

The Association of Lipoprotein(a) Levels with Atherosclerotic Cardiovascular Disease in Thailand: A Cross-Sectional Study

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Purpose: The optimal plasma lipoprotein(a) [Lp(a)] cutoff level for predicting atherosclerotic cardiovascular disease (ASCVD) in Southeast Asian populations remains limited. Therefore, our study aimed to identify the optimal plasma Lp(a) cutoff for predicting ASCVD in Thai patients.

Patients and Methods: We conducted a retrospective analysis of patients who underwent Lp(a) measurement at Siriraj Hospital between January 2019 and August 2024. Inclusion criteria included Thai ethnicity and age ≥ 15 years. Baseline characteristics, comorbidities, laboratory data, and Lp(a) levels were extracted from medical records. Lp(a) levels were compared between ASCVD and non-ASCVD groups. Odds ratios (OR) for ASCVD and coronary artery disease (CAD) were calculated using Lp(a) < 25 nmol/L as the reference.

Results: A total of 2341 patients (age 54.4 ± 17.7 years, 42.0% male) were included. Among them, 413 (17.6%) had ASCVD, 254 (10.9%) had CAD, 186 (7.9%) had ischemic stroke, 21 (0.9%) had peripheral arterial disease (PAD), and 14 (0.6%) had abdominal aortic aneurysm. Median Lp(a) levels (nmol/L) were significantly higher in patients with ASCVD [37.2 vs 24.4, $p < 0.001$], CAD [43.8 vs 24.5, $p < 0.001$], and AS [51.6 vs 25.3, $p = 0.002$] compared to those without diseases. After adjusting for other risk factors, Lp(a) ≥ 40 nmol/L was associated with increased risks of ASCVD [OR 1.538 (1.203–1.958)] and CAD [OR 1.877 (1.407–2.505)]. A multivariate model incorporating Lp(a) ≥ 40 nmol/L with other risk factors demonstrated 70–80% sensitivity and specificity for predicting ASCVD and CAD.

Conclusion: Elevated plasma Lp(a) levels are significantly associated with ASCVD and CAD. An Lp(a) cutoff of ≥ 40 nmol/L predicted ASCVD and CAD risk in Thai.

Keywords: lipoprotein(a), atherosclerotic cardiovascular disease, coronary artery disease, aortic valve stenosis, Asian

Introduction

Lipoprotein(a) [Lp(a)] levels exhibit significant variation across self-reported racial and ethnic groups. Studies have consistently shown that individuals of East Asian and White descent tend to have lower median Lp(a) levels compared to Black individuals of African descent and South Asian populations.¹ For instance, data from the UK Biobank, which examined the risk of atherosclerotic cardiovascular disease (ASCVD) associated with Lp(a) levels, measured in nanomoles per liter (nmol/L), in a diverse cohort of 460,000 individuals using a validated immunoturbidometric assay aligned with World Health Organization/International Federation of Clinical Chemistry reference standards, revealed a median Lp(a) of 19.6 nmol/L across the entire population. Median levels were reported as 19 nmol/L in White participants, 31 nmol/L in South Asians, 75 nmol/L in Black individuals, and 16 nmol/L in Chinese individuals. The study also identified higher median Lp(a) levels among women (22 nmol/L) compared to men (17 nmol/L).¹ Despite these insights, data regarding Lp(a) levels in Southeast Asian populations remain limited. A previous study in Malaysia

found significantly lower plasma Lp(a) concentrations in Malays compared to Bidayuh individuals [6.6 (2.8–14.6) vs 16.9 (8.2–32.7) mg/dL, $p < 0.001$].² Such population-specific differences underscore the importance of regionally focused research to better understand Lp(a) distributions and their clinical implications in different ethnic groups.

Elevated plasma Lp(a) has been firmly established as an independent risk factor for ASCVD, myocardial infarction, and aortic valve stenosis (AS).^{3–5} The relationship between Lp(a) levels and ASCVD risk follows a log-linear pattern above the population median, with progressively higher levels conferring an increased risk of cardiovascular events. However, clinical guidelines vary regarding the Lp(a) threshold for high cardiovascular risk. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines⁶ define high Lp(a) as ≥ 50 mg/dL (≥ 125 nmol/L), whereas the Canadian Cardiovascular Society (CCS) guidelines⁷ and the National Lipid Association (NLA) scientific statement⁸ recommend a cutoff of ≥ 100 nmol/L. In contrast, the European Atherosclerosis Society (EAS)⁹ classifies Lp(a) levels as normal when < 30 mg/dL (< 75 nmol/L), intermediate between 30–50 mg/dL (75–125 nmol/L), and abnormal when > 50 mg/dL (> 125 nmol/L).

Given the paucity of data in Southeast Asian populations, particularly in Thailand, we aimed to determine the optimal plasma Lp(a) cutoff for predicting coronary artery disease (CAD) and ASCVD in Thai patients. Understanding these population-specific thresholds could improve cardiovascular risk stratification and inform clinical decision-making in this population. Although some guidelines, including the 2022 European Atherosclerosis Society (EAS) consensus statement, recommend measuring Lp(a) levels at least once in all adults, other guidelines such as those in Thailand¹⁰ advise Lp(a) measurement only in selected high-risk groups. These include patients with established ASCVD, familial hypercholesterolemia (FH), those at high cardiovascular risk, or individuals with a family history of premature cardiovascular disease. Therefore, identifying appropriate thresholds for Lp(a) in Thai patients may support more effective implementation of guideline-based risk assessment.

Materials and Methods

Study Design and Population

This retrospective cohort study analyzed patient data from the Faculty of Medicine Siriraj Hospital, Mahidol University, between January 2019 and August 2024. Eligible participants were individuals of Thai ethnicity, aged ≥ 15 years, who had undergone plasma Lp(a) measurement during the study period. Baseline demographic, clinical, and laboratory data were retrieved from the hospital's electronic medical records. The study was approved by the Siriraj Institutional Review Board (COA No. Si 460/2024). The informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data. Patient data confidentiality was protected, and the study was conducted in accordance with the Declaration of Helsinki.

Data Collection

Baseline characteristics, including age, sex, comorbidities, lipid-lowering medications, lipid profiles, and Lp(a) levels, were extracted from the medical database. Additional clinical information, such as smoking status, family history of ASCVD, systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI), was manually reviewed from the medical records. Smoking status was categorized as current smoker or ex-smoker. For laboratory and clinical parameters, data from the visit closest to the Lp(a) measurement, within a 6-month window, were utilized.

Definition of Comorbidities

Comorbidities were identified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). CAD was defined using ICD-10 codes I20, I21, I24, and I25, with additional supporting evidence of coronary angioplasty implant or graft (code Z95.5), aortocoronary bypass graft (code Z95.1), or ICD-9 code 88.56 for coronary arteriography with two catheters. In cases of uncertainty, medical records were reviewed for confirmation. AS was defined using ICD-10 code I35, supported by echocardiographic findings or documentation of prosthetic valve replacement (code Z95.2). Ischemic stroke was identified by ICD-10 codes I63–I66, I67.2, I67.8, I67.9, I69.3, I69.4, and I69.8. Peripheral arterial disease (PAD) was defined by ICD-10 codes I73.9 and I74,

while abdominal aortic aneurysm (AAA) was defined by ICD-10 code I71. Diabetes mellitus (DM) was identified using ICD-10 codes E10, E11, E13, and E14, and hypertension was defined using ICD-10 code I10. Chronic kidney disease (CKD) stages 3–5 was identified by ICD-10 codes N18.3, N18.4, and N18.5. Venous thromboembolism (VTE) was defined using ICD-10 code I80, and heart failure was identified with ICD-10 code I50. For the purpose of this study, ASCVD was defined as the presence of CAD, ischemic stroke, PAD, or AAA.

Lipoprotein(a) and Laboratory Measurement

Lp(a) levels were measured using the Tina-quant Lipoprotein (a) Gen. 2 assay (catalog code: 05852625190), a particle-enhanced immunoturbidimetric assay performed on the cobas® 8000 analyzer, c502 module (Roche Diagnostics, Mannheim, Germany). The assay employed a five-level calibration with an analytical measurement range of 7–240 nmol/L and was traceable to the International Federation of Clinical Chemistry (IFCC) reference material SRM2B. All testing was performed in the central laboratory of Siriraj Hospital. Cholesterol and triglyceride levels were measured using enzymatic colorimetric methods, while HDL-cholesterol was analyzed using homogeneous enzymatic colorimetric methods on the c702 module.

Assay performance was assessed according to the Clinical and Laboratory Standards Institute (CLSI) EP15-A3 protocol.¹¹ The coefficients of variation for repeatability (CV_R) and within-laboratory imprecision (CV_{WL}) were calculated. For Lp(a), the CV_R ranged from 0.89% to 1.26%, and the CV_{WL} ranged from 1.41% to 1.47%. For cholesterol, triglycerides, and HDL-cholesterol, the CV_R ranged from 1.14% to 1.52%, 0.50% to 0.72%, and 0.82% to 1.10%, respectively, while the CV_{WL} ranged from 1.36% to 1.88%, 0.66% to 0.80%, and 1.24% to 1.79%, respectively. These performance metrics indicate high assay reliability, ensuring robust and reproducible measurements for the study analyses.

Statistical Analysis

All statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA) and Python version 3.10 (Python Software Foundation). Data was assessed for normality using the Shapiro–Wilk test and visual inspection of histograms and Q-Q plots. Continuous variables with normal distributions were presented as mean ± standard deviation (SD), while non-normally distributed continuous variables were presented as median with interquartile range (IQR). Categorical variables were expressed as frequencies with corresponding percentages.

Comparisons between groups were conducted using appropriate statistical tests based on data type and distribution. For normally distributed continuous variables, an independent samples *t*-test was used. For non-normally distributed continuous variables, the Mann–Whitney *U*-test was applied. Categorical variables were compared using the Chi-square test, with Fisher’s exact test employed when the expected cell count was less than five.

Univariable analyses were initially performed to assess the relationship between plasma Lp(a) levels and the presence of ASCVD or CAD. Subsequently, binary logistic regression analysis with the enter method was conducted to identify independent associations between Lp(a) levels and ASCVD or CAD, adjusting for potential confounders, including age, sex, DM, hypertension, CKD, and smoking status. Lp(a) was analyzed both as a continuous variable and as a categorical variable using clinically relevant cutoffs based on existing guideline thresholds.⁹ Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported to quantify the strength of associations.

Model calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test, and multicollinearity among independent variables was assessed by examining the variance inflation factor (VIF), with a VIF >10 indicating problematic multicollinearity. The predictive performance of Lp(a) in identifying ASCVD and CAD was further assessed using Receiver Operating Characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated to quantify discriminatory power, with values closer to 1.0 indicating superior diagnostic performance. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were derived at various Lp(a) cutoff levels to identify the optimal threshold for ASCVD and CAD prediction. The Youden index was utilized to determine the optimal cutoff. All statistical tests were two-sided, with a *p*-value <0.05 considered statistically significant.

Results

During the study period, 2461 patients underwent plasma Lp(a) measurement. After excluding non-Thai patients ($n=30$) and aged <15 years ($n=90$), 2341 remained for analysis. The mean age was 54.4 ± 17.7 years, and 42.0% were male. ASCVD was present in 413 patients (17.6%), including CAD in 254 patients (10.9%), ischemic stroke in 186 patients (7.9%), PAD in 21 patients (0.9%), and AAA in 14 patients (0.6%). Smoking status and family history of ASCVD were documented in 48.2% and 17.6% of patients, respectively.

Compared with the non-ASCVD group, patients with ASCVD were significantly older, more often male, and had a higher prevalence of DM, hypertension, CKD, smoking, and heart failure. They more frequently used lipid-lowering therapies (statins, ezetimibe, PCSK9 inhibitors, cholestyramine, omega-3 fatty acids) and had lower total and LDL cholesterol levels ($p < 0.05$). Median plasma Lp(a) level was 25.8 (9.6–25.8) nmol/L overall, 27.8 (10.8–74.3) in females, and 20.7 (8.7–63.5) in males. Plasma Lp(a) levels were significantly higher in females than in males in both ASCVD and non-ASCVD groups. Detailed characteristics are shown in [Table 1](#).

[Table 2](#) presents the median plasma Lp(a) levels stratified by disease status. Median plasma Lp(a) levels were significantly higher in patients with ASCVD (37.2 nmol/L, IQR 11.6–107.6), CAD (43.8 nmol/L, IQR 12.9–113.3), and AS (51.6 nmol/L, IQR 18.1–106.5) compared with those without these conditions (all $p < 0.05$). Patients with PAD (44.5 nmol/L, IQR 13.8–115.1) and VTE (50.3 nmol/L, IQR 23.6–120.8) also had higher plasma Lp(a) levels, but these differences were not statistically significant.

A multivariate logistic regression analysis was conducted to identify independent predictors of ASCVD and CAD. As presented in [Table 3](#), the analysis revealed that elevated plasma Lp(a) levels, along with age, male sex, diabetes, hypertension, and CKD, were independently associated with an increased risk of ASCVD and CAD. Notably, high plasma Lp(a) levels (≥ 40 nmol/L) were significantly associated with both ASCVD and CAD. The risk of ASCVD in patients with plasma Lp(a) ≥ 40 nmol/L was comparable to that observed in patients with DM and CKD stage 3–5 (OR 1.538 vs 1.562 vs 1.484, respectively). Similarly, for CAD, the risk associated with elevated Lp(a) levels was comparable to the risk seen in patients with DM and CKD (OR 1.877 vs 1.660 vs 1.594, respectively). Lp(a) remained independently associated with ASCVD and CAD after adjustment for on treatment LDL-C ([Supplemental Table 1](#)). These findings underscore the clinical relevance of Lp(a) ≥ 40 nmol/L as a potential threshold for cardiovascular risk stratification, similar in magnitude to well-established risk factors such as DM and CKD.

ROC curve analysis was performed to evaluate the predictive performance of plasma Lp(a) levels for ASCVD and CAD after adjusting for age, sex, diabetes mellitus, hypertension, and CKD stage 3–5. As shown in [Figure 1](#). The AUC for Lp(a) cutoff ≥ 40 nmol/L for predicting ASCVD and CAD were 0.823 ± 0.021 and 0.827 ± 0.023 respectively indicating good discrimination between patients with and without diseases. Plasma Lp(a) ≥ 40 nmol/L had a sensitivity of 48.4% and specificity of 64.0% for predicting ASCVD, which increased to 82.8% and 69.0% with the model. For CAD, sensitivity and specificity were 53.5% and 63.6%, improving to 78.0% and 76.1% with the model.

The relationship between plasma Lp(a) levels and the risk of ASCVD and CAD was analyzed using both univariate and multivariate models across predefined Lp(a) categories, using Lp(a) < 25 nmol/L as reference. As illustrated in [Figure 2](#), univariate analysis demonstrated a positive association between increasing plasma Lp(a) levels and the presence of ASCVD and CAD. In multivariate analysis, after adjusting for age, sex, diabetes mellitus, hypertension, and CKD stage 3–5, plasma Lp(a) levels ≥ 75 nmol/L, and ≥ 125 nmol/L remained significantly associated with higher odds of CAD and ASCVD, respectively. The adjusted ORs increased progressively with higher Lp(a) levels, suggesting a level-dependent relationship.

Discussion

Our study demonstrates a significant association between elevated plasma Lp(a) levels and the risk of ASCVD and CAD in the Thai population. We identified a plasma Lp(a) threshold of ≥ 40 nmol/L as an optimal cutoff for predicting these cardiovascular conditions, providing important insights into the role of Lp(a) in cardiovascular risk stratification for this population.

Table 1 Baseline Characteristic of Patients with Non-ASCVD and ASCVD (n=2341)

	Overall (n=2341)	Non ASCVD (n=1928)	ASCVD (n=413)	P-values
Age (years)	54.4±17.7	52.1±17.6	65.1±14.0	<0.001
Male, n (%)	984 (42.0)	742 (38.5)	242 (58.6)	<0.001
BMI (kg/m²)	24.8±5.1	24.8±5.2	25.0±4.5	0.586
Comorbidity, n (%)				
Diabetes	567 (24.2)	367 (19.0)	200 (48.4)	<0.001
Hypertension	976 (41.7)	632 (32.8)	344 (83.3)	<0.001
CKD 3–5	224 (9.6)	121 (6.3)	103 (24.9)	<0.001
CAD	254 (10.9)	0	254 (61.5)	-
Ischemic stroke	186 (7.9)	0	186 (45.0)	-
AAA	14 (0.6)	0	14 (3.4)	-
PAD	21 (0.9)	0	21 (5.1)	-
AS	45 (1.9)	19 (1.0)	26 (6.3)	<0.001
VTE	16 (0.7)	16 (0.8)	0	0.092
Heart failure	101 (4.3)	34 (1.8)	67 (16.2)	<0.001
Smoking, n (%)	237 (21.0)	147 (16.6)	90 (37.0)	<0.001
Family history of ASCVD, n (%)	94 (22.8)	76 (22.1)	18 (26.5)	0.432
Medication, n (%)				
Statin	1127 (48.1)	744 (38.6)	383 (92.7)	<0.001
Ezetimibe	145 (6.2)	73 (3.8)	72 (17.4)	<0.001
PCSK9_inhibitor	25 (1.1)	13 (0.7)	12 (2.9)	<0.001
Nicotinic acid	5 (0.2)	2 (0.1)	3 (0.7)	0.041
Fibrates	76 (3.2)	63 (3.3)	13 (3.1)	0.901
Cholestyramine	8 (0.3)	5 (0.3)	3 (0.7)	0.153
Omega_3_acid	7 (0.3)	3 (0.2)	4 (1.0)	0.021
SBP (mmHg)	130.8±18.2	130.1±17.7	134.3±19.8	<0.001
DBP (mmHg)	74.5±11.7	74.5±11.5	74.3±12.5	0.744
Total cholesterol (mg/dL)	188.8±52.5	195.5±51.0	156.3±47.2	<0.001
Triglyceride (mg/dL)	100 (73,137)	98 (71,135)	106 (80,146)	0.004
HDL-cholesterol (mg/dL)	57.0±17.0	58.8±16.9	48.4±14.6	<0.001
Calculated	109.1±46.5	113.8±45.8	83.5±41.4	<0.001
LDL-cholesterol (mg/dL)				
Lipoprotein(a), nmol/l	25.8 (9.6, 25.8)	24.4 (9.5, 63.6)	37.2 (11.6, 107.6)	<0.001
Lp(a) in male, nmol/l	20.7 (8.7, 63.5)	19.0 (7.9, 56.5)	29.9 (10.0, 78.3)	<0.001
Lp(a) in female, nmol/l	27.8 (10.8, 74.3)	26.8 (10.4, 69.4)	44.4 (15.5, 136.6)	<0.001

Notes: Data were present as mean±standard deviation, median (interquartile range), n(%).

Abbreviations: CKD, Chronic kidney disease; CAD, Coronary artery disease; AAA, Abdominal aortic aneurysm; PAD, Peripheral arterial disease; AS, Aortic valve stenosis; VTE, Venous thromboembolism; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

Consistent with finding across multiple ethnic groups, including White, Black and Asian populations,^{1,4,12–14} our findings confirm the strong positive association between elevated Lp(a) levels and ASCVD risk. In our cohort, the median Lp(a) level in ASCVD group was 37.2 nmol/L, closely aligning with global data reporting a median Lp(a) level of 37.2 nmol/L in Asian individuals with ASCVD.¹⁴ Ethnic disparities in Lp(a) concentrations have been well documented, with the highest levels observed in Black populations, followed by White, Hispanic, and East Asian populations.^{1,4,12,13} Even within Asian subpopulations, notable differences exist, with South Asians exhibiting the highest Lp(a) levels, followed by Southeast Asians and East Asians.^{13,15} The variability in Lp(a) levels among ethnic groups is largely attributed to genetic determinants, including differences in the copy number of Kringle IV type 2 (KIV-2) repeats, single nucleotide polymorphisms (SNPs) in and around the LPA gene locus, and other genetic factors influencing Lp(a) metabolism.^{12,16} Interestingly, our study found that Lp(a) levels were higher in females compared to males in both the ASCVD and non-ASCVD groups, a trend consistent with previous studies.^{17,18} The observed sex-related differences in

Table 2 Median Plasma Lipoprotein(a) [Lp(A)] Levels in Patients with and without Various Cardiovascular Diseases

Cardiovascular Disease	Lp(a) Level (nmol/L)		P-value
	Yes	No	
ASCVD	37.2 (11.6, 107.6) (n=413)	24.4 (9.5, 63.6) (n= 1928)	<0.001
CAD	43.8 (12.9, 113.3) (n=254)	24.5 (9.5, 64.5) (n= 2087)	<0.001
Stroke	27.5 (10.1, 78.0) (n=186)	25.7 (9.6, 69.2) (n=2155)	0.390
AAA	46.7 (6.0, 81.1) (n=14)	25.7 (9.6, 69.5) (n=2327)	0.611
PAD	44.5 (13.8, 115.1) (n=21)	25.5 (9.6, 69.4) (n=2320)	0.052
AS	51.6 (18.1, 106.5) (n=45)	25.3 (9.6, 68.5) (n=2296)	0.002
VTE	50.3 (23.6, 120.8) (n=16)	25.6 (9.6, 69.2) (n=2325)	0.057

Notes: Data are presented as median (interquartile range). Plasma Lp(a) levels are reported in nmol/L.

Abbreviations: Lp(a), Lipoprotein(a); ASCVD, Atherosclerotic Cardiovascular Disease; CAD, Coronary Artery Disease; AAA, Abdominal Aortic Aneurysm; PAD, Peripheral Arterial Disease; AS, Aortic Stenosis; VTE, Venous Thromboembolism.

Table 3 Multivariate Logistic Regression Analysis for Predictors of ASCVD and CAD

	ASCVD		CAD	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age (years)	1.024 (1.015, 1.033)	<0.001	1.022 (1.012, 1.033)	<0.001
Male	2.146 (1.683, 2.735)	<0.001	2.269 (1.696, 3.037)	<0.001
Diabetes	1.562 (1.205, 2.024)	0.001	1.660 (1.225, 2.249)	0.001
Hypertension	5.374 (3.932, 7.345)	<0.001	4.862 (3.254, 7.263)	<0.001
CKD stage 3–5	1.484 (1.069, 2.059)	0.018	1.594 (1.113, 2.284)	0.011
Lp(a)≥40 nmol/L	1.538 (1.203, 1.958)	<0.001	1.877 (1.407, 2.505)	<0.001

Notes: The model included age, sex, diabetes, hypertension, CKD stage 3–5, and Lp(a)≥40 nmol/L. Odds ratios represent the relative increase in odds of ASCVD or CAD associated with each variable. P-values were derived using multivariate logistic regression.

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; Lp(a), Lipoprotein(a).

Lp(a) levels may be partly explained by hormonal influences, as estrogen is known to modulate Lp(a) concentrations, leading to variations between sexes.¹⁹ The lower LDL-C levels observed in the ASCVD group are likely a result of intensive lipid-lowering therapy, particularly statins, which were used in over 90% of this group. As such, LDL-C values reflect on-treatment levels rather than baseline lipid status. Nevertheless, Lp(a) remained independently associated with ASCVD and CAD after adjustment for LDL-C, reinforcing its value as a residual and independent risk marker.

Large cohort studies and genetic analyses have provided strong evidence supporting a causal relationship between elevated Lp(a) levels and ASCVD, as well as AS.^{1,5,20–24} The UK Biobank study demonstrated that each 50 nmol/L increment in Lp(a) concentration was associated with an 11% increased risk of ASCVD, with similar hazard ratios observed across different ethnic groups (HR 1.11, 1.10, and 1.07 for White, South Asian, and Black individuals, respectively).¹ Similarly, the Copenhagen City Heart Study reported a stepwise increase in myocardial infarction risk with rising Lp(a) levels, with no apparent threshold effect.⁵ In line with these findings, our study also observed that higher Lp(a) levels were associated with increased odds of ASCVD and CAD compared to lower Lp(a) levels (<25 nmol/L as reference). Patients with CAD and AS exhibited significantly higher Lp(a) levels than those without these conditions. However, no significant differences in Lp(a) levels were observed among patients with and without stroke, PAD, AAA, or heart failure. This may suggest that an extremely high Lp(a) level is required to establish a significant association with these conditions, as previously reported in other studies.⁹ The Copenhagen General Population Study (CGPS) further supports this concept, demonstrating that individuals with Lp(a)>83 nmol/L had a significantly higher risk of myocardial infarction, ischemic heart disease, AS, and heart failure (men only), compared to those with Lp(a)

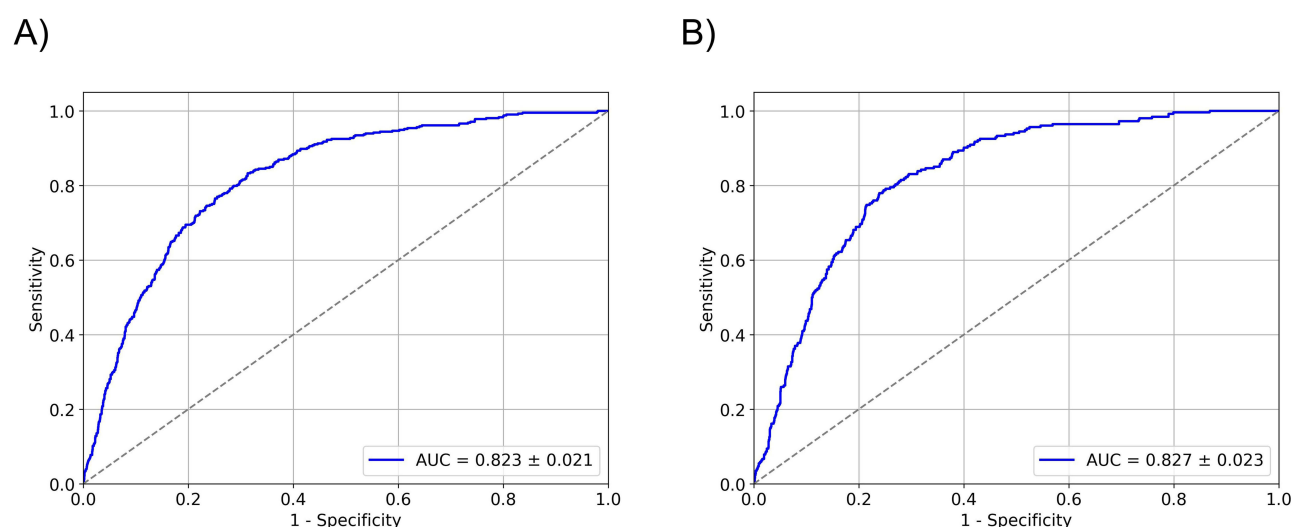


Figure 1 Receiver Operating Characteristic (ROC) curves for plasma Lp(a) ≥ 40 nmol/L in predicting ASCVD (A) and CAD (B) adjusting for age, sex, diabetes, hypertension, and CKD.

< 18 nmol/L.¹⁸ Interestingly, a separate analysis of the same CGPS cohort identified a significant relationship between extremely elevated Lp(a) levels (> 199 nmol/L or above the 96th percentile) and ischemic stroke. These findings suggest that while moderate elevations in Lp(a) primarily influence CAD and AS risk, an exceptionally high Lp(a) concentration may be required to confer a significant association with ischemic stroke and other vascular conditions.²⁵

Although there was a continuous increase in ASCVD and CAD risk with rising Lp(a) levels rather than a distinct threshold effect, defining clinically relevant cut-off values remains crucial for practical application. Given the variability in guideline-recommended Lp(a) thresholds, ranging from 75 nmol/L⁹ to higher values in other populations, and the ethnic diversity in Lp(a) distribution, we selected 40 nmol/L—corresponding to the median Lp(a) level in our ASCVD and CAD cohorts—as an optimal threshold for further analysis. From multivariate analysis, Lp(a) levels ≥ 40 nmol/L were associated with an OR of 1.538 for ASCVD, a risk comparable to well-established cardiovascular risk factors such as diabetes mellitus (OR 1.562) and CKD (OR 1.484). The predictive utility of Lp(a) ≥ 40 nmol/L demonstrated 48.4% sensitivity and 64.0% specificity for ASCVD and 53.5% sensitivity and 63.6% specificity for CAD. Notably, incorporating Lp(a) ≥ 40 nmol/L into a multivariate model that included other ASCVD risk factors significantly improved predictive accuracy, enhancing sensitivity and specificity to 70–80%. These findings suggest that the Thai population may exhibit heightened susceptibility to the cardiovascular effects of Lp(a) at lower levels compared to White populations. However, the INTERHEART study previously reported higher Lp(a) levels in Southeast Asians compared to Europeans in both control and myocardial infarction cases,¹³ highlighting the need for further large-scale prospective studies in the Thai population to validate these observations. The ROC curve analysis further supports the clinical relevance of Lp(a) levels in risk stratification, with an AUC of 0.823 for ASCVD and 0.827 for CAD, indicating good discriminative performance. The predictive performance of Lp(a) was enhanced when combined with other cardiovascular risk factors, highlighting the potential utility of Lp(a) measurement in routine clinical practice. In the 2018 guideline on the management of blood cholesterol from the American College of Cardiology (ACC),²⁶ Lp(a) ≥ 125 nmol/L was identified as one of the risk-enhancing factors used to discuss the initiation of statin therapy in patients with borderline and intermediate risk of ASCVD. In agreement with the ACC guideline, our study found that Lp(a) ≥ 125 nmol/L was associated with higher risk of both ASCVD and CAD as compared to the low Lp(a) group after adjusting for other risk factors, supporting the use of plasma Lp(a) as one of the risk-enhancing factors. Although 92.7% of patients in the ASCVD group were receiving statin therapy, prior evidence has shown that statins do not have a significant effect on plasma Lp(a) concentrations.²⁷ Therefore, the use of statins is unlikely to confound the association between Lp(a) levels and ASCVD observed in our study.

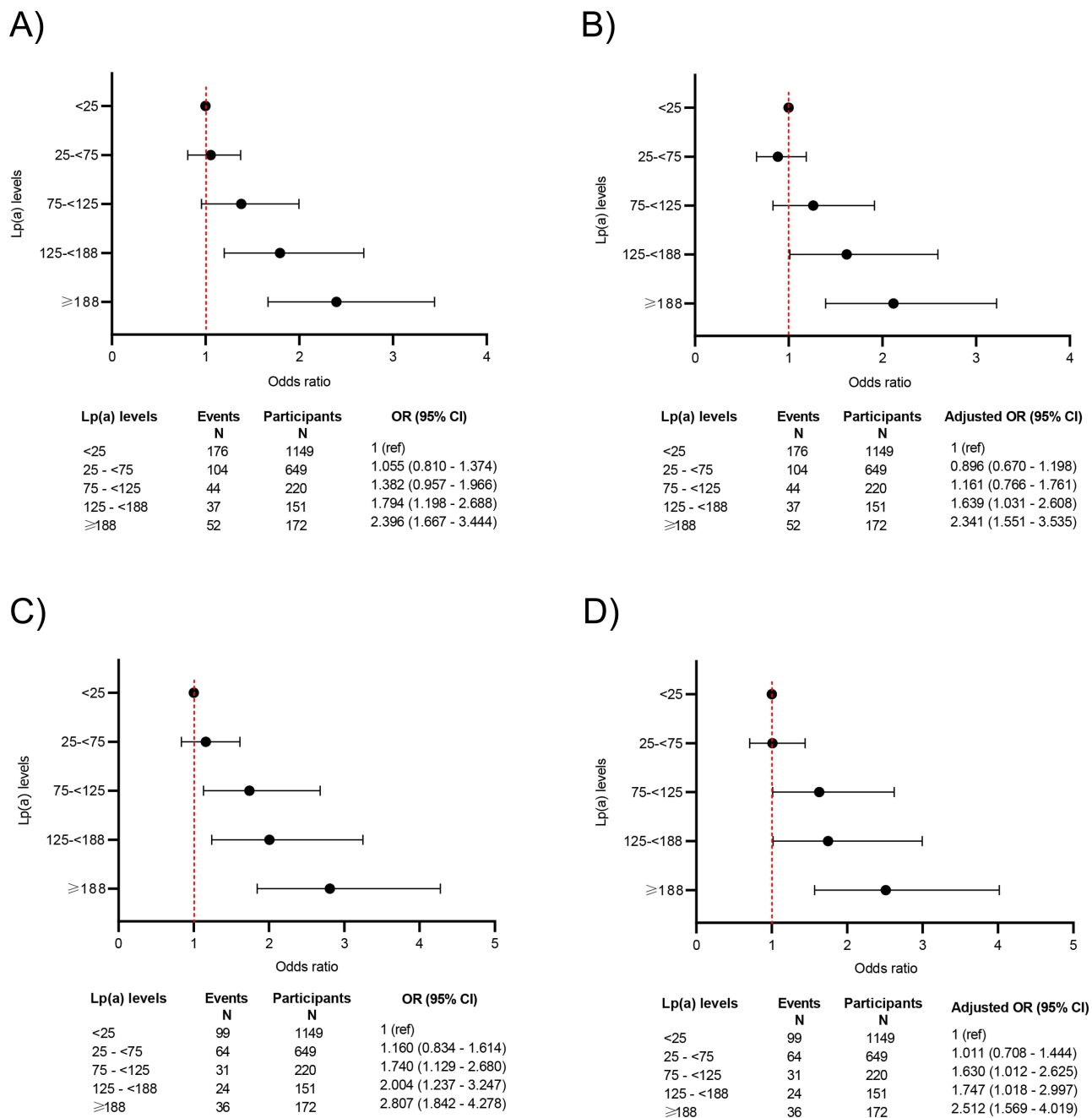


Figure 2 Univariate and Multivariate analysis of plasma Lp(a) levels for ASCVD and CAD Risk. This figure presents the odds ratios with 95% confidence intervals for ASCVD (**A** and **B**) and CAD (**C** and **D**) across different plasma Lp(a) level categories. The left panels show results from univariate analysis, while the right panels display adjusted ORs from multivariate analysis, which were adjusted for age, sex, diabetes mellitus, hypertension, and CKD stage 3–5. Odds ratios were calculated using plasma Lp(a) <25 nmol/L as the reference category. The red dotted line was drawn at an OR=1.

To the best of our knowledge, this study represents the first investigation in Thailand exploring the association between Lp(a) and ASCVD in a large patient cohort. A major strength of our study is the use of real-world hospital data, including comprehensive clinical and laboratory parameters, which allowed us to perform robust multivariate analyses adjusting for key cardiovascular risk factors. Furthermore, the inclusion of ICD-10 and procedural codes provided a reliable identification of CAD and AS cases. Our study also benefits from the use of a standardized Lp(a) measurement assay that is traceable to international reference materials, ensuring high accuracy and reproducibility. Additionally, the

determination of an optimal Lp(a) cutoff specific to the Thai population enhances the applicability of our findings in regional clinical practice and cardiovascular risk assessment.

Despite these strengths, our study has some limitations. First, its retrospective design and reliance on electronic medical records may introduce selection and information biases, as data collection was dependent on available hospital records rather than a controlled study design. Second, LDL-C levels in this study represent on-treatment values, particularly in the ASCVD group, which may underestimate the patients' baseline lipid burden. This could introduce bias when evaluating the relative contribution of Lp(a) compared to LDL-C. However, Lp(a) remained significantly associated with ASCVD and CAD even after adjusting for LDL-C, reinforcing its value as residual and independent risk marker ([Supplemental Table 1](#)). Third, our study was limited to patients receiving care at a single tertiary hospital, restricting generalizability to the broader Thai population. Additionally, we were unable to access information on patients with documented ASCVD who sought follow-up care at other institutions, potentially leading to an underestimation of Lp(a)-associated cardiovascular risk. Lastly, the sample size for certain cardiovascular conditions, such as PAD and AAA, was relatively small, which may have reduced statistical power and limited the ability to detect significant associations in these subgroups. Future studies with larger cohorts and multi-center data collection are warranted to further validate our findings.

Conclusion

Our findings suggest that plasma Lp(a) levels ≥ 40 nmol/L are independently associated with increased risks of ASCVD and CAD in the Thai population. This threshold may serve as a useful marker for cardiovascular risk stratification, particularly when used alongside traditional risk factors. Future prospective studies with larger sample sizes and longer follow-up periods are needed to validate these findings and explore their implications in clinical practice.

Data Sharing Statement

The collection of data for this study is available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no conflicts of interest in this work.

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