INTRODUCTION

Carotid plaque formation represents a significant global health challenge, while the associated carotid artery atherosclerotic disease is a life-threatening condition. Blood lipid levels are pivotal factors in carotid plaque development. Therefore, maintaining low low-density lipoprotein cholesterol (LDL-C) levels to reduce carotid plaque formation is crucial, and statins are used to achieve this goal. However, despite the successful lowering of LDL-C levels through statin therapy, residual risks have been increasingly recognized. The principal residual risk factor for carotid plaque formation is lipoprotein(a) [Lp(a)], a heparically synthesized lipoprotein that shares a structural resemblance with LDL. Its formation involves the binding of apolipoprotein(a) to apolipoprotein B100, a constituent of LDL. Lp(a) is considered more atherogenic than LDL due to its heightened ability to permeate arterial walls, inciting inflammatory responses and thrombus formation. Genetic factors predominantly influence Lp(a) levels,
while the impact from environmental factors is minimal. In patients with dyslipidemia who experience a reduction in LDL-C levels due to statin therapy, Lp(a) levels resist significant decrease and may even exhibit slight elevation. Several studies have shown a correlation between Lp(a) levels and vascular diseases, such as myocardial infarction, stroke, and peripheral arteriopathy. Various types of research, including epidemiological studies, meta-analyses, Mendelian randomization studies, and genome-wide association studies, have shown that elevated Lp(a) level is a risk factor for cerebrovascular and cardiovascular diseases. Although evidence suggests that elevated Lp(a) levels contribute to the progression of carotid plaque formation, this remains a topic of debate. Several studies have suggested that high Lp(a) levels are associated with presence of carotid plaques, while other studies have reported no relationship between them. Furthermore, one study on asymptomatic Japanese women reported that lower Lp(a) levels are associated with increased carotid intima-media thickness (IMT).

This study aimed to determine the correlation between Lp(a) levels and carotid plaque formation in the general population.

SUBJECTS AND METHODS

1. Study Subjects and Data Collection

We selected healthy participants who underwent both screening Lp(a) measurements and carotid ultrasonography at Gangnam Severance Hospital between January 2017 and December 2022.

Data collected from the enrolled participants included sex, age, history of hypertension (HTN), diabetes mellitus (DM), dyslipidemia, smoking, body mass index (BMI), fasting glucose, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL-C.

Data are summarized as mean values with standard deviations for continuous variables and counts with percentages for categorical variables.

2. Measurement of Lp(a) Levels

Lp(a) levels were assessed using the latex agglutination method, which involved an anti-human Lp(a) monoclonal antibody and a commercial kit from Lp(a) Daiichi Pure Chemicals Co., Ltd. (Tokyo, Japan). This analysis was performed in conjunction with an autoanalyser (Hitachi 7600-110; Hitachi Technologies Co., Tokyo, Japan) to ensure accurate measurements across diverse apo(a) isoforms. The cutoff level for Lp(a) was set at 50 mg/dL.

3. Carotid Artery Ultrasound

Carotid artery ultrasound examinations were performed by board-certified radiologists using various ultrasound machines, including the Philips iU22 and Philips EPIQ 5G. Longitudinal images of the bilateral proximal and distal common and internal carotid arteries were acquired separately. Carotid plaque was defined as a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness, or demonstrated thickness greater than or equal to 1.5 mm.

4. Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Co., Armonk, NY, USA). Logistic regression analysis was used to examine the relationship between Lp(a) levels and presence of carotid plaques. Univariate analysis was conducted for the Lp(a) levels and carotid artery ultrasound results. Multivariate analysis, which included variables such as sex, age, HTN, dyslipidemia, DM, smoking, BMI, glucose, cholesterol, triglycerides, HDL-C, and LDL-C, was also performed.

RESULTS

A total of 4,896 participants were selected for the analysis. The mean age was 57.1±10.6 years and 65.7% were men. The prevalence rates of HTN, DM, dyslipidemia, and smoking were 30.9%, 10.7%, 28.2%, and 16.2%, respectively. The mean BMI was 24.8±3.6 kg/m². The mean levels of glucose, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL-C were 106.2±23.3 mg/dL, 200.8±43.4 mg/dL, 137.4±89.3 mg/dL, 55.3±13.4 mg/dL, and 122.5±36.3 mg/dL, respectively. The mean level of Lp(a) was 15.5±18.1 mg/dL, with 6.0% of participants having Lp(a) levels ≥50 mg/dL. Carotid artery plaques were de-
tected in 41.8% of the participants (Table 1).

When comparing participants based on the presence or absence of carotid artery plaque, those with carotid plaques were, on average, older than those without plaques (62.2±9.2 years vs. 53.6±10.2 years, respectively, \( p<0.001 \)). A higher proportion of men was observed among the participants with plaques than among those without plaques (70.2% vs. 62.5%; \( p<0.001 \)). Participants with plaques had a higher prevalence of HTN (43.9% vs. 21.5%, \( p<0.001 \)), DM (16.7% vs. 6.5%, \( p<0.05 \)), and dyslipidemia (38.0% vs. 21.1%, \( p<0.001 \)) than those without plaques. There was no significant difference in smoking history between the two groups (\( p=0.353 \)). In the group with carotid artery plaques, glucose (110.7±26.0 vs. 103.0±20.6, \( p<0.001 \)) and triglycerides (140.5±87.4 vs. 135.1±90.6, \( p=0.040 \)) levels were significantly higher, while HDL-C (54.0±12.8 vs. 56.1±13.7, \( p<0.001 \)) levels were significantly lower. Contrary to the expected outcomes, cholesterol (193.9±46.1 vs. 205.8±40.7, \( p<0.001 \)) and LDL-C (117.5±38.7 vs. 126.2±34.0, \( p<0.001 \)) levels were found to be significantly lower in the group with carotid artery plaques. Participants with carotid plaques had significantly higher mean Lp(a) levels compared to those without plaques (16.9±20.1 vs. 14.5±16.5, \( p<0.001 \)). Furthermore, a greater proportion of individuals with Lp(a) levels ≥50 mg/dL were found in the group with carotid plaques than in those without plaques (7.4% vs. 5.1%, \( p<0.001 \)) (Table 1).

Univariate (unadjusted) and multivariate logistic regression analysis were performed using SPSS version 26. Because of the significant correlations among cholesterol, triglycerides, and LDL-C, only the latter was included in the multivariate analysis. A stepwise method was employed to remove variables while selecting the model with the highest receiver operating characteristic (ROC) curve. The univariate logistic regression analysis revealed a significant association between Lp(a) levels ≥ 50 mg/dL and the presence of carotid plaques, with an unadjusted odds ratio (OR) of 1.508 (\( p<0.001 \), 95% confidence interval [CI]: 1.192–1.907). The multivariate logistic regression analysis was conducted, including the variables age, sex, HTN, DM, dyslipidemia, smoking, BMI, glucose, HDL-C, LDL-C, and Lp(a) ≥50 mg/dL. HDL-C and BMI were removed using a stepwise method. Consequently, the final

### Table 1. Demographic and clinical characteristics of the study population categorized by the presence or absence of carotid plaque

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=4,896)</th>
<th>Carotid plaques (yes) (n=2,046)</th>
<th>Carotid plaques (no) (n=2,850)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.2±10.6</td>
<td>62.2±9.2</td>
<td>53.6±10.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex: Men (%)</td>
<td>3,218 (65.7)</td>
<td>1,437 (70.2)</td>
<td>1,781 (62.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>1,512 (30.9)</td>
<td>899 (43.9)</td>
<td>613 (21.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>526 (10.7)</td>
<td>341 (16.7)</td>
<td>185 (6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>1,380 (28.2)</td>
<td>778 (38.0)</td>
<td>602 (21.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>794 (16.2)</td>
<td>320 (15.6)</td>
<td>474 (16.6)</td>
<td>0.353</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>24.8±3.6</td>
<td>25.0±3.3</td>
<td>24.7±3.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>106.2±23.3</td>
<td>110.7±26.0</td>
<td>103.0±20.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>200.8±43.4</td>
<td>193.9±46.1</td>
<td>205.8±40.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>137.4±89.3</td>
<td>140.5±87.4</td>
<td>135.1±90.6</td>
<td>0.040</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>55.3±13.4</td>
<td>54.0±12.8</td>
<td>56.1±13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>122.5±36.3</td>
<td>117.5±38.7</td>
<td>126.2±34.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>15.5±18.1</td>
<td>16.9±20.1</td>
<td>14.5±16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lp(a) ≥50 (mg/dL)</td>
<td>296 (6.0)</td>
<td>152 (7.4)</td>
<td>144 (5.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are represented as mean±standard deviation, while categorical variables are depicted as counts (n) and percentages (%).

DM, diabetes mellitus; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).
model included the following variables: age, sex, HTN, DM, dyslipidemia, smoking, glucose, LDL-C, and Lp(a) $\geq$ 50 mg/dL. Lp(a) levels $\geq$ 50 mg/dL were significantly associated with the presence of carotid plaques, with an adjusted OR of 1.318 ($p$=0.038, 95% CI: 1.015–1.711). This indicates a persistent and significant association between Lp(a) levels $\geq$ 50 mg/dL and the presence of carotid plaques even after adjusting for age, sex, HTN, DM, dyslipidemia, smoking, glucose, LDL-C, and Lp(a) $\geq$50 mg/dL (Table 2, Fig. 1).

**DISCUSSION**

This study aimed to elucidate the association between Lp(a) levels and carotid plaque formation. Despite the widespread use of statins to lower LDL-C levels, further decrease of cerebrovascular risk necessitates the exploration of additional risk factors such as Lp(a). Our study indicates that Lp(a) levels $\geq$50 mg/dL are significantly associated with the presence of carotid artery plaques, reinforcing the hypothesis that Lp(a) is an independent risk factor for carotid plaque formation.

Consistent with previous epidemiological studies and genetic analyses, our data support the hypothesis that Lp(a) levels are closely linked to atherogenesis. This is corroborated by our multivariate logistic regression analysis, which maintained the association of Lp(a) level with carotid plaques even after adjusting for other conventional risk factors such as age, sex, HTN, and dyslipidemia. These findings align with existing evidence on the fact that Lp(a) proinflammatory and prothrombotic properties exacerbate vascular disease pathogenesis.\(^{25,26}\)

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**Table 2. The results of unadjusted and adjusted logistic regression analyses**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>Lower limit</td>
<td>Upper limit</td>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Age</td>
<td>1.097</td>
<td>1.089</td>
<td>1.104</td>
<td>$&lt;0.001$</td>
<td>1.094</td>
<td>1.086</td>
</tr>
<tr>
<td>Sex: Men</td>
<td>1.416</td>
<td>1.254</td>
<td>1.599</td>
<td>$&lt;0.001$</td>
<td>1.616</td>
<td>1.400</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.860</td>
<td>2.524</td>
<td>3.241</td>
<td>$&lt;0.001$</td>
<td>1.632</td>
<td>1.412</td>
</tr>
<tr>
<td>DM</td>
<td>2.881</td>
<td>2.385</td>
<td>3.48</td>
<td>$&lt;0.001$</td>
<td>1.364</td>
<td>1.072</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.291</td>
<td>2.018</td>
<td>2.601</td>
<td>$&lt;0.001$</td>
<td>1.318</td>
<td>1.128</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.929</td>
<td>0.796</td>
<td>1.085</td>
<td>0.353</td>
<td>1.286</td>
<td>1.073</td>
</tr>
<tr>
<td>BMI</td>
<td>1.022</td>
<td>1.006</td>
<td>1.039</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>1.016</td>
<td>1.013</td>
<td>1.019</td>
<td>$&lt;0.001$</td>
<td>1.006</td>
<td>1.002</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.988</td>
<td>0.984</td>
<td>0.992</td>
<td>$&lt;0.001$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.993</td>
<td>0.992</td>
<td>0.995</td>
<td>$&lt;0.001$</td>
<td>1.002</td>
<td>1.000</td>
</tr>
<tr>
<td>Lp(a) $\geq$50 mg/dL</td>
<td>1.508</td>
<td>1.192</td>
<td>1.907</td>
<td>$&lt;0.001$</td>
<td>1.318</td>
<td>1.015</td>
</tr>
</tbody>
</table>

Unadjusted odds ratios (OR) and 95% confidence intervals (CI) are presented for each variable. The adjusted OR with their corresponding 95% CIs after controlling for other variables are provided where applicable.

DM, diabetes mellitus; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).
Nevertheless, in our study, traditional risk factors such as cholesterol and LDL-C levels were lower in participants with carotid plaques. Additionally, in the univariate logistic regression analysis, the unadjusted OR for LDL-C were <1. These findings may be related to the high prevalence of dyslipidemia among patients with carotid plaques. Consequently, these patients are more likely to receive dyslipidemia treatment, which could explain the lower cholesterol and LDL-C levels observed. However, data on dyslipidemia medication use were lacking, which is a limitation in our study.

These results underscore the need for a paradigm shift in cerebrovascular risk assessment and disease management. Currently, statin therapy is the cornerstone of dyslipidemia treatment; however, it has little effect on Lp(a) levels. Therefore, our study further emphasizes the need for targeted therapies such as proprotein convertase subtilisin-kexin 9 (PCSK9) inhibitors or antisense oligonucleotides to reduce Lp(a) levels.27-30

Our study has several strengths, including a large sample size and incorporation of a comprehensive set of cerebrovascular risk factors. However, there are several limitations. First, the cross-sectional nature of the study prevented the establishment of a causal relationship between Lp(a) levels and carotid plaques. Second, data on the use of lipid-lowering medications, particularly statins, were lacking. Given the high prevalence of dyslipidemia in the group with carotid plaques, it is likely that a substantial proportion of participants were receiving statin therapy, which could have influenced Lp(a) levels. Third, our data did not include information on plaque characteristics. Differences in plaque composition between the groups may have influenced the results. Fourth, most participants were from a single ethnic group undergoing health screening, which may have limited the generalizability of our findings.

In conclusion, our analysis provides further evidence on the significant role of Lp(a) in the pathogenesis of carotid plaques. However, prospective studies are required to evaluate the effectiveness of Lp(a)-lowering therapies on reducing carotid plaque formation and incidence of cerebrovascular events. Furthermore, our findings support the inclusion of Lp(a) level assessments in the routine evaluation of atherosclerotic cerebrovascular disease risk.

Ethics Statement
This study was approved with a waiver of informed consent by the Severance Hospital, Yonsei University Health System Institutional Review Board (3-2023-0157), ensuring adherence to ethical guidelines and the protection of participants’ rights and welfare.

Availability of Data and Material
The datasets generated or analyzed during the study are available from the corresponding author upon reasonable request.

Author Contributions
Minsoo Sung and Kyung-Yul Lee designed the study; Minsoo Sung and Young Hoon Yoon were responsible for data acquisition; Minsoo Sung and Yo Han Jung analyzed the data; Minsoo Sung wrote the first draft; Yo Han Jung and Kyung-Yul Lee critically reviewed the manuscript; Kyung-Yul Lee supervised the project. All authors have read and approved the final manuscript.

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Conflicts of Interest
No potential conflicts of interest relevant to this article were reported.

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