High Level of Lipoprotein(a) as Predictor for Recurrent Heart Failure in Patients with Chronic Heart Failure: a Cohort Study

Jianlong Yan,[1] Yanbin Pan,[2*] Junhui Xiao,[1] Wenxue Ma,[1] Li Li,[1] Mingjiang Zhong,[1] Haiquan Long,[1] Fanliang Kong,[1] Wenming Shao[3]*

Huadu District People's Hospital, Southern Medical University – Cardiology,[1] Guangzhou – China

Huadu District People's Hospital, Southern Medical University - Intensive Care Unit.,[2] Guangzhou – China

The First Affiliated Hospital of Jinan University – Emergency,[3] Guangzhou – China

** Jianlong Yan and Yanbin Pan were co-first authors, they contributed equally to this study.*

Abstract

Background: **Elevated plasma levels of Lipoprotein(a) [Lp(a)] are recognized as a significant risk factor for atherosclerotic vascular disease. However, there are limited data regarding association between Lp(a) and recurrent heart failure (HF) in patients with chronic HF caused by coronary heart disease (CHD).**

Objective: **Elevated levels of Lp(a) might have a prognostic impact on recurrent HF in patients with chronic HF caused by CHD.**

Methods: **A total of 309 patients with chronic HF caused by CHD were consecutively enrolled in this study. The patients were divided into 2 groups according to whether Lp(a) levels were above or below the median level for the entire cohort (20.6 mg/dL): the high Lp(a) group (n = 155) and the low Lp(a) group (n = 154). A 2-sided $p < 0.05$ was statistically considered significant.**

Results: **During the median follow-up period of 186 days, 31 cases out of a total of 309 patients (10.03%) could not be reached during follow-up. A Kaplan–Meier analysis demonstrated that patients with higher Lp(a) levels had a higher incidence of recurrent HF than those with lower Lp(a) levels (log-rank < 0.0001). A multivariate Cox regression analysis revealed that Lp(a) levels were independently correlated with the incidence of recurrent HF after adjustment of potential confounders (hazard ratio: 2.720, 95 % confidence interval: 1.730-4.277, $p < 0.0001$).**

Conclusions: **In Chinese patients with chronic HF caused by CHD, elevated levels of Lp(a) are independently associated with recurrent HF. (Arq Bras Cardiol. 2019; 113(2):197-204)**

Keywords: **Lipoproteins; Apolipoproteins; Heart Failure; Coronary Artery Disease; Hypertension; Diabetes Mellitus; Echocardiography/methods; Cohort Studies.**

Introduction

Heart failure (HF) is a global, severe public health issue.[1] According to previous reports, the prevalence of HF is stable, at approximately 1% to 2% of the general population, but this number sharply increases to 20% in those aged over 80 years.[2] Among most developed and developing countries, the increasing number of HF patients has already become a significant epidemic and a major cause of hospitalizations, morbidity, and mortality despite advances in the treatment of HF.[3-6]

Elevated plasma levels of Lipoprotein(a) [Lp(a)] are recognized as a significant risk factor for atherosclerotic cardiac and cerebrovascular disease.[7-11] Lp(a) consists of one molecule of a low density lipoprotein (LDL)-like particle, containing apolipoprotein B-100 (apoB) and one molecule of a large highly polymorphic glycoprotein, named apolipoprotein(a) (apoA), which are connected by a single disulfide bond.[12] Studies have shown that Lp(a) contributes to cardiovascular disease (CVD) risk through multiple mechanisms, such as proatherogenic, proinflammatory, and potentially antifibrinolytic mechanisms.[13-15]

In the current studies, high levels of Lp(a) have been shown to be an independent risk factor for myocardial infarction,[8] stroke,[7] aortic stenosis,[16] and, as now shown, HF.[17] However, no studies have illustrated the significant association between Lp(a) levels and recurrent HF in participants with chronic HF caused by coronary heart disease (CHD). Therefore, our study sought to evaluate the association between plasma levels of Lp(a) and recurrent HF in patients with chronic HF caused by CHD.

Methods

Research design and population

In total, 309 hospitalized patients who were diagnosed with chronic HF due to CHD in the First Affiliated Hospital of Jinan University Guangzhou, China, were consecutively

Mailing Address: Junhui Xiao •
Huadu District People's Hospital, Southern Medical University, 48 Xinhua Road, Huadu, Guangzhou, Guangdong, 510800 - China
E-mail: xiaojunhui2009@hotmail.com
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enrolled over a continuous period between January 2014 and December 2016. Chronic HF was diagnosed by two cardiologists based on 2016 European Society of Cardiology guidelines.[18] Patients were enrolled based on the following criteria: 1) The etiology of chronic HF is CHD; 2) patients with HF in New York Heart Association functional class II to IV. Patients were excluded according to the following criteria: 1) chronic HF secondary to other heart diseases, such as valvular heart disease, obstructive hypertrophic cardiomyopathy, and myocarditis and pericardial disease; 2) complicated with infectious diseases, autoimmune diseases, malignant tumors, severe liver and end-stage kidney disease with dialysis and systemic disease such as hyperthyroidism; 3) removal of patients who lack clinical data; 4) administration of medications that affect Lp(a) levels (nicotinic acid including niceritrol, tocopherol nicotinate, and nicomol).

Data at the first admission were collected for patients with multiple hospitalizations. Hypertension was defined as systolic blood pressure (BP) $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg on repeated measurements, or the use of antihypertensive medication. Diabetes mellitus (DM) was defined according to the World Health Organization criteria.[19] We assessed the estimated glomerular filtration rate (eGFR) according to the Chinese Modification of Diet in Renal Diseases equation based on serum creatinine, age, and gender.[20] This study was approved by the ethics committee of the First Affiliated Hospital of Jinan University and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants involved in the study.

Laboratory measurements

The venous blood samples were usually obtained on the 2nd morning of admission after an 8-hour fasting. Serum Lp(a) levels were measured by latex agglutination immunoassays and apolipoproteins were determined by fixed-rate immunonephelometric assay using a HITACHI 7600 chemistry autoanalyzer (Hitachi High-Technologies Corporation, Tokyo, Japan).

Echocardiography

Transthoracic echocardiographic examination was performed on each enrolled patient by an experienced ultrasonographist using a Philips IE33 (Philips Healthcare, the Netherlands) cardiac ultrasound system machine within 24 to 48 hours after admission and within 24 hours after the primary PCI. Left ventricular ejection fraction (LVEF) was estimated with the modified Simpson method.

Clinical outcome and follow-up

The primary outcome evaluated in the present study was recurrent HF. The patients included in this study were followed for 1, 3, 6, 9, and 12 months after discharge with 1) access to medical records, outpatient electronic workstations, and medical insurance system; 2) telephone or face-to-face visits. For follow-up failures, we contacted the patients' family or neighbors, or even their workplaces.

Statistical analysis

First, continuous variables with normal distribution were expressed as mean (standard deviation [SD]); non-normal variables were reported as median (interquartile range [IQR]). Categorical variables were described as numbers and/or percentages. Means of 2 continuous normally distributed variables were compared by independent samples Student's *t* test. Mann-Whitney U test was employed to compare means of 2 groups of variables not normally distributed. The frequencies of categorical variables were compared using Pearson χ^2 test.

Second, patients were divided into 2 groups according to whether Lp(a) levels were above or below the median level for the entire cohort (20.6 mg/dL): the high Lp(a) group (n = 155) and the low Lp(a) group (n = 154). The event-free rate for recurrent HF was plotted using Kaplan−Meier method with the log-rank test.

Third, we analyzed the association of plasma Lp(a) levels as a continuous variable and as categorical variables with recurrent HF. Cox proportional hazards models were used to evaluate these associations, both with and without adjustment for confounding variables. In the adjusted regression model I, number of stents, multiple lesions, aldosterone antagonists, LN-NT-proBNP, SBP, and NYHA class were included. Model II was further adjusted for the same variables as Model I plus the following risk factors: gender, DM, atrial fibrillation (AF), hypertension, LAD lesion, prior PCI, two lesions, diuretics, ACEI/ARBs, digoxin, beta-blockers, anti-diabetic drugs, heart rate, total cholesterol (TC), potassium, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides, hemoglobin, LVEF, age, body mass index (BMI), and eGFR.

The MedCalc software, version 15.2.2, was used to calculate the clinical outcomes with relative risk and 95% confidence interval (CI). The Cox proportional hazards models analyses was performed using the EmpowerStats statistical software (http://www.empowerstats.com, X&Y Solutions, Inc. Boston, MA) and the statistical package R (http://www.R-project.org). A 2-sided $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 309 patients with chronic HF caused by CHD were enrolled in this study. 31 patients (10.03%) could not be reached during follow-up. The mean age of the patients was 68.6 $\pm$ 11.6 years, and 174 (56.3%) were males. The medians (IQR) of two groups of Lp(a) levels were 12.0 (7.6-16.6) mg/dL and 35.3 (25.4-52.0) mg/dL, respectively ($p < 0.001$).

Baseline characteristics and laboratory results, past medical history, and medications at discharge are shown in Table 1. There were differences in NYHA class, LVEF, NT-proBNP and Lp(a) levels, prior MI, prior PCI, multiple lesions, and number of stents between 2 groups. Meanwhile, there were no differences regarding medication at discharge, age, male gender, current smoker, BMI, heart rate, eGFR, conventional lipid profile, DM, AF, hypertension, and prior CABG.

Table 1 – Baseline characteristics of the study population

Variables	All patients (n = 309)	Low-Lp (a) Group (n = 154)	High-Lp (a) Group (n = 155)	p value
Age (years)	68.6 ± 11.6	68.5 ± 11.7	68.8 ± 11.6	0.833
Male gender (%)	174 (56.3)	79 (51.3)	95 (61.3)	0.077
Current smokers (%)	72 (23.3)	31 (20.1)	41 (26.5)	0.189
Alcohol intake (%)	15 (4.9)	6 (3.9)	9 (5.8)	0.435
Heart rate (beats/min)	81.6 ± 18.5	81.7 ± 18.0	81.5 ± 19.1	0.920
BMI (kg/m^2)	21.9 ± 4.5	22.4 ± 4.5	21.5 ± 4.5	0.087
SBP (mmHg)	142.5 ± 28.1	146.0 ± 29.3	139.0 ± 26.4	0.801
NYHA class (%)				**< 0.001**
II	154 (49.8)	103 (66.9)	51 (32.9)	
III	102 (33.0)	32 (20.8)	70 (45.2)	
IV	53 (17.2)	19 (12.3)	34 (21.9)	
Potassium (mmol/L)	3.9 ± 0.4	3.9 ± 0.4	4.0 ± 0.4	0.754
Sodium (mmol/L)	141.1 ± 4.2	141.2 ± 3.9	141.0 ± 4.4	0.633
Hemoglobin (g/dL)	131.0 ± 17.8	130.6 ± 16.3	131.2 ± 19.2	0.760
NT-proBNP (pg/ml)	3109.0 (1500.0-6313.0)	1534.5 (1075.0-2523.5)	5977.0 (3222.0-8835.0)	< 0.001
LN-NT-proBNP (pg/ml*)	8.0 ± 0.8	7.4 ± 0.7	8.6 ± 0.6	< 0.001
LVEF (%)	48.3 ± 4.2	49.2 ± 3.8	47.4 ± 4.4	< 0.001
eGFR (mL/min/1.73 m^2)	85.3 ± 29.8	88.4 ± 28.1	82.1 ± 31.1	0.063
TC (mg/dL)	156.7 (129.7-190.4)	161.0 (135.3-187.9)	156.0 (127.3-191.9)	0.974
Lp(a) (mg/dL)	20.6 (12.0-35.3)	12.0 (7.6-16.6)	35.3 (25.4-52.0)	< 0.001
HDL-C (mg/dL)	42.6 (36.4-50.3)	42.8 (36.1-50.3)	42.6 (37.0-49.5)	0.762
LDL-C (mg/dL)	90.3 (72.6-118.1)	92.1 (74.9-111.2)	88.4 (64.3-121.8)	0.609
TG (mg/dL)	117.8 (82.3-167.3)	125.7 (81.5-189.5)	112.5 (83.7-155.4)	0.133
LAD lesion(%)	278 (90.0)	137 (89.0)	141 (91.0)	0.557
Two lesions(%)	91 (29.4)	41 (26.6)	50 (32.3)	0.277
Multiple lesions(%)	89 (28.8)	34 (22.1)	55 (35.5)	0.009
Number of stents (%)				**< 0.001**
0	141 (45.6)	87 (56.5)	54 (34.8)	
1	96 (31.0)	47 (30.5)	49 (31.6)	
2	50 (16.2)	11 (7.1)	39 (25.2)	
3	14 (4.5)	5 (3.2)	9 (5.8)	
4	8 (2.6)	4 (2.6)	4 (2.6)	
History of				
DM(%)	130 (42.1)	57 (37.0)	73 (47.1)	0.073
AF(%)	32 (10.4)	18 (11.7)	14 (9.0)	0.444
Hypertension (%)	251 (81.2)	131 (85.1)	120 (77.4)	0.085
Prior MI(%)	91 (29.4)	33 (21.4)	58 (37.4)	0.002
Prior CABG(%)	2 (0.6)	2 (1.3)	0 (0.0)	0.475
Prior PCI(%)	164 (53.1)	66 (42.9)	98 (63.2)	<0.001
Medications at discharge				
Diuretics (%)	183 (59.2)	88 (57.1)	95 (61.3)	0.458
Digoxin (%)	12 (3.9)	5 (3.2)	7 (4.5)	0.564
ACEI/ARBs (%)	285 (92.2)	140 (90.9)	145 (93.5)	0.386

Continuation

Beta-blockers (%)	276 (89.3)	133 (86.4)	143 (92.3)	0.093
Aldosterone antagonists (%)	171 (55.3)	83 (53.9)	88 (56.8)	0.611
antiplatelet drugs(%)	296 (95.8)	146 (94.8)	150 (96.8)	0.389
Statins (%)	303 (98.1)	150 (97.4)	153 (98.7)	0.405
Anti-diabetic drugs(%)	125 (40.5)	55 (35.7)	70 (45.2)	0.091

*AF: atrial fibrillation; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; Lp(a): lipoprotein(a); LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; LAD: lesion left anterior descending artery lesion; NYHA class: New York Heart Association class; NT-proBNP: N-terminal pro-B type natriuretic peptide; Prior MI: prior myocardial infarction; Prior CABG: prior coronary artery bypass grafting; Prior PCI: prior percutaneous coronary intervention; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides. *LN-NT-proBNP was the natural logarithm of NT-proBNP. Data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]) or n (%).*

Clinical outcomes

The median follow-up period was 186 days, with a maximum of 365 days. Clinical outcomes between groups are summarized in Table 2. The recurrent HF was significantly different between the 2 groups, but cardiac death, acute coronary syndrome, and ischemic stroke were not. The presence of elevated Lp(a) levels was associated with a greater rate of the recurrent HF (51.3% vs 78.1%, $p < 0.0001$).

Kaplan-Meier survival analysis

Kaplan-Meier survival analysis demonstrated that patients in the high Lp(a) group had a significantly higher incidence rate of the recurrent HF compared with those in the low Lp(a) group (log-rank $p < 0.0001$) (Figure 1).

Hazard ratio (95% confidence interval) for recurrent HF events

Considering Lp(a) < 20.6 as the reference group, Lp(a) ≥ 20.6 had higher risks for recurrent HF, with HR of 3.071 (95% CI, 2.283-4.130, $p<0.0001$). When adjusted for clinical parameters such as number of stents, multiple lesions, aldosterone antagonists, LN-NT-proBNP, SBP, NYHA class, the HR of Lp(a) ≥ 20.6 was 2.244 (95% CI, 1.493-3.371, $p = 0.0001$). The HR from adjusted II was further increased after further adjustment for other known confounding variables. Compared with the reference, the HR of Lp(a) ≥ 20.6 was 2.720 (95% CI, 1.730-4.277, $p = 0.0001$). In addition, analyses with the plasma Lp(a) levels as a continuous variable were conducted for the overall population, which showed these associations remained statistically significant after adjustment in Adjust I and Adjust II (Table 3).

Discussion

To our knowledge, this is the first study to analyze the association between baseline Lp(a) levels and recurrent HF in patients with chronic HF due to CHD. We found that a higher Lp(a) level is an independent predictor of the occurrence of recurrent HF in patients with chronic HF caused by CHD.

Previous several studies have demonstrated the association between Lp(a) levels and cardiac and cerebrovascular events. High levels of Lp(a) are associated with increased risk of myocardial infarction in a prospective general population study with 16 years of follow-up.[8] One study revealed that Lp(a) levels at admission were independently correlated with the occurrence of MACCE in patients with STEMI.[21] Another study suggested that an elevated Lp(a) level was significantly associated with long-term mortality following coronary angiography or percutaneous coronary intervention.[22] Although many studies have shown that LP(a) is an independent risk factor for adverse cardiac and cerebrovascular outcomes, limited data are available on the association between baseline Lp(a) levels and recurrent HF. In our study, we showed that baseline levels of Lp(a) ≥ 20.6 mg/dL was associated with significantly increased risk of recurrent HF with an HR of 2.720 (95% CI, 1.730-4.277; $p < 0.0001$) in patients with chronic HF due to CHD during the one-year follow-up, even after adjustment for major covariables. This observed association is consistent with the findings from a large-scale prospective study in a Danish overall population that consisted of 98,097 participants aged 48–67 y at baseline, followed for up to 21 years (mean of 7). The population attributable risk of HF was 9% for elevated Lp(a) levels.[17]

Currently, there are a few possible reasons for HF. Two possible mechanisms might explain this association between Lp(a) and HF occurrence:1) The increased HF risk due to elevated Lp(a) levels was partially mediated by myocardial infarction and/or aortic valve stenosis,[17,23] which can also be observed in our study. However, most part cannot be explained through both sides. 2) Given its proatherogenic properties, increased arterial stiffness, including vascular noncompliance in the aorta, was strongly associated with increased risk of HF.[24] Because echocardiography data were not collected, we could not assess the associations of Lp(a) levels, aortic stenosis, arterial stiffness and HF in our study. Compared with previous studies, our study included patients with a history of chronic HF. In addition, patients have poor left ventricular systolic function. The abovementioned fact is the possible cause of HF recurrence.

Additionally, the median value of Lp(a) is also different among different ethnicities, such as non-Hispanic Caucasians (median, 12 mg/dL [IQR, 5-32 mg/dL]), and Japanese individuals (median, 13 mg/dL [IQR, 5-26 mg/dL]).[25] In our study, Lp(a) was higher than in other populations (median, 20.6 mg/dL [IQR, 12.0-35.5 mg/dL]). Apo (a) contains 10 KIV repeated

Table 2 – Clinical outcomes

Variables	Low-Lp (a) Group (n = 154)	High-Lp (a) Group (n = 155)	RR	95% CI	p value
Recurrent HF	79 (51.3)	121 (78.1)	1.52	1.28-1.81	< 0.0001
Ischemic stroke	1 (0.6)	3 (1.9)	2.98	0.31-28.34	0.3419
ACS	1 (0.6)	5 (3.2)	4.97	0.59-42.03	0.1412
NSTEMI	0 (0)	2 (1.3)	4.97	0.24-102.65	0.2995
STEMI	1 (0.6)	3 (1.9)	2.98	0.31-28.34	0.3419
Cardiac death	0 (0)	2 (1.3)	4.97	0.24-102.65	0.2995

ACS: acute coronary syndrome; CI: confidence interval; HF: heart failure; NSTEMI: non-ST-segment elevation myocardial infarction; RR: relative risk; STEMI: ST-segment elevation myocardial infarction. Data are presented as n (%).

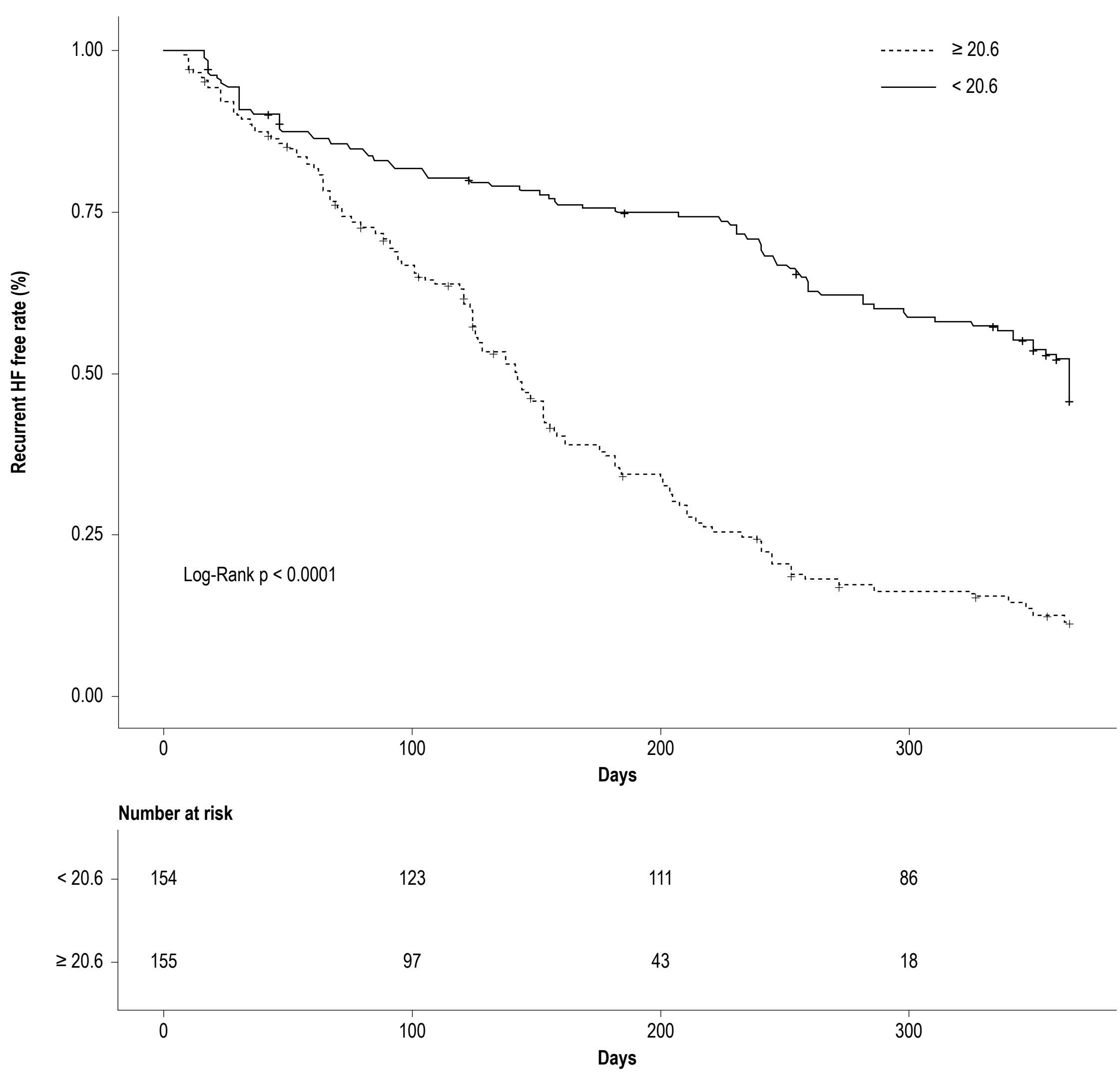

Figure 1 – *Kaplan-Meier curve for recurrent HF free rate according to Lp(a) levels. HF: heart failure.*

subtypes comprised of a single copy of KIV1, multiple copies of KIV2, a single copy of KIV3 ~ 10.[12] Lp(a) levels are genetically determined by the variation of the copy number of kringle IV type 2 (KIV-2) repeats on the *LPA* gene and various single nucleotide polymorphisms.[25] The number of repeats was inversely associated with Lp(a) levels.[25] In addition, Frischmann et al.[26] observed that increased plasma LP(a) levels were associated with renal dysfunction. In our study, the

Table 3 – Associations between baseline Lp(a) with recurrent heart failure

Exposure	Non-adjusted HR (95%CI)	p value	Adjust I HR (95%CI)	p value	Adjust II HR (95%CI)	p value
LP(a)	1.022 (1.016-1.028)	< 0.0001	1.014 (1.006-1.023)	0.0008	1.018 (1.009-1.027)	0.0001
LP(a)						
< 20.6	1.0		1.0		1.0	
≥ 20.6	3.071 (2.283-4.130)	< 0.0001	2.244 (1.493-3.371)	0.0001	2.720 (1.730-4.277)	< 0.0001

AF: atrial fibrillation; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; LDL-C: low-density lipoprotein cholesterol; LAD: lesion left anterior descending artery lesion; Lp(a): lipoprotein(a); NYHA class: New York Heart Association class; NT-proBNP: N-terminal pro-B type natriuretic peptide; Prior PCI: prior percutaneous coronary intervention; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides. Non-adjusted model adjust for: none. Adjust I model adjust for: number of stent, multiple lesions, aldosterone antagonists, LN-NT-proBNP, SBP, NYHA class.

included subjects had lower glomerular filtration rate, which led to reduced clearance of Lp(a), and higher plasma levels than in other previously studied Chinese populations.

In our study, the rates of statin use were up to 97.4% and 98.7% in patients with low-Lp(a) group and high-Lp(a) group, respectively, and most patients adhered to statin therapy during follow-up, but statins were originally intended to lower LDL-C levels. Moreover, previous studies have shown that statin therapy did not easily alter Lp(a) levels.[27,28] About the Lp(a) reduction treatment, early treatment with nicotinic acid, with the increase in nicotinic acid treatment dose, also correspondingly resulted in lower serum levels of Lp(a), and a maximum reduction in Lp(a) levels of up to 30-40%.[29] Because of the significant side effects such as facial blushing and liver toxicity, it is no longer widely used.[30] Recently, new Lp(a)-lowering treatments have emerged. The novel lipid-lowering drug Mipomersen is a synthetic inhibitor of apoB that indirectly reduces the synthesis of Lp(a) by reducing the synthesis of apo B, which can significantly reduce Lp(a) levels in patients with CHD.[31] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce the level of LP(a) by inhibiting the degradation of low-density lipoprotein receptors (LDLR).[32] In the present study, none of the subjects used the abovementioned drugs. For patients with chronic HF due to CHD, further multicenter prospective randomized controlled trials are needed to verify whether lowering the levels of serum Lp(a) can reduce the risk of cardiovascular and cerebrovascular events.

Conclusion

In conclusion, in Chinese patients with chronic HF caused by CHD, our study demonstrates that elevated levels of Lp(a) significantly predict recurrent HF.

Limitations

Our study has several limitations. First, it was a retrospective, observational and single-center study with selection bias. Therefore, whether the associations between LPA, B and HF are actually established, further multicenter prospective randomized controlled trials are needed to verify them in the future. Second, although we adjusted several known confounding variables in the multivariable Cox proportional hazards models, other unknown factors might have played roles in recurrent HF. Third, the detection of events may have been incomplete due to follow-up failures. 31 cases out of a total of 309 patients (10.03%) could not be reached during follow-up. Fourth, our study did not differ between HF with preserved and reduced ejection fraction when assessing the association between Lp(a) and recurrent HF in patients with chronic HF who have CHD.

Author contributions

Conception and design of the research: Yan J, Pan Y, Xiao J; Acquisition of data: Yan J, Pan Y; Analysis and interpretation of the data: Yan J, Pan Y, Xiao J, Zhong M, Long H; Statistical analysis: Yan J, Pan Y, Xiao J, Ma W, Li L, Zhong M, Long H, Kong F; Writing of the manuscript: Yan J, Pan Y, Shao W; Critical revision of the manuscript for intellectual content: Yan J, Pan Y, Ma W, Li L, Kong F, Shao W.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the The First Affiliated Hospital of Jinan University under the protocol number 017. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014; 63(12):1123-1133.
2. Udelson JE, Stevenson LW. The Future of Heart Failure Diagnosis, Therapy, and Management. Circulation. 2016; 133(25):2671-86.
3. Desai AS. Intensive Management to Reduce Hospitalizations in Patients With Heart Failure. Circulation. 2016; 133(17):1704-7.
4. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33(14):1787-847.
5. Khatibzadeh S, Farzadfar F, Oliver J, Ezzati M, Moran A. Worldwide risk factors for heart failure: a systematic review and pooled analysis. Int J Cardiol. 2013; 168(2):1186-94.
6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013; 128(16):1810-52.
7. Erqou S, Kaptoge S, Perry PL, Di AE, Thompson A, White IR, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009; 302(4):412-23.
8. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009; 301(22):2331-9.
9. Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2012; 125(2):241-9.
10. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009; 361(26):2518-28.
11. Erqou S, Thompson A, Di AE, Saleheen D, Kaptoge S, Marcovina S, et al. Apolipoprotein(a) isoforms and the risk of vascular disease: systematic review of 40 studies involving 58,000 participants. J Am Coll Cardiol. 2010; 55(19):2160-7.
12. Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). J Lipid Res. 2016; 57(8):1339-59.
13. van der Valk FM, Bekkering S, Kroon J, Yeang C, Van den Bossche J, van Buul JD, et al. Oxidized Phospholipids on Lipoprotein(a) Elicit Arterial Wall Inflammation and an Inflammatory Monocyte Response in Humans. Circulation. 2016; 134(8):611-24.
14. Hancock MA, Boffa MB, Marcovina SM, Nesheim ME, Koschinsky ML. Inhibition of plasminogen activation by lipoprotein(a): critical domains in apolipoprotein(a) and mechanism of inhibition on fibrin and degraded fibrin surfaces. J Biol Chem. 2003; 278(26):23260-9.
15. Berglund L, Ramakrishnan R. Lipoprotein(a): an elusive cardiovascular risk factor. Arterioscler Thromb Vasc Biol. 2004; 24(12):2219-26.
16. Capoulade R, Chan KL, Yeang C, Mathieu P, Bossé Y, Dumesnil JG, et al. Oxidized Phospholipids, Lipoprotein(a), and Progression of Calcific Aortic Valve Stenosis. J Am Coll Cardiol. 2015; 66(11):1236-1246.
17. Kamstrup PR, Nordestgaard BG. Elevated Lipoprotein(a) Levels, LPA Risk Genotypes, and Increased Risk of Heart Failure in the General Population. JACC Heart Fail. 2016; 4(1):78-87.
18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016; 18(8):891-975.
19. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15(7):539-53.
20. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006; 17(10):2937-44.
21. Mitsuda T, Uemura Y, Ishii H, Takemoto K, Uchikawa T, Koyasu M, et al. Lipoprotein(a) levels predict adverse vascular events after acute myocardial infarction. Heart Vessels. 2016; 31(12):1923-9.
22. Feng Z, Li HL, Bei WJ, Guo XS, Wang K, Yi SX, et al. Association of lipoprotein(a) with long-term mortality following coronary angiography or percutaneous coronary intervention. Clin Cardiol. 2017; 40(9):674-678.
23. Feng Z, Li HL, Bei WJ, Guo XS, Wang K, Yi SX. Association of lipoprotein(a) with long-term mortality following coronary angiography or percutaneous coronary intervention. Clin Cardiol. 2017; 40(9):674-8.
24. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. J Am Coll Cardiol. 2012; 60(16):1455-69.
25. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010; 31(23):2844-53.
26. Frischmann ME, Kronenberg F, Trenkwalder E, Schaefer JR, Schweer H, Dieplinger B, et al. In vivo turnover study demonstrates diminished clearance of lipoprotein(a) in hemodialysis patients. Kidney Int. 2007; 71(10):1036-43.
27. Nicholls SJ, Tang WH, Scoffone H, Brennan DM, Hartiala J, Allayee H, et al. Lipoprotein(a) levels and long-term cardiovascular risk in the contemporary era of statin therapy. J Lipid Res. 2010; 51(10):3055-61.
28. Kostner GM, Gavish D, Leopold B, Bolzano K, Weintraub MS, Breslow JL. HMG CoA reductase inhibitors lower LDL cholesterol without reducing Lp(a) levels. Circulation. 1989; 80(5):1313-9.
29. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. Pharmacol Ther. 2010; 126(3):314-45.
30. Cooper DL, Murrell DE, Roane DS, Harirforoosh S. Effects of formulation design on niacin therapeutics: mechanism of action, metabolism, and drug delivery. Int J Pharm. 2015; 490(1-2):55-64.
31. Santos RD, Raal FJ, Catapano AL, Witztum JL, Steinhagen-Thiessen E, Tsimikas S. Mipomersen, an antisense oligonucleotide to apolipoprotein B-100, reduces lipoprotein(a) in various populations with hypercholesterolemia: results of 4 phase III trials. Arterioscler Thromb Vasc Biol. 2015; 35(3):689-99.
32. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015; 372(16):1489-99.