Lipoprotein (a) is a residual risk of atherosclerotic renal artery stenosis in hypertensive patients: a population-based cross-sectional study.

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Research

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Abstract

**Background:** Low-density lipoprotein cholesterol (LDL-c) has been proven to be a risk factor for atherosclerotic cardiovascular disease (CVD), while lipoprotein (a) (Lp(a)) is a residual risk factor for CVD, even though LDL-c is well controlled by statin use. Importantly, the role of Lp(a) in atherosclerotic renal artery stenosis (ARAS) is still unknown.

**Methods:** For this cross-sectional population-based study, patients who simultaneously underwent coronary and renal angiography were examined. ARAS was defined as a 50% reduction in the cross-sectional (two-dimensional plane) area of the renal artery. Data were collected and compared between ARAS and non-ARAS groups, including clinical history and metabolite profiles. Univariate analysis, three tertile LDL-c-based stratified analysis, and multivariate-adjusted logistic analysis were conducted, revealing a correlation between Lp(a) and ARAS.

**Results:** A total of 170 hypertensive patients were included in this study, 85 with ARAS and 85 non-RAS. Baseline information indicated comparability between the two groups. Univariate analysis showed that systolic blood pressure and peripheral arterial disease were positively correlated with ARAS while coronary artery disease was negatively associated. Stratified analysis of LDL-c revealed a significant increase in the incidence of ARAS in patients who had high Lp(a) concentrations at low LDL-c levels (OR: 4.77, 95%CI:1.04-21.79, P = 0.044). Further logistic analysis with adjusted covariates also confirmed the result, indicating that high Lp(a) levels were independently associated with ARAS (OR: 8.16, 95%CI 1.12-59.12, P = 0.037). This relationship increased with increasing Lp(a) concentration based on a curve fitting graph. These results were not present in the low and intermediate LDL-c-level groups.

**Conclusion:** In hypertensive patients who present low LDL-c, high Lp(a) was significantly associated with atherosclerotic renal artery stenosis and thus is a residual risk factor.

**Background**

Cardiovascular disease (CVD) is the leading cause of death in China. A large proportion of CVD cases are caused by arteriosclerotic cardiovascular disease (ASCVD), which has rapidly and substantially increased, being responsible for > 2.4 million deaths in 2016 and accounting for 25% of total deaths [1]. Mendelian randomization studies and RCTs have consistently demonstrated that low-density lipoprotein cholesterol (LDL-c) is causally associated with the risk of ASCVD [2–7]. The American Heart Association/American College of Cardiology and European Society of Cardiology guidelines provide recommended LDL-c levels based on CVD risk stratification. In a recent ESC article, lipoprotein(a) [Lp(a)] was highlighted as a CVD risk estimator [8]. Studies from the past few decades have revealed that populations with well-regulated LDL-c levels still had a considerably high residual cardiovascular risk, and that Lp(a) is responsible for this phenomena [9–14].

Atherosclerotic renal artery stenosis (ARAS), which represents an important proportion of ASCVD cases, is generally recognized to cause renal damage and accounts for 5–15% of patients who develop end-stage renal disease [15–17]. The incidence of symptomless ARAS has been reported to be high in patients undergoing angiography for extrarenal atherosclerotic vascular disease, especially in hypertensive patients [18], reflecting the prevalence of ARAS in systemic atherosclerosis, and that it is commonly overlooked [19–20]. Hypertension can accelerate the progress of ARAS by facilitating lipid deposition, in addition to other traditional CVD risk factors, such as age [21, 22], diabetes [23], smoking [24], occurrence of peripheral artery disease (PAD) [19], and coronary artery disease (CAD)[25], which are also related to ARAS. This raises the question: does Lp(a) act as a "residual risk" factor for ARAS? Recent studies have suggested a relationship between Lp(a) and ARAS, but further evidence is required to clarify this relationship, which was the aim of this study.

**Methods**

**Study population and data collection**

This study was designed as a cross-sectional analysis. From October 2013 to September 2014, patients with hypertension who had simultaneously undergone both coronary and renal angiography with hypertension were consecutively selected from a single catheter center in China. Initially, patients underwent coronary angiography because of CAD, and renal angiography was also
performed if the patient satisfied any of the following conditions: patients who developed hypertension before age 30; patients who developed severe hypertension after age 55; patients with rapid, refractory, malignant, or suddenly aggravated hypertension; patients with deteriorated renal function (as marked by a >30% increase in serum creatinine) after treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; patients with unexplained renal atrophy or >1.5-cm difference in length of kidney; patients with unexplained sudden exacerbated and/or refractory pulmonary edema; patients with coronary multivesSEL disease, cerebrovascular disease, or peripheral atherosclerotic disease; patients with unexplained exacerbation of renal failure (including patients undergoing dialysis or kidney transplantation); or patients with unexplained congestive heart failure. Exclusion criteria include a history of cancer, coagulation disorder, or renal stenting.

All experimental data were collected from the case database of the medical center and recorded by two authors (Yang and Li).

Definitions and laboratory examination

In all patients, hypertension was diagnosed according to the European Society of Cardiology guidelines as SBP $\geq 140$ and/or DBP $\geq 90$ mmHg, which is equivalent to a 24-h ambulatory blood pressure monitoring average of $\geq 130/80$ mmHg, or a home blood pressure monitoring average of $\geq 135/85$ mmHg for two measurements at least 3 days [26]. Blood cell test was detected using a Sysmex-XE5000 through impedance technology. HDL-cholesterol, LDL-cholesterol, total-cholesterol, Lp(a), albumin, uric acid, creatinine, and cystatin C were detected using a Backman AU5800 spectrophotometer via colorimetry or immunoturbidimetry. Aldosterone, renin, and angiotensin II were detected using a PETECK96-I through a chemiluminescence immunoassay. The evaluated glomerular filtration rate (EGFR) ($\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{m}^{-2}$) was calculated using the Cockroft–Gault formula.

Coronary and renal angiography was performed by the Judkins technique. CAG and renal angiography were performed simultaneously with radial approach, and the femoral artery was used in a minority of patients as clinically necessary. Catheter 5-Fr or 6-Fr Judkins left and right diagnostic catheters (Cordis, Bridgewater, NJ, USA) were used for left and right coronary angiography, respectively. Renal angiography was performed using a 5-Fr Judkins right or 5-Fr Multi-Purpose diagnostic catheter engaged in or directed to the renal artery ostium, with contrast medium flowing back from the renal artery. Both renal arteries were visualized in anterior-posterior projections. All angiograms were independently reviewed by an experienced angiographer. Lesion severity in the coronary tree and the renal vasculature was assessed by visual estimation. ARAS was defined as a 50% reduction in the area of cross-sectional or two-dimensional plane of the renal artery, as presented by renal arterial lumen loss (RALL) $\geq 50%$. Coronary artery stenosis as measured by angiography that was $\geq 70%$ was regarded as CAD. Existing carotid, peripheral arterial, or aorta plaques were considered to represent PAD.

Statistical analysis

Statistical analysis was performed in three steps. First, the baseline characteristics of the participants were measured according to following principles after they were divided into two groups (ARAS and non-ARAS): (1) continuous variables were expressed as the means ± standard deviations (for normal distribution) or medians/quartiles (for skewed distribution), and categorical variables were shown as the frequencies with percentages; (2) one-way ANOVA (normal distribution), Kruskal–Wallis H (skewed distribution) test, and chi-square test (categorical variables) were used to determine significant differences between the groups. Next, an LDL-c-based stratified analysis was conducted to assess the relation between Lp(a) and ARAS. Third, all of the risk factors mentioned previously were pooled for multivariate adjustment by logistic analysis and used to assemble generalized additive models to identify non-linear relationships where Lp(a) was a continuous variable. If an incremental effect model was present, it was trimmed into three tertiles to determine the threshold point for risk assessment. Comparisons where P < 0.05 (two-sided) were considered to be statistically significant. All of the analyses were performed with Stata 15.0, R (version 3.4.3) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA).

Result

Baseline information

A total of 170 hypertensive patients were analyzed in this study. Based on the RALL range, these patients were divided into two groups: ARAS (RALL $\geq 50%$) and non-ARAS (RALL <50%). All baseline characteristics are included in Table 1. The median age of the participants was 69 years and male accounted for 64.71% of the study population. Of these, 22 patients had bilateral renal
artery stenosis, 63 patients had unilateral renal artery stenosis, and 85 patients did not have renal artery stenosis. Age, SBP, PAD, and CAD were found to be significantly different between two groups. Table 2 details the metabolites levels for the patients, in which creatinine, EGFR, and aldosterone were significantly different between the patient groups.

Table 1 Baseline characteristics of ARAS and non-ARAS patients.

Table 2 Metabolites in ARAS and non-ARAS patients.

Univariate and stratified analysis

Univariate analysis of ARAS was performed and SBP and PAD were positively correlated with ARAS, while CAD was negatively correlated (Table 3). Current smoking status, gender, age, body mass index (BMI) and diabetes mellitus (DM) were not associated with ARAS. In order to explore the relationship between Lp(a) and ARAS in a low LDL-c population, a stratified analysis was performed using three tertiles. In a low LDL-c population, patients with high Lp(a) levels had significantly higher rates of ARAS than patients with low Lp(a) levels (Table 4, OR: 4.77; 95%CI: 1.04-21.79; P = 0.044).

Table 3 Univariate analysis for ARAS.

Illustration: “Low” (OR = 1) as the reference

Table 4 LDL-c-based stratified analyses for Lp(a) and ARAS by three tertiles.

Illustration: “Low” (OR = 1) as the reference.

Logistic analysis

A logistic analysis was performed to identify additional risk factors besides Lp(a) among populations with low LDL-c levels. The incidence of ARAS dramatically increased in patients with high Lp(a) levels after adjusting for other influence (OR: 8.16, 95%CI 1.12-59.12, P = 0.037), including current smoking status, SBP, gender, age, BMI, DM, PAD, and CAD (Figure 1). Interestingly, we also observed that CAD was associated with reduced incidence of ARAS (OR: 0.10; 95%CI 0.01-0.73; P = 0.024).

Figure 1. Forest plot for multivariate analysis with ARAS in a low LDL-c population by logistic regression.

The relationship between Lp(a) and ARAS in a low LDL-c population

Based on the logistic regression analysis, the incidence of ARAS was set as the endpoint, with the Lp(a) concentration acting as the main influence factor in plotting the fitting graph and adjusting for other covariates. The relationship between Lp(a) and ARAS was non-linear, with ARAS levels leveling off at a certain concentration of Lp(a) (Figure 2a). As Lp(a) was a continuous variable, three points could be used to represent different thresholds of morbidity. Compared with the low Lp(a) concentration group, the high Lp(a) concentration group was significantly related to the incidence of ARAS (P = 0.037), while differences in comparison to the intermediate group were not significant (P = 0.64). The probability of a patient with low LDL-c levels suffering from ARAS was calculated for different levels of Lp(a) (Figure 2b).

Figure 2a. Non-linear relationship and tertile points between Lp(a) and ARAS adjusted covariates.

Illustration: External image: the x-axis is Lp(a) concentration. The y-axis is the incidence of ARAS, with the shaded area representing a 95% confidence interval. (linear trend, p: 0.018). Internal image: the x-axis is Lp(a) concentration. The y-axis is the incidence of ARAS when dividing Lp(a) concentrations into three tertiles. The reference group (low Lp(a)) was set to 1.0.

2b. Population-based ARAS prevalence corresponding to different concentrations of Lp(a) levels in patients with low LDL-c levels.

Illustration: Blue color indicates the prevalence of ARAS at different Lp(a) levels among a low LDL-c population.

The distribution of Lp(a) in population
Setting Lp(a) concentration as the continuous variable, the concentration demarcation point was set using the Lp(a) tertile method on the study population in order to obtain risk stratification. The distribution of Lp(a) was positively skewed to the right, and ARAS risk was significantly increased in the upper tertile in low LDL-c patients (Figure 3).

**Figure 3.** Distribution of Lp(a) concentrations in a population.

*Illustration: Red bars (Lp(a)>245mg/l) represent increased possibility of suffering from ARAS at low LDL-c levels.*

**Discussion**

This cross-sectional study indicated that, in a hypertensive Chinese population with low levels of LDL-c, Lp(a) was identified as a significant residual risk factor for ARAS.

The result was performed in five parts. First, a univariate analysis revealed that SBP and history of PAD were positively associated with ARAS, while history of CAD was negatively correlated. Current smoking status, gender, age, BMI, and DM were not associated with ARAS. The role of SBP in ARAS can be easily understood, as this protein accelerates the progression of atherosclerosis, which directly promotes serum lipid deposition on renal artery walls. Regarding PAD, as atherosclerosis is a systemic arterial disease, the presence of PAD is inevitably accompanied by lesion formation in the renal artery. This also suggests that lipid accumulation in the peripheral and renal arteries may be homogeneous. CAD was not identified as a risk factor of ARAS in this study which was unexpected. This may be due to CAD being defined as coronary stenosis over >70% lumen area, excluding those patients with mild to intermediate plaque lesions. Interestingly, these lesion were present even when other atherogenic risk factors we absent. In addition, we analyzed different concentrations of Lp(a) in a low LDL-c population, revealing that high-levels of Lp(a) were associated with a high incidence rate of ARAS, further supporting the hypothesis that ARAS and Lp(a) levels are related. Next, logistic analysis that adjusted for other covariates in this low LDL-c population to further confirmed the hypothesis. After controlling for current smoking, SBP, gender, age, BMI, DM, PAD, and CAD, we found that there was a significant effect of Lp(a) on ARAS in a low LDL-c population. Subsequently, in order to more intuitively demonstrate this relationship with ARAS, a concentration-prevalence fitting curve was plotted, revealing that incremental increases in Lp(a) concentration of Lp(a) initially caused increased ARAS levels, before leveling off at a certain rate. At the same time, Lp(a) concentration was divided into three tertiles in order to generate a line chart to estimate risk proportions. Finally, the distribution of Lp(a) concentrations in hypertensive patients was analyzed to distinguish between population tertiles based on ARAS risk. Thus, to our knowledge, we are the first to demonstrate an independent association between Lp(a) concentration and ARAS in a hypertensive low LDL-c population.

Pathophysiologically, the mechanisms by which Lp(a) increases CVD risk are driven by proatherogenic and prothrombotic states, including endothelial disorder, smooth muscle proliferation, foam cell formation, and local coagulation disturbances[13]. Molecularly, Lp(a) is similar to LDL-c, as it is a particle covalently bound by apoB and apo(a), which carries pathogenic LDL-c and leads to atherosclerosis[27]. However, Lp(a) is more atherogenic than LDL-c due to presence of apo(a), which can induce inflammation that is mediated by oxidized phospholipids and antifibrinolytic effects that result from inhibiting plasminogen activation[27–30]. Lp(a) shares similarities to LDL-c, which may account for the associated risk of Lp(a) leading to atherosclerosis initiation and progression in a low LDL-c environment. In this study, Lp(a) levels were significantly associated with ARAS at low LDL-c levels. One explanation for this effect is that the impact of Lp(a) is reduced at high LDL-c concentrations. Although Lp(a) has a stronger pathogenicity, LDL-c is still a significant factor in atherosclerosis progression. Together, this underscores the importance of Lp(a) in the context of low LDL-c levels and promotes further study of the related residual risks.

Clinical trials and systematic reviews over the past several decades have revealed a strong relationship between Lp(a) concentration and CVD[31–34]. For example, the JUPITER trial of low LDL-c participants demonstrated that baseline Lp(a) concentrations were associated with increased CVD risk[14]. Similar results were obtained from AIM-HIGH and LIPID trials in which participants underwent LDL-c lowering therapy[35, 36]. These data suggest that high Lp(a) levels act as a latent pathogenic factor during the development and treatment of CVD wherein common risks are treated. This study examining the relationship between ARAS and Lp(a) supports these observations, indicating that Lp(a) is a determinant for residual risk in hypertensive patients with low LDL-c levels. In the general population, LPA IS THE MAJOR GENE CONTROLLING THE LP(A) FEATURE AND EXPLAINS 70–90% of the variance in LP(A) LEVELS[37]. In this study, most patients had undergone primary angiographic without statin
treatment, so their baseline Lp(a) levels were mostly controlled by genetics, suggesting that the study’s results are applicable to those with naturally high Lp(a) levels. This cannot be inferred across the entire population, as widespread use of statins have been demonstrated to increase Lp(a) concentrations by 10%−20% [38, 39]. Statin use may cause cholesterol to “escape” coordination with LDL-c receptors to form more Lp(a)[40], which indicates a need to monitor populations that are treated with statins.

The impact of Lp(a) on ARAS has raised and seriously questioned in previous studies, as both positive and negative results have been reported [25, 41–43]. Park et al.[41] performed renal arteriography at the time of cardiac catheterization in 270 patients and screened 28 ARAS (≥ 50% narrowing of renal artery) and 242 non-ARAS patients, concluding that Lp(a) was not associated with ARAS (median, ARAS:143 mg/l vs. non-ARAS:188 mg/l). In contrast, Scoble et al.[42] examined the lipoprotein profiles in a small number of patients with (n = 32, ≥ 30% narrowing of renal artery on angiography) or without (n = 32, matched with ARAS patients for clinical baseline features but no angiography performed) ARAS in a case-controlled study, revealing that serum Lp(a) levels were higher in the non-ARAS group (mean ± SD, ARAS:310 ± 210 mg/l vs. non-ARAS:580 ± 450 mg/l; P < 0.01). The negative relationship between ARAS and Lp(a) was explained by an Apo(a) polymorphism. Zhang et al.[25] performed a cross-sectional study of 1200 Chinese patients who underwent renal arteriography immediately after coronary angiography, and found that Lp(a) was significantly higher in patients with mild and advanced ARAS (≥ 30% narrowing of renal artery to artery) by univariate logistic regression (percentage of high serum Lp(a), ARAS:24.2% vs. Non-ARAS:17.5%; P = 0.039). Catena et al.[43] examined 50 hypertensive patients with ARAS (in those with mild and advanced ARAS (≥ 70% narrowing of renal artery on angiography) and 58 hypertensive patients with comparable cardiovascular risk factor burden but non-ARAS (assessed by angio-MRI or angio-CT scan and/or renal angiography) in a cross-sectional study, which demonstrated that Lp(a) levels in the highest tertile had greater risk than the lowest tertile (OR:3.70; P = 0.016). Further analyzing their results, we revealed that some studies had insufficient sample sizes for analysis, while one study diagnosed ARAS by non-invasive imaging methods, which could have resulted in variability in patient assignment. In addition, few studies have taken the effect of Lp(a) at low LDL-c levels into account, resulting in studies with insufficient information to establish coherent conclusions. In this study, angiography was used to assess a 50% narrowing of renal artery in order to classify patients in either the ARAS group or non-ARAS, as opposed to non-invasive imaging, and this meets the gold standard of diagnosis. In addition, this study’s data were thoroughly and expansively collected compared to prior studies and therefore can provide higher quality evidence. It must be noted, however, that there are still some limitations to this study. First, as this study utilized cross-sectional data studies, only correlations can be inferred, rather than causality, which established the findings as a reference tool for clinical practice. Second, as the study patients needed to undergo simultaneous renal angiography and coronary angiography needs to be accurately assessed, the number of cases available to be assessed was limited. Third, patients with poor kidney function may also have proteinuria, causing the liver to produce more lipoprotein, including Lp(a) and potentially effecting serum Lp(a) levels.

Great progress has been made in understanding the role of Lp(a) in ARAS, but much remains to be explored. Patients under therapy have more clinical events of ARAS than are prevented, indicating that residual risk factors, such as Lp(a), need to be examined and taken into account. Given the potential CVD risks of Lp(a), treatment is now an urgent task. In the era of comprehensive lipid-lowering medications, there is greater importance given to reducing LDL-c levels, and, by extension, to understanding the impact of Lp(a). The 2019 European Society of Cardiology guidelines recommend measuring Lp(a) concentration at least once in each adult person’s lifetime and consider 180 mg/dL of Lp(a) to be a very high inherited level that indicates danger for ACSVD (Class IIa, Grade C)[8]. It must be noted that, currently, no known medications that directly lower Lp(a) levels have been approved for use.

**Conclusion**

Early identification of renal artery stenosis provides an opportunity to slow down the progression of renal dysfunction, enhance the quality of life, and improve chances of survival. Various factors are related to the development of atherosclerosis in renal arteries, and this study revealed that in hypertensive patients with low LDL-c levels, the high Lp(a) concentration is independently and significantly associated with atherosclerotic renal artery stenosis and thus is a residual risk factor. Further studies will investigate mechanisms by which this information regarding Lp(a) may be leveraged for new treatments.

**Abbreviations**
Declarations

Ethics approval and consent to participate

This study was conducted under the guiding principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the Guangdong Provincial People's Hospital. All participants were verbally informed of the study.

Consent for publication

Not applicable.

Availability of data and materials

The data set analyzed in this study can be reasonably obtained from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XMH contributed to the data analyse and drafting of the manuscript. YX, XDL and DML collected and collated the data. YLZ and HJD contributed to the ideas and critical revisions of the manuscript and approved the final version of the manuscript to submit. All authors read and approved the final manuscript.

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References


Tables

Due to technical limitations, Tables 1 - 4 are only available for download from the Supplementary Files section.

Figures

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<th>Variable</th>
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Figure 1

Forest plot for multivariate analysis with ARAS in a low LDL-c population by logistic regression.

Figure 2

2a. Non-linear relationship and tertile points between Lp(a) and ARAS adjusted covariates. Illustration: External image: the x-axis is Lp(a) concentration. The y-axis is the incidence of ARAS, with the shaded area representing a 95% confidence interval. (linear
trend, \( p: 0.018 \). Internal image: the x-axis is \( \text{Lp(a)} \) concentration. The y-axis is the incidence of ARAS when dividing \( \text{Lp(a)} \) concentrations into three tertiles. The reference group (low \( \text{Lp(a)} \)) was set to 1.0. 2b. Population-based ARAS prevalence corresponding to different concentrations of \( \text{Lp(a)} \) levels in patients with low LDL-c levels. Illustration: Blue color indicates the prevalence of ARAS at different \( \text{Lp(a)} \) levels among a low LDL-c population.

**Figure 3**

Distribution of \( \text{Lp(a)} \) concentrations in a population. Illustration: Red bars (\( \text{Lp(a)} > 245 \text{mg/l} \)) represent increased possibility of suffering from ARAS at low LDL-c levels.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.doc
- Table3.doc
- Table4.doc
- Table1.doc