Association between lipoprotein (a) and heart failure with reduced ejection fraction development

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Abstract

Background: The current study aimed to evaluate the relationship between baseline serum lipoprotein (a) [Lp(a)] level and heart failure with reduced ejection fraction (HFrEF) development.

Methods: This was a retrospective study, and participants were enrolled from the outpatient clinic. All data were extracted from the electronic health record of the outpatient clinic system. The follow-up was performed through reviewing the clinical notes at the outpatient clinic system, and study outcome of the current study was the first diagnosis of HFrEF. Participants were divided into low Lp(a) (<30 mg/dl, \( n = 336 \)) and high Lp(a) (≥30 mg/dl, \( n = 584 \)) groups.

Results: Individuals in the high Lp(a) group were more likely to be men and have diabetes mellitus (DM) and dyslipidemia. Increased Lp(a) at baseline was positively associated with serum N-terminal pro-B natriuretic peptide level while negatively associated with left ventricular ejection fraction (LVEF) at follow-up. After adjusting for covariates, per 10 mg/dl increase in baseline Lp(a) remained significantly associated with HFrEF, with odds ratio of 1.17 (95% confidence interval of 1.05, 1.46). The magnitude of association between baseline Lp(a) level and HFrEF was greater in men and in individuals with DM or coronary heart disease (CHD), while it was weaker in individuals treated with beta-blocker at baseline.

Conclusion: Increased Lp(a) at baseline was associated with HFrEF development. The adverse effects of Lp(a) were greater on men and individuals with DM or CHD, which were mitigated by beta-blocker therapy. These findings together underscore the possibility and usefulness of Lp(a) as a new risk factor to predict HFrEF.

KEYWORDS
heart failure, lipoprotein (a), relationship

1 | INTRODUCTION

Heart failure (HF) is a leading cause of morbidity and mortality in China and worldwide.\(^1\)\(^-\)\(^3\) Considering the adverse impacts of HF on the prognosis and quality of life, the identification and characterization of new risk factor for HF is clinically relevant as it will help better predict the risk of HF development,\(^4\)\(^-\)\(^6\) which in turn would help guide clinical management in an efficient and effective way. Among these, lipoprotein (a) [Lp(a)] has been recognized as a potential target.\(^7\)\(^,\)\(^8\)

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Several studies have demonstrated that Lp(a) is an independent risk factor for atherosclerotic cardiovascular disease due to its proatherosclerotic and pro-thrombotic effects. In addition, high serum Lp(a) level was related to an increased risk of acute ischemic events, incident HF, and cardiovascular mortality. For example, our prior study has indicated that among individuals with acute coronary syndrome undergoing percutaneous coronary intervention, compared to those with low serum Lp(a) level, individuals with high serum Lp(a) level had a higher risk of developing congestive HF during hospitalization. Interestingly, results from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort study suggested that increased serum Lp(a) level at baseline was associated with incident HF only in the White but not in the Black, Hispanic, or Chinese populations. Differences in the clinical characteristics might partially explain the discrepant findings. It is important that the MESA study also has shown that compared with the other racial/ethnic groups, Chinese Americans appeared to have a lower serum Lp(a) level. These results suggested that Lp(a) might confer ethnic-specific impacts on cardiovascular system. Further studies are needed to clarify whether increased serum Lp(a) level is independently associated with incident HF in Chinese populations.

Accordingly, we conducted a retrospective study to evaluate whether baseline serum Lp(a) level was associated with incident HF with reduced ejection fraction (HFrEF). In addition, we performed an exploratory analysis to evaluate whether age, sex, comorbid conditions, and medication use at baseline would modify the relationship between serum Lp(a) level and incident HFrEF.

2 | METHODS

2.1 | Study participants

The current study was approved by the Institutional Review Board of the Fuwai Hospital Chinese Academy of Medical Science, Shenzhen, China, and written informed consent was waived due to the retrospective design. All the processes were performed in accordance with the Declaration of Helsinki. Individuals who were seen in the cardiovascular outpatient clinic of our hospital during January 2019 and June 2020 were screened for the eligibility of the current study. The included criteria were as follows: >18 years old, had serum Lp(a) level at baseline, and at least had one follow-up at the outpatient clinic of our hospital. The excluded criteria were as follows: had documented HF at baseline, was treated with a PCSK9 inhibitor at baseline, had prior history of myocardial infarction, prior revascularization, valvular heart disease, or cardiomyopathy (e.g., idiopathic dilated), had chronic kidney disease (CKD) with stage 4–5, or had familial hyperlipidemia. The study flowchart is presented in Figure 1.

2.2 | Data collection

All data were extracted from the electronic health record of the outpatient clinic system by independent investigators. Baseline data, including demographics (age and sex), vital signs (blood pressure and heart rate), and comorbid conditions (smoking, obesity, hypertension, diabetes mellitus [DM], dyslipidemia, atrial fibrillation, coronary heart disease [CHD], ischemic stroke/transient ischemic stroke, and peripheral vascular disease), were collected. Laboratory parameters included lipid panel, fasting plasma glucose (FPG), serum levels of creatinine, C-reactive protein (CRP), and Lp(a). Creatinine was used to calculate the estimated glomerular filtration rate (eGFR) using the MDRD formula. Medications used at baseline were also extracted.

2.3 | Follow-up and study outcome

The follow-up was performed through reviewing the clinical notes at the outpatient clinic system. Study outcome of the current study was the first diagnosis of HFrEF, which was based on the following criteria: the presence of HF symptoms (e.g., dyspnea at rest or during exercise).

A total of 2696 patients were screened during January of 2019 and June of 2020. 1263 patients were excluded due to without serum Lp(a) level at baseline. 513 patients were excluded due to the following: 128 had HF at baseline, 76 were being treated with PCSK9 inhibitor, 159 without any follow-up, 150 with myocardial infarction, prior revascularization, valvular heart disease, cardiomyopathy, chronic kidney disease stage 4–5, or familial hyperlipidemia.

FIGURE 1 Study flowchart
exercise) and signs (e.g., pulmonary rales or peripheral edema), elevated serum level of N-terminal pro-B-type natriuretic peptide (NT-proBNP), echocardiographic examination (e.g., left ventricular ejection fraction [LVEF] <40%), and medications used for HFrEF (e.g., loop diuretic). All the events were adjudicated by an experienced cardiologist.

2.4 Statistical analysis

Continuous variables with normal distribution were presented as mean ± standard deviation, otherwise were presented as median (interquartile range). Categorical variables were presented as number and percentage. Participants were separated into low Lp(a) (<30 mg/dl) and high Lp(a) (≥30 mg/dl) groups based on prior recommendation. Between-group differences were assessed using the Student t test or Mann–Whitney U test for continuous variables, and the chi-squared test for categorical variables. Linear regression analysis was performed to evaluate baseline serum Lp(a) level with serum NT-proBNP level and LVEF at follow-up. Coefficient beta (β) and associated 95% confidence interval (CI) were reported. To examine whether elevated Lp(a) was an independent risk factor for HFrEF, logistic regression analysis was performed and the low Lp(a) group was served as the reference group. Odds ratio (OR) and associated 95% CI were reported. To further examine whether age, sex, comorbid conditions and medication use at baseline would modify the relationship between Lp(a) and incident HFrEF, the interaction analysis was performed and a p-value for interaction was reported. All analyses were conducted using SPSS 23.0 statistical software, and a two-sided p-value < 0.05 was considered as statistical significance.

3 RESULTS

3.1 Baseline characteristics

Comparisons of baseline characteristics are presented in Table 1. Compared with those in the low Lp(a) group (n = 336), individuals in the high Lp(a) group (n = 584) were more likely to be men (66.1% vs. 54.8%) and have DM (32.5% vs. 29.2%) and dyslipidemia (52.7% vs. 42.0%), and had higher serum levels of triglyceride, CRP and Lp(a). There were no differences in medication use at baseline except that individuals in the high Lp(a) group were more likely to receive statins (50.9% vs. 45.8%) and less likely to receive beta-blocker (33.6% vs. 19.7%). The serum NT-proBNP and LVEF at baseline were comparable between these two groups.

3.2 Relationship between baseline Lp(a) level with serum NT-proBNP level and LVEF at follow-up

To evaluate whether baseline serum Lp(a) level was associated with serum NT-proBNP level and LVEF at follow-up, linear regression analysis was performed. As shown in Table 2, after adjusting for multiple potential covariates including baseline NT-proBNP and LVEF, increased Lp(a) at baseline was associated with increased serum NT-proBNP level at follow-up, with coefficient β of 1.04 (95% CI 0.82, 1.24), while increased Lp(a) at baseline was associated with decreased LVEF at follow-up, with coefficient β of −0.62 (95% CI −0.35, −0.89).

3.3 Association between Lp(a) and incident HFrEF

Among these 920 participants, 48 (5.2%) were diagnosed as HFrEF based on the outpatient clinical notes at follow-up. To examine whether baseline Lp(a) level predicted the incident HFrEF, multivariable regression analysis was performed. As shown in Table 3, in the unadjusted model, per 10 mg/dl increase in baseline Lp(a) was associated with 85% higher risk of incident HFrEF. After stepwise adjusting for covariates, per 10 mg/dl increase in baseline Lp(a) remained significantly associated with incident HFrEF, with odds ratio of 1.17 (95% CI 1.05, 1.46).

3.4 Interaction analysis of baseline Lp(a) level and incident HFrEF

We further examined whether baseline characteristics would modify the relationship between baseline Lp(a) level and incident HFrEF. As presented in Table 4, there were significant interactions according to sex, comorbid condition, and medication use at baseline. In specific, the magnitude of the association between baseline Lp(a) level and incidence HFrEF was greater in men and in individuals with DM or CHD, while it was weaker in individuals treated with beta-blocker at baseline.

4 DISCUSSION

The current study should be the first few studies to evaluate the relationship between Lp(a) and incident HFrEF among Chinese populations. There are two main findings of the current study. First, compared to those with low serum Lp(a) level, individuals with high serum Lp(a) level at baseline had a higher risk of developing HFrEF during follow-up. Also, after adjusting for multiple covariates, elevated Lp(a) remained significantly associated with a higher risk of developing HFrEF. Second, the interaction analysis indicated that elevated Lp(a) appeared to be associated with a greater risk of HFrEF in men and in individuals with DM or CHD, and a lower risk in individuals on beta-blocker therapy. These findings suggest that Lp(a) might be a risk factor for HFrEF among Chinese populations, especially for men and those with DM or CHD. Beta-blocker therapy might mitigate the risk.

With the extended life expectancy in the general populations, the prevalence of HF is increasing continuously in China and around
the world.1,2,17 Although the prognosis and quality of life have been improved for HFrEF populations in the last three decades, the 5-year survival rate remains suboptimal.18–20 Identifying novel risk factor for HF has two important clinical implications. On the one hand, it will help accurately predict the risk of HF in the population and individual level. On the other hand, it will facilitate the implementation of primary prevention, which in turn may help reduce the incidence of HF. Some studies from the Western populations have suggested that Lp(a) might be a useful marker to predict HF development. For example, in the MESA study, Steffen et al reported that Lp(a) was associated with a greater risk of HF only in White, and compared to those with Lp(a) <30 mg/dl, individuals with Lp(a) ≥30 mg/dl had 69% higher risk of developing HF.14 Findings from the Mendelian randomization study further demonstrated that increased serum Lp(a) level and corresponding LPA risk genotypes were associated with 22% increased risk of incident HF.21 Racial/ethnic differences in Lp(a) have been documented extensively,11,22,23 and it is therefore important and necessary to evaluate whether Lp(a) is a risk factor

| Variables                          | Lp(a) <30 mg/dl | Lp(a) ≥30 mg/dl | p-Value |
|------------------------------------|----------------|----------------|---------|
| n                                  | 336            | 584            |         |
| Age (years)                        | 49.3 ± 7.4     | 50.2 ± 8.6     | 0.64    |
| Men, n (%)                         | 184 (54.8)     | 386 (66.1)     | <0.0001 |
| Systolic blood pressure (mm Hg)    | 132 ± 17       | 134 ± 15       | 0.43    |
| Diastolic blood pressure (mm Hg)   | 76 ± 13        | 74 ± 14        | 0.51    |
| Heart rate (beat per minute)       | 79 ± 16        | 80 ± 17        | 0.25    |
| Current smoker, n (%)              | 136 (40.5)     | 229 (39.2)     | 0.84    |
| Obesity, n (%)                     | 95 (28.3)      | 153 (26.2)     | 0.37    |
| Hypertension, n (%)                | 182 (54.2)     | 322 (55.1)     | 0.62    |
| Diabetes mellitus, n (%)           | 98 (29.2)      | 190 (32.5)     | 0.04    |
| Dyslipidemia, n (%)                | 158 (47.0)     | 308 (52.7)     | 0.01    |
| Atrial fibrillation, n (%)         | 30 (8.9)       | 55 (9.4)       | 0.93    |
| Coronary heart disease, n (%)      | 129 (38.4)     | 236 (40.4)     | 0.19    |
| Ischemic stroke/TIA, n (%)         | 41 (12.2)      | 65 (11.1)      | 0.32    |
| Peripheral vascular disease, n (%) | 33 (9.8)       | 59 (10.1)      | 0.66    |
| Fasting plasma glucose (mmol/L)    | 5.8 ± 0.6      | 5.8 ± 0.5      | 0.87    |
| Total cholesterol (mmol/L)         | 5.1 ± 0.7      | 5.2 ± 0.9      | 0.48    |
| LDL-C (mmol/L)                     | 3.0 ± 0.6      | 3.1 ± 0.5      | 0.72    |
| HDL-C (mmol/L)                     | 1.0 ± 0.4      | 1.0 ± 0.5      | 0.28    |
| Triglyceride (mmol/L)              | 1.8 (0.8–2.9)  | 2.0 (0.9–3.1)  | 0.04    |
| Lipoprotein (a) (mg/dl)            | 16.2 (9.4–27.2)| 89.5 (47.8–188.5)| <0.0001|
| C-reactive protein (mg/dl)         | 4.5 ± 1.2      | 8.6 ± 2.5      | 0.003   |
| NT-proBNP (pg/ml)                  | 24.3 (12.2–38.7)| 21.9 (10.8–36.4)| 0.42    |
| Creatinine (umol/L)                | 73.4 ± 16.8    | 74.5 ± 17.2    | 0.65    |
| eGFR (ml/min/1.73m²)               | 70.5 ± 15.4    | 68.6 ± 13.6    | 0.26    |
| CKD, n (%)                         | 55 (16.4)      | 109 (18.7)     | 0.07    |
| Aspirin, n (%)                     | 216 (64.3)     | 407 (69.7)     | 0.09    |
| Clopidogrel, n (%)                 | 19 (5.7)       | 24 (4.1)       | 0.20    |
| Statins, n (%)                     | 154 (45.8)     | 297 (50.9)     | 0.03    |
| Beta-blocker, n (%)                | 113 (33.6)     | 115 (19.7)     | 0.01    |
| ACEI/ARB, n (%)                    | 175 (52.1)     | 296 (50.7)     | 0.14    |
| Calcium channel blocker, n (%)     | 80 (23.8)      | 127 (21.7)     | 0.35    |
| Oral antidiabetics, n (%)          | 74 (22.0)      | 148 (25.3)     | 0.07    |
| Insulin, n (%)                     | 18 (5.4)       | 35 (6.0)       | 0.11    |
| LVEF (%)                           | 58 ± 15        | 57 ± 13        | 0.85    |

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TIA, transient ischemic attack.
for HF in Chinese population. Leveraging the electronic health record from the outpatient clinic, we performed a retrospective study to investigate whether elevated Lp(a) at baseline portended an increased risk of developing HFrEF. Consistent with prior reports, our study further demonstrated that patients with elevated Lp(a) at baseline had 17% higher risk of developing HFrEF after adjusting for multiple covariates. However, the exact pathophysiological mechanisms are undetermined yet, and the two following theories might be applied to explain these findings. First, through pro-atherosclerotic and pro-thrombotic effects, elevated Lp(a) might cause micro- or macro-thrombosis in the coronary artery, which in turn impair cardiac perfusion and performance. Indeed, prior studies had shown that the association between Lp(a) and HF was partly explained by myocardial infarction. Second, accumulating evidence has demonstrated that Lp(a) is an independent risk factor for aortic valve stenosis. Notably, aortic valve stenosis results in chronic elevation of left ventricular afterload, which is associated with cardiac necrosis and fibrosis. Myocardial maladaptation usually predisposes to HF. Study of the Mendelian randomization study also had shown that the risk of Lp(a) on HF development can be partly attributed to aortic valve stenosis. Further studies are needed to elucidate whether reduction in Lp(a) can prevent HFrEF development in the general populations.

To the best of our knowledge, this should be the first study to report that the relationship between Lp(a) and HFrEF differed by sex, comorbid status and use of medication. Specifically, we observed that the magnitude of the association between Lp(a) and incident HFrEF was greater in men than in women. This observation might be partly explained by the cardioprotective effect of estrogen in women. It is noted that in individuals with DM or CHD, the magnitude of the association between Lp(a) and HFrEF was greater than their counterparts without DM or CHD. Indeed, individuals with DM or CHD are at an increased risk of developing HFrEF. Therefore, Lp(a) elevation might exert additive effects on HFrEF development. Unexpectedly, we also observed that individuals who were treated with beta-blocker at baseline had a lower risk of HFrEF than their counterparts without beta-blocker. The mechanism is unclear. However, one might speculate that inhibiting sympathetic nervous system with beta-blocker might result in decreased heart rate and cardiac workload, which in turn helps preserve cardiac function. Further studies are needed to corroborate the current findings.

In conclusion, the findings of the current study support the notion that increased Lp(a) at baseline was associated with HFrEF development. In addition, the adverse effects of Lp(a) were greater in
men and individuals with DM or CHD. Notably, these effects were mitigated by beta-blocker therapy. These findings together underscore the possibility and usefulness of Lp(a) as a new risk factor to predict HFrEF in Chinese populations.

4.1 Study limitation

There are some limitations of the current study. First, this was an observational study and any causal relationship cannot be drawn from the findings of the current study. Second, the current study was performed in the Chinese populations and whether these findings can be extrapolated to other racial/ethnic groups were unknown. Third, although we have adjusted for multiple covariates, unmeasured and unknown covariates might remain exist and influence the relationship between Lp(a) and HFrEF. Fourth, in the current study we only evaluated the relationship between Lp(a) and HFrEF, and whether there was also a significant relationship between Lp(a) and HF with preserved ejection fraction was unknown. Considering the increasing prevalence of HF with preserved ejection fraction worldwide, further studies are needed to address this issue.

CONFLICT OF INTEREST

All authors declare that they do not have any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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