI, with higher proportion of family history of CAD, current smoker, drinking history, and chronic coronary syndrome. Moreover, compared with subjects in the other four groups, those with Lp(a) quintile 1 were more likely to have lower LDL cholesterol, HDL cholesterol, total cholesterol, and hsCRP, as well as higher triglycerides, estimated glomerular filtration rate, and LVEF. Detailed baseline characteristics data are summarized in ►**Table 1**. In addition, baseline characteristics of study patients according to Lp(a) quartiles are presented in ►**Supplementary Table S3** (available in the online version).

Association between Lp(a) Level and Clinical Outcomes

During a median follow-up of 2 years (IQR: 2.0–2.1 years), 2,747 (17.0%) bleeding and 525 (3.3%) major bleeding were recorded. Kaplan–Meier analysis demonstrated that incidences of long-term bleeding were significantly higher in patients with Lp(a) quintile 1 (log-rank test $p < 0.001$), when compared with patients with Lp(a) quintiles 2 to 5 (►**Fig. 2A**). However, the incidences of 2-year major bleeding seemed to be similar among the two groups (►**Fig. 2B**). Similar results were presented when comparing patients in Lp(a) quintile 1 group with patients from any other group (►**Supplementary Fig. S1**, available in the online version). The results obtained from grouping patients by quartiles of Lp(a) were consistent with those obtained from grouping patients by quartiles of Lp(a) (►**Supplementary Figs. S2** and **S3,** available in the online version).

A significant association was observed between Lp(a) and 2-year bleeding by univariable analysis, whereas there was no significant association between Lp(a) and long-term major bleeding (►**Table 2**, ►**Supplementary Table S4** [available in the online version]). As shown in ►**Table 2** and ►**Supplementary Table S4** (available in the online version), Lp(a) remained its significant association with bleeding in Cox proportional hazard model 1 (adjusted for age and sex), model 2 (additionally adjusted for BMI, hypertension, family history of CAD, and drinking history), and model 3 (further adjusted for LDL cholesterol, total cholesterol, hsCRP, LVEF, β-blocker, CCB, and oral anticoagulants) (►**Table 2**: hazard ratio [HR] 0.86, 95% confidence interval [CI]: 0.79–0.95; HR: 0.87, 95% CI: 0.80–0.95; HR: 0.89, 95% CI: 0.81–0.97; respectively) (►**Supplementary Table S4** [available in the online version]: HR: 0.88, 95% CI: 0.81–0.96; HR: 0.89, 95% CI: 0.82–0.97; HR: 0.91, 95% CI: 0.83–0.99, respectively).

To access the predictive utility of Lp(a) on a continuous scale, RCS with four-knot based on Cox proportional hazard model 3 was employed and the corresponding result in ►**Fig. 3** revealed that there was an L-shaped association of Lp(a) with the risk of bleeding at 2-year follow-up, even after adjustment for potential confounding factors (p for nonlinearity < 0.05).

Subgroup Analysis

Subgroup analysis was further performed for evaluation of the associations between Lp(a) and the long-term primary endpoint in different populations according to age, sex, BMI, hypertension, family history of CAD, drinking history, and use of oral anticoagulants. All variables in model 3 excepting those used for stratification were fully adjusted (►**Fig. 4**). The result of subgroup analysis presented comparable interactions following 2-year bleeding between two groups and those covariates mentioned above (all p for interactions > 0.05).

Discussion

In this real-world, large-sample, prospective and multicenter cohort study, we reported the following three important findings: (1) Lp(a) was inversely and significantly associated with the incidence of long-term bleeding in patients with CAD, while the risk of major bleeding was similar between individuals in Lp(a) quintile 1 and subjects in Lp(a) quintiles 2 to 5; (2) the results were robust when splitting patients by Lp(a) quartiles; and (3) the association of Lp(a) with the risk of bleeding at 2-year follow-up was an L-shaped one.

Dyslipidemia management is a key therapeutic strategy in the primary and secondary prevention of ASCVD.[1,22] Even when LDL cholesterol concentrations are well-controlled, the residual cardiovascular risk remains, which may be attributed to different atherogenic factors, including inflammation, Lp(a), and other lipid profiles.[2,23] Lp(a), which is a complex polymorphic lipoprotein including an LDL cholesterol-like particle covalently combined with apolipoprotein (a), has been regarded as a potential therapeutic target to reduce residual cardiovascular risk.[2] Compelling evidence from genetic, epidemiologic, and observational investigations strongly supports that elevated levels of Lp(a) are causally associated with increased ASCVD risk.[3,4,24] As a result, proprotein convertase subtilisin/kexin type 9 inhibitors that reduce Lp(a) modestly have been recommended by current guidelines.[25] Emerging gene-silencing approaches, like the antisense oligonucleotide pelacarsen and the small-interfering RNA olpasiran, have demonstrated their potent Lp(a)-reducing effects and safety.[16,17] Previous studies have mainly focused on the association of elevated Lp(a) levels with increased risk of ischemic adverse events during follow-up, while the relationship between Lp(a) and long-term bleeding risk has been rarely mentioned, especially in the CAD population, who strongly need to balance the risk of ischemia versus the risk of bleeding during medication.[1,26]

Recently, a mendelian randomization study which examined 109,169 individuals from two prospective cohort studies in the Danish general population concluded that high concentrations of serum Lp(a) were associated with lower risk of cerebral and airway bleeding causally and observationally, which indicates Lp(a) may play a special role in wound healing and hemostasis.[9] Another previous literature enrolled 10,494 community-dwelling participants from Japan found that, during more than 10 years' follow-up, subjects with the highest Lp(a) (in the third tertile) had a significantly lower risk of cerebral hemorrhage, both in men and women (HR: 0.34, 95%

Table 1 Baseline characteristics of study patients according to lipoprotein(a) quintiles

Characteristics	Lp(a) 1st quintile, ≤6.8 mg/dL	Lp(a) 2nd quintile, 6.8–13.6 mg/dL	Lp(a) 3rd quintile, 13.6–24.9 mg/dL	Lp(a) 4th quintile, 24.9–51.3 mg/dL	Lp(a) 5th quintile, ≥51.3 mg/dL	*p*-Value
Number	3,230	3,230	3,230	3,230	3,230	
Lp(a), mg/dL	4.0 (2.6–5.4)	9.7 (8.2–11.6)	18.2 (15.7–21.3)	34.9 (29.5–41.9)	80.4 (64.1–100.4)	<0.001
Age, y	60.3 (53.0–67.0)	61.5 (54.0–68.0)	61.8 (54.0–68.0)	62.0 (54.0–68.5)	62.0 (54.0–68.6)	<0.001
Men, %	2,606 (80.7)	2,431 (75.3)	2,446 (75.7)	2,343 (72.5)	2,252 (69.7)	<0.001
BMI, kg/m^2	26.0 (24.2–28.1)	25.7 (23.7–27.8)	25.7 (23.6–27.8)	25.6 (23.6–27.8)	25.4 (23.5–27.7)	<0.001
Diabetes mellitus, %	1,093 (33.8)	1,056 (32.7)	1,018 (31.5)	1,046 (32.4)	1,017 (31.5)	0.234
Hypertension, %	2,126 (65.8)	2,114 (65.4)	2,063 (63.9)	2,138 (66.2)	2,123 (65.7)	0.326
Family history of CAD, %	585 (18.1)	516 (16.0)	507 (15.7)	529 (16.4)	482 (14.9)	0.010
Previous stroke, %	499 (15.4)	511 (15.8)	494 (15.3)	496 (15.4)	544 (16.8)	0.403
Previous MI, %	594 (18.4)	530 (16.4)	527 (16.3)	572 (17.7)	655 (20.3)	<0.001
Previous PCI/ CABG, %	862 (26.7)	770 (23.8)	810 (25.1)	871 (27.0)	982 (30.4)	<0.001
Current smoker, %	794 (24.6)	735 (22.8)	787 (24.4)	740 (22.9)	578 (17.9)	<0.001
Drinking history, %	1,584 (49.0)	1,441 (44.6)	1,478 (45.8)	1,412 (43.7)	1,350 (41.8)	<0.001
Diagnosis on admission, %						<0.001
Chronic coronary syndrome	2,017 (62.4)	1,790 (55.4)	1,671 (51.7)	1,723 (53.3)	1,944 (60.2)	
Acute coronary syndrome	1,213 (37.6)	1,440 (44.6)	1,559 (48.3)	1,507 (46.7)	1,286 (39.8)	
LDL cholesterol, mg/dL	81.1 (63.7–105.0)	88.4 (68.7–113.9)	91.9 (71.8–117.4)	92.7 (73.4–119.7)	96.1 (76.4–121.2)	<0.001
HDL cholesterol, mg/dL	39.8 (33.6–47.5)	40.5 (34.4–48.6)	40.9 (34.4–48.6)	41.3 (34.7–49.0)	42.1 (35.9–50.6)	<0.001
Total cholesterol, mg/dL	145.2 (121.6–174.1)	150.2 (126.6–179.5)	154.1 (131.3–183.0)	155.2 (132.0–185.7)	160.2 (136.3–188.4)	<0.001
Triglycerides, mg/dL	136.3 (96.5–195.8)	125.7 (91.2–174.3)	122.1 (90.3–166.6)	121.2 (91.2–165.5)	123.9 (92.9–162.8)	<0.001
eGFR, mL/min/ 1.73 m^2	87.4 (75.5–99.7)	85.9 (74.0–99.2)	86.6 (74.3–99.9)	86.2 (73.8–98.4)	84.8 (71.8–96.6)	<0.001
hsCRP, mg/L	1.6 (0.8–3.7)	2.0 (0.9–4.4)	2.3 (1.0–6.2)	2.4 (1.1–6.2)	2.0 (1.0–5.1)	<0.001
Left main/three-vessel disease, %	1,307 (40.5)	1,227 (38.0)	1,404 (43.5)	1,424 (44.1)	1,559 (48.3)	<0.001
SYNTAX score	11.0 (6.0–18.0)	11.0 (7.0–18.7)	12.0 (7.0–19.0)	12.0 (7.0–19.5)	12.0 (7.0–19.5)	<0.001
LVEF, %	62.0 (58.0–65.0)	61.0 (57.8–65.0)	60.0 (57.0–65.0)	60.0 (56.0–65.0)	60.0 (57.0–65.0)	<0.001
Medications at discharge, %						
Dual antiplatelet therapy	3,150 (97.5)	3,170 (98.1)	3,158 (97.8)	3,141 (97.2)	3,148 (97.5)	0.161
β-Blocker	2,594 (80.3)	2,435 (75.4)	2,496 (77.3)	2,524 (78.1)	2,596 (80.4)	<0.001
ACEI/ARB	1,717 (53.2)	1,723 (53.3)	1,781 (55.1)	1,765 (54.6)	1,701 (52.7)	0.219
CCB	1,399 (43.3)	1,312 (40.6)	1,301 (40.3)	1,325 (41.0)	1,413 (43.7)	0.008
Statin	3,070 (95.0)	3,088 (95.6)	3,097 (95.9)	3,059 (94.7)	3,080 (95.4)	0.188
Oral anticoagulants	369 (11.4)	348 (10.8)	354 (11.0)	391 (12.1)	406 (12.6)	0.121

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SYNTAX, synergy between PCI with taxus and cardiac surgery.
Note: Data were expressed as *n* (%) or median (interquartile range).

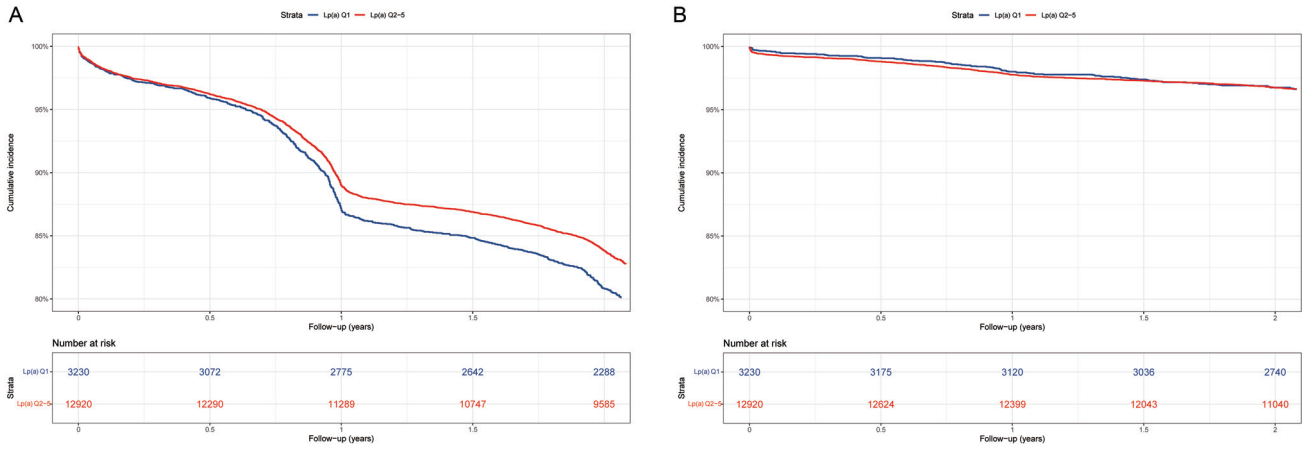

Fig. 2 Kaplan–Meier curves of 2-year bleeding (**A**) and 2-year major bleeding (**B**) according to Lp(a) level (quintile 1 vs. quintiles 2–5). Lp(a), lipoprotein(a).

Table 2 Multivariable Cox regression analyses for the primary and secondary endpoints

			Univariable		Model 1		Model 2		Model 3	
		Events/ subjects	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Bleeding	Lp(a) quintile 1	625/ 3,230	Reference	–	Reference	–	Reference	–	Reference	–
	Lp(a) quintiles 2–5	2,122/ 12,920	0.84 (0.77–0.92)	<0.001	0.86 (0.79–0.95)	0.001	0.87 (0.80–0.95)	0.003	0.89 (0.81–0.98)	0.012
Major bleeding	Lp(a) quintile 1	105/ 3,290	Reference	–	Reference	–	Reference	–	Reference	–
	Lp(a) quintiles 2–5	420/ 12,920	1.01 (0.81–1.25)	0.958	0.98 (0.79–1.22)	0.875	0.98 (0.79–1.22)	0.886	0.97 (0.78–1.21)	0.793

Abbreviations: CI, confidence interval; HR, hazard ratio; Lp(a), lipoprotein(a).
Note: Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, BMI, hypertension, family history of CAD, and drinking history.
Model 3: adjusted for age, sex, BMI, hypertension, family history of CAD, drinking history, LDL cholesterol, total cholesterol, hsCRP, LVEF, dual antiplatelet therapy, β-blocker, CCB, and oral anticoagulants.

CI: 0.15–0.76; HR: 0.44, 95% CI: 0.21–0.96, respectively), compared with those with the lowest Lp(a) (in the first tertile), which suggested that a lower level of Lp(a) may be a marker of the cerebral hemorrhagic risk in the general Japanese population.[8] Moreover, in the secondary prevention settings, similar evidence presented that among 860 patients with incident peritoneal dialysis from a retrospective study in China, serum Lp(a) concentrations were independently and inversely associated with the risk of hemorrhagic stroke.[10] However, a knowledge gap toward the association of Lp(a) with long-term bleeding risk still exists in the secondary prevention of patients with CAD, who require long-term aspirin as the base medication and 12-month DAPT after PCI. Based on the background that the East Asian individuals usually have a higher risk of bleeding than their European or American counterparts, it is of great need to explore whether lower Lp (a) concentrations would increase the incidence of bleeding events concomitantly, especially in treated CAD patients who might be at a higher risk of bleeding.[15]

To the best of our knowledge, our novel findings first reported that, after adjusting for confounding risk factors, there is an inverse association between serum Lp(a) concentration and long-term bleeding risk in this analysis of over 16,000 participants with established CAD.

Interestingly, the results displayed in ►**Fig. 2A** indicate that both the Lp(a) quintile 1 curve and the Lp(a) quintiles 2 to 5 curve exhibit inflection points at the 1-year follow-up. This finding can be attributed to the fact that a majority of participants in this study underwent PCI and required DAPT for a period of 1 year. Consequently, the difference in bleeding incidence between the two patient groups increased during the 12-month follow-up period, while the difference in bleeding incidence remained stable during the subsequent 12-month follow-up period. Similar results are also shown in ►**Supplementary Fig. S2A** (available in the online version). According to RCS analysis, there was an L-shaped association of Lp(a) with the risk of bleeding at 2-year follow-up, consistent with the findings of an inverse association of Lp(a) and 2-year bleeding risk. Subgroup analysis presented comparable interactions following 2-year bleeding between two groups and some meaningful covariates (age, sex, BMI, hypertension, family history of

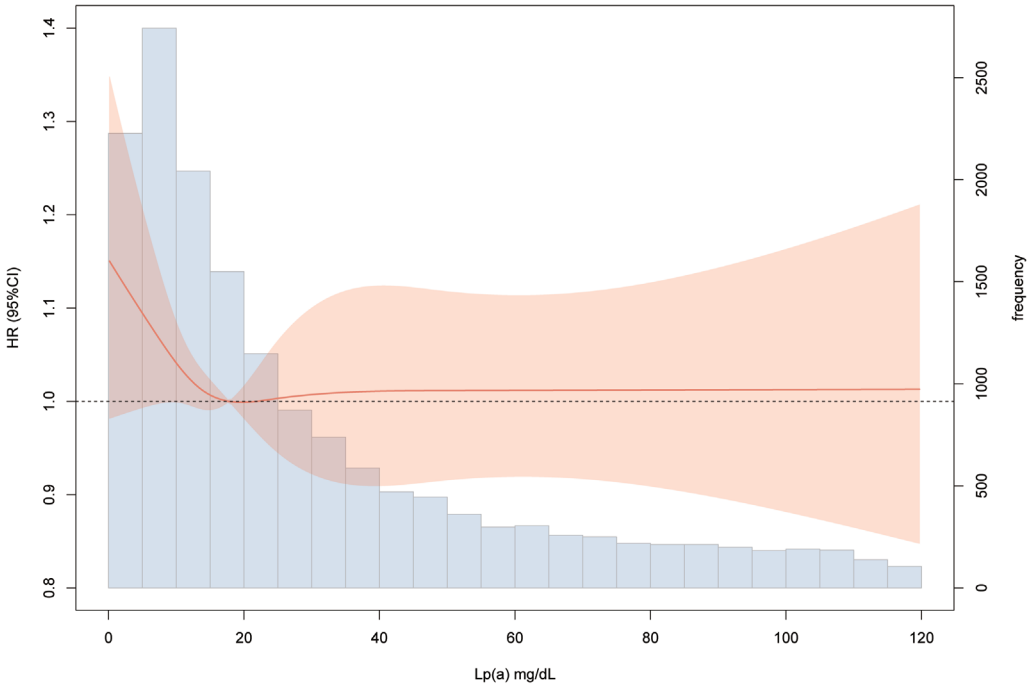

Fig. 3 Multivariable adjusted hazard ratios for long-term bleeding according to lipoprotein(a) levels. Solid red lines are multivariable-adjusted hazard ratios, and light red shade indicates 95% confidence intervals derived from restricted cubic spline regressions with four knots. The hazard ratio of no association of 1.0 is also shown as a dashed line. The light blue shadow illustrates the distribution histogram of Lp(a). Cox regressions were adjusted for age, sex, BMI, hypertension, family history of CAD, drinking history, LDL cholesterol, total cholesterol, hsCRP, LVEF, dual antiplatelet therapy, β-blocker, CCB, and oral anticoagulants. BMI, body mass index; CAD, coronary artery disease; CCB, calcium-channel blocker; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LVEF, left ventricular ejection fraction.

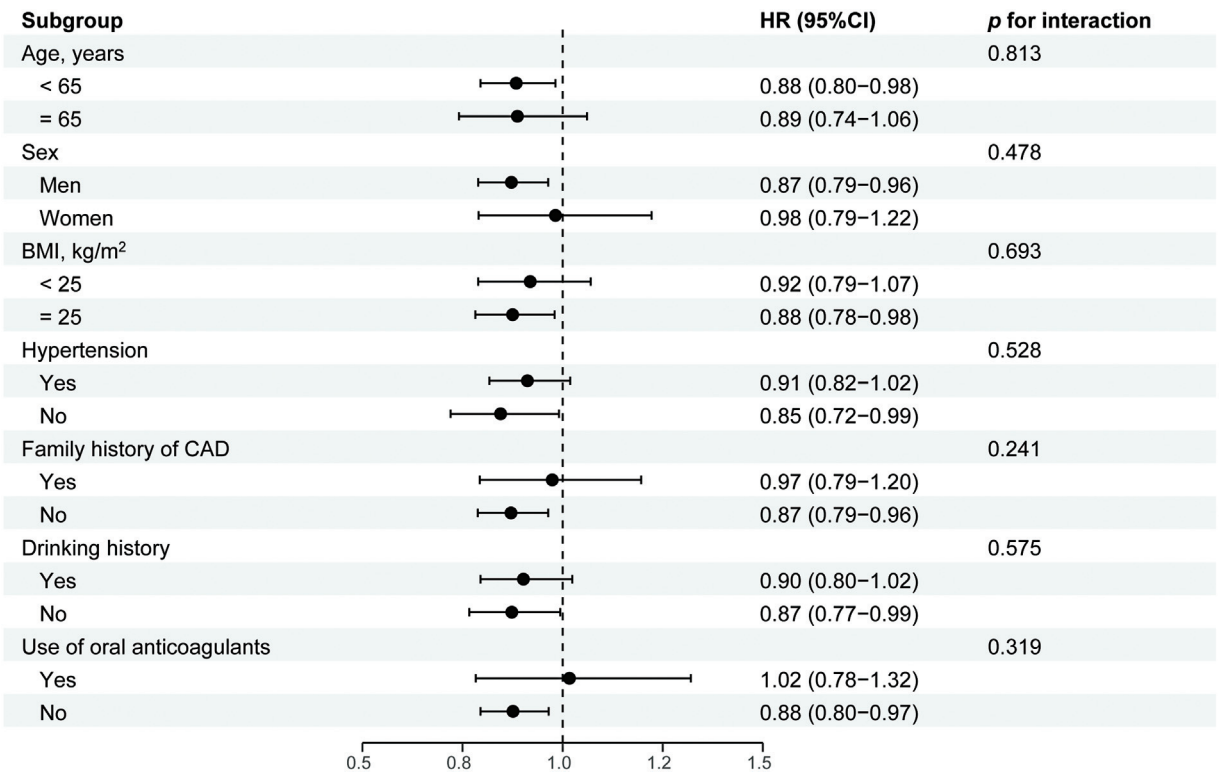

Fig. 4 Subgroup analysis according to different subsets. Adjusted model included age, sex, BMI, hypertension, family history of CAD, drinking history, LDL cholesterol, total cholesterol, hsCRP, LVEF, dual antiplatelet therapy, β-blocker, CCB, and oral anticoagulants. HR, hazard ratio; CI, confidence interval; BMI, body mass index; CAD, coronary artery disease; CCB, calcium-channel blocker; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

CAD, drinking history, and use of oral anticoagulants). Interestingly, according to the regression coefficients for adjusted variables in model 3, age and hsCRP had significant inverse associations with the risk of bleeding (►**Supplementary Table S2** [available in the online version]). Future studies are expected to explore the relationship between these two factors and bleeding risk in CAD patients with different Lp(a) levels. Our findings underscored the importance of Lp(a) assessment and more effort should be made to promote clinician awareness of the Lp(a) as a novel marker for bleeding risk and how to interpret this inverse relationship and L-shaped association. However, this investigation did not find similar association of Lp(a) levels with long-term major bleeding (BARC type 2, 3, or 5 bleeding) risk, which might be interpreted by heterogeneity in the pathophysiology of bleeding in different organs and inconsistent definitions of major bleeding by different consensus.[9,12,21] Further RCTs concerning the association between Lp(a) levels and the risk of long-term bleeding in the secondary prevention of CAD patients on a global scale are needed to warrant our findings.

Since the role of Lp(a) in bleeding has not been investigated previously, we may only speculate the underlying mechanisms to explain our findings. As a complex atherogenic lipoprotein, Lp(a) particles possess unique anabolic and catabolic functions secondary to its protein component of Apo(a), which is encoded by the LPA gene and whose structure resembles plasminogen, a key constituent in the fibrinolysis cascade.[27] In the normal physiological state, plasminogen circulates in a closed, activation-resistant conformation and chooses an open form, when it is converted into active plasmin by various enzymes through binding to fibrin clots.[28,29] Apo(a) bounding covalently to Lp(a) has repeated copies of kringle-IV, similar to those found in plasminogen.[30] Therefore, activation of plasminogen, generation of plasmin, and fibrinolysis are all impaired.[31] Consistently, previous literatures have demonstrated that the fibrin clots forming at bleeding sites display plasminogen receptors with affinity for both Apo(a) and plasminogen.[32,33] Another plausible explanation for the association of Lp(a) with the risk of long-term bleeding may be related to its clot-disrupting properties, such as promotion of tissue factor expression in monocytes, binding and inhibition of the tissue factor pathway inhibitor, and overproduction of plasminogen activator inhibitor 1 induced by oxidized Lp(a).[34] As a result, due to the unique structural similarity and other factors interfering the clot biology, the competitive inhibition of plasmin activation and function by Lp(a) may inhibit fibrinolysis and lower level of Lp (a) may induce bleeding eventually.[35]

This study has several notable strengths. It is the first, prospective, real-world cohort investigation with a large sample size and the long follow-up, focusing on the role of Lp(a) with long-term bleeding in patients with CAD, who were consecutively enrolled from nine regional and representative medical centers in China. Moreover, we evaluated the nonlinear correlation between Lp(a) and 2-year bleeding risk and proposed an L-shaped association between Lp (a) and poor prognosis toward bleeding in patients with CAD for the first time. However, this research also has its shortcomings. First, due to the nature of observational research, we could not entirely adjust for potential confounding factors adequately in this study. Further RCTs are necessary to validate our findings. Second, Lp(a) concentrations were only measured at baseline. In fact, dynamic assessments might enable bleeding risk prediction more accurately. Third, given significant differences in Lp(a) levels across ethnicity, whether our findings could be generalized to other populations needs to be confirmed in the future.[36] Fourth, there might be some reporting bias, although a systematic methodology for capturing bleeding events had been used. Fifth, although the sensitivity analysis showed the robustness of the results to the cutoff value (6.8 mg/dL), this value was not derived from the systematic analysis and was stemmed from an exploratory analysis where the cutoff point might separate the risk by chance. Further studies are needed to confirm the significance of this cutoff point in the future.

Conclusion

In conclusion, our findings first demonstrated the inverse and L-shaped association of serum Lp(a) levels with the risk of bleeding at 2-year follow-up in patients with CAD. A global attention and effort should be made to increase the clinician awareness of Lp(a)'s role as a novel marker for bleeding risk to better guide shared-decision making in clinical practice. Additionally, the underlying mechanisms of the inverse and L-shaped association need to be further studied.

What is known about this topic?

- Elevated lipoprotein(a) levels are causally related to adverse ischemic events.
- High lipoprotein(a) levels exert physiological effects in the process of wound healing and tissue repairing.

What does this paper add?

- This study first reported that there was an inverse and L-shaped association of lipoprotein(a) with bleeding risk in patients with coronary artery disease.
- A global effort should be made to increase clinician awareness of lipoprotein(a)'s role, as a novel marker for bleeding risk, to better guide shared-decision making in clinical practice.

Authors' Contribution

P.W., D.Y., J.Y., and Y.H. contributed to the study design. P. Z., L.J., N.X., R.L., Y.C., J.X., Y.S., Y.Y., and X.T. participated in the collection, analysis, or interpretation of data. P.W. and D.Y. performed the statistical analysis and drafted the manuscript. J.Y., Y.H., R.G., X.W., Y.F., Z.Z., Z.L., Y.Z., Q.W., Z. W., X.G., and X.Z. critically revised the manuscript. All authors read and approved the final submitted version.

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Conflict of Interest
None declared.

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