ORIGINAL RESEARCH

Correlations Between Coronary Artery Disease, Coronary Artery Calcium Score, and Lipoprotein(a) Level in Korea

Joan Kim [ID][1], Seung Woo Choi [ID][1], Young Shin Lee [ID][1], Jung Myung Lee [ID][1], Hyemoon Chung [ID][1], Jong Shin Woo [ID][1], Woo-Shik Kim [ID][1], Yun Young Choi [ID][2], Weon Kim [ID][1]

[1]Department of Cardiology, Kyung Hee University Hospital, Seoul, Korea; [2]Department of Medicine, Graduate School, Kyung Hee University, Seoul, Korea

Correspondence: Weon Kim, Tel +82 2 958 8176, Email mylovekw@hanmail.net

Background: Lipoprotein(a) (Lp(a)) levels are associated with coronary artery disease (CAD) and aortic valve calcification. This study aimed to determine the correlation between Lp(a) levels and coronary artery calcium (CAC) scores in patients who underwent coronary computed tomography angiography (CCTA).

Methods: This was a single-center observational study. The patients had not been previously diagnosed with CAD and underwent CCTA and Lp(a) measurement in a three-month timeframe. Coronary angiography and further management were performed according to the physician's decision. Of the 252 patients, 81 and 171 patients underwent coronary revascularization and received medical treatment only, respectively. To examine the relationship between Lp(a) and CAC score and between Lp(a) and CAD, we divided the patients by Lp(a) level (50 mg/dL) and CAC score (400).

Results: No relationship was observed between Lp(a) and CAD or other risk factors for CAD. There were no differences in the ratio of patients who underwent coronary revascularization or in the CAC score according to an Lp(a) level of 50 mg/dL. There was no difference in Lp(a) level at a CAC score of 400. The proportion of patients who underwent coronary revascularization was high in the high CAC score group (50.6% vs 23.7%, p = 0.000). No association was observed between Lp(a) level and CAC score in the Spearman correlation (0.000, p < 0.998).

Conclusion: Correlations between Lp(a) level and CAC score and between Lp(a) and CAD were not observed in this Korean cohort study. However, a high CAC score was correlated with coronary revascularization.

Keywords: lipoprotein(a), coronary calcium score, coronary artery disease

Introduction

Lipoprotein(a) (Lp(a)) is a particle that is structurally similar to low-density lipoprotein cholesterol (LDL) and contains apolipoprotein(a) bound to apolipoprotein B100 via a disulfide bond.[1] Some studies have suggested that high concentrations of plasma Lp(a) are associated with a high risk of aortic valve stenosis[2] and coronary artery disease (CAD).[3,4] There are several hypotheses regarding the pathophysiology of Lp(a). Similar to LDL, Lp(a) can be pro-atherogenic because excess Lp(a) is deposited into the subendothelial arterial space and oxidized.[5] In addition, Lp(a) can be prothrombotic because the structure of apolipoprotein(a) is similar to plasminogen and may compete with plasminogen, thus leading to interference with the fibrinolytic system.[6]

However, the relationships between Lp(a) and CAC, and between Lp(a) and CAD, are very complex and have not yet been precisely established. Many studies have shown different relationships between Lp(a) levels and CAD, particularly with regard to race.[7] For example, according to Virani et al, the Lp(a) levels of Black subjects were higher than those of white subjects, and had a stronger positive correlation with cardiovascular disease events compared to that observed in white subject.[8] In contrast, a large prospective cohort study in China (n = 3884) found that plasma Lp(a) levels were not strongly associated with CAD, death, or stroke.[11] In addition, various studies have found different correlations of Lp(a)

with coronary artery calcification. In a community-based study, sex-specific associations between Lp(a) and coronary artery calcium (CAC) score were supported,[12] and another study reported that Lp(a) was strongly associated with high CAC score in women with type 2 diabetes mellitus (DM).[13] Meanwhile, some studies reported negative results.[10,14]

The purpose of this study was to determine the correlation between Lp(a) level and CAC score in Korean patients, and to determine the relationship between Lp(a) and CAD.

Materials and Methods

Study Participants

This was a single-center, cross-sectional, observational study. The patients consisted of 252 individuals who visited Kyung Hee University Hospital from March 2020 to February 2021 for the evaluation of chest pain, CAD risk evaluation for non-cardiac surgery, stroke, or healthcare examination. Among the visitors for healthcare examination, those who had cardiac hypertrophy on CXR or high CAC score (>400) or significant stenosis on coronary computed tomography angiography (CCTA) were included. The patients underwent CCTA and an Lp(a) test in a three-month timeframe. They had not previously been diagnosed with CAD (defined as myocardial infarction (MI), coronary revascularization, angiographic significant stenosis, or positive stress test), and were 27 to 89 years old. Of the 252 eligible patients, 81 patients underwent coronary revascularization and 171 received medical treatment only. Coronary angiography was performed according to the physician's decision. Coronary revascularization was performed on lesions with stenosis greater than 70% and/or FFR <0.8. Coronary revascularization was not performed on lesions clinically judged to be impossible for PCI or those for which it was thought that intervention would not be beneficial (eg, distal lesions or too-small vessels).

The exclusion criterion was a history of coronary disease.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kyung Hee University Hospital (protocol code: KHUH 2021-10-077).

Clinical and Laboratory Values

Information on the age, sex, DM, hypertension (HTN), prior stroke history, smoking, and alcohol consumption of the patients was obtained from their medical records. Body mass index was obtained by dividing weight (kg) by the square of height (m^2). The creatinine, glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, LDLcholesterol, and high-sensitivity C-reactive protein concentrations were measured using an AU-5800 Chemistry Analyzer (Beckman Coulter Inc., Brea, CA, USA). The Lp(a) level was measured by an immunoturbidimetry technique calibrated with the IFCC reference material, using the same analyzer. HbA1c was measured using an automated Glycohemoglobin Analyzer HLC-723G8 (Tosoh G8; Tosoh Bioscience, Inc., Japan).

Computed Tomography Scans

Computed tomography (CT) scans were performed with a 128-slice scanner (Ingenuity CT cor 128, Philips Medical Systems, Cleveland, OH, USA), and the standard scanning parameters were 64 mm × 0.625 mm section collimation, 400 ms rotation time, 120 kV tube voltage, and 39.5 mAs (395 mA × 0.1 s) tube current under ECG-gated dose modulation. The Agatston score was calculated using standard calcium scoring.

Statistical Analysis

Statistical analyses of the data were performed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA). Data are reported as mean ± standard deviation for continuous variables and as proportions for categorical variables. The Spearman correlation statistical method was used to analyze the correlations between Lp(a) and the risk factors of CAD and between Lp(a) and CAC score. Student's *t*-tests and chi-square tests were used to compare the coronary intervention group and medical management only group, the low and high Lp(a) groups, and the low and high CAC groups.

Results

Baseline Participant Characteristics

Table 1 shows a summary of the baseline characteristics. The mean age was 68.2 years, and 58.7% of the patients were male. The mean CAC score was 478.4, and the Lp(a) level was 24.8 mg/dL. The number of patients who underwent coronary intervention was 81 (32%).

Evaluation of anginal chest pain was the most common reason for CCTA (n = 161, 64%). Following this, the other reasons for examination were risk evaluation of non-cardiac surgery (n = 50, 19.8%), coronary evaluation of patients with stroke (n = 26, 10.3%), and healthcare examination (n = 15, 5.9%).

Associations Between Lp(a) and CAD and Various CAD Risk Factors

Spearman correlations did not reveal any associations between Lp(a) and other lipid, metabolic, or inflammatory parameters. The analysis was also conducted by dividing the patients into the medical treatment only and coronary revascularization groups. However, the results were almost the same between the two groups (Table 2).

As many studies suggest that Lp(a) levels above 50 mg/dL be designated as abnormal,[9] we divided the patients into two groups according to an Lp(a) level of 50 mg/dL to determine the differences between the two groups. There was no difference between the two patient groups with regard to the lipid, metabolic, or inflammatory parameters. In addition, there were no significant differences in the number of patients who underwent coronary intervention (69 (31.1%) vs 12 (40.0%), p = 0.326) or the CAC scores (474.2 ± 744.3 vs 509.8 ± 824.2, p = 0.808) between the two groups (Table 3).

Associations Between Lp(a) Level and CAC Score

Figure 1 shows biased distributions of Lp(a) level and CAC score. All patients were divided into two groups according to a calcium score of 400, which is a level generally considered to have prognostic value.[10,11] There was no significant difference in the Lp(a) level between the two groups (25.4 ± 26.0 vs 23.6 ± 20.0, p = 0.601). However, the mean age of the high CAC score group was higher than that of the low CAC score group (70.9 ± 8.9 vs 67.0 ± 10.1, p = 0.003), the proportion of men was higher (49 (62.0%) vs 65 (37.6%), p = 0.004) in the high CAC score group, and the ratio of patients who had

Table 1 Baseline Participant Characteristics

	Total (n = 252) Mean ± SD or n (%)
Age, years	68.2 ± 9.9
Gender, male	148 (58.7%)
DM	88 (34.9%)
HTN	190 (75.4%)
Prior stroke	40 (15.9%)
Current smoker	66 (26.2%)
BMI (kg)	25.4 ± 5.0
Creatinine (mg/dL)	1.03 ± 1.37
HbA1c (%)	6.5 ± 3.74
Total cholesterol (mg/dL)	168.4 ± 44.9
Triglyceride (mg/dL)	147.9 ± 81.2
HDLc (mg/dL)	50.7 ± 15.1
LDLc (mg/dL)	101.4 ± 32.0
Hs-CRP (mg/dL)	0.34 ± 0.92
Lp(a) level (mg/dL)	24.8 ± 24.2
CAC score	478.4 ± 752.6
Patients who underwent revascularization	81 (32%)

Note: Mean ± SD for continuous variables and n (%) for categorical variables.
Abbreviations: DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a); CAC, coronary artery calcium.

Table 2 Spearman Correlations of Lipid, Metabolic, and Inflammatory Parameters with Plasma Lp(a) Levels

	Total (n = 252)	Optimal Medical Treatment Only Group (n = 171)	Coronary Revascularization Group (n = 81)
Total cholesterol	0.119 (p = 0.064)	0.062 (p = 0.434)	0.218 (p = 0.052)
TG	−0.013 (p = 0.840)	−0.099 (p = 0.200)	0.136 (p = 0.225)
HDLc	0.039 (p = 0.537)	0.005 (p = 0.953)	0.121 (p = 0.283)
LDLc	0.139 (p = 0.028)	0.103 (p = 0.180)	0.198 (p = 0.076)
Glucose	−0.12 (p = 0.061)	−0.105 (p = 0.181)	−0.075 (p = 0.503)
HbA1c	−0.008 (p = 0.895)	−0.041 (p = 0.593)	−0.124 (p = 0.269)
Creatinine	−0.096 (p = 0.128)	−0.080 (p = 0.296)	−0.036 (p = 0.751)
BMI	−0.12 (p = 0.853)	0.041 (p = 0.593)	−0.113 (p = 0.317)
Hs-CRP	0.002 (p = 0.977)	−0.000 (p = 0.999)	−0.015 (p = 0.907)

Abbreviations: TG, triglyceride; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; BMI, body mass index; Hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a).

Table 3 Lipid, Metabolic, and Inflammatory Parameters; CAC Score; and Number of Patients Who Underwent Coronary Revascularization According to Lp(a) Level

	Lp(a) < 50 mg/dL (n = 222) Mean ± SD or n (%)	Lp(a) ≥ 50 mg/dL (n = 30) Mean ± SD or n (%)	p-value
Age, years	68.5 ± 10.1	66.1 ± 8.5	0.217
Gender, male	151 (68.0%)	17 (56.7%)	0.807
DM	78 (35.1%)	10 (33.3%)	0.846
HTN	169 (76.1%)	21 (70.0%)	0.465
Prior stroke	36 (16.2%)	4 (13.3%)	0.685
Current smoker	59 (26.6%)	7 (23.3%)	0.705
BMI (kg)	25.5 ± 5.2	24.4 ± 4.0	0.289
Creatinine (mg/dL)	1.1 ± 1.5	0.84 ± 0.16	0.438
HbA1c (%)	6.5 ± 4.0	6.3 ± 1.1	0.781
Total cholesterol (mg/dL)	167.4 ± 44.5	176.1 ± 48.0	0.335
TG (mg/dL)	147.0 ± 82.8	153.3 ± 69.3	0.699
HDLc (mg/dL)	50.6 ± 15.3	51.1 ± 13.7	0.859
LDLc (mg/dL)	100.6 ± 31.1	107.4 ± 37.7	0.275
Hs-CRP (mg/dL)	0.34 ± 0.94	0.34 ± 0.86	0.988
Lp(a) level (mg/dL)	17.5 ± 11.6	78.7 ± 25.4	-
CAC score	474.2 ± 744.3	509.8 ± 824.2	0.808
Patients who underwent coronary revascularization	69 (31.1%)	12 (40.0%)	0.326

Note: Mean ± SD for continuous variables and n (%) for categorical variables.
Abbreviations: DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; TG, triglyceride; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a); CAC, coronary artery calcium.

HTN was higher (68 (86.1%) vs 122 (70.5%), p = 0.008) in the high CAC score group. The number of patients who underwent coronary intervention was higher in the high CAC score group (40 (50.6%) vs 41 (23.7%), p = 0.000) (Table 4).

The correlation between Lp(a) and CAC score could not be observed in all patients by using the Spearman correlation (Spearman correlation: 0.053, p = 0.403). The results were the same in the group receiving medical therapy only (Spearman correlation: 0.057, p = 0.46) and in the coronary intervention group (Spearman correlation: 0.002, p = 0.986).
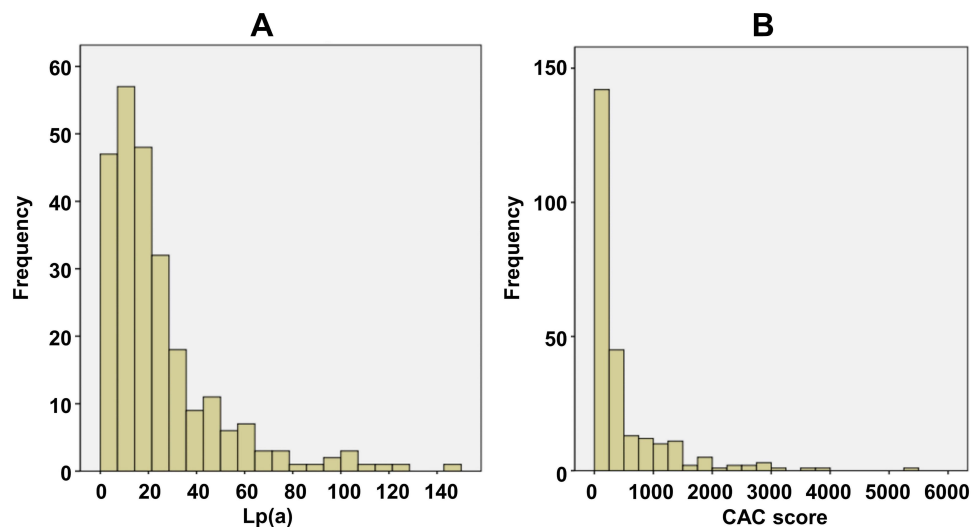
Figure 1 (**A**) Distribution of Lp(a): n=252, mean: 24.75 mg/dL, SD=24.29 mg/dL, median: 18.3 mg/dL, IQR 20.7. (**B**) Distribution of CAC score: n=252, mean: 478.4 mg/dL, SD=752.6 mg/dL, median: 185.26 mg/dL, IQR 491.4.

Discussion

Lp(a) is found in atherosclerotic plaques and is associated with vascular smooth muscle proliferation and endothelial cell damage.[12] In a recent large-scale study targeting multi-ethnic participants, Lp(a) was related to CAD independently of CAC score.[13] However, other studies suggest that the relationship between Lp(a) and CAD may appear differently depending on age, sex, race, and comorbidities.[7,14–16] The results of our study showed no strong relationship between Lp(a) and CAD in a Korean cohort, and this finding can be explained by the results of previous studies.

Table 4 Lipid, Metabolic, and Inflammatory Parameters; Lp(a) Level; and Number of Patients Who Underwent Coronary Revascularization According to CAC Score

	CAC Score < 400 (n = 173) Mean ± SD or n (%)	CAC Score ≥ 400 (n = 79) Mean ± SD or n (%)	p-value
CAC score	114.6 ± 118.6	1275.2 ± 924.7	-
Age, years	67.0 ± 10.1	70.9 ± 8.9	p = 0.003
Gender, male	65 (37.6%)	49 (62.0%)	p = 0.004
DM	56 (32.4%)	32 (40.5%)	p = 0.209
HTN	122 (70.5%)	68 (86.1%)	p = 0.008
Prior stroke	27 (15.6%)	13 (16.5%)	p = 0.864
Current smoker	45 (26%)	21 (26.6%)	p = 0.924
BMI (kg)	25.5 ± 5.1	25.3 ± 5.1	p = 0.831
Creatinine (mg/dL)	0.93 ± 1.08	1.24 ± 1.86	p = 0.164
HbA1c (%)	6.6 ± 4.4	6.4 ± 1.4	p = 0.717
Total cholesterol (mg/dL)	170.7 ± 45.1	163.1 ± 44.3	p = 0.221
TG (mg/dL)	148.0 ± 85.6	146.3 ± 71.3	p = 0.840
HDLc (mg/dL)	50.5 ± 14.6	51.2 ± 16.2	p = 0.734
LDLc (mg/dL)	103 ± 32.4	96.4 ± 30.5	p = 0.096
Hs-CRP (mg/dL)	0.33 ± 0.89	0.36 ± 0.99	p = 0.822
Lp(a) level (mg/dL)	25.4 ± 26.0	23.6 ± 20.0	p = 0.601
Patients who underwent coronary revascularization	41 (23.7%)	40 (50.6%)	p = 0.000

Note: Mean ± SD for continuous variables and n (%) for categorical variables.
Abbreviations: CAC, coronary artery calcium; DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; TG, triglyceride; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a).

In our study, no correlation was found between Lp(a) and CAC scores. There are two recent studies on the correlation between Lp(a) and CAC in Korea. The study of Chung et al showed that in asymptomatic male patients over 45 years of age, the level of Lp(a) was significantly higher for patients with CAC scores greater than 0 than the Lp(a) level of patients with CAC scores of 0 (16.74±20.53 vs 13.97±16.10, p = 0.006).[18] Sung et al[19] also demonstrated a positive correlation between Lp(a) level and CAC score in a large cohort in Korea. However, unlike our study, these two studies were conducted on asymptomatic health check-up patients, and the cut-off of the patients' CAC scores was much lower than that in our study (0 vs 400). In general, CAC score indicates the burden of atherosclerosis in the coronary artery,[17] and the general cutoff for increasing CAD risk has been identified as approximately 350–400; therefore, it can be said that these studies showed correlation between preclinical atherosclerosis and Lp(a). By contrast, our study divided patients on the basis of a CAC of 400, and the clinical significance of our study is the comparison of the differences of the actual clinical outcome, that is, whether a coronary revascularization was performed.

The number of patients included in the present study was only 252, and this small sample size was a disadvantage of this study. Nevertheless, the results clearly indicate relationships between CAD and other well-known risk factors for CAD (eg, CAC score, age, gender, and HTN). This suggests that the patients in this study sufficiently reflect the characteristics of the general population. Another disadvantage of this study was the heterogeneity of the patients. However, the included patients mostly had angina, high coronary risk in the preoperative evaluation, or stroke. Only 5.9% of patients underwent CT scans for health check examination and these patients had risk for CAD (eg, cardiac hypertrophy, high CAC score, and/or significant stenosis on CCTA). Therefore, most of the subjects were at high risk of coronary disease. This is supported by the fact that the average CAC score of the patients in this study was 478.4, which is quite high.

In this cross-sectional study, the analysis was conducted by dividing the patients into one group that received the intervention and a second group that did not. All patients who received the intervention were stable angina patients, and patients with acute coronary syndrome were not included. Therefore, follow-up cohort studies on endpoints such as survival rate, MI, and stroke are necessary in future. In addition, as the level of Lp(a) in the blood is largely determined by the gene, in future studies, it is necessary to conduct Lp(a) genetic study, such as Apo(a) size polymorphism or SNP analysis, on Korean cohort and compare the results with those of large-scale international studies.[20,21]

In conclusion, significant correlations between Lp(a) level and CAC score and between Lp(a) and CAD were not observed in this Korean cohort study. However, a high CAC score was significantly correlated with coronary revascularization.

Data Sharing Statement

The data are not publicly available because data export was not approved by the Institutional Review Board. The data presented in this study are available on request from the Institutional Review Board.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Kyung Hee University Hospital (protocol code: KHUH 2021-10-077 and date of approval: 2021.11.01).

Informed Consent Statement

Patient consent was waived because this study is a RETROSPECTIVE study; consent waiver was approved by the Institutional Review Board.

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Disclosure

The authors declare no conflicts of interest in this work.

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